Victor R. Preedy *Editor*

Handbook of Anthropometry

Physical Measures of Human Form in Health and Disease

Volume 1 • Parts 1–6

Springer

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ISBN 978-1-4419-1787-4 e-ISBN 978-1-4419-1788-1
DOI 10.1007/978-1-4419-1788-1
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011935369

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

There are a variety of theoretical and practical definitions of anthropometry, but in its simplest form anthropometry is the physical measurement of the human body and its parts. Methods can be very simple. On the other hand, advances in technology and computing have given rise to the development of more sophisticated apparatus which can be used to measure and characterise individual tissues and organs. Thus, anthropometric devices can range from a simple tape to measure head circumference to expensive electromagnetic image-capturing systems for characterising limb shapes. These methods can be used to obtain information on normal people at various life stages. Alternatively, anthropometry can be used and applied to understanding disease, including the responses to treatments, or to generate reference data. Understanding and applying concepts and techniques of anthropometry require a good source of written material that covers not only the theoretical basics but the practical applications in health and disease. Hitherto such sources on human anthropometry have been fragmentary, covering single facets without any cross-fertilisation between disciplines or sciences or between different intellectual divides. These deficiencies are, however, addressed in *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, where all facets and features of anthropometry are described. The book is divided into 26 different parts as follows:

Part I:	Tools and Techniques in Anthropometry: General Methods
Part II:	Tools and Techniques in Anthropometry: Water, Hydration and Surface Area
Part III:	Tools and Techniques in Anthropometry: Muscle
Part IV:	Tools and Techniques in Anthropometry: Adipose Tissue, Other Compartments and Relationships
Part V:	Regions and Anatomical Areas of the Body: Head and Face
Part VI:	Regions and Anatomical Areas of the Body: Limbs, Extremities and Bones
Part VII:	Regions and Anatomical Areas of the Body: Joints and Digits
Part VIII:	Regions and Anatomical Areas of the Body: Abdominal and Trunk Regions
Part IX:	Regions and Anatomical Areas of the Body: Sensory Organs
Part X:	Regions and Anatomical Areas of the Body: Internal Organs, Other Tissues and Regions
Part XI:	Anthropometry of Pregnancy: Prenatal and Postnatal Aspects
Part XII:	Anthropometry of Infants and Children

Part XIII: Anthropometry of Puberty and Adolescence in Health and Disease
Part XIV: Anthropometry of Middle-Aged and Aged in Health and Disease
Part XV: Anthropometry in Genetic Disease and Polymorphisms
Part XVI: Anthropometry in Cancer
Part XVII: Anthropometry in Exercise and Sport Activities
Part XVIII: Anthropometry in Metabolic Disease and Obesity
Part XIX: Anthropometry in Diabetes
Part XX: Anthropometry in Cardiovascular Disease
Part XXI: Anthropometry in Organ Disease
Part XXII: Anthropometry in Special Conditions and Circumstances
Part XXIII: Anthropometry in Ethnic Groups and Cultural and Geographical Diversity
Part XXIV: Anthropometry and Nutrition: General Aspects
Part XXV: Anthropometry and Nutrition: Micro- and Macro-Nutrients
Part XXVI: Biomechanical and Ergonomic Aspects

The chapters are written by national and international experts who are specialists in their field. Each chapter is self-contained. Sometimes experts in one field are novices in another. To bridge this intellectual divide, the authors have incorporated sections on applications to other areas of health and disease, practical methods and techniques, guidelines, and key points or features. The summary points presented in bullet form are designed for easier intellectual digestion. This book is for health scientists, doctors, nurses, physiologists, nutritionists and dietitians, public health scientists, epidemiologists, health workers and practitioners, exercise physiologists, physiotherapists, university faculty, undergraduates and graduates. It is also designed for policy makers, designers and ergonomists.

Biography

Victor R. Preedy is currently Professor of Nutritional Biochemistry in the Department of Nutrition and Dietetics, King's College London, and Honorary Professor of Clinical Biochemistry in the Department of Clinical Biochemistry, King's College Hospital. He is also Director of the Genomics Centre, Kings College London. He is presently a member of the School of Medicine, King's College London. King's College London is one of the leading universities, currently ranked consistently within the top 25 in the world. Professor Preedy gained his Ph.D. in 1981, and in 1992 he received his Membership of the Royal College of Pathologists (MRCPath), based on his published works. He was elected a Fellow of the Royal College of Pathologists (FRCPath) in 2000. In 1993, he gained his second doctoral degree (D.Sc.) for his outstanding contribution to protein metabolism. In 2004, Professor Preedy was elected as a Fellow to both the Royal Society for the Promotion of Health (FRSH) and the Royal Institute of Public Health (FRIPHH). In 2009, he was elected as a Fellow of the Royal Society for Public Health (FRSPH). He is also a Fellow of the Society of Biology (FSB). Professor Preedy has written or edited over 550 articles, which include over 160 peer-reviewed manuscripts based on original research and 85 reviews and 30 books. His interests pertain to matters concerning nutrition and health at the individual and societal levels.

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Part I
Tools and Techniques in Anthropometry: General Methods

Chapter 1
Calculating Sample Size in Anthropometry

Carine A. Bellera, Bethany J. Foster, and James A. Hanley

Abstract Sample size estimation is a fundamental step when designing clinical trials and epidemiological studies for which the primary objective is the estimation or the comparison of parameters. One may be interested in the prevalence of overweight children in a given population; however, the true prevalence will remain unknown and cannot be observed unless the whole population is studied. Statistical inference is the use of statistics and random sampling to make inferences concerning the true parameters of a population. By choosing a representative sample, inference based on the observed prevalence leads to an estimation of the true parameter. But how many subjects should be sampled to obtain an accurate estimate of the prevalence? Similarly, how many subjects should we sample to show that this parameter is different from some fixed value?

We first review basic statistical concepts including random variables, population and sample statistics, as well as probability distributions such as the binomial and normal distributions. Principles of point and interval estimation, as well as hypothesis testing, are presented. We consider several commonly used statistics: single proportions, differences between two proportions, single means, differences between two means, and reference limits. For each parameter, point estimators are presented as well as methods for constructing confidence intervals. We then review general methods for calculating sample sizes. We first consider precision-based estimation procedures, where the sample size is estimated as a function of the desired degree of precision. Next, although there is greater emphasis on precision-driven estimation procedures, we also briefly describe power-based estimation methods. This approach requires defining a priori the difference one wishes to detect, the desired significance level, and the desired power of the test. Sample size estimation procedures are presented for each parameter, and examples are systematically provided.

Abbreviations and Notations

N	Population size
n	Sample size
ME	Margin of error
ε	Precision

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_1,

μ	Population mean
m	Sample mean
σ^2	Population variance
s^2	Sample variance
π	Population proportion
p	Sample proportion
H_0	Null hypothesis
H_A	Alternative hypothesis
α	Type I error rate
β	Type II error rate
z_p	$100p\%$ standard normal deviate
BMI	Body mass index
DBP	Diastolic blood pressure

1.1 Introduction

Sample size estimation is a fundamental step when designing clinical trials and epidemiological studies for which the primary objective is the estimation or the comparison of parameters. One may be interested in the prevalence of a given health condition, e.g. obesity, in a specific population; however, the true prevalence will always remain unknown and cannot be determined unless the whole population is observed. Statistical inference is the use of statistics and random sampling to make inferences concerning the true parameters of a population. By selecting a representative sample, inference based on the **observed** prevalence leads to an estimation of the **true** parameter. But how many subjects should be sampled to obtain an accurate estimate of the prevalence?

Sample size estimation can be either precision-based or power-based. In the first scenario, one is interested in estimating a parameter, such as a proportion, or a difference between two means, with a specific level of precision. On the other hand, one might only be interested in testing whether two parameters differ. The sample size will be estimated as a function of the size of the difference one wishes to detect as well as the degree of certainty one wishes to obtain.

To understand the process of sample size estimation, it is important to be familiar with basic statistical concepts. We first review statistical principles, as well as general concepts of statistical inference, including estimation and hypothesis testing. Methods for sample size estimation are presented for various parameters using precision-based and power-based approaches, although there is greater emphasis on precision-driven estimation procedures (Gardner and Altman 1986, 1988).

Most concepts presented in this chapter are available in introductory statistical textbooks (Altman et al. 2000; Armitage et al. 2002) and texts focusing on the methodology of clinical trials (Machin et al. 1997; Friedman et al. 1998; Sackett 2001; Piantadosi 2005). We refer the interested readers to these works.

1.2 Basic Statistical Concepts

1.2.1 Random Variable

A random variable assigns a value to each subject of a population, such as weight, hair colour, etc. By random, it is implied that the true value of the variable cannot be known until it is observed. A variable

(for simplicity, we will often discard the term *random* throughout the rest of this chapter) is either **quantitative** or **qualitative**.

A quantitative variable is one that can be measured and can take a range of values, for example, waist circumference, size, age, or the number of children in a household. Quantitative variables include **discrete** and **continuous** variables. A discrete variable is one that can take only a limited range of values, or similarly, the possible values are distinct and separated, such as the number of children in a household. On the other hand, a continuous variable can take an infinite range of values, or similarly, can assume a continuous uninterrupted range of values, such as height or age.

A qualitative or categorical variable is one that cannot be numerically measured, such as the presence or absence of a disease, gender, or the colour of hair. A **dichotomous** or binary variable is one that can take one of two values, such as the presence or absence of a trait or state, or whether or not one is overweight.

1.2.2 Population Versus Sample Statistics

Suppose we are interested in describing the size of 10-year old girls attending English schools. Height in this population can be summarized by various quantities, such as the mean, the median or the variance. These quantities are called **population statistics** and are usually represented with Greek letters. Unless all 10-year old girls attending English schools are measured, the true value of population statistics, such as the mean height in our example, cannot be observed and is **unknown**. It is however possible to **estimate** the true value with some degree of certainty. This involves randomly sampling from the whole population of interest. Based on a random sample of 10-year old girls attending English schools, one observes the distribution of heights in this sample and calculates the observed mean. Quantities derived from an **observed sample** are called **sample statistics**, and are usually denoted using Roman letters.

Two random samples of equal size will usually not yield the same value of the sample statistic. The possible differences between the estimates from all possible samples (conceptual), or between each possible estimate and the true value are referred to as **sampling variation**. As a result, it is not possible to conclude that the observed sample mean corresponds to the true population mean. By using appropriate statistical methods, sample statistics can be used to make inferences about population statistics. In the next section, we present commonly used statistics.

1.2.3 Summarizing Data

1.2.3.1 Categorical Variables

Summarizing categorical variables involves counting the number of observations for each category of the variable. These counts are usually referred to as frequencies. The proportion of such counts among the total can also be represented.

1.2.3.2 Quantitative Variables

Continuous variables can be summarized using measures of **location** and **dispersion**. Measures of location, such as the mean or the median, represent the central tendency of distributions. Dispersion measures, such as the variance, represent the repartition of a variable around the central tendency.

Given a population of size N and a variable X with observed values $x_1,\ldots,x_N$, the population mean is given by: $\mu = \sum_{i=1}^{N} \frac{x_i}{N}$. If only a random sample of size n is available, the sample mean m is calculated similarly and given by $m = \sum_{i=1}^{n} \frac{x_i}{n}$.

If observations are ordered in increasing order, the median is the middle observation of the sample. If the number of observations in a sample is odd, the median is the value of the $\frac{1}{2}(n+1)^{\text{th}}$ observation of the ordered sample, while it is the mean of the values of the two middle observations if the number of observations is even.

The most common measure of dispersion is the variance, or its square root, the standard deviation. Given a population of size N, the variance σ^2 is given by $\sigma^2 = \frac{\sum_i (x_i - \mu)^2}{N}$, where μ is the population mean. The population standard deviation is $\sigma = \sqrt{\frac{\sum_i (x_i - \mu)^2}{N}}$. If a sample of size n is available, the sample variance s^2 is provided by $s^2 = \frac{\sum_i (x_i - m)^2}{n-1}$, where m is the sample mean. The denominator is slightly different from that of a population variance. This correction ensures that the parameter s^2 is an unbiased estimator of the population variance σ^2. Similarly, the sample standard deviation, usually denoted as SD, is calculated as $\text{SD} = \sqrt{\frac{\sum_i (x_i - m)^2}{n-1}}$.

Other measures of dispersion include the range, the inter-quartile range and reference limits. The range corresponds to the difference between the maximum and the minimum values. When in increasing order, the first or lower quartile corresponds to the value below which 25% of the data fall. The third or upper quartile corresponds to the value below which 75% of the data fall. There are several methods to compute quartiles: one involves calculating the first and third quartiles as the rank of the $\frac{1}{4}(n+1)$ th and $\frac{3}{4}(n+1)$ th observed values. Other methods are available, but will usually lead to relatively close results (Armitage et al. 2002).

The inter-quartile range is the difference between the upper and lower quartiles. Note that the second or middle quartile corresponds to the value below which 50% of the data fall, and as such, is equivalent to the median.

More generally, the 100p% reference limit, where $0 < p < 1$, is the value below which 100p% of the values fall. For example, the median is equivalent to the 50% reference limit. Reference limits are also called reference values, percentiles, or quantiles.

Example: A random sample of ten 20-year-old women leads to the following observed weights (in kg): 50, 55, 60, 61, 45, 52, 62, 54, 48, 53. The variable of interest X is the weight, which is a continuous variable. We first reorder this random sequence of $n = 10$ observations: 45, 48, 50, 52, 53, 54, 55, 60, 61, 62. Based on previous formulae, we have the following results:

- The sample mean is calculated as $m = \sum_{i=1}^{10} \frac{x_i}{10} = \frac{45 + \cdots + 62}{10} = 54$ kg
- The sample median is calculated as $\text{med} = \frac{53 + 54}{2} = 53.5$ kg

Table 1.1 Sample probability distribution for the categorical variable X defined as the number of copies of allele A

x	0	1	2
$P(X = x)$	3/10	5/10	2/10

- The sample variance is calculated as $s^2 = \dfrac{\sum_i (x_i - 54)^2}{10-1} = \dfrac{(45-54)^2 + \cdots + (62-54)^2}{9} = 32\ \text{kg}^2$
- The range is given by 62–45 = 17 kg

1.2.4 Probability Distributions

A distribution is defined as the set of frequencies of the values or categories of a measurement made on a group of persons. The distribution tells us either how many or what proportion of the group was found to have each value (or each range of values) out of all of the possible values that the quantitative measure can have (Last 2001).

Consider the variable X corresponding to the number of copies of a certain allele A. The variable X can take three distinct values: 0, 1, 2. Ten subjects are randomly selected from the general population and the following series of outcomes is observed: 0, 0, 2, 1, 1, 2, 1, 0, 1, 1. This series is called a random series, since previous values cannot be used to predict future observation. One can then calculate the proportion of subjects carrying two copies of the allele. This observed proportion equals 2/10 in our example. If subjects are randomly sampled indefinitely, this proportion will tend towards a limiting value, called the **probability** of carrying two alleles, denoted by $P(X = 2) = \pi$. The sample probability distribution of the variable X is represented in Table 1.1.

We have the following result: $\sum P(X = x) = 1$. This leads us to a fundamental property of probability distributions: for a given variable, the sum of the probabilities of each possible event equals 1.

1.2.4.1 Bernoulli and Binomial Distributions

Consider a dichotomous random variable X whose values can be either one state or the other, or the absence or presence of a specific trait. The true (unknown) proportion of the population that is in the index category of the state or trait (the probability that a randomly selected individual would be in this category ($X = 1$)) is denoted as π and the probability of being in the other (reference) category ($X = 0$) is thus $1 - \pi$. The parameter π defines the probability distribution of X, and is called the **Bernoulli distribution** (after J Bernoulli, a Swiss mathematician). The variable X is said to follow a Bernoulli distribution with parameter π. If, as here, the variable X is coded as 0 (reference category) or 1 (index category), its mean and variance are given respectively by $\text{mean}(X) = \pi$ and $\text{var}(X) = \pi(1-\pi)$.

Define the random variable Y as the observed number of subjects with a particular state of interest out of n randomly selected subjects. If the probability that this state is present is π, the variable Y, that is, the sum of Bernoulli random variables with parameter π, is said to follow a **binomial distribution** with mean and variance given respectively by $\text{mean}(Y) = n\pi$ and $\text{var}(Y) = n\pi(1-\pi)$. The probability that this state is present for k out of n subjects is given by: $P(Y = k) = C_n^k \pi^k (1-\pi)^{n-k} = \dfrac{n!}{(n-k)!k!}\pi^k(1-\pi)^{n-k}$.

Table 1.2 Probability distribution for the categorical variable *Y* defined as the number of subjects with state *S* out of 3 randomly selected subjects

y	0	1	2	3
$P(Y = y)$	1/8	3/8	3/8	1/8

When n is large, the distribution of Y will converge to a normal distribution with mean $n\pi$ and variance $n\pi(1-\pi)$.

Example: The presence of a health state S is assessed in $n = 3$ randomly selected subjects. The variable Y corresponds to the number of subjects with state S out of the $n = 3$ subjects, and can thus have 4 possible values: 0, 1, 2, or 3. Assume that the state S is present in $\pi = 50\%$ of the population. The probability of observing $k = 2$ subjects with state S out of $n = 3$ randomly selected subjects is given by: $P(Y=2) = C_3^2\pi^2(1-\pi)^{3-2} = \frac{3!}{(3-2)!2!}(0.50)^2(0.50)^{3-2} = \frac{3}{8}$.

The complete probability distribution of Y can be computed and is represented in Table 1.2.

1.2.4.2 The Normal Distribution

Consider a continuous random variable with values that vary between –∞ and +∞. The most important continuous probability distribution is the **Gaussian distribution** (after Karl Gauss, a German mathematician), also called the **normal distribution**, which is indexed by two parameters: the mean and the variance. If X follows a normal distribution with mean μ and variance σ^2, we use the following notation: $X \sim N(\mu,\sigma^2)$.The curve representing the normal distribution is symmetric, so that the mean and the median fall at the centre of the symmetry. It is described by the function $f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}$. The probability that a random variable falls between two values, A and B, is represented graphically by the area under the curve of the probability distribution and between the two vertical lines with coordinates $x = A$ and $x = B$, as illustrated in Fig. 1.1.

Numerically, this probability is obtained by computing the integral $P(A < x < B) = \int_A^B f(x)dx = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2} dx$. Calculation of this integral is not feasible using simple calculation tools; however, the properties of the normal distribution simplify the probability estimation in some cases. For example, the probability that any random normal variable $X \sim N(\mu,\sigma^2)$ falls within one standard deviation of the mean is known to be about 68%, that is $P(\mu - \sigma < x < \mu + \sigma) = 68\%$, as presented in Fig. 1.2.

Similarly, about 95% of the distribution falls within two standard deviations of the mean ($P(\mu - 2\sigma < x < \mu + 2\sigma) = 95\%$), and 99.7% within three standard deviations ($P(\mu - 3\sigma < x < \mu + 3\sigma) = 99.7\%$). For other values of the normal distribution, one has to either calculate the integral $P(A < x < B) = \int_A^B f(x)dx$ (by hand or using a mathematical or statistical software) or rely on statistical tables for which these probabilities are tabulated for values of μ and σ. There is however an infinite number of values for these parameters, and it is therefore not possible to have tables for all of them. Interestingly, every normal distribution with parameters μ and σ can be expressed in terms of a normal distribution with mean 0 and variance 1, called the **standard normal distribution**. Indeed, if $X \sim N(\mu,\sigma^2)$, then one can define the variable Z such that $Z = \frac{X-\mu}{\sigma}$. It can be shown that $Z \sim N(0,1)$.

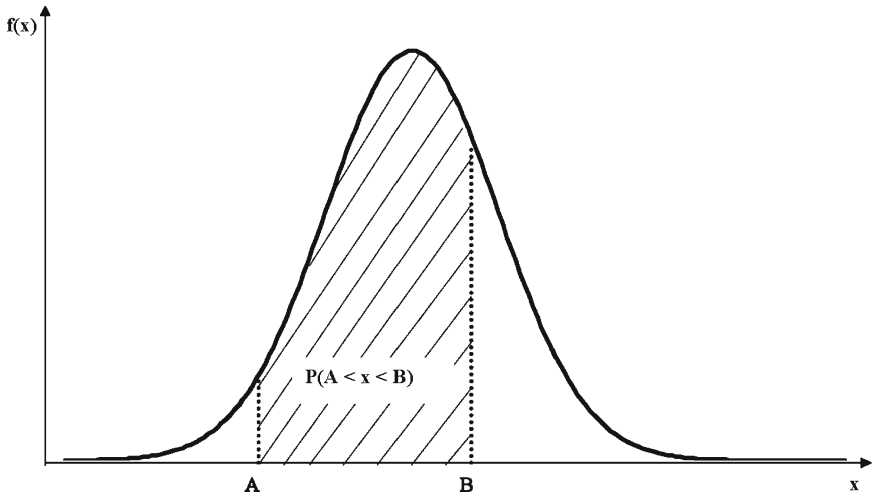

Fig. 1.1 Normal probability distribution function for a variable *X*. The *shaded area* represents the probability that the variable *X* falls between *A* and *B*. Numerically, this probability is obtained by computing the integral $P(A < x < B) = \int_A^B f(x)dx = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2} dx$

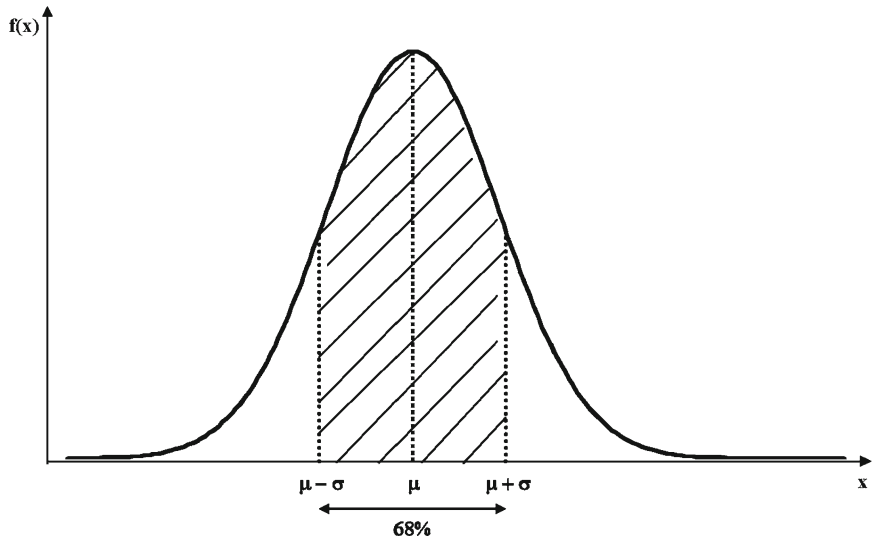

Fig. 1.2 Probability distribution function for a normal random variable *X* with mean μ and variance σ^2. The *shaded area* represents the probability that the normal variable *X* falls within the interval from the mean minus one standard deviation to the mean plus one standard deviation, that is $P(\mu - \sigma < x < \mu + \sigma)$, which is about 68%

Thus, computing the probability that a variable $X \sim N(\mu,\sigma^2)$ belongs to the interval [A;B], is equivalent to computing the probability that a variable $Z \sim N(0,1)$ belongs to the interval $\left[\frac{A-\mu}{\sigma}; \frac{B-\mu}{\sigma}\right]$. Tables of the standard normal distribution are available in most statistical textbooks. Important tables are associated with the standard normal distribution, including the table $P(z)$, which provides for each

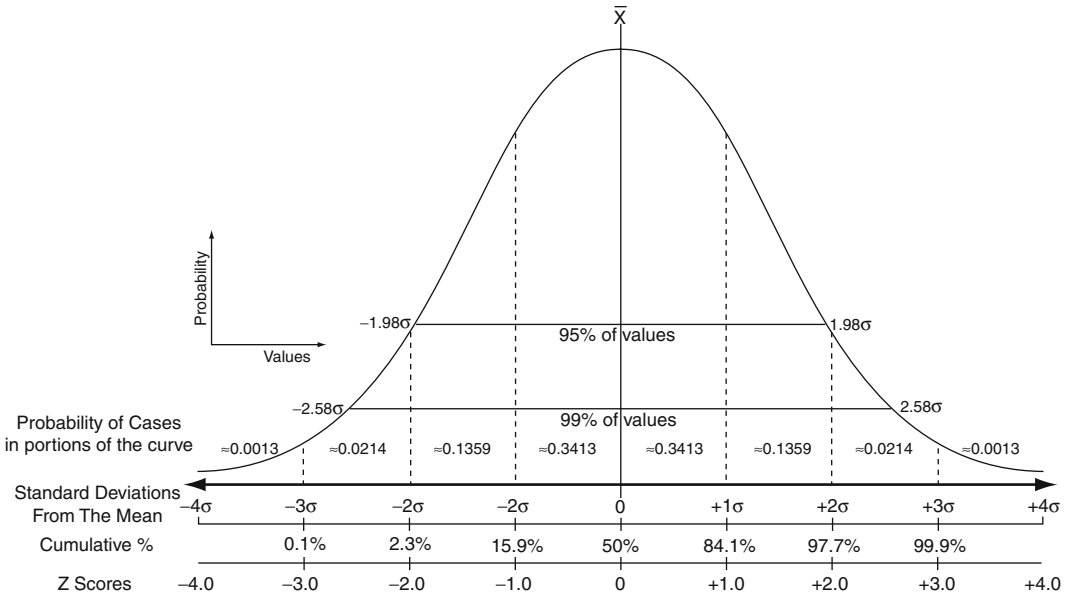

Fig. 1.3 The normal distribution. This plot illustrates standard results of the normal distribution including standard deviations from the means and the *Z*-scores

value of z, the probability that Z falls outside the interval $[-z; z]$: $P(z) = P(Z < -z \text{ or } Z > z) = 1 - P(-z < Z < z)$. Some standard normal values are commonly used: $P(1.64) = 0.10$ and $P(1.96) = 0.05$, that is, $P(-1.96 < Z < 1.96) = 95\%$. Thus, if a standard normal variable is randomly selected, there is a 95% chance that its value will fall within the interval [–1.96; 1.96]. Equivalently, the probability that a standard normal random variable $Z \sim N(0,1)$ falls outside the interval [–1.96; 1.96] is 5%. Given the symmetry of the normal distribution, $P(Z > 1.96) = P(Z < -1.96) = 2.5\%$. These standard results are illustrated in Fig. 1.3. The *Z*-values are usually referred to as the *Z*-scores and are commonly used in anthropometry. They are discussed in greater detail in a subsequent chapter.

The normal distribution is commonly used in anthropometry, in particular to construct reference ranges or intervals. This allows one to detect measurements which are extreme and possibly abnormal. A typical example is the construction of growth curves (WHO Child growth standards 2006). In practice, however, data can be skewed (i.e. not symmetric) and thus observations do not follow a normal distribution (Elveback et al. 1970). In such cases, a transformation of the observations, such as logarithmic, can remove or at least reduce the skewness of the data (Harris and Boyd 1995; Wright and Royston 1999).

1.3 Principles of Statistical Estimation

There are two estimation procedures: **point estimation** and **interval estimation**. Point estimation provides a value that we hope to be as close as possible to the true unknown parameter value. Interval estimation provides an interval that has a fixed a priori probability of containing the true parameter value.

1.3.1 Point Estimation

1.3.1.1 Point Estimator and Point Estimate

Point estimation is the process of assigning a value to a population parameter based on the observation of a sample drawn from this population. The resulting numerical value is called the **point estimate**; the mathematical formula/function used to obtain this value is called the **point estimator**. While the point estimator is identical whatever the sample, the point estimate varies across samples.

1.3.1.2 Point Estimation for a Proportion

The variable of interest is binary, such as the presence or absence of a specific health condition. We are interested in π, the true prevalence of this condition. Assume we randomly draw a sample of n subjects and denote the observed number of subjects with the condition of interest by k. The point estimator of π is given by $p = \frac{k}{n}$, while point estimates correspond to the numerical values $p_1, p_2, \ldots,$ obtained from distinct samples of n observations.

1.3.1.3 Point Estimation for a Mean and a Variance

X is a continuous variable with population mean and variance denoted respectively by μ and σ^2. If n subjects are randomly selected with subjects i=1 to n having respectively observed values x_1 to x_n, the mean μ, the variance σ^2 and the standard deviation SD are estimated respectively by $m = \sum_{i=1}^{n} \frac{x_i}{n}$, $s^2 = \sum_{i=1}^{n} \frac{(x_i - m)^2}{n-1}$ and $\mathrm{SD} = \sqrt{\sum_{i=1}^{n} \frac{(x_i - m)^2}{n-1}}$.

1.3.1.4 Point Estimation for a Reference Limit

Let $X_1, X_2, \ldots, X_n$ be the measurements for a random sample of n individuals. The $100p\%$ reference limit, where $0 < p < 1$, is the value below which $100p\%$ of the values fall. Reference limits may be estimated using nonparametric or parametric (i.e. distribution-based) approaches (Wright and Royston 1999).

The simplest approach is to find the empirical reference limit, based on the order statistics. The k^{th} order statistic, denoted as $X_{(k)}$, of a statistical sample is equal to its k$^{\text{th}}$-smallest value. Thus, given our initial sample $X_1, X_2, \ldots, X_n$, the order statistics are $X_{(1)}, X_{(2)}, \ldots, X_{(n)}$, and represent the observations with first, second, …, n^{th} smallest value, respectively. An empirical estimation of the $100p\%$ reference limit is given by the value which has rank $[p(n+1)]$, where [.] denotes the nearest integer. For example, for a sample of size $n = 199$ and $p = 0.025$, $[p(n+1)]$=5, and thus the value of the fifth order statistic, $X_{(5)}$, provides a point estimate of the 2.5% reference limit.

Reference limits can also be estimated based on parametric methods. Assume that the observations follow a normal distribution with mean μ and variance σ^2. For a random sample of size n, the sample mean and sample standard deviation are given by m and SD, respectively. The $100p\%$ reference limit is then estimated as $m + z_p \mathrm{SD}$, where z_p is the $100p\%$ standard normal deviate.

1.3.2 Interval Estimation

1.3.2.1 Principles

A single-value point estimate, without any indication of its variability, is of limited value. Because of sample variation, the value of the point estimate will vary across samples, and it will not provide any information regarding precision. One could provide an estimation of the variance of the point estimator. However, it is more common to provide a range of possible values. A **confidence interval** has a specified probability of containing the parameter value (Armitage et al. 2002). By definition, this probability, called the coverage probability, is $(1-\alpha)$, where $0<\alpha<1$. If one selects a sample of size n at random, using say a set of random numbers, then the sample that one gets to observe is just one sample from among a large number of possible samples one might have observed, had the play of chance been otherwise. A different set of n random numbers would lead to a different possible sample of the same size n and a different point estimate of the parameter of interest, along with its confidence interval. Of the many possible interval estimates, some $100(1-\alpha)\%$ of these intervals will capture the true value. This implies that we cannot be sure that the $100(1-\alpha)\%$ confidence interval calculated from the actual sample will capture the true value of the parameter of interest. The computed interval might be one of the possible intervals (with proportion $100\alpha\%$) that do not contain the true value. The most commonly used coverage probability is 0.95, that is $\alpha = 0.05 = 5\%$, in which case the interval is called a 95% confidence interval.

1.3.2.2 Interval Estimation for a Proportion

In this situation, the variable of interest is binary, such as the presence or absence of a specific health condition, and we are interested in π, the prevalence rate of this condition. Given a random sample of n subjects, a point estimator for the proportion π is given by $p = \frac{k}{n}$, where k is the observed number of subjects with the condition of interest in the sample. When n is large, the sampling distribution of p is approximately normal, with mean π and variance $\frac{\pi(1-\pi)}{n}$. Thus, a $100(1-\alpha)\%$ confidence interval for π is given by $\left[p \pm z_{1-\alpha/2}\sqrt{\frac{p(1-p)}{n}} \right]$. In smaller samples ($np < 5$ or $n(1-p)<5$), exact methods based on the binomial distribution should be applied rather than a normal approximation to it (Machin et al. 1997).

Example: Assume one is interested in estimating π, the proportion of overweight children. In a selected random sample of $n = 100$ children, the observed proportion of overweight children is $p = 40\%$.A 95% confidence interval $\left(z_{1-\alpha/2} = 1.96\right)$ for the true proportion π of overweight children is given by $\left[0.40 \pm 1.96\sqrt{\frac{0.40(0.60)}{100}} \right]$, that is [30%; 50%].

1.3.2.3 Interval Estimation for the Difference Between Two Proportions

The variables of interest are binary, and we are interested in π_1 and π_2, the prevalence rates of a specific condition in two independent samples of size n_1 and n_2. Let k_1 and k_2 denote the number of

observed subjects with the condition of interest in these two samples. A point estimator for the difference $\pi_1 - \pi_2$ is given by $p_1 - p_2 = \frac{k_1}{n_1} - \frac{k_2}{n_2}$, where p_1 and p_2 are the two sample proportions. When n_1 and n_2 are large, the sampling distribution of $p_1 - p_2$ is approximately normal with mean $\pi_1 - \pi_2$ and variance $\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}$. Thus, a 100(1 − α)% confidence interval for the true difference in proportions $(\pi_1 - \pi_2)$ is given by $\left[(p_1 - p_2) \pm z_{1-\alpha/2}\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}\right]$. In case of smaller samples ($n_1 p_1 < 5$ or $n_1(1 - p_1) < 5$ or $n_2 p_2 < 5$ or $n_2(1 - p_2) < 5$), exact methods based on the binomial distribution should be applied rather than a normal approximation to it (Machin et al. 1997).

Example: Assume a randomized trial is conducted to compare two physical activity interventions for reducing waist circumference. A total of 110 and 100 subjects are assigned to receive intervention A or B, respectively. The observed success rate is 40% in group A and 20% in group B. A 95% confidence interval for the true difference in success rates is given by

$$\left[(0.40 - 0.20) \pm 1.96\sqrt{\frac{0.40 \times 0.60}{110} + \frac{0.20 \times 0.80}{100}}\right],$$ that is, [8%; 32%].

1.3.2.4 Interval Estimation for a Mean

The variable of interest is continuous with true mean μ and true variance σ^2. We are interested in estimating the true population mean μ. A total of n subjects have been randomly selected from this population of interest. When n is large ($n > 30$), the distribution of the sample mean m is approximately normal with mean μ and variance $\frac{\sigma^2}{n}$. A 100(1–α) confidence interval for μ is thus given by $\left[m \pm z_{1-\frac{\alpha}{2}}\sqrt{\frac{\sigma^2}{n}}\right]$. One can use s^2 as an estimate of the population variance, unless the variance σ^2 is known. If the sample size is small, and if the variable of interest is known to be normal, then a 100(1–α) confidence interval for μ is given by $\left[m \pm t_{n-1,\alpha}\sqrt{\frac{s^2}{n}}\right]$, where $t_{n-1,\alpha}$ corresponds to the α% tabulated point of the $t_{n-1,\alpha}$ distribution.

Example: One is interested in estimating the average weight of 15-year-old girls. After selecting a random sample of 100 girls, the observed average weight is 55 kg, and the standard deviation is 15 kg. A 95% confidence interval for the mean weight of 15-year-old girls is thus given by: $\left[55 \pm 1.96\sqrt{\frac{15^2}{100}}\right]$, that is [52; 58].

1.3.2.5 Interval Estimation for the Difference Between Two Means

Given two independent samples of size n_1 and n_2 with respective means μ_1 and μ_2, and variances σ_1^2 and σ_2^2, a point estimator for the difference $\mu_1 - \mu_2$ is given $m_1 - m_2$, where m_1 and m_2 correspond

to the two sample means. When n_1 and n_2 are large, the distribution of m_1–m_2 is approximately normal with mean μ_1–μ_2 and variance $\frac{\sigma_1^2}{n_1}+\frac{\sigma_2^2}{n_2}$. A 100(1–$\alpha$)% confidence interval for the true difference in means is then given by $\left[(m_1-m_2)\pm z_{1-\alpha/2}\sqrt{\frac{\sigma_1^2}{n_1}+\frac{\sigma_2^2}{n_2}}\right]$. Unless the variances σ_1^2 and σ_2^2 are known, one can use the sample variances s_1^2 and s_2^2 as their respective estimates: $\left[(m_1-m_2)\pm z_{1-\alpha/2}\sqrt{\frac{s_1^2}{n_1}+\frac{s_2^2}{n_2}}\right]$.

Example: One wishes to compare the diastolic blood pressure (DBP) between two populations of subjects A and B. In a sample of 50 randomly selected subjects from population A, the observed DBP mean is 110 mmHg, while the mean DBP in 60 patients randomly selected from population B is about 100 mmHg. The observed standard deviations are, respectively, 10 mmHg and 8 mmHg. A 95% confidence interval for the true difference in DBP means is thus $\left[(110-100)\pm 1.96\times\sqrt{\frac{10^2}{50}+\frac{8^2}{60}}\right]$, that is, [6.6; 13.4].

1.3.2.6 Interval Estimation for a Reference Limit

Using a nonparametric approach, a confidence interval for a reference limit can be expressed in terms of order statistics (Harris and Boyd 1995). An approximate 100(1–α)% confidence interval for the 100p% reference limit is given by the order statistics $x_{(r)}$ and $x_{(s)}$, where r is the largest integer less than or equal to $np+\frac{1}{2}-z_{\frac{\alpha}{2}}\sqrt{np(1-p)}$, and s is the smallest integer greater than or equal to $np+\frac{1}{2}+z_{\frac{\alpha}{2}}\sqrt{np(1-p)}$.

Example: In their example, Harris and Boyd are interested in the 90% confidence interval $\left(z_{1-\alpha/2}=1.645\right)$ for the 2.5% (p=0.025) reference limit based on a random sample of size n=240 (Harris and Boyd 1995). The lower bound of this interval corresponds to the value of the r^{th} order statistic, where r is the largest integer less than or equal to $np+\frac{1}{2}-z_{\frac{\alpha}{2}}\sqrt{np(1-p)}=240\times 0.025+\frac{1}{2}-1.645\sqrt{100\times 0.025\times 0.975}$, that is, 2. Similarly, the upper bound corresponds to the value of the s^{th} order statistic, where s is the smallest integer greater than or equal to $np+\frac{1}{2}+z_{\frac{\alpha}{2}}\sqrt{np(1-p)}$, that is, 11. Referring to the ordered observations, bounds of the 90% confidence interval for the 2.5% reference limit are thus provided by the values of the second and eleventh order statistics.

Confidence intervals can also be built using parametric methods. Assume that the observations follow a normal distribution with mean μ and variance σ^2. For a random sample of size n, the sample mean and sample standard deviation are given by m and SD, respectively. The parametric estimator of the $100p\%$ reference limit is $m+z_p\text{SD}$, where z_p is the $100p\%$ standard normal deviate. The variance of this estimator is given by $\frac{\sigma^2}{n}\left(1+\frac{z_p^2}{2}\right)$. A $100(1-\alpha)\%$ confidence interval for the $100p\%$ reference limit is thus $\left[m+z_p\text{SD}\pm z_{1-\frac{\alpha}{2}}\sqrt{\frac{\text{SD}^2}{n}\left(1+\frac{z_p^2}{2}\right)}\right]$. See Harris and Boyd for worked examples (Harris and Boyd 1995).

1.4 Precision-Based Sample Size Estimation

Sample size can be computed using either a precision-based or power-based approach. In anthropometry, however, there is greater emphasis on precision-driven estimation procedures (Gardner and Altman 1986, 1988).

For any given parameter, the length of the confidence interval is a function of the sample size. More specifically, the larger the sample, the narrower the confidence interval. Thus, the main purpose of confidence intervals is to indicate the (im)precision of the sample study estimates as population values (Gardner and Altman 1988). Conversely, one can fix the desired length of the interval and estimate the number of subjects needed accordingly. Formulae are available to estimate the sample size as a function of the precision, which can be expressed in two ways.

One can express the length of the interval in absolute terms based on the **absolute margin of error**, ME, which represents half the width of the confidence interval, and is the quantity often quoted as the "plus or minus" in lay reports of surveys. In such case, the confidence interval is expressed as "estimate ± ME". It is also possible to express the length of the interval in **relative** terms based on the **precision** usually denoted by ε. In such cases, the confidence interval is expressed as "estimate $\pm\varepsilon\times$ estimate". There is a direct relationship between the margin of error and the precision since ME $=\varepsilon\times$ estimate; sample size can thus be estimated as a function of either parameter.

Note that the term *error* is often a source of confusion when dealing with sample size and power calculations. Therefore, it is always very important to provide a precise definition of this term, that is, to clarify whether we are referring to an absolute or relative error.

Throughout this section, we consider that observations from the same sample are independent. In the case of two-sample problems, we consider that the two samples are independent.

1.4.1 Dichotomous Variables

1.4.1.1 Sample Size for Estimating a Single Proportion with a Given Precision

A $100(1-\alpha)\%$ confidence interval for the true proportion π given a sample size n and an anticipated value p is given by: $\left[p\pm z_{1-\frac{\alpha}{2}}\sqrt{\frac{p(1-p)}{n}}\right]$. The width of the confidence interval is thus given by

$2 \times z_{1-\frac{\alpha}{2}} \sqrt{\frac{p(1-p)}{n}}$ and depends on the number of subjects in the sample. Conversely, the number of subjects needed to estimate the proportion will depend on the degree of precision (indicated by the maximum width of the confidence interval) one is willing to accept. The margin of error, ME, is half the width of the confidence interval. If one wants the absolute margin of error to be at most ME, that is, one wants $z_{1-\frac{\alpha}{2}} \sqrt{\frac{p(1-p)}{n}} \leq \text{ME}$, then the number of subjects should be at least $n = \frac{z^2_{1-\frac{\alpha}{2}} p(1-p)}{\text{ME}^2}$.

This problem can also be expressed in terms of precision (or relative error). The confidence interval $\left[p \pm z_{1-\frac{\alpha}{2}} \sqrt{\frac{p(1-p)}{n}} \right]$ can be rewritten as $[p \pm \varepsilon p]$, implying that the estimation of π is provided to within $100\varepsilon\%$ of its anticipated value, where ε is the precision of the estimation. Since $\text{ME} = p\varepsilon$,the required sample size can thus be expressed as $n = \frac{z^2_{1-\frac{\alpha}{2}} (1-p)}{p\varepsilon^2}$. Note that the sample size is maximized for $p = 0.50$.

If either np or $n(1-p)$ are small (i.e. below 5), exact approximations based on the binomial distribution should be applied rather than a normal approximation to it (Machin et al. 1997).

Example: One is interested in estimating the prevalence of overweight children with an absolute margin of error smaller than 0.05 (ME = 0.05). If the prevalence, π, is expected to be around 50% ($p = 0.50$), and interest is in estimating a 95% confidence interval $\left(z_{1-\frac{\alpha}{2}} = 1.96 \right)$, the minimum number of subjects needed should be $\frac{1.96^2 0.5(1-0.5)}{0.05^2}$, that is, at least 384 subjects.

1.4.1.2 Sample Size for Estimating the Difference Between Two Proportions with a Given Precision

Given two proportions π_1 and π_2 for two independent samples of size n_1 and n_2, a $100(1-\alpha)\%$ confidence interval for the true difference in proportions $(\pi_1 - \pi_2)$ is estimated by $\left[(p_1 - p_2) \pm z_{1-\alpha/2} \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}} \right]$, where p_1 and p_2 are the observed sample proportions.

The width of the confidence interval is given by $2 \times z_{1-\alpha/2} \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$. Assuming samples are of equal size $n = n_1 = n_2$ and an absolute margin of error ME, the number of subjects in each sample should be at least $n = \frac{z^2_{1-\alpha/2} \left(p_1(1-p_1) + p_2(1-p_2) \right)}{\text{ME}^2}$. In terms of precision ε or relative error, where $\text{ME} = \varepsilon(p_1 - p_2)$, the required sample size is expressed as $n = \frac{z^2_{1-\alpha/2} \left(p_1(1-p_1) + p_2(1-p_2) \right)}{\varepsilon^2 (p_1 - p_2)^2}$. Similar formulae have been derived for the case of unequal sample sizes (Machin et al. 1997).

***Example*:** A study is set up to compare a new physical activity intervention to a standard one for overweight subjects. The aim is to reduce the body mass index (BMI) down to 30 cm/kg^2 or lower. The anticipated success rates are expected to be approximately $p_1 = 10\%$ and $p_1 = 25\%$ for the new and standard interventions respectively. The investigator would like to recruit two groups of patients with equal sample sizes $n = n_1 = n_2$, and provide a 95% confidence interval for difference in success rates with an absolute margin of error ME = 10%. The minimum number of subjects per group should be at least $n = \dfrac{1.96^2\left(0.10 \times 0.90 + 0.25 \times 0.75\right)}{0.10^2}$, that is, 107 subjects per group.

1.4.2 Continuous Variables

1.4.2.1 Sample Size for Estimating a Single Mean with a Given Precision

A 100(1–α)% confidence interval for a mean μ given anticipated mean m and assuming a large sample is given by $\left[m \pm z_{1-\frac{\alpha}{2}} \dfrac{\sigma}{\sqrt{n}}\right]$. The width of the confidence interval is $2 \times z_{1-\frac{\alpha}{2}} \dfrac{\sigma}{\sqrt{n}}$. If we want the absolute margin of error to be at most ME, then the number of subjects has to be greater than $n = \dfrac{z^2_{1-\frac{\alpha}{2}} \sigma^2}{\mathrm{ME}^2}$. If one wishes to express the sample size in terms of precision ε, where ME = εm, the required sample size is expressed as $n = \dfrac{z^2_{1-\frac{\alpha}{2}} \sigma^2}{\varepsilon^2 m^2}$. Unless the variance σ^2 is known, one can use a literature-based or experience-based s^2 as an estimate of the population variance.

Example: An investigator is interested in estimating diastolic blood pressure (DBP) in a specific population. The mean DBP and standard deviation are anticipated to be about 105 mmHg ($m = 105$) and 20 mmHg (SD = 20). If the desired relative precision is 5% ($\varepsilon = 5\%$), the required sample size for estimating a 95% confidence interval for the mean DBP should be at least $n = \dfrac{1.96^2\, 20^2}{0.05^2 105^2}$, that is 56 subjects.

1.4.2.2 Sample Size for Estimating the Difference Between Two Means with a Given Precision

Assuming independent samples of size n_1 and n_2, with respective sample means m_1 and m_2 and common variance σ^2, a 100(1–α)% confidence interval for the true difference in means is given by $\left[(m_1 - m_2) \pm z_{1-\alpha/2}\sigma\sqrt{\dfrac{1}{n_1} + \dfrac{1}{n_2}}\right]$. The width of the confidence interval is thus given by $2 \times z_{1-\alpha/2}\sigma\sqrt{\dfrac{1}{n_1} + \dfrac{1}{n_2}}$. Assuming samples of equal size $n = n_1 = n_2$ and a margin of error ME, the number of subjects in each sample should be at least $n = \dfrac{2\, z^2_{1-\alpha/2} \sigma^2}{\mathrm{ME}^2}$. If one wishes to express the

sample size in terms of precision ε, where ME = $\varepsilon(m_1 - m_2)$, the required sample size is expressed as $n = \frac{2\, z^2_{1-\alpha/2}\, \sigma^2}{\varepsilon^2 (m_1 - m_2)^2}$. Unless the variance σ^2 is known, one can use a literature-based or experience-based s^2 as an estimate of the population variance. Similar formulae have been derived for the case of unequal sample sizes (Machin et al. 1997).

Example: An investigator is interested in evaluating two treatments (A and B) aimed at decreasing cholesterol level. The anticipated mean cholesterol levels following treatments A and B are, respectively, 200 and 250 mg/dL, with a 20 mg/dL common standard deviation. To obtain a 95% confidence interval for the difference in cholesterol levels after treatment with (relative) precision $\varepsilon = 10\%$, the sample size should be at least $n = \frac{2 \times 1.96^2 \times 20^2}{0.10^2 (200 - 250)^2}$, that is 123 subjects per group.

1.4.2.3 Sample Size for Estimating a Regression-Based Reference Limit with a Given Precision

In some cases, the variable of interest might be indexed by a secondary variable. Suppose we have a continuum of distributions indexed by a covariate. For example, assume that we are studying BMI in a group of children of different ages. Instead of the mean BMI, we might be interested in other parameters of the BMI distribution, more particularly in the 95% reference limit of the BMI distribution for various ages. How many children should we sample in order to have a precise estimate of this reference limit and for every possible value of age? This question can be answered by applying linear regression techniques to estimate the reference limit as a function of age. Methods have been developed to estimate sample sizes for regression-based reference limits under various situations (Bellera and Hanley 2007). We provide an overview of these approaches, and refer the interested reader to this literature for additional details.

It is assumed that the mean value of the response variable of interest (e.g., BMI) varies linearly with the covariate (e.g., age), and that the response values are approximately normally distributed around this mean. The response variable and the covariate of interest are denoted by Y and X, respectively. Assume that at any given value x_0 of age, the mean value of interest, such as BMI, is an approximate linear function of X and that individual BMI values are normally distributed around this mean (the latter eventually after a suitable transformation) with constant variance: $Y \,|\, x_0 \sim N\left(\beta_0 + \beta_1 x_0, \sigma^2\right)$. The 100$p$% reference limit for Y at this specific age point x_0 is given by: $Q_0 = \beta_0 + \beta_1 x_0 + z_p \sigma$, where z_p is the standard normal deviate corresponding to the 100p% reference limit of interest.

Given n selected individuals with data points $\left((x_i, y_i), i = 1, \ldots, n\right)$, a point estimator for the 100p% reference limit is given by: $\hat{Q}_0 = \hat{\beta}_0 + \hat{\beta}_1 x_0 + z_p s_{Y|X}$, where $\hat{\beta}_0$ and $\hat{\beta}_1$ are obtained by least-squares estimation of the regression coefficients β_0 and β_1, and $s_{Y|X}$ is the observed root mean square error.

Sample size estimation for regression-based reference limits requires defining the following parameters:

- The 100p% reference limit of interest, where $0 < p < 1$, and the corresponding one-sided standard normal deviate, z_p. For example, if we are interested in the 95% reference limit, the one-sided standard normal deviate is $z_{0.95} = 1.64$.

- The 100(1–α)% confidence interval for the reference limit of interest, and its corresponding two-sided standard normal deviate $z_{1-\frac{\alpha}{2}}$, where $0 < \alpha < 1$. For example, if we want the 95% confidence interval, then $\alpha = 0.05$ and $z_{1-\frac{\alpha}{2}} = 1.96$.
- The 100(1–β)% reference range, which encompasses 100(1–β)% of the values (e.g., BMI) as well as its corresponding two-sided standard normal deviate $z_{1-\frac{\beta}{2}}$, where $0 < \beta < 1$. For example, if we want the 95% reference range, then $\beta = 0.05$ and $z_{1-\frac{\beta}{2}} = 1.96$.
- The relative margin of error Δ, defined as the ratio of the width of the 100(1-α)% confidence interval for the reference limit to the width of the 100(1–β)% reference range. This means that we want a sample size large enough so that the width of the 100(1–α)% confidence interval for our reference limit is small when compared to the width of the 100(1–β)% reference range (we usually take $\alpha = \beta$).
- The design of the study, that is, the distribution of the covariate (e.g., age) in the sample investigated, which will influence the computation of the sample size.

Once the above parameters have been specified, we can estimate the sample size. Assume, first that we choose our sample so that the covariate (e.g., age) follows a uniform distribution. In such cases, the variance of the estimator $\hat{Q}$ of the reference limit is approximately equal to $\text{var}(\hat{Q}_0) = \frac{\sigma^2}{n}\left(4 + \frac{z_p^2}{2}\right)$. The width of the 100(1–α)% confidence interval for the 100p% reference limit at the *extreme* value of age is therefore $2z_{1-\frac{\alpha}{2}}\sigma\frac{\sqrt{4+\frac{z_p^2}{2}}}{\sqrt{n}}$. Assume we want a relative error of Δ, defined as the ratio of the width of the 100(1–α)% confidence interval for the reference limit to the width of the 100(1–β)% reference range. The width of the 100(1–α)% reference range is given by $2z_{1-\frac{\beta}{2}}\sigma$. Thus, if we want the ratio of the width of the 100(1–α)% confidence interval for the reference limit to the width of the 100(1–β)% reference range to be smaller than the relative error Δ, we require $\frac{z_{1-\frac{\alpha}{2}}\sqrt{4+\frac{z_p^2}{2}}}{z_{1-\frac{\beta}{2}}\sqrt{n}} \le \Delta$. That is, the minimum sample size, n, required to estimate the 100(1–α)% confidence interval for the 100p% reference limit, with a relative margin of error of Δ, when compared to the 100(1–β)% reference range, should be at least $n = \frac{z_{1-\frac{\alpha}{2}}^2\left(4+\frac{z_p^2}{2}\right)}{z_{1-\frac{\beta}{2}}^2\Delta^2}$. Similar formulae have been derived assuming other sampling strategies (Bellera and Hanley 2007). For example, instead of a uniform age distribution, one might take one-third of the sample at one age extreme, one-third at the midpoint, and one-third at the other age extreme. In this study design, the minimum

sample size requirement is then $\frac{z^2_{1-\frac{\alpha}{2}}\left(\frac{5}{2}+\frac{z_p^2}{2}\right)}{z^2_{1-\frac{\beta}{2}}\Delta^2}$. Similarly, we can also expect that the age distribution in the sample will follow a normal distribution. If we assume that the range of X is approximately 4 times the standard deviation of X, then we show that the sample size requirement becomes: $\frac{z^2_{1-\frac{\alpha}{2}}\left(5+\frac{z_p^2}{2}\right)}{z^2_{1-\frac{\beta}{2}}\Delta^2}$.

Notice that the previous formulae were derived under the "worst-case" scenario, that is, assuming that we are interested in estimating the reference limit at the extreme end of age, where the variability is highest, and thus the largest sample size is needed. If one is interested in the $100p\%$ reference limit at the average age value (where the variability is minimized), then the sample size is reduced to $\frac{z^2_{1-\frac{\alpha}{2}}\left(1+\frac{z_p^2}{2}\right)}{z^2_{1-\frac{\beta}{2}}\Delta^2}$, for any given age distribution (or similarly, assuming a homogeneous population not indexed by a covariate). Put simply, information from either side of the average age adds strength to the information at the average age. In contrast, information at the extremes of the age distribution can only gather "strength" from one side of the age distribution; on the other side, there is infinite uncertainty.

Several other factors can impact the sample size (Cole 2006), such as for example the range of the covariate of interest. If one is interested in the height of children, a larger sample will be needed when considering birth to 18 years than when considering 5–12 years. Non-constant variability can also affect the sample size, since the variance of the estimator, $\text{var}(\hat{Q}_0)$, is proportional to $\frac{\sigma^2}{n}$, where σ^2 varies with age. This ratio can be made constant across age groups by ensuring that the sample size n is proportional to σ^2. Thus, at the ages at which the variability is increased, for example during puberty, the sample size needs to be increased appropriately to compensate (Goldstein 1986; Cole 2006). Similarly, in case of heteroscedasticity of the variable of interest across the covariate, regression techniques can be used to model the standard deviation as a function of the mean, and previous formulae can still be used as a rough guide for sample size planning. Notice that the variation σ^2 to be used in planning includes both the true inter-individual variability and the variability of the measuring instruments used: measurement tools with differing precisions will provide different sample size estimates. Finally, the nature of the relation between the covariate and the variable of interest can also affect the sample size, as more subjects will be needed to capture "wiggles" in the relation compared to a simple linear relation. If there is some nonlinearity in the covariate, such as for example a quadratic relationship, the formulae can also be accommodated by adjusting the point estimator of the reference limit of interest.

Example: We are interested in estimating a specific BMI reference limit as a linear function of age. Specifically, we wish to produce a 95% confidence interval $\left(z_{1-\frac{\alpha}{2}}=1.96\right)$ for the 95% BMI reference

limit ($z_{0.95} = 1.64$), with a relative margin of error $\Delta = 10\%$, when compared with the 95% reference range $\left(z_{1-\frac{\beta}{2}} = 1.96 \right)$. If age is uniformly distributed in the sample, then the minimum required sample size is $n = \frac{1.96^2 \left(4 + 1.64^2\right)}{1.96^2 0.10^2}$, i.e., we would need at least 536 observations to obtain this precise an estimate of the 95% BMI reference limit at any place in the age range. If, on the other hand, one is interested in the 95% reference limit only at the average age value, or in a homogeneous population not indexed by a covariate, then we would need at least $n = \frac{1.96^2 \left(1 + 1.64^2\right)}{1.96^2 0.10^2}$, that is, 236 observations.

1.5 Principles of Hypothesis Testing

We have presented formulae for the estimation of the sample size required to estimate various parameters with a desired degree of precision. Similarly, one may want to ensure that a sufficient number of subjects are available to show a difference between two parameters. We discuss here some basic principles of hypothesis testing which can be found in introductory statistical textbooks, as well as works devoted to clinical trials or epidemiology (Lachin 1981; Friedman et al. 1998; Armitage et al. 2002).

One wishes to compare two groups, A and B, with true prevalence rates, π_A and π_B. From a statistical point of view, this comparison is expressed in terms of a **null hypothesis**, called H_0, which states that no difference exists between the two groups: H_0: $\pi_A - \pi_B = 0$. Hypothesis testing consist in testing whether or not H_0 is true, more specifically, whether or not it should be rejected. Thus, until otherwise proven, H_0 is considered to be true. The true prevalence rates, π_A and π_B are unknown. If two groups of subjects are properly sampled, one can obtain appropriate estimates P_A and P_B. Although π_A and π_B might not differ, it is possible that by chance alone, the observed proportions P_A and P_B are different. In such cases, one might falsely conclude that the two groups have different prevalence rates. Such a false-positive error is called **a type 1 error**, and the probability of making such an error corresponds to the **significance level** and is denoted by α. The probability of making a type 1 error should be minimized. However, decreasing the significance level increases the sample size. The probability of observing a difference as extreme as or more extreme than the difference actually observed, given that the null hypothesis is true, is called the ***p-value*** and is denoted by P. The null hypothesis H_0 will be rejected if $p < \alpha$.

If the null hypothesis is not correct, then an **alternative hypothesis**, denoted by H_A must be true, that is H_A:$\pi_A - \pi_B = \delta$, where $\delta \neq 0$. It is possible that by chance alone, the observed proportions P_A and P_B differ only by a small amount. As a result, the investigator may fail to reject the null hypothesis. This false-negative error is called **a type 2 error**, and the probability of making such error is denoted by β. The probability of correctly accepting H_0 is thus $1-\beta$ and is referred as the **power**. It defines the capability of a statistical test to reveal a given difference between two parameters, if this difference really exists. The power depends on the size of the difference we wish to detect, the type 1 error, and the number of subjects. That is, if the type 1 error and the sample size are held constant, a study will have a larger power if one wishes to detect a large difference compared to a small one.

1.6 Power-Based Sample Size Estimation

The number of subjects needed should be planned carefully in order to have sufficient power to detect significant differences between the groups considered. To provide a power-based (or test-based) estimation of sample size requires defining a priori the difference one wishes to detect, the desired significance level and the desired power of the test.

As will be discussed below, sample size formulae involve the ratio of the variance of the observations over the difference one wishes to detect, or more generically, a noise–signal ratio, where the signal corresponds to the difference one wishes to detect, and the noise (or uncertainty) is the sum of all the factors (sources of variation) that can affect the signal (Sackett 2001).

Note that we only discuss the case of independent observations. In clinical trials, for example, it may not always be possible to randomize individuals. For example, a physical activity intervention might be implemented by randomizing schools. Individuals are then grouped or clustered within schools. They cannot be considered as statistically independent, and the sample size needs to be adapted since standard formulae underestimate the total number of subjects (Donner et al. 1981; Friedman et al. 1998).

1.6.1 Dichotomous Variables

1.6.1.1 Sample Size for Comparing a Proportion to a Theoretical Value

The variable of interest is dichotomous. For example, one is interested in the prevalence of obese children π_1. Based on a random sample, the objective is to compare this proportion to a target (fixed) value p_0. The null and alternative hypotheses are given respectively by $H_0: \pi_1 = p_0$ and $H_A: \pi_1 \neq p_0$. The minimum number of subjects needed to perform this comparison assuming an observed prevalence rate p_1, a significance level α and power $1-\beta$ is $n = \dfrac{\left(z_{1-\frac{\alpha}{2}}\sqrt{p_0(1-p_0)} + z_{1-\beta}\sqrt{p_1(1-p_1)} \right)^2}{(p_1 - p_0)^2}$.

Example: One is interested in evaluating a specific diet aimed at reducing weight in obese subjects. A success is defined as reducing a BMI down to 25 or lower. One wishes to test whether this new diet has a better success rate than the standard diet for which the efficacy rate is known to be $p_0 = 20\%$. The anticipated efficacy rate of the new diet is $p_1 = 40\%$. The sample size needed to show a difference between the efficacy rate of the new diet and the target efficacy rate p_0 assuming a significance level $\alpha = 0.05$ $\left(z_{1-\frac{\alpha}{2}} = 1.96 \right)$, and power $1-\beta = 0.90$ ($z_{1-\beta} = 1.28$) is at least $n = \dfrac{\left(1.96\sqrt{0.20(1-0.20)} + 1.28\sqrt{0.40(1-0.40)}\right)^2}{(0.40-0.20)^2}$, i.e., 36 patients. If the anticipated efficacy rate is $p_1 = 30\%$, that is, one wishes to detect a smaller difference, then the sample size must be increased to at least $n = \dfrac{\left(1.96\sqrt{0.20(1-0.20)} + 1.28\sqrt{0.30(1-0.30)}\right)^2}{(0.30-0.20)^2}$, that is, 137 subjects.

Note that the calculated sample sizes are quite low. This is because we are comparing one sample to one historical (or literature-based) sample. In practice, one will usually be comparing two samples (next section), as in clinical trials. In this case, the resulting sample size is much higher as variability of the second sample has to be accounted for.

1.6.1.2 Sample Size for Comparing Two Proportions

The outcome of interest is dichotomous and two independent groups of equal size are being sampled and compared. The objective is to detect a difference between two proportions π_0 and π_1, that is, the null and alternative hypotheses are given respectively by H_0: $\pi_1-\pi_0=0$ and H_A: $\pi_1-\pi_0=\delta$, where $\delta\neq 0$. The size of each sample required to detect an anticipated difference p_1-p_0, assuming a significance level α, and power β is $n=\dfrac{\left(z_{1-\frac{\alpha}{2}}\sqrt{2\bar{p}(1-\bar{p})}+z_{1-\beta}\sqrt{p_0(1-p_0)+p_1(1-p_1)}\right)^2}{(p_1-p_0)^2}$, where $\bar{p}$ is the average of the two anticipated proportions p_0 and p_1. Similar formulae are available for the case of unequal sample sizes (Piantadosi 2005).

Example: A trial is set up to compare two physical activity interventions with anticipated success rates of 50% and 30%. The sample size per group needed to show a difference between the two interventions assuming a difference in success rates $\delta=50\%-30\%=20\%$, a significance level $\alpha=0.05$ $\left(z_{1-\frac{\alpha}{2}}=1.96\right)$, and power $1-\beta=0.90$ $\left(z_{1-\beta}=1.28\right)$ is $n=\dfrac{\left(1.96\sqrt{0.40(1-0.40)}+1.28\sqrt{0.30(1-0.30)+0.50(1-0.50)}\right)^2}{0.20^2}$ that is, 84 subjects per group.

1.6.2 Continuous Variables

1.6.2.1 Sample Size for Comparing a Mean to a Theoretical Value

The variable of interest is continuous. For example, one is interested in the mean waist circumference, μ_1, following a physical activity intervention. Based on a random sample of subjects, the objective is to compare this mean circumference to a target mean value m_0. The null and alternative hypotheses are thus given respectively by H_0: $\mu_1=m_0$ and H_A: $\mu_1\neq m_0$. For this one sample problem, the number of subjects needed to perform this comparison assuming an anticipated mean value m_1, a standard deviation σ, significance level α and power $1-\beta$ is $n=\dfrac{\sigma^2\left(z_{1-\frac{\alpha}{2}}+z_{1-\beta}\right)^2}{(m_1-m_0)^2}$. Unless the variance σ^2 is known, one can use a literature-based or experience-based s^2 as an estimate of the population variance.

Example: One wishes to test whether mean waist circumference in a given population following a new physical activity intervention is reduced compared to a standard intervention. Following the standard intervention, the mean waist circumference is known to be about $m_0 = 140$ cm. It is anticipated that the new intervention will reduce this circumference to $m_1 = 130$ cm. The sample size needed to show a difference between the mean waist circumference with the new intervention and a target value m_0, assuming a significance level $\alpha = 0.05$ $\left(z_{1-\frac{\alpha}{2}} = 1.96\right)$, a 90% power $\left(z_{1-\beta} = 1.28\right)$ and standard deviation SD = 20cm, is $n = \frac{20^2\left(1.96+1.28\right)^2}{\left(130-140\right)^2}$, that is, 42 patients.

1.6.2.2 Sample Size for Comparing Two Means

The variable of interest is continuous and two independent groups of equal size are being sampled and compared. The objective is to detect a difference between two means, that is, the null and alternative hypotheses are given respectively by $H_0: \mu_1 - \mu_0 = 0$ and $H_A: \mu_1 - \mu_0 = \delta$, where $\delta \neq 0$. The sample size of each group required to detect this difference assuming an anticipated difference $m_1 - m_0$, common variance σ^2, significance level α and power β is $n = \frac{2\sigma^2 \times \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{(m_1 - m_0)^2}$. Unless the variance σ^2 is known, one can use a literature-based or experience-based s^2 as an estimate of the population variance.

Example: In their example, Armitage et al. are interested in comparing two groups of men using the forced expiratory volume (FEV) (Armitage et al. 2002). From previous work, the standard deviation of FEV is 0.5 L. A two-sided significance level of 0.05 $\left(z_{1-\frac{\alpha}{2}} = 1.96\right)$ is to be used with an 80% power ($z_{1-\beta} = 0.842$). In order to show a mean difference of 0.25 L between the groups, and assuming samples of equal sizes, the total number of men should be at least $n = \frac{2 \times 0.5^2 \times \left(1.96 + 0.842\right)^2}{0.25^2}$, that is, 63 men per group.

1.7 Other Parameters, Other Settings

Sample sizes can be estimated for various parameters and under various settings. As such, it is not possible to cover all possible situations into a single book chapter! We have reviewed formulae for the estimation of sample sizes for commonly used parameters such as means, proportions and reference limits. Other parameters such as time-to-event outcomes (Freedman 1982; Schoenfeld 1983; Dixon and Simon 1988), correlation coefficients (Bonett 2002), concordance coefficients (Donner 1998), or even multiple endpoints can be considered (Gong et al. 2000). Similarly, methods for calculating sample size assuming other designs have been investigated. Instead of detecting a specific difference, one might be interested in showing equivalence or noninferiority (Fleming 2008); observations may be clustered (Donner et al. 1981; Hsieh 1988), etc. Sample size estimation procedures have been developed for these settings and we refer the interested reader to specialized literature or general works on sample size (Friedman et al. 1998; Machin et al. 1997; Altman et al. 2000; Piantadosi 2005).

Finally, although they should be used with caution, several statistical software packages, such as nQuery® (nQuery Advisor ® 6.0), or East® (Cytel), are available to compute sample size and power for means, proportions, survival analysis, etc.

1.8 Application to Other Areas of Health and Disease

The methods presented in this chapter can be applied to many areas of research and study design, including anthropometry, but also fundamental biology, epidemiology, clinical trials, social sciences, demography, or economics.

Summary Points

- Before estimating a sample size, the nature and the distribution of the variable of interest must be defined. The parameter of interest (mean, proportion, reference limit) can then be identified.
- Before estimating a sample size, the type of sample has to be identified: one single sample? Two samples?
- Sample size estimation can be either precision-based or power-based.
- When performing precision-based sample size estimation, the anticipated value of the parameter as well as the level of significance and the precision (absolute or relative) must be defined a priori.
- When performing power-based sample size estimation, the anticipated value of the parameter as well as the level of significance and the power must be defined a priori.

Key Features of Sample Size Estimation

Table 1.3 Sample-size required for the estimation of a 100(1–α)% confidence interval for various parameters (*assuming an absolute margin of error* ME)

Parameter of interest	Sample size
Proportion (assuming an anticipated value P)	$n = \frac{z^2_{1-\frac{\alpha}{2}}\, p(1-p)}{\mathrm{ME}^2}$
Difference between 2 proportions (assuming independent samples with the same sample size and anticipated proportions p_1 and p_2)	$n\ (\text{per group}) = \frac{z^2_{1-\alpha/2}\left(p_1(1-p_1)+p_2(1-p_2)\right)}{\mathrm{ME}^2}$
Mean (assuming sample variance s^2)	$n = \frac{z^2_{1-\frac{\alpha}{2}}\, s^2}{\mathrm{ME}^2}$
Difference between 2 means (assuming independent samples with the same sample size and common sample variance s^2)	$n\ (\text{per group}) = \frac{2\, z^2_{1-\alpha/2}\, s^2}{\mathrm{ME}^2}$
Regression-based reference limit for the 100p% reference limit (assuming a uniform distribution for the covariate and a relative margin of error of Δ when compared to the 100(1–β)% reference range)	$n = \frac{z^2_{1-\frac{\alpha}{2}}\left(4+\frac{z_p^2}{2}\right)}{z^2_{1-\frac{\beta}{2}}\Delta^2}$

Table 1.4 Sample-size required for the comparison, via a test, of various parameters (assuming significance level α, and power $1-\beta$

Comparison of interest	Sample size
Single proportion π_1 (with anticipated value p_1) to a theoretical value p_0	$n = \dfrac{\left(z_{1-\frac{\alpha}{2}}\sqrt{p_0(1-p_0)} + z_{1-\beta}\sqrt{p_1(1-p_1)}\right)^2}{(p_1-p_0)^2}$
Two proportions (assuming independent samples of equal size, with anticipated proportions p_0 and p_1 and where $\bar{p} = (p_0+p_1)/2$)	n (per group) $= \dfrac{\left(z_{1-\frac{\alpha}{2}}\sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta}\sqrt{p_0(1-p_0)+p_1(1-p_1)}\right)^2}{(p_1-p_0)}$
Single proportion μ_1 (with anticipated value m_1) to a theoretical value m_0 (assuming sample variance s^2)	$n = \dfrac{s^2\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{(m_1-m_0)^2}$
Two means (assuming independent samples of equal size with common sample variance s^2)	n (per group) $= \dfrac{2s^2 \times \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{(m_1-m_0)^2}$

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Chapter 2
Use of Percentiles and *Z*-Scores in Anthropometry

Youfa Wang and Hsin-Jen Chen

Abstract Percentiles and *Z*-scores are often used to assess anthropometric measures to help evaluate children's growth and nutritional status. In this chapter, we first compare the concepts and applications of percentiles and *Z*-scores and their strengths and limitations. Compared to percentiles, *Z*-scores have a number of advantages: first, they are calculated based on the distribution of the reference population (mean and standard deviation), and thus reflect the reference distribution; second, as standardized quantities, they are comparable across ages, sexes, and anthropometric measures; third, *Z*-scores can be analyzed as a continuous variable in studies. In addition, they can quantify extreme growth status at both ends of the distribution. However, *Z*-scores are not straightforward to explain to the public and are hard to use in clinical settings. In recent years, there has been growing support to the use of percentiles in some growth and obesity references. We also discuss the issues related to cut point selections and outline the fitting/smoothing techniques for developing reference curves. Finally, several important growth references and standards including the previous and new WHO growth reference/standards and the US 2000 CDC Growth Charts, are presented and compared. They have been developed based on different principles and data sets and have provided different cut points for the same anthropometric measures; they could, thus, provide different results. This chapter will guide readers to understand and use percentiles and *Z*-scores based on recent growth references and standards.

Abbreviations

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
IOTF	International Obesity Task Force
HAZ	Height- or length-for-age *Z*-score
MGRS	Multicentre Growth Reference Study
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
SD	Standard deviation
WHO	World Health Organization
WHZ	Weight-for-age *Z*-score

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_2,

2.1 Introduction

Anthropometric assessment for children and adolescents involves the use of growth standards and/or growth references for assessing their growth, nutritional status and well being (Wang et al. 2006; WHO 1995). A growth standard reflects optimal growth, suggesting that all children have the potential to achieve that level, while a growth reference is simply the distribution used for comparison (WHO MGRSG 2006a).

Percentiles and *Z*-scores in anthropometric measures have been widely used to help assess young people's nutritional status and growth, such as undernutrition (e.g., underweight, stunting and wasting) and overnutrition (i.e., overweight and obesity), see Tables 2.1 and 2.2. Often, percentiles (such as the 5th, 85th, 95th, 97th, 99th percentiles) and *Z*-scores (e.g., -2 and +2) are used to classify various health conditions, and sex-age-specific anthropometric measures cut-points (based on *Z*-scores or percentiles) are provided in tables and as smoothed curves on growth charts (see Figs. 2.1 and 2.2).

For the past four decades, the World Health Organization (WHO) has recommended the use of growth reference (or "growth chart"), mainly based on *Z*-scores of anthropometric measures, to assess children's nutritional status and growth. These growth charts were developed based on data

Table 2.1 Comparison of percentiles and *Z*-scores in anthropometry

	Percentiles	*Z*-scores
1. Definition	The percentage of observations (or population) falls below the value of a variable	The number of standard deviation (SD) away from the mean, when the distribution is normal
2. Scale	Rank scale	Continuous scale (from $-\infty$ to ∞)
3. Strengths	(a) Intuitively more understandable	(a) Allowing comparisons across ages and sexes
	(b) Indicating the expected prevalence	(b) Able to quantify the extreme values
		(c) Good for assessing the longitudinal changes in growth status
4. Limitations	(a) Not comparable across different anthropometries	Difficult to perceive than percentiles, especially for the public
	(b) Extreme values are lumped to the highest/lowest percentile	
	(c) Not suitable for assessing longitudinal growth status	

5. Under normal distribution, a percentile must correspond to a fixed *Z*-score.

Following is a list of usually used percentile-*Z*-score conversion values.

0.2nd	–3
2.3rd	–2
2.5th	–1.96
5th	–1.64
15th	–1.04
16th	–1
50th (median)	0
84th	+1
85th	+1.04
95th	+1.64
97.5th	+1.96
97.7th	+2
99.8th	+3

This table lists the key definitions and scales of percentiles and *Z*-scores, and compares their strengths and limitations. In practical setting, users would often face the task to convert *Z*-scores to percentiles or vice versa. Thus, this table also shows the corresponding values between percentiles and *Z*-scores

Table 2.2 The 1995 WHO growth reference: use of percentiles and *Z*-scores

Outcomes	Anthropometric measures and cut points	Indication of growth/nutrition problems
Infants and children (<10 years)		
Stunting	HAZ < –2 *Z* score, or <3rd percentile	Chronic malnutrition
Wasting/thinness	WHZ < –2 *Z* score, or <3rd percentile	Acute malnutrition, current malnutrition
Overweight	WHZ > 2 *Z* score	Overweight
Adolescents (> =10 years)		
Stunting	HAZ <–2, or <3rd percentile	Chronic malnutrition
Thinness	BMI-for-age < 5th percentile	Underweight
At risk of overweight	BMI-for-age > =85th percentile	Overweight
Obese	BMI-for-age > =85th percentile and triceps and subscapular skinfold thickness-for-age > =90th percentiles	Obesity

This table summarizes the cut-points of percentiles and *Z*-scores to define problematic growth status in children and adolescents when using anthropometric measures. These cut-points based on statistical distribution are often adopted by other growth references/standards including the recent new WHO growth standards and references
HAZ: Height- or length-for-age *Z*-score; *WHZ*: Weight-for-age *Z*-score; *BMI*: Body mass index (WHO 1995)

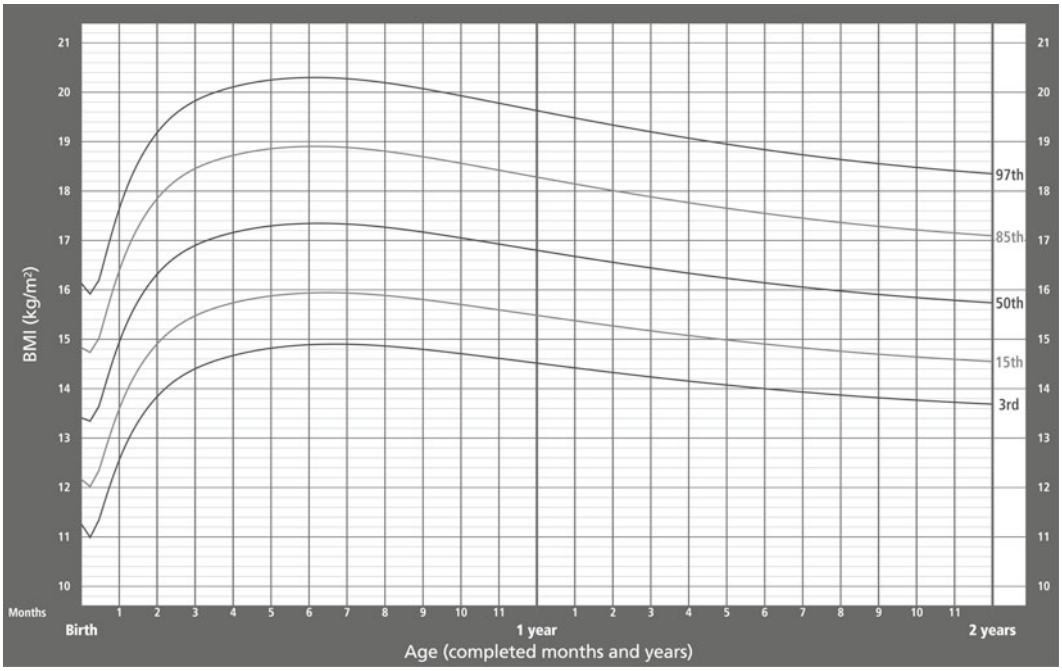

Fig. 2.1 The 2006 WHO growth standards: BMI-for-age percentiles for boys under 2-year-old. The curves for the 3rd, 15th, 50th, 85th, and 97th percentiles of 0–2 year-old boys' BMI-for-age are presented in this growth chart (Preprinted from WHO Growth Standards website, with permission)

collected in the United States (Wang et al. 2006). In 1995, WHO recommended the use of the sex-age-specific percentiles of some anthropometric measures for adolescents (WHO 1995). Historically, the WHO international growth references focused more on undernutrition problems, including wasting, stunting and underweight, even as the need to address a growing obesity problem in many countries has risen over the past two decades. The earlier versions of WHO growth

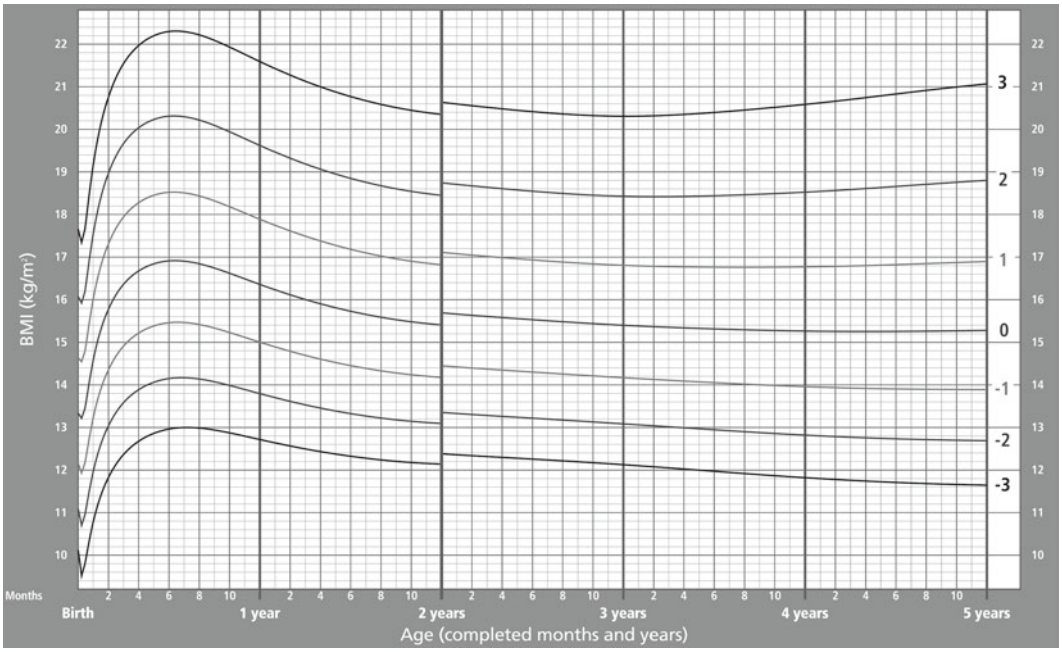

Fig. 2.2 The 2006 WHO growth standards: BMI *Z*-scores growth chart for preschool girls (0–5 years). This growth chart juxtaposes 0–2 year-old and 2–5 year-old girls' BMI-for-age *Z*-score curves. This chart provides curves for *Z*-scores of 0, ±1, ±2, and ±3. The disjunction at 2 years old addresses the issue of differential measurements between recumbent length and standing height. The length-for-age curves are averagely 0.7 cm larger than height-for age curves at 2-year-old (Reprinted from WHO Growth Standards website, with permission)

references were based on US data, whereas the new 2006 WHO Growth Standards for preschool age children have been developed based on data collected from several countries (see below).

Pediatric growth charts have been widely used globally by researchers, pediatricians, nurses and parents to assess the growth and nutritional status of children, but often users might not be aware of their limitations (Wang et al. 2006). For example, growth charts were not designated as a sole diagnostic instrument. Instead, they contribute to forming an overall clinical impression of the child being measured (CDC 2000). In addition, many users are not aware of the differences between "growth standard" and "growth reference" as these two terms are often used interchangeably.

In this chapter, we first describe the concepts and application of percentiles and *Z*-scores in anthropometry and compare their limitations and strengths. Next, we address two important issues: the selection of anthropometric measure cut points and the statistical methods and techniques for growth curve fitting and smoothing. Finally, we describe several international growth references including the 2006 WHO Growth Standards, growth references based on the US population, and an international reference for childhood obesity. In some of these references, anthropometric values corresponding to certain *Z*-scores and percentiles are provided.

2.2 The Use of *Z*-Scores

The use of *Z*-scores is recommended for several reasons (Table 2.1). First, *Z*-scores are calculated based on the distribution of the reference population (both the mean and the standard deviation [SD]); thus, they reflect the reference distribution. Second, as standardized measures, *Z*-scores are comparable

Fig. 2.3 *Z*-score and the corresponding cumulative probability and percentile (proportion). For normal distribution, the *Z*-score of 0 divides the total area into two equal halves. Thus, the *Z*-score of 1 corresponds to the 84th percentile (=0.5 + 0.34), i.e., 84% of the population are measured lower than *z*-score of 1. A *Z*-score is calculated as dividing the difference between measured value (x) and the mean (μ) by standard deviation (σ)

across age, sex and measure (as a measure of "dimensionless quantity"). Third, a group of *Z*-scores can be subject to summary statistics such as mean and SD and can be studied as a continuous variable. In addition, *Z*-score values can quantify the growth status of children outside of the percentile ranges (WHO 1995). However, the major limitation of *Z*-scores is that they are not straightforward to explain to the public and may be of limited use in clinical settings. The WHO and US Centers for Disease Control and Prevention (CDC) have ever developed a statistical software to help researchers to calculate *Z*-scores based on the 1978 WHO/NCHS (National Center for Health Statistics) references.

In statistical terms, *Z*-scores are a special application of transformation rules. The *Z*-score for a measure (e.g., height or BMI), indicates how far and in what direction (positive vs. negative) a measured value deviates from the population mean, expressed in units of the population SD. It is a dimensionless quantity derived from dividing the difference between individual value (x) and the population mean (μ) by the population SD (σ). The transformed *Z*-scores' distribution will have a mean of zero and a SD of one (i.e., mean = 0, SD = 1). This conversion process is called standardizing or normalizing.

$$Z = \frac{x - \mu}{\sigma}$$

Z-scores are sometimes called "standard scores". The *Z*-score transformation is especially useful when seeking to compare the relative standings of different measures (e.g., height vs. BMI, or the measures of boys' vs. girls') from distributions with different means and/or different SDs. *Z*-scores are especially informative when the distribution to which they refer is normal. In every normal distribution, the area under the curve between the mean and a given *Z*-score value corresponds to a fixed proportion of the total area (Fig. 2.3). Based on this characteristic, statisticians have created tables indicating the value of these proportions for various *Z*-scores.

2.3 The Use of Percentiles

A percentile is the value of a variable below which a certain percentage of observations (or population) falls, i.e., the percentile refers to the position of an individual on a given reference distribution. Percentiles are easier to understand and use in practice, both by health professionals and the public.

In addition, a percentile dictates the expected percentage of a population should be above (or below) it (see Table 2.1). Often age-sex-specific percentiles are recommended to assess children's growth and nutritional status based on anthropometric measures as well as other health conditions such as blood pressure. During recent years, there is a growing consensus on using sex- and age-specific BMI percentiles as cut-offs instead of weight-for-height *Z*-scores (WHZ) for assessing overweight and obesity as well as thinness/underweight in children over 2 years old (Kuczmarski et al. 2002; Wang et al. 2006; WHO 2006). The widely used percentiles include the 3rd, 5th, 50th (median), 85th, 95th, 97th, 99th.

In statistics, the term percentile and the related term percentile rank are often used in descriptive statistics as well as in the reporting of scores from norm-referenced tests. Percentiles are often represented graphically, using a normal curve (Fig. 2.3). A normal curve is always represented with some key features. The peak or the center of the bell-shaped curve stands the point of the mean of the distribution. The mean ($z = 0$) halves the normal distribution into two equal and symmetric areas. On both the right and left sides each, the graph can be shown as divided into three parts, according to *Z*-scores of 1, 2, and 3 SD to the right and -1, -2, -3 SD to the left, respectively. At each point of these SDs, the corresponding percentile (or cumulative probability) is fixed. In other words, as long as the distribution is normal, every SD unit on the *x*-axis has a specific percentile which is always paired with them. Therefore, on a normal curve, 34.13% of the data lies between 0 and -1 (or +1), 13.59% between -1 and -2 (or between +1 and +2), and 2.14% between -2 and -3 (or between +2 and +3). The remaining 0.14% of the data lies below -3 (or above +3).

A limitation of using percentiles is that the same interval of percentile values corresponds to different ranges in absolute values for different measurements. For instance, increments from 85th to 90th percentile correspond to different ranges in subscapular and in triceps skinfold thickness. Even within the distribution of one measurement, same increments at different percentile levels could correspond to different changes in both *Z*-scores and absolute measures. In addition, it does not allow for quantifying the change in percentile values near the extremes of the reference distribution (e.g., people in the uppermost 1st percentile can have very different absolute values). For these reasons, we suggest that percentiles should not be used to assess change in status over time, while change in *Z*-scores is a better measure. *Z*-scores are more useful in research while percentiles are easier for use in clinical settings and by the public.

Z-scores and percentiles can be converted to each other, but the commonly used cut points of each are not at exactly comparable levels. For example, *Z*-scores of 2 and -2 correspond to the 97.7th and 2.3rd percentiles, while the 85th and 5th percentiles correspond to *Z*-scores of 1.04 and -1.65, respectively.

2.4 Selection of Anthropometric Measure Cut Points

In growth references and standards based on international data or those from individual countries, *Z*-scores of +2 and -2, and/or certain percentiles (e.g., 5th, 85th, and 95th), have often been chosen as cut points to classify problematic growth/nutritional status such as malnutrition or obesity. These criteria are based on statistical distribution rather than on the risks of health outcomes (see Table 2.2). Ideally, the criteria should be established based on their associations with higher health risks, and cut points should be chosen for the particular purpose. The classification of "higher risk" individuals and population groups should be based on the evidence of increased risk for morbidity, mortality, or/and impaired function performance (WHO 1995).

However, to assess the relationship between different indicators and health outcomes is often more difficult in children than in adults. It is even harder to choose cut points for "higher risk". In children, two types of health outcomes need to be considered for studying the association with anthropometric measurement/indicators: (a) the short- and intermediate-term health outcomes during childhood and adolescence, and (b) long-term health outcomes in adulthood. Before well-designed long-term longitudinal studies provided sufficient information for these purposes, the International Obesity Task Force (IOTF) recommended sex-age-specific cut points for overweight and obese children and adolescents. These cut points are distinct from other statistical criteria based on growth reference/standards: they correspond to the overweight and obesity status in adulthood. (Cole et al. 2000, see below) Even with these unprecedented features, more solid evidence regarding the association between growth status and health outcomes are necessary.

In addition to connecting the deviations in anthropometric indicators and health/functional consequences, Pelletier suggested two more considerations for selecting cut points to assess growth and nutritional status: (1) Variation in age, maturation, gender, ethnicity, and other "technical" factors that affect anthropometry "independently" or in conjunction with health or social causes or consequences; and (2) The intended or potential applications of the anthropometric cut points, such as clinical diagnosis, policy formulation, social utility as well as advocacy for particular problems and solutions. (Pelletier 2006) He further argued that different indicators and cut points are needed for different application purposes. However, this notion may not be agreed upon by various user communities, including international expert groups, because universal cut points of simple indicators are considered easier to use and better for international comparisons.

Nevertheless, given the increasing understanding of the complexity of assessing children's growth and the new reality of a growing global obesity epidemic, as well as that many developing countries are facing a double burden of under- and over-nutrition problems, the international community and the public might take a new position if appropriate single cut points for simple indicators cannot be developed (Wang et al. 2006). For example, although the WHO has been recommending to use the BMI cut points of 25 and 30 for adults to classify overweight and obesity since the mid 1990s (WHO 1995), later research suggested that different BMI cut points may be more appropriate for specific populations and for different purposes, for example, lower BMI cut points of 23 and 25 for some Asian Pacific populations (Inoue et al. 2000; WHO Expert Consultation 2004).

2.5 Statistical Methods/Techniques Used for Curve-Fitting or Smoothing

Growth references/standards are used to compare an individual's measurements with that of the population. To develop sex-age-specific growth curves of critical percentile or *Z*-score cut points is important. Several different curve-fitting and smoothing techniques have been used in the development of existing growth references. When the 1978 WHO/NCHS growth curves were developed, a least-squares-cubic-spline technique was used (Hamill et al. 1979). The BMI and skinfold thickness percentiles being recommended by the WHO for international use were developed based on data collected in the US using the LOWESS method (LOcally WEighted regression Scatter-plot Smoothing) (Must et al. 1991). Several recent growth and obesity references, such as the 2000 CDC Growth Charts, the 2006 WHO Growth Standards, and the 2007 WHO Growth references (see below) used the LMS (lambda, mu, and sigma) estimation procedure or its modified approach to accommodate the distributions of different anthropometric measurements. The LMS method was introduced in the 1980s (Cole et al. 1992). For example, the CDC Growth Charts were carried out in

two stages: curve smoothing and transformation. The LMS method was modified for the transformation stage (Kuczmarski et al. 2002). In general, methods which summarize the centiles as an underlying distribution, such as the LMS method, "borrow strength" from neighboring ages and centiles and thus make better use of the data than the separate percentile-fitting methods used in the 1978 WHO/NCHS reference (Wang et al. 2006).

Based on the smoothed percentile curves over ages, the normalized distribution can be reconstructed and the *Z*-scores can be estimated. Theoretically, under normal distribution, each percentile should correspond to a *Z*-score (see below). Thus, the transformation procedure of the data is then carried out. For example, to develop the US 2000 CDC Growth Charts, Box-Cox transformation procedure and/or LMS (lambda, mu, and sigma) method were conducted for correcting the skewness of distribution at each age month, and then converting the percentile into *Z*-score. Given the LMS equation for specific indicator and the estimated parameters λ (L, the power in the Box-Cox transformation for "correcting" the skewness), μ (M, median), and σ (S, a coefficient of variation) for each age of month, child's anthropometric measurements can be converted to *Z*-scores and percentiles (see below).

These different methods may affect the final curves and cut points. For example, the BMI percentiles developed by Must et al. and Hammer et al. based on the First National Health and Nutrition Examination Survey (NHANES) data are not identical (Hammer et al. 1991; Must et al. 1991). Take the 5th percentile for 18-year-old white adolescents as an example, Must et al.'s figure vs. Hammer et al.'s was 17.5 vs. 18.3 for males and 16.9 vs. 17.2 for females, respectively. For the 95th percentile, the figures were 29.9 vs. 29.7 for males and 29.2 vs. 31.0 for females, respectively. Hence, different curve-fitting and smoothing techniques could lead to different results.

2.6 Practical Methods and Techniques: How to Use Growth References/Standards

To use a growth reference or standard to help assess individual or groups of children's growth and nutritional status, one will need to compare the subject(s)'s measure against the cut points provided in such growth references or standards, provided either in tables or growth charts (called growth curves). To use the growth charts, the users plot the observations on them. Since the growth charts were designated applicable to different sexes and age ranges, users need to choose the appropriate one.

Figure 2.4 is an example showing how to use the 2000 CDC Growth Charts to monitor a girl's growth in weight. This is a weight-for-age chart, and the girl's body weight measurements at 11 months after birth were plotted on the chart. The chart shows reference curves for the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles from birth to 36 months old. These curves can be used to evaluate the position of a child's anthropometric measurement relative to the reference population. The girl's weight-for-age was first generally between the 50th and 75th percentile curves after birth, but faltered to below the 10th percentile after 15 months old. This indicated failure of growth and the need of more careful examination and care such as better nutrition and/or appropriate treatment to the underlying causes. Similarly, one can use the growth charts for different anthropometric indicators provided by other growth references and standards.

Another way to use the recent growth references and standards, in particular, for research, is to calculate exact percentile and *Z*-score values for the subjects' measured values, compared to the selected reference or standard. The WHO 2006 and 2007 growth standards and reference and the 2000 CDC Growth Charts utilized similar techniques of smoothing and transformation (the LMS method).

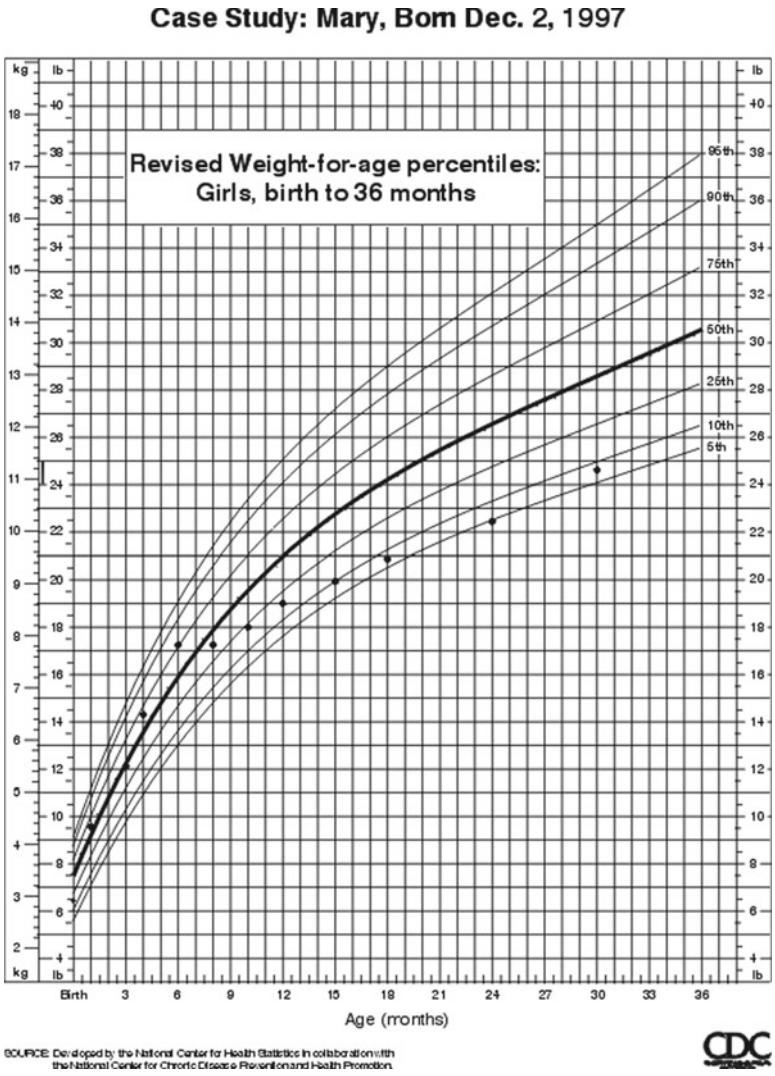

Fig. 2.4 An example from CDC of how to use growth chart to monitor individual child's growth (Adapted from http://www.cdc.gov/growthcharts/case_mary.htm). This figure uses a case to show how to apply a growth chart to assess a child's growth trajectory and health status. It shows a girl who had experienced growth faltering after age of 6 months. More details were provided in text (Reprinted from CDC website: http://www.cdc.gov/growthcharts/case_mary.htm)

They all provide the sex-age-specific LMS parameters that allow users to calculate the *Z*-score corresponding to each individual child's measured value. The formula for calculating *Z*-score is:

$$z = \frac{\left(y/M\right)^{L} - 1}{SL} \text{ when } L \neq 0; \quad z = \frac{\ln\left(y/M\right)}{S} \text{ when } L = 0;$$

where y is the individual observation, while the LMS parameters for the individual's age and sex need to be applied. For example, to calculate the WHZ for a 60-month-old (or 5 year-old) boy with a body weight of 15 kg based on the 2000 CDC Growth Reference, the reference table of weight-for-age

children of 2–20 years of age should be used. The estimated LMS parameters for boys aged 60.0–60.9 months old are listed on the reference table as -1.000453886 for *L*, 18.48592413 for *M*, and 0.129879257 for *S*. Thus, the boy's WHZ is -1.79 according to the formula.

As for percentile, it can be calculated after the *Z*-score is obtained, because the distributions of anthropometric measurements are close to normal under the Box-Cox transformation. In the above case, where the WHZ is -1.79, the corresponding percentile is the 3.7th. Namely, within the normal distribution with a mean of 0 and SD of 1, the cumulative probability below -1.79 SD from mean is 0.037. This can be calculated using a statistical software or by looking up the *Z*-table. This boy's body weight was below the lowest 5% compared to 60-month-old boys in the 2000 CDC reference. If the CDC's weight-for-age chart for children aged 2–20 was used, this boy's body weight would be plotted between the 3rd and 5th percentile curves.

Additional attention should be paid to including the 2006 WHO Growth Standard's formulas to adjust distorted extreme values and the 2000 CDC Growth Reference's formula for special occasions when *L* parameter equals to 0 (CDC 2000; WHO MGRSG 2006a). Furthermore, the formula for *Z*-scores of different anthropometric indicators may vary in the 2006 WHO Growth Standards (WHO MGRSG 2006a). Users should read the manuals carefully before applying these formulae. Furthermore, even though the recent growth charts from the CDC and the WHO since 2000 are developed using similar statistical techniques, the reference populations and data used to develop them are quite different (see below).

2.7 The WHO Growth References and Standards

Since the 1970s the WHO has published several versions of growth references, recommended for international use to help assess children's growth and nutritional status. Thus far, there are three widely known and used versions: the 1978 WHO/NCHS Growth References (for children up to age 10), the WHO Growth References (for children and adolescents up to age 19), and the 2006 WHO Growth Standards (for preschool children, under 6 years of age).

Most of the earlier versions are based on growth references developed and used in the US. The US CDC NCHS developed growth references based on national survey data collected in the 1960s and 1970s. These NCHS Growth Charts included anthropometric measurements such as weight-for-height, weight-for-age, height-for-age, and head circumference-for-age. They were developed based on several national surveys (namely NHES II, NHES III, and NHANES I) and a local study for infants (the Fels Longitudinal Study). More details about the history of the WHO growth references are provided elsewhere (WHO 1995; Wang et al. 2006; WHO MGRSG 2006a).

2.7.1 The 1978 WHO/NCHS Growth References

In 1978, the WHO/CDC produced a normalized version of the US CDC/NCHS growth curves, showing *Z*-scores instead of absolute anthropometric values. It was called the 1978 WHO/NCHS Growth References, and has been widely used all over the world since then. However, it has a number of limitations (Wang et al. 2006). For example, one of its main limitations is about representativeness, because the growth reference for infants was developed based on data collected from the Fels Longitudinal Study, which followed mainly formula-fed children in an area in Ohio State in mid-west of the USA. Moreover, these children were followed with large time intervals, which

Table 2.3 Key anthropometric measures and indicators provided in recent WHO and US CDC growth references/standards

	2000 CDC growth reference		2006 WHO growth standards		2007 WHO growth reference
Applicable age range (years)	0–3	2–20	0–2	2–5	5–19
Length/height/stature-for-age	v	v	v	v	v
Weight-for-age	v	v	v	–	v
Weight-for-length	v	–	v	–	–
Weight-for-height/stature	–	v	–	v	–
BMI-for-age	–	v	v	v	v
Head circumference-for-age	v	–	v	–	–
Arm circumference-for-age	–	–	v[a]	v	–
Subscapular skinfold-for-age	–	–	v[a]	v	–
Triceps skinfold-for-age	–	–	v[a]	v	–

This table lays out the anthropometric measures included in the three sets of recent growth references/standards. The first two are widely used by people in different countries

"v" indicates available measures

[a]From 3 months to 5 years (CDC 2000; de Onis et al. 2007; WHO 2006)

provided insufficient data to describe the rapid and changing rate of growth in early infancy (Kuczmarski et al. 2002). Recent studies have shown that the growth pattern of breast-fed infants differed from that of formula-fed infants (Victora et al. 1998; de Onis and Onyango 2003). To overcome these limitations, new growth references and standards have been developed in the US in 2000 and by the WHO in 2006, respectively (see below).

2.7.2 The 1995 WHO Growth References

In 1995, a WHO Expert Committee reviewed existing growth references and research findings, and then re-endorsed the use of the 1978 WHO/NCHS Growth Charts. In addition, for adolescents, the committee recommended use of the sex- and age-specific BMI ≥ the 85th percentile and both triceps and subscapular skinfold thickness ≥ the 90th percentile for classifying "at risk of overweight" and "overweight" (WHO 1995). These percentiles were developed based on the US data. Previously the WHO had not made specific recommendation for adolescents. The committee acknowledged the weaknesses of the NCHS infant growth charts, and some potential problems when using these US adolescent BMI percentiles in other populations. For example, their predictability to future health risk and generalizability for children from developing countries was unknown. The committee recommended the use of these references on a provisional basis, until better reference data became available (WHO 1995).

2.7.3 The 2006 WHO Growth Standards for Preschool Children

On April 27, 2006, the WHO released new growth standards for children from birth to the age of 60 months (5 years old, see Tables 2.3 and 2.4). In order to establish growth standards for different races/ethnicities, the Multicentre Growth Reference Study (MGRS) recruited affluent, breast-fed, and healthy infants/children whose mothers did not smoke during or after delivery from six cities in

Table 2.4 Estimated children/adolescents' percentiles and *Z*-scores corresponding to the recommended BMI cut points for adults for the classification of thinness grade 2 (BMI < =17), overweight (BMI > =25), and obesity (BMI > =30)

		Boys						Girls					
		Percentiles corresponding to			*Z*-scores corresponding to			Percentiles corresponding to			*Z*-scores corresponding to		
	Data Source	BMI = 17	BMI = 25	BMI = 30	BMI = 17	BMI = 25	BMI = 30	BMI = 17	BMI = 25	BMI = 30	BMI = 17	BMI = 25	BMI= 30
WHO (2007)[a]	USA	–	–	–	–	1	2	–	–	–	–	1	2
IOTF (2000, 2007)[b]	Brazil	3	95.3	99.9	–1.9	1.7	3.1	2	84.8	98.0	–2.0	1.0	2.1
	Hong Kong	9	88.3	96.9	–1.3	1.2	1.9	6	90.2	98.2	–1.6	1.3	2.1
	The Netherlands	2	94.5	99.7	–2.2	1.6	2.7	3	93.5	99.7	–1.9	1.5	2.7
	Singapore	6	89.5	98.3	–1.5	1.3	2.1	9	93.0	99.0	–1.3	1.5	2.3
	UK	2	90.4	99.1	–2.2	1.3	2.7	2	88.3	98.8	–2.0	1.2	2.3
	USA	1	81.9	96.7	–2.4	0.9	1.8	3	83.5	96.0	–2.0	1.0	1.8

This table summarizes the corresponding percentiles and *Z*-scores which correspond to the specific BMI cut-points at the age (e.g., 18 or 19 years old) of transitioning to adulthood

[a]WHO (2007)2007 growth reference, BMI equal to these cut points at age 19 years old (de Onis et al. 2007)

[b]The IOTF reference, at age of 18 years on each country's data set (Cole et al. 2000, 2007)

Brazil, Ghana, India, Norway, Oman, and the USA. This study included a longitudinal sample followed from birth to 24-month-old and a cross-sectional sample recruiting 18- to 71-month-old children. The MGRS data showed great similarities in growth across all study centers, with only about 3% of the total variation in growth was contributed by race/country. Hence, the multicenter data were pooled for a more powerful sample (WHO MGRSG 2006a). The data demonstrate that preschool children in different regions of the world have the same growth potential to achieve similar levels of heights and weights when their nutrition and health care needs are met. However, this conclusion was based on children from birth to 6 years (72 months) of age. Genetic influence on inter-individual variation in the ultimate height in adulthood cannot be ruled out.

The WHO recommends these new standards in replace of the old versions for international use among preschool children, although some countries still use their own growth references/standards. The 2006 WHO Growth Standards include anthropometric indicators such as length/height-for-age, weight-for-age, weight-for-length/height, BMI-for-age, head circumference-for-age, arm circumference-for-age, subscapular skinfold-for-age, and triceps skinfold-for-age. Recumbent length-for-age was used for indicator of stature from birth to age of 24 months, while standing height-for-age from 2 to 5 years old. Due to the differential measurements of body length and body height, a 0.7 cm taller in length at 24-month-old was observed. Thus, to address this issue, weight-for-length for 0–2 year-old children and weight-for-height for 2–5 year-old children were presented on separate charts. Meanwhile, growth charts for all other indicators that involve length/height show a disjunction between the curves for 0–24 months-old and those for 24–60 month-old, like the BMI-for-age chart in Fig. 2.2. The WHO provides growth charts and tables of percentiles and *Z*-scores, separately for girls and boys. On the *Z*-score growth charts, the curves for 0, ±2, and ±3 SD from the age specific median of certain indicator were plotted. As for the percentile charts, five curves for the 3rd, 15th, 50th, 85th, and 97th percentiles were shown for each indicator. In the tables, the values of indicator at 0, ±1, ±2, and ±3 SD, and for percentiles of 1st, 3rd, 5th, 15th, 25th, 50th, 75th, 85th, 97th and 99th were provided for each age of month.

The 2006 WHO Growth Standards differ from the existing growth charts in many ways. They suggest "how children should grow", which is developed using a prescriptive approach, not just a descriptive one. They show that all children can attain similar levels of healthy height and weight as long as they have adequate feeding and health care. A key characteristic of the new standards is that it presumed breastfeeding as a biological norm. Furthermore, the pooled sample from the six participating countries creates better international standards, in contrast to the previous growth reference based on children from a single country. The standards can serve as tools for detecting both under-nutrition and obesity. The standards go beyond the previous references and include indicators like BMI and skinfolds. These charts are particularly useful in monitoring childhood obesity, which is relevant to public health in both developed and developing countries (WHO MGRSG 2006a; WHO 2006).

2.7.4 The 2007 WHO Growth Reference for School-Age Children and Adolescent

Based on recommendations made in 2006 by a group of international experts including the lead author, in particular, regarding the limitation of the previous growth references and the needs of better ones for assessing both overweight and undernutrition (Wang et al. 2006), the WHO released another set of growth reference for children and adolescents aged 5–19 years in 2007 (de Onis et al. 2007). To our knowledge, this reference has not been widely used yet. The references were derived based on the same US dataset as for the 1978 WHO/NCHS growth references but used different growth curve

smoothing techniques. The references include three indicators: BMI-for-age, weight-for-age, and height-for-age (Tables 2.3 and 2.4). For each indicator, charts and tables for percentiles and *Z*-scores were provided. The percentiles charts draw the 3rd, 15th, 50th, 85th, and 97th percentile curves, while the tables provided the values of anthropometric measures for more percentiles (1st, 3rd, 5th, 15th, 25th, 50th, 75th, 85th, 95th, 97th, and 99th). Regarding *Z*-scores of these three indicators, the curves for 0, ±1, ±2, ±3 *Z*-scores from median were shown on charts, and the values for these cut points were provided in tables.

The WHO recommended the cut points for overweight and obesity based on the BMI-for-age *Z*-scores. With the smoothing methods, it showed that the BMI-for-age *Z*-score = 1 at 19 year-old was 25.4 for boys and 25.0 for girls, which equals or is close to the WHO BMI cut point of 25 used in adults. Thus, the reference curve of *Z*-score = 1 was recommended to classify "overweight", while that of *Z*-score > 2 for classifying "obesity" based on the same idea. BMI-for-age *Z*-score < -2 and < -3 were set as the cut-points for thinness and severe thinness, respectively (WHO MGRSG 2006b).

2.8 The 2000 International Obesity Task Force (IOTF) Reference for Classification of Childhood Obesity

To define "overweight" and "obesity" among children aged 2–18 years, the IOTF endorsed a series of sex-age-specific BMI cut points. Based on data from multinational surveys, the cut points were developed from sex-specific BMI-age curves that pass through a BMI of 25 for overweight and 30 for obesity at age of 18 years old, respectively (Cole et al. 2000). Thus, these classifications of overweight and obesity in young people would be more biologically or pathologically meaningful compared to those references just based on distribution (i.e. percentiles or *Z*-scores). Given the concern for the differences among races/ethnicities, the reference was developed based on nationally representative data from six countries/regions: Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the USA. The LMS methods with Box-Cox transformation was used to construct percentile curves. At age of 18 years, the BMI *Z*-score corresponding to 25kg/m^2 ranged from 0.91 to 1.68 across the six countries/regions, while the pooled data of the WHO MGRS data showed that this BMI for 19 year-old was about at the *Z*-score of 1 for boys and girls (Table 2.4). This IOTF reference used pooled data to calculate sex-age-specific BMI cut points for overweight and obesity.

The cut points were reported for children from 2 to 18 years old in every half year in age for clinical use. For epidemiological studies, Cole et al. recommended that the mid-year cut points could be used for the year group to obtain unbiased prevalence estimate (e.g., using the cut point at 7.5 years for the age group 7.0–7.9). However, these BMI cut points for obesity may be less precise than those for overweight because of the larger variations in the percentile curves for obesity among the 6 datasets.

The IOTF reference has been recommended for international use due to its unique strengths: First, it is based on large data sets from six countries or regions and covers different races/ethnicities. Second, the BMI cutoffs are linked to adult cutoffs for overweight and obesity, which are good indicators of risks for adverse health outcomes. On the other hand, there are also concerns about this reference (Wang 2004). There is great variation in the prevalence of overweight and obesity across the six countries/regions that the IOTF reference population was based on Cole et al. (2000).

Moreover, recently the same procedure was applied using the same data for generating the cut point curve for thinness in children and adolescents, using the WHO-recommended cut point for adults of BMI < 17 for grade 2 thinness (Cole et al. 2007). They intentionally used the term "thinness" rather than "underweight". Because these cut-points were only based on BMI-for-age, they want to make this distinct from wasting and stunting. The 2007 WHO Growth Reference also used the term thinness rather than underweight for BMI-Z < 2.

2.9 The US 2000 CDC Growth Charts

As mentioned above, the US CDC/NCHS has developed several versions of growth charts since the 1970s, and some of them had been recommended by the WHO for international use. In order to address the limitations of the previous growth charts, the CDC/NCHS released new growth charts in 2000, which were developed based on data of infants and children from birth to 5 years old in the Third National Health and Nutrition Examination Survey (NHANES III) to replace the Fels Longitudinal Study, and on the other data from earlier national surveys.

The growth charts consist of a series of percentile curves of selected anthropometric measures, including weight-for-age, length-for-age, weight-for-length, and head circumference-for-age from birth to 36 months of age. For children above 2 years old, there are weight-for-age, stature-for-age, BMI-for-age, and weight-for-stature charts for children taller than 77cm (Table 2.3) (CDC 2000; Kuczmarski et al. 2002). The charts are presented separately for 0–2 year-old and for 2–20 year-old children, thus, the issue of disjunction between length and height measurements at the age of 2 years is not observable on the charts.

Growth curves for these anthropometric measurements were laid out as two sets of charts, "Individual Growth Charts" and "Clinical Growth Charts." Each chart is printed on one page, namely "Individual Growth Charts." As for "Clinical Growth Charts", length/stature-for-age and weight-for-age were graphed on a same page, and so were the head circumference-for-age and weight-for-length charts displayed together. The growth charts and tables present the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th percentile curves. The 85th percentile curve is in addition provided, on the BMI-for-age and weight-for-stature growth charts for 2–20 year-old children because this is a recommended cut point for childhood overweight. Regarding the *Z*-score for the indicators, only tables provide the detailed corresponding values indicator-for-age at 0, ±0.5, ±1, ±1.5, and ±2.

2.10 Comparisons of Using Different International and Local Growth References/Standards

As many previous studies have used the earlier growth references and various recent and new growth references/standards will continue to be used in the future, it is important to know how comparable the results are if these references and standards are applied on the same study population. A number of studies have attempted to address this issue. Following highlighted some of the related findings (see Table 2.5 for a summary). Overall, they showed that the estimated unhealthy growth status can vary when different growth reference/standards are applied.

One recent study showed that the Bangladeshi, Dominican Republic, and North American/European children aged 0–12 months had higher prevalence of overweight and stunting but lower prevalence of underweight, when the 2006 WHO Growth Standards was used compared to the 2000 CDC Growth Charts. In addition, according to the 2000 CDC Growth Charts, these children's WHZ decreased as age increased but were relatively stable based on the 2006 WHO Growth standards (de Onis et al. 2006). The US children showed a higher prevalence in stunting but lower prevalence in wasting when using the WHO 2006 Growth Standards versus the 2000 CDC Growth Charts, but they used the percentiles as cut points (5th for undernutrition and 95th for overweight) (Mei et al. 2008). Schwarz et al., compared the prevalence of undernutrition among Gabonese children based on three growth references/standards, namely the 1978 WHO/NCHS, the 2000 CDC and the 2006 WHO ones. They found that the prevalence of wasting and stunting was significantly higher when applying the 2006 WHO Growth Standards among 3-month-old children, while for 15-month-old

Table 2.5 Comparisons of prevalence (%) of growth/nutritional status problems assessed based on The 1978 WHO/NCHS reference, The 2000 CDC Growth Charts and The 2006 WHO Growth Standards

Country/settings, data collection year, sample	WHO/NCHS (1978)	CDC (2000)	WHO (2006)	References
Bangladesh, 1996–1997 4,787 children aged 0–60 months	N/A	Stunting: 54.4% Wasting: 56.5%	Stunting: 60.1% Wasting: 52.9%	de Onis et al. (2006)
Gabon, 2002 (baseline) 289 children aged 3 months 289 children aged 15 months (at follow-up)	Stunting: 10–15% Wasting: 0.7% Stunting: ~30% Wasting: ~15%	Stunting: 10–15% Wasting: 1.0% Stunting: ~15% Wasting: ~20%	Stunting: 23.5% Wasting: 4.0% Stunting: ~30% Wasting: ~5%	Schwarz et al. (2008)
Madagascar, 2004 969 children aged 6–59 months	Stunting: 35.8% Wasting: 3.2%	Stunting: 30.0% Wasting: 12.2%	N/A	Roberfroid et al. (2006)
US, 1999–2004 (NHANES) 3,920 children aged 0–59 months	N/A	Stunting: 3.7% Wasting: 5.0% Overweight: 9.2%	Stunting: 7.0% Wasting: 2.8% Overweight: 12.9%	Mei et al. (2008)
Dominican Republic, 2004 10,381 children aged 0–60 months	N/A	Overweight: 6.4%	Overweight: 8.6%	de Onis et al. (2006)

This table shows selected studies that compared the results based on different growth references/standards, and they have revealed considerable differences. Except for the US study, stunting is defined as length/height-for-age z scores < –2, wasting as weight-for-age *z*-scores (WHZ) < –2, and overweight as weight-for-length/height *z*-scores >2. Findings in the US study were based on the 5th or 95th percentiles for weight-for-age, length-for-age, and weight-for-height, respectively

children, the prevalence of stunting was lowest based on the 2000 CDC reference (Schwarz et al. 2008). Comparing the 1978 WHO/NCHS Growth References and the 2000 CDC Growth Charts, Roberfroid et al. (2006) demonstrated that for children aged 6–59 months in Madagascar, the estimated prevalence of stunting and underweight were different. The prevalence of stunting was higher using the 1978 reference, while the prevalence of underweight was more salient when applying the 2000 CDC references.

These findings suggest that, when the CDC 2000 Growth Charts replaced the Fels Longitudinal Study with the NHANES III data, the reference was representative of a heavier preschool subpopulation. Thus, the prevalence of wasting became higher. It is important to consider the reference population and methods used for developing the references/standards when choosing a growth reference/standard for assessing problematic growth outcomes.

Table 2.6 summarizes the main references and classifications having been used to define overweight and obesity in children and adolescents. Table 2.7 shows that according to one of our recent studies, the obesity prevalence estimated for Chinese children aged 6–18 years old in Beijing could vary between 5.8% and 9.8%, but in relative term, by 69% (Shan et al. 2010). Prevalence of overweight in Dominican and the US children was lower when using the 2000 CDC Growth Charts than using the 2006 WHO Growth Standards, regardless of the cut points (de Onis et al. 2006; Mei et al. 2008; Table 2.5). These findings indicate considerable differences in the prevalence of overweight/obesity based on different references, and the need of more research in these areas to help understand and guide appropriate applications of such references in different populations and for various purposes (Wang 2004; Wang et al. 2006).

Table 2.6 Different classifications/references for child and adolescent overweight and obesity

Standards/references	Overweight	Obesity	Data and reference population	References
2006 WHO Growth Standards for preschool children[a]	BMI-for-age or weight-for-length/height *Z*-score > 2	BMI-for-age or weight-for-length/height *Z*-score>3	Multicenter Growth Reference Study	WHO Training Course (2006)
2007 WHO Growth Reference for school age children	BMI-for-age *Z*-score > 1	BMI-for-age *Z*-score > 2	Same data as the CDC growth charts	de Onis et al. (2007)
2000 IOTF Reference	≥BMI-for-age cutoffs derived from BMI-age curves passed BMI of 25 at age 18	≥BMI-for-age cutoffs derived from BMI-age curves passed BMI of 30 at age 18	Data from the US, Brazil, Britain, Hong Kong, the Netherlands, and Singapore	Cole et al. (2000)
US 2000 CDC Growth Chart	≥BMI 85th percentile	≥BMI 95th percentile	US NHANES data (1971–1994)	Kuczmarski et al. (2002)
Europe-French BMI reference	≥BMI 90th percentiles	≥BMI 97th percentiles	Data collected for the French population	Poskitt (1995); Rolland-Cachera et al. (1991)

This table compares the evolving definition for childhood problematic growth status in different growth references/standards. See Table 2.1 for the corresponding values between percentiles and *Z*-scores, e.g., a *Z*-score of 2 corresponds to the 97.7th percentile, and *Z*-score of 1, the 84th percentile

[a]The 2006 WHO Growth Standards for preschool children recommends using BMI-for-age or weight-for-length/height Z scores of 1–2 to classify "at risk of overweight"

Table 2.7 Prevalence (%) of overweight and obesity among Chinese children and adolescents aged 2–18 years old in Beijing based on four local and international BMI references (Shan et al. 2010)

Age group (years)	Overweight (not obese)				Obesity			
	IOTF	WHO	CDC	WGOC[a]	IOTF	WHO	CDC	WGOC[a]
2–5	7.6	3.7	8.0	No ref.	3.5	2.3	6.8	No ref.
6–9	11.2	12.1	10.1	9.5	6.3	10.0	10.4	11.4
10–12	16.7	17.9	13.8	13.2	7.2	11.9	12.0	11.9
13–15	13.7	13.5	11.5	11.7	5.3	7.4	8.1	8.7
16–18	11.8	11.6	9.2	12.8	3.6	4.2	4.9	5.9
6–18	13.6	14.0	11.4	11.9	5.8	8.7	9.2	9.8
All, 2–18	13.1	13.2	11.1	No ref.	5.6	8.2	9.0	No ref.

Data source: Shan et al. (2010)

This table demonstrates the different results in prevalence of childhood obesity when different growth references/standards were used. IOTF, the 2000 International Obesity Task Force reference; WHO, The 2006 and 2007 WHO standards/references; CDC, the 2000 CDC Growth Charts; WGOC, the local reference developed by the Working Group on Obesity in China, which corresponded to the BMI cut points of 24 and 28 at age 18, respectively. BMI cut points of 24 and 28 are used in China to define overweight and obesity in adults, respectively

[a]WGOC' BMI reference: BMI cut points were only provided for children at age of 7–18 years

In summary, key issues for consideration before one chooses and uses a growth reference/standard include: (a) Whether it is a reference population or optimal growth pattern that one wants to compare to? (b) Whether the plotting on the charts or calculating the exact percentiles/*z*-scores for individual children is more feasible and/or useful? (c) Whether percentile or *z*-score can serve the purpose of application? (d) What age-sex- and anthropometric indicator- specific references are provided? These issues also suggest the directions for future research, including validating the generalizability of existing reference/standards to different countries, and deciding the cut points for unhealthy growth status which associated with future health risk.

2.11 Applications to Other Areas of Health and Diseases

People can use the percentiles and *Z*-scores of anthropometric measures in various growth standards or references to assess children's growth and nutritional status problems including malnutrition (e.g., stunting, wasting, underweight) and overnutrition (e.g., overweight and obesity). In addition, percentiles of other health measures such as blood pressure has been used to help classify elevated blood pressure (or called "hypertension") in young people (National High Blood Pressure Education Program 1996). This means that blood pressure readings are ranked according to where they fall against the percentage of the reference population of all children, while taking into account variations in gender, height, age, and other developmental parameters. For example, in the USA, the updated blood pressure tables were developed based on the NHANES 1999–2000 data, and included the 50th, 90th, 95th, and 99th percentiles (NHLBI 2004). The 50th percentile indicates the midpoint of normal blood pressure range, and is additionally compared to earlier guidelines. "Prehypertension" is defined as average systolic and/or diastolic blood pressure (SBP/DBP) ≥ 90th and < 95th percentiles (previously defined as "high normal"). Hypertension is defined based on the 95th percentile, and the 99th percentile allows more precise staging of hypertension.

Summary Points

- Percentile and *Z*-score of anthropometry are statistical tools to help assess child growth and nutritional status, relative to a reference or standard population.
- Percentile and *Z*-score can be converted to each other when the distribution is normal.
- Percentile indicates the percentage of observations that fall below a certain value. It is easier to use and for the public to understand, but may not be a good quantitative tool.
- *Z*-score is the distance and direction of an observation away from the population mean. Although it is not very intuitively perceivable, this dimensionless quantity can be used for comparison across indicators and populations. Individual children's measurments can be transformed to *Z*-scores based on growth reference, and *Z*-scores can be used as a continuous variable in research.
- Usually a growth reference is developed based on data collected from a representative sample of a population and shows the growth pattern of the reference population, which may not be an optimal growth pattern.
- A growth standard derived from a healthy and affluent child population can be regarded as an optimal distribution of growth.
- Various statistical methods and techniques have been used for curve-fitting and smoothing to help derive the related cut points for anthropometric measures in existing growth references and standards. These methods/techniques can affect the derived cut points.
- The 2006 WHO Growth Standards for preschool children differ from the other existing references, and show "how children should grow." It is developed based on a prescriptive approach for evaluating children's growth rather than a descriptive one.
- The 2006 WHO Growth Standards provide a tool for detecting both under nutrition and obesity, and thus address the double burden of under- and over-nutrition problems. They are relevant to both developed and developing countries.
- The US 2000 CDC Growth Charts have a number of improvements when compared to earlier versions of CDC growth references, but may not be appropriate for use in other populations, in particular, developing countries.

- Prevalence of problematic growth or nutrition status patterns can be different when estimated based on different growth references/standards.
- More research is needed to assess and guide the appropriate application of international growth references and standards in different populations, in particular, in developing countries.

Acknowledgments This work was supported in part by research grants from the NIH/NIDDK (R01DK81335-01A1, 1R03HD058077-01A1, R03HD058077-01A1S1) and the Nestle Foundation. We also thank Irwin Shorr for his comments on an earlier draft of this chapter.

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Chapter 3
Use of Bioelectrical Impedance: General Principles and Overview

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Abstract The present chapter clarifies some of the basic concepts of bioimpedance and discusses its significance with regard to biophysical models and their limitations. The focus is on bioimpedance body composition models, which have become popular under the term Bioelectrical Impedance Analysis (BIA) and Bioelectrical Impedance Spectroscopy (BIS). The intention is to provide the novice reader who is unfamiliar with biophysics, electromagnetics, and circuit theory with a comprehensive, easy-to-follow, and interdisciplinary introduction to the technical and biophysical concepts underlying current BIA and BIS techniques. Such knowledge is considered important to carefully perform and interpret bioimpedance results in clinical and research settings. The main sections of the chapter build on each other in a logical order, but can also be used independently as future reference by the experienced reader. In brief, the present chapter starts with an explanation of the raw data obtained from bioimpedance measurements. This serves as a basis for reviewing the passive electrical properties of human cells and tissue and for showing how these properties can be represented by electrical equivalent circuits. This goes on to explain the frequency-dependent nature of the electrical properties of biological tissue and clarify the differences between single-frequency, multi-frequency BIA, and BIS. Subsequently, safety considerations and general measurement principles such as electrode arrangements are also addressed in order to highlight how deep-tissue measurements can be obtained non-invasively without the use of needle electrodes. This is followed by a detailed outline of the fundamental biophysical model underlying most bioimpedance body composition applications. The weak points of present biophysical models are identified by comparing conventional whole-body BIA approaches to alternative techniques such as proximal electrode configurations or segmental measurements. Examples are used to show how to improve segmental measurements by performing multiple measurements along the limbs, thus "slicing" the limbs in various cross-sections such as during MRI scanning. Finally, the chapter assesses the reliability of bioimpedance measurements by discussing several endogenous and exogenous sources of error, and concludes with a guideline for standardizing bioimpedance measurement procedures. This serves as the basis for a discussion of selected applications in the following chapters on bioelectrical impedance and is therefore intended to complement each other.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_3,

Abbreviations

Latin letters

A	Area [m^2]
BIA	Bioelectrical Impedance Analysis
BIS	Bioelectrical Impedance Spectroscopy
C	Capacitance [F]
C_m	Membrane capacitance [F]
f	Frequency [Hz]
f_c	Characteristic frequency [Hz]
l	Length [m]
L	Liter
R	Resistance [Ω]
R_0	Resistance at zero frequency [Ω]
R_∞	Resistance at infinite frequency [Ω]
R_e	Extracellular resistance [Ω]
R_i	Intracellular resistance [Ω]
V	General volume [L]
X	Reactance [Ω]
X_c	Capacitive reactance [Ω]
Z	General impedance (magnitude) [Ω]

Greek letters

ρ	Resistivity [Ω·m]
ε	Permittivity [$F \cdot m^{-1}$]
σ	Conductivity in general [$S \cdot m^{-1}$]
τ	Time constant [s]
φ	Phase angle [°]
ω	Angular frequency ($2\pi f$) [Hz]
Ω	Ohm

3.1 Introduction

Presently, the term bioimpedance measurements refer to all methods based on the characterization of the passive electrical properties of biological tissue. Some biological tissues show active electrical properties, as they are capable of generating electrical potentials, the passive electrical properties of biological tissues relate to their response to the injection of external electrical energy. Different measurement techniques and various bioelectrical properties form a collection of methods that are now employed for multiple applications. Generally, these methods can be classified according to the following four groups: transimpedance, transmission line, microwave, inductive, and finally a combination of the preceding. Furthermore, all methods can be based on either single- or multiple-channel measurements. The latter have also been associated with the term tomography as they focus on characterizing the spatial distribution of the passive electrical properties. Presently, single-channel transimpedance methods are most widespread due to their extensive research history and ease of application, and have become popular under the term bioelectrical impedance analysis (BIA). They reconstruct the passive electrical properties of biological tissue by injecting alternating currents into

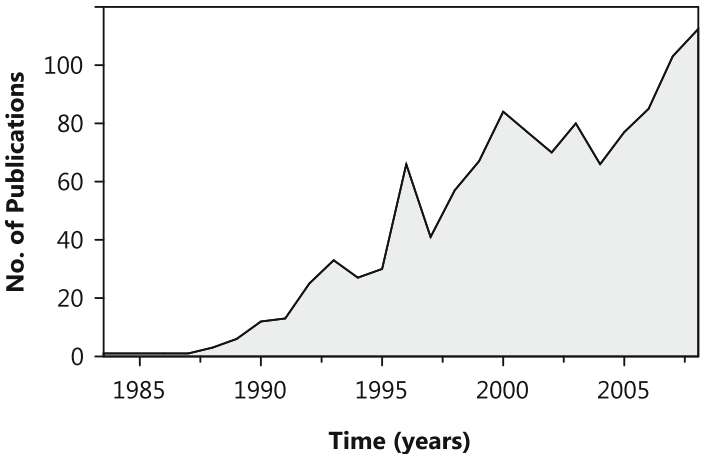

Fig. 3.1 Number of annual peer-reviewed publications on BIA since 1980. Results based on PubMed search using the following citation: (bioelectrical impedance analysis [Title/Abstract]) AND ("Year/MM/DD"[PDAT]: " Year/MM/DD "[PDAT])

an object via electrodes and measuring the potential differences between select points of interest. Because of the different passive electric properties of biological tissue and their frequency-dependent response to an alternating current, impedance magnitude and phase can provide diagnostic information about physiological properties and events of the body or body segment under consideration. While the basic idea of this approach can be generally adopted for cellular measurements (i.e. Coulter counter principle), volume changes (transthoraic impedance cardiography for stroke volume measurements), tissue classification and tissue monitoring (i.e. ischemia detection), most research and developments have focused on body composition applications. The significant impact of this technology can be traced to its main advantages:

- It is non-invasive.
- It is relatively inexpensive.
- It can be easily operated.
- It enables continuous (online) monitoring.
- It is rapid.
- It is portable.

These benefits are important characteristics in designing new medical instrumentation and are still a major reason for the permanent refinement of existing techniques and the investigation of new applications. A survey of publications on BIA, retrieved using Boolean methods through the internet database 'PubMed' revealed that the number of papers per annum between 1990 and 2000 increased seven-fold, and continues to rise gradually at a growth rate of nearly 22% (Fig. 3.1).

The need for further research on BIA has also been confirmed by various expert panels stating that a vast number of questions about BIA still remain unanswered today and the full range of applications of the technique has yet to be investigated.

3.2 Impedance, Phase Angle, Resistance, and Reactance

In spite of the growing accessibility and use of BIA, there are still a lot of misconceptions concerning the appropriate analysis of BIA results. The basic concept of in-vivo bioimpedance monitoring is the injection of an alternating current between two specific points of the human body (usually the wrist and ipsilateral ankle for body composition assessments) and the measurement of the resulting voltage

Table 3.1 Key concepts of bioelectrical impedance

Concept	Definition	Equation	Unit
Impedance (Z)	Electrical impedance is a measure of the total opposition of a conductor against an alternating current. This opposition is directly proportional to voltage across the two points and inversely proportional to the current between them. Given that the human body can be electrically modeled as an array of resistors and capacitors, the electrical impedance of the human body comprises both a real part (resistance R) and an imaginary part (reactance X). Since in an alternating-current circuit voltage and current change as a function of frequency, impedance comprises both information about both the direction (phase) as well as the magnitude of impedance. Consequently, it is expressed as a complex number which can be graphically depicted as a vector.	$Z = R + jX$	[Ω]
Magnitude of impedance (Z)	The magnitude of impedance is a scalar quantity as it only refers to the distance of the impedance vector. It can be calculated as the vector sum of resistance and reactance.	$Z = \sqrt{R^2 + X_c^2}$	[Ω]
Phase (φ)	Phase reflects the delay between voltage and current. Hence, it indicates to the direction of complex impedance. Graphically, it is represented as the angle between impedance and the x-axis.	$\varphi = tan^{-1}\left(\frac{X_c}{R}\right)$	[°]
Resistance (R)	Resistance refers to the real part of complex impedance. It is the opposition offered by a resistor to the flow of electrons due to friction. It is limited by the area and length of the conductor as well as its specific resistivity, the temperature-dependent intrinsic property of material to conduct a current.	$R = \rho\frac{l}{A}$	[Ω]
Reactance (X_c)	Reactance refers to the imaginary part of complex impedance. It is the opposition generated by the storage and release of charges by a capacitor in an alternating current-circuit. Given that reactance is inversely proportional to frequency it decreases with increasing frequency.	$X_c = \frac{1}{2\pi fC}$	[Ω]
Extracellular resistance (R_e)	At very low frequencies or rather zero frequency obtained from extrapolation by bioimpedance spectroscopy, an alternating current will be able to penetrate the cell membrane. Accordingly, a measurement of resistance is only a reflection of the extracellular space and therefore termed extracellular resistance.	$R_0 = R_e$	[Ω]
Intracellular resistance (R_i)	Intracellular resistance refers to the resistance of the intracellular space only. It cannot be measured, but computed from extracellular and infinite resistance using Kichhoff's laws.	$R_i = \frac{R_0 R_\infty}{R_0 - R_\infty}$	[Ω]
Infinite resistance (R_∞)	At very high frequencies or rather infinite frequency, cell membranes are continuously charged and recharged, so that virtually a current is also "conducted" in the intracellular space. Accordingly, resistance is a reflection of the extracellular and intracellular resistance. Infinite resistance can be extrapolated by bioimpedance spectroscopy and is related to intra- and extracellular resistance by Kichhoff's laws.	$\frac{1}{R_\infty} = \frac{1}{R_e} + \frac{1}{R_e}$	[Ω][Ω]

The table above summarizes important key concepts underlying bioimpedance measurements, starting with the most important key point, impedance. Phase-sensitive analyzers additionally allow the differentiation between reactance and resistance. Extracellular resistance and intracellular resistance require performance of a bioimpedance spectroscopy, where measurements are performed between a range of frequencies (15–500) between 5 kHz and 1 MHz

drop between these points. The data obtained from this measurement are impedance, phase angle, resistance, and reactance. To effectively interpret BIA results, a basic physical understanding of these concepts and their implications for physiologic processes is mandatory. To provide a simple and clear introduction to these concepts, they are first addressed in a general context from a physical perspective. In the following subsection they will then be linked to biological cells and tissues. The key concepts underlying these two subsections are summarized in Table 3.1.

3.2.1 Ohm's Law

Electrical impedance is a measure of the total opposition of a conductor against an alternating current. It is defined by Ohm's law, stating that the opposition of a conductor against an alternating current is directly proportional to voltage across the two points and inversely proportional to the current between them. Hence, if a known current is applied to a subject and voltage is measured, the underlying impedance can be calculated. Since in an alternating-current circuit voltage and current change as a function of frequency, impedance comprises information about both the direction (phase) as well as the magnitude of impedance. Whereas for direct currents resistance is simply defined as the ratio of voltage to current, the mathematical expression for impedance takes into account the dependence of voltage and current on frequency. This is summarized in the following equation:

$$Z = \frac{v(t)}{i(t)} = \frac{V_{\max}\sin(\omega t + \varphi_v)}{I_{\max}\sin(\omega t + \varphi_i)}[\Omega]. \tag{3.1}$$

where Z is impedance, $v(t)$, $i(t)$, $V_{\max}$, and $I_{\max}$ denote instantaneous voltage, instantaneous current, maximum voltage, and maximum current, respectively. t is the time since the waveform started, ω is angular frequency, and φ_v and φ_i are the phase angle of voltage and current, respectively.

While pure resistors offer resistance to a flow of current due to friction against the motion of electrons, electrical circuits can also comprise reactance, which can be understood as inertia against the motion of electrons. Taken together, resistance and reactance determine the direction and magnitude of impedance.

3.2.2 Resistance

Resistance is referred to as the real part of impedance and expressed in Ohm. Assuming uniform current density, resistance (R) can be defined by the physical geometry and resistivity of the conductor. Specific resistivity is commonly denoted by ρ (Ω·m).·It·is a measure of the material's ability to transmit electrical current that is independent of the geometrical constraints. The geometrical constraints are given by the cross-sectional area A (m^2) of the conductor and its length l (m) as indicated in

$$R = \rho\frac{l}{A}[\Omega]. \tag{3.2}$$

3.2.3 Reactance

The imaginary part of impedance is termed reactance and also measured in Ohm. Reactance can be traced to capacitive and inductive sources. The latter, however, do presently not play a significant role in most bioimpedance models, and will therefore not be considered in the following (Ward et al. 1999; Gluskin 2003; Riu 2004).

Capacitors are able to store and release charges, but do not permit a direct, physical flow of charges. However, by changing the polarization, they can virtually "conduct" current in proportion to the rate of voltage change. Hence, they will pass more current for faster-changing voltages (as they charge and discharge to the same voltage peaks in less time), and less current for slower-changing voltages. This frequency-dependent opposition is termed capacitive reactance (X_c) and defined as

$$X_c = \frac{1}{2\pi fC}[\Omega]. \tag{3.3}$$

where f is frequency (Hz), and C is capacitance (F). Capacitance depends on the dimensions of the capacitor as well as the composition between the capacitor plates. For simple structures (i.e. parallel-plate capacitors), capacitance can be defined as

$$C = \varepsilon_0 \varepsilon_r \frac{A}{d} [F]. \tag{3.4}$$

where A (m^2) is the cross-sectional area of the plates, d (m) is the distance between the plates, ε_0 is permittivity of free space (8.854 e−12 $F \cdot m^{-1}$), and ε_r is the relative permittivity of the permittivity of the material between the plates, i.e. the dielectric (dimensionless). The latter indicates the ease with which localized electrical charge can be polarized by the application of an electrical field, thus affecting C.

3.2.4 Impedance and Phase

Electrical impedance comprises both the opposition to current related to resistance and reactance.

In Cartesian form, electrical impedance can be defined as

$$Z = R + jX \, [\Omega]. \tag{3.5}$$

where Z denotes impedance, j is an imaginary unit ($\sqrt{-1}$) and is used instead of i to avoid confusion with the current symbol. Since, in alternating-current circuits, voltage and current change as a function of frequency, impedance is also dynamic because it changes in direction and amplitude. Consequently, impedance cannot be represented by a scalar quantity, which only reflects a single dimension. To represent both direction (i.e. phase shift) and amplitude (i.e. distance or magnitude) complex numbers are used to denote impedance. For these reasons complex impedance is sometimes written in bold to distinguish it from the magnitude of impedance. For simplification, Z is used to denote complex impedance as well as general impedance (magnitude) throughout in this text. Graphically, complex impedance can be depicted as a vector. It has a definite direction and a definite length. Thus, it comprises the information of both dimensions. The relationships between Z, R and X_c can also be graphically depicted in a complex plane. Figure 3.2 shows an example of such as plane for a resistor-capacitor (RC) circuit.

Due to the representation of R and X_c as vectors, the magnitude of Z can be calculated as the vector sum of its individual components. The geometrical relationship between R and X_c is also characterized by the phase angle (φ), which varies between 0 degree and −90 degrees. φ represents the delay between voltage and current, and is caused by the ability of the capacitor to store and release charges. For an ideal capacitor, φ is −90 degrees and Z is purely reactive. In contrast, if an alternating-current circuit is purely resistive, i.e. it consists of resistors only, the phase shift between the voltage and current is zero, and hence, Z is equal to R. As a result,

$$Z = \frac{v(t)}{i(t)} = \frac{V_{max} \sin(\omega t + \varphi_v)}{I_{max} \sin(\omega t + \varphi_i)} = \frac{V_{max}}{I_{max}} \angle 0 = \frac{V_{max}}{I_{max}} [\Omega]. \tag{3.6}$$

The frequency-dependent response of X_c is also reflected in φ. An example for a simple resistor-capacitor (RC) circuit in series is given in Fig. 3.3.

The behavior of the transfer functions can be explained straightforwardly. In a direct current circuit, once the applied voltage reaches a maximum, no more charges can accumulate on the plates of the

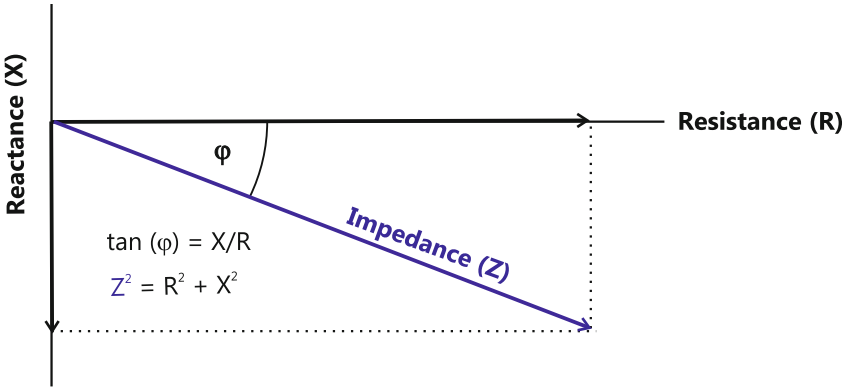

Fig. 3.2 Complex impedance plane of an RC circuit. Complex impedance can be graphically visualized as a vector. The vector indicates both magnitude (or distance) and direction (or phase) of impedance. The magnitude can be computed as the sum of the vectors of resistance (*R*) and reactance (*X*). The phase angle is expressed in degrees and can be calculated as the inverse tangent of *X* and *R*. Presently, except for a few exceptions *X* is expected to be purely attributed is to capacitive sources in human body composition models. Reactance is therefore also commonly denoted by the subscript c for capacitance (X_c)

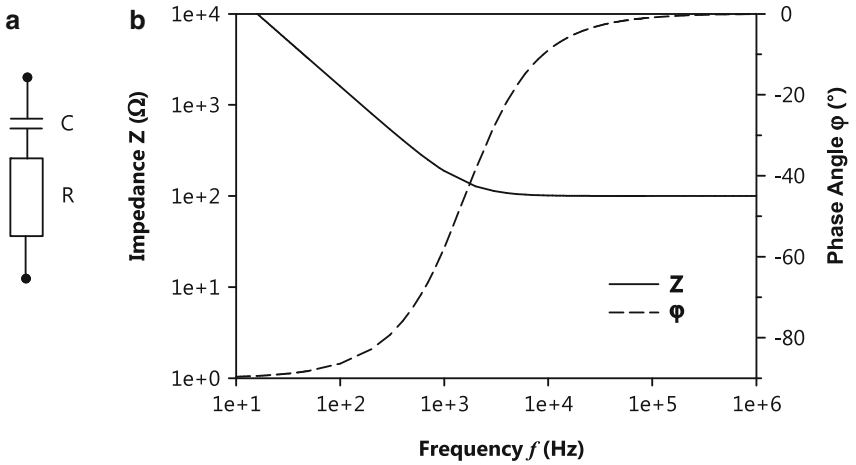

Fig. 3.3 Schematic presentation of serial RC circuit and its corresponding Bode plot. (**a**) Serial RC circuit (**b**) Bode plot for a serial RC circuit with $C = 1$ μF and $R = 100$ Ω, depicting magnitude and phase as a function of frequency. Abscissa and ordinate are both expressed in logarithm to base 10 for magnitude. Bode plot Magnitude *Z* (*solid line*), phase *φ* (*dashed line*)

capacitor. Hence, no further current will pass through the circuit. For these reasons, it is commonly said that capacitors block direct current. Similarly, in an alternating-current circuit, at very low frequencies, capacitors nearly block the current, as the periodic accumulation of charges on the plates of the capacitor occurs at a low rate. Hence, as frequency decreases and converges towards 0, the opposition of the capacitor to the flow of current increases. In contrast, at high frequencies, the capacitor is continuously charged and discharged with regard to frequency, creating a continuous flow of electrons. Thus, it is said that alternating current "passes" capacitors as a function of frequency. Finally, for frequencies converging towards infinity, the capacitor is short-circuited and the opposition of the capacitor diminishes. Consequently, as indicated in Fig. 3.3b the magnitude of impedance is equal to 100 Ω and the phase converges to zero.

3.3 Cells and Tissue and Their Electrical Equivalent Circuits

3.3.1 The Passive Electrical Properties of Biological tissue and Cells

Biological tissue can be defined as a group of similar cells and associated intercellular matter acting together to perform specific functions in an organism. Each cell is surrounded by a semipermeable phospholipid bilayer, called the cell membrane, which physically separates the intracellular components from the extracellular environment. It consists of two layers of phospholipid molecules, each having a hydrophobic tail pointing toward the inside of the membrane and a hydrophilic head forming the inner and outer surfaces of the membrane (Fig. 3.4).

Since the lipid bilayer is immiscible with the extra- and intracellular fluid, it has a static separation effect for water-soluble substances such as ions. Due to its thickness of ≈5–10 nm (Pocock et al. 1999), the cell membrane can therefore electrically be modeled as a capacitor.

On the other hand, both intra- and extracellular liquids contain ions that are free to migrate, and can therefore be considered as electrolytes. By far the most important ions for extracellular conductance are sodium (Na^+) and chloride (Cl^-). In the cytoplasm potassium (K^+), negatively charged proteins, hydrogen phosphate $\left(HPO_4^{2-}\right)$, sulfate $\left(SO_4^{2-}\right)$ and organic acids constitute the dominant charge carriers. The contribution of bicarbonate $\left(HCO_3^-\right)$ is marginal compared to overall conductivity. Indirect effects of $\left(HCO_3^-\right)$ on the conductivity of body fluids are, however, possible by influencing the ionic exchange across the cell membrane. For small changes in ion concentrations, a linear relationship with the changes in conductivity can be assumed (Scharfetter et al. 1997a).

In summary, due to the composition of the cell membrane and extra- and intracellular fluids, biological tissue would be expected to exhibit both reactive and resistive properties, when an alternating current is applied. If tissue impedance is measured over a broad frequency range between a few kHz and several GHz, such a frequency-dependent response can be observed. In addition, the passive electrical properties of biological tissue are not only highly frequency-dependent, but also vary significantly with the type of tissue. This is summarized for selected tissues at 5, 50 and 500 kHz in Fig. 3.5. It should be noted that conductivity is the inverse of resistivity.

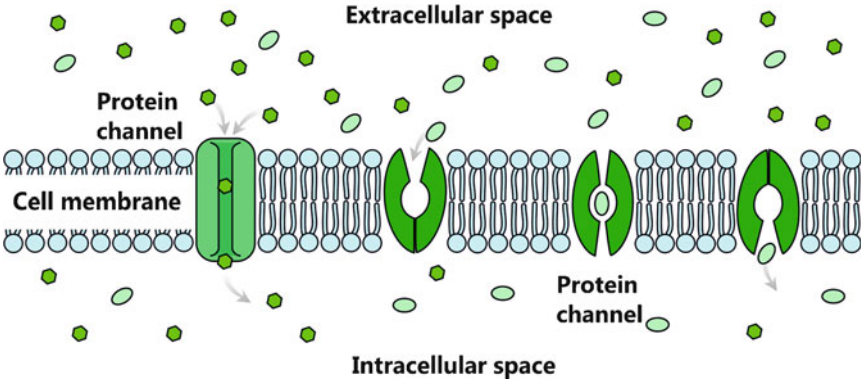

Fig. 3.4 Two-dimensional structure of the cell membrane. The basic structure of the cell membrane consists of two layers of phospholipid molecules. As a result, the cell membrane has a static separation effect for water-soluble substances such as ions. Exchange of ions is therefore facilitated via specialized proteins channels. The proteins embedded in the lipid bilayer may be peripheral (situated on either side of the membrane) or extend from one end to the other (transmembrane or integral proteins)

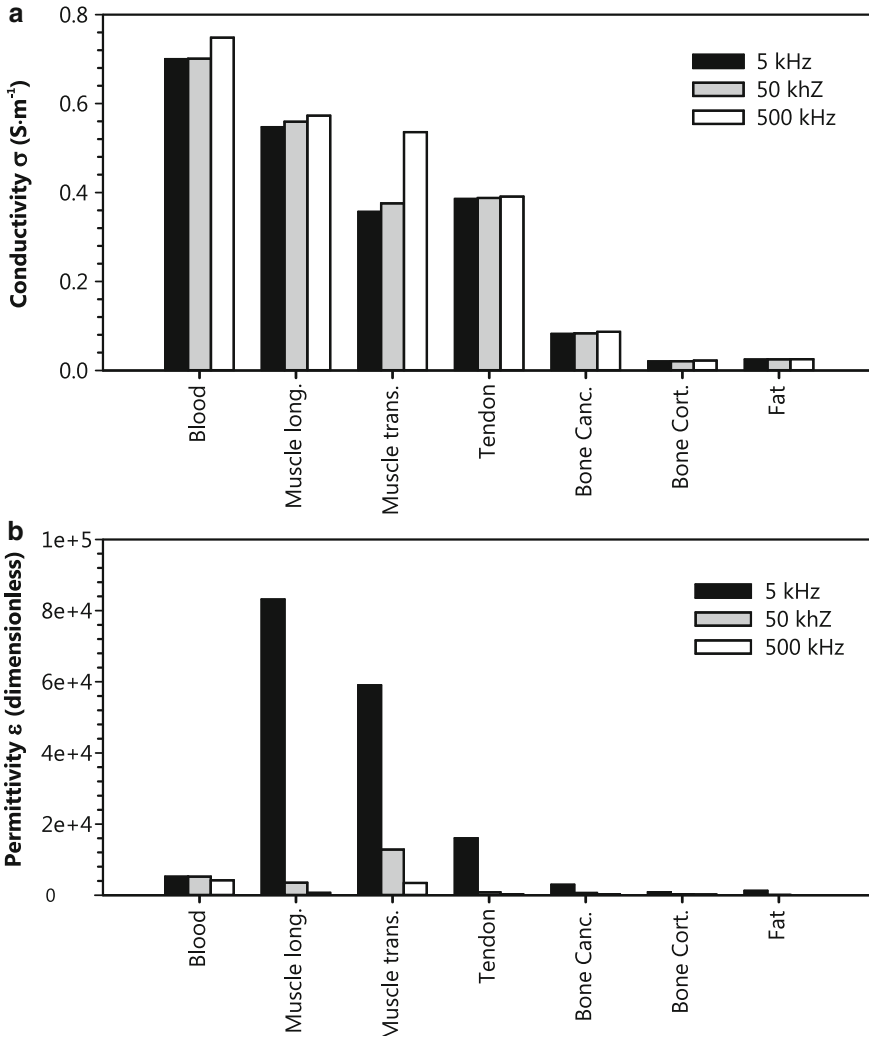

Fig. 3.5 Conductivity and permittivity at low and high frequencies for selected tissue samples. (**a**) Conductivity (inverse of resistivity) and (**b**) permittivity of selected tissue samples at 5, 50, and 500 kHz. Conductivity increases as a function of frequency. This effect is most pronounced for highly anisotropic tissue such as muscle fibers. In addition, the frequency-dependence for muscle tissue is also clearly observable for permittivity. As frequency increases, permittivity decreases. Data based on Gabriel et al. (1996). Muscle long., skeletal muscle tissue measured in longitudinal direction; Muscle trans., skeletal muscle tissue measured in transverse direction; Bone canc., cancellous bone; Bone cort., cortical bone tissue

As frequency increases, permittivity decreases while conductivity increases. The individual quantities, however, vary significantly. Due to their high content of electrolytes, blood and muscle have very high conductivity compared to fat and bone. Furthermore, it is clearly shown that some tissues exhibit strong anisotropic effects. For instance, the conductivity for muscle in longitudinal direction at 5 and 50 kHz is ≈1.5 times higher than conductivity for muscle in the transverse direction. This discrepancy can be explained by the alignment of muscle fibers and muscle cell membranes which exhibit high capacitive effects and therefore increase reactance when arranged perpendicular to the applied current. This is in accordance with the observation that at high frequencies (500 kHz) the difference in conductivity diminishes.

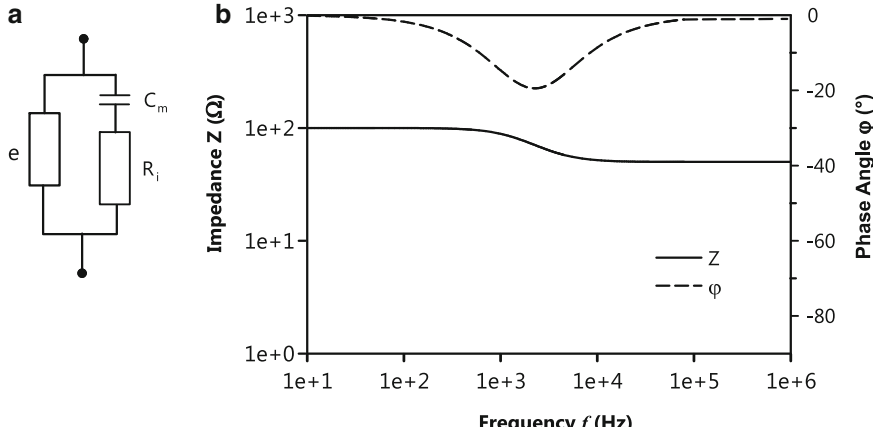

Fig. 3.6 Equivalent electrical circuit analogous to the Fricke and Morse model and its corresponding Bode plot. (**a**) Schematic presentation of equivalent electrical circuit analogous to the Fricke and Morse model. The extracellular compartment is represented by a resistor, and the intracellular compartment is represented by a resistor and capacitor in series. (**b**) Bode plot for a resistor (R_e = 100 Ω) in parallel with a series combination of a resistor (R_i = 100 Ω) and a capacitor (C_m = 1 μF). It should be noted that the electrical system depicted could also be represented by two resistors in series with a capacitor in parallel because it is possible to obtain the same immittance (impedance or admittance) values for both arrangements. In fact, the electrical properties of a system as a whole unit can be described by 'lumping' all its capacitive and resistive properties into a single equivalent capacitance and resistance component, respectively. The arrangement of these components in parallel or series depends on the investigator's choice. Though the parallel version is best characterized by admittance, the use of impedance is frequently employed in the present work for consistency and simplicity, in spite of the parallel electrical circuit depicted here. The impact of circuit choice is, however, important with regard to the imaginary and real part since their parallel and series equivalents are not identical. The quantities measured by bioimpedance analyzers yield components corresponding to their series equivalent (Neves and Souza 2000). R_e, extracellular resistance, R_i, intracellular resistance; C_m, membrane capacitance; Z, impedance; φ, phase

3.3.2 Electrical Equivalent Circuits of Biological Tissue

3.3.2.1 Fricke and Morse Model

In 1925, Fricke proposed a theoretical model for the passive electrical properties of living tissues. Fricke and Morse (1925) found that their measurements on suspensions of red blood cells could be explained by a circuit consisting of a resistor in parallel with the series combination of a resistor and capacitor (Fig. 3.6a).

Due to the phospholipid bilayer, Fricke and Morse assumed that the cell membrane could be modeled by a capacitor (C_m). Furthermore, they represented the intracellular and extracellular electrolytic medium each with a pure resistor (R_i and R_e respectively). This means that when a potential difference is applied across a cell suspension, C_m is charged by ions moving under the influence of the electric field. Consequently, at low frequencies, the membranes have high X_c so the cells behave as non-conductors in a conducting medium. Thus, most of the current is considered to flow around the cells, resulting in a relatively high Z and equal to R_e (Fig. 3.7). At high frequencies, however, X_c is low and an increasing amount of current can penetrate the membranes and flow through the relatively highly conducting cytoplasm of the cells. Thus, the current is able to flow through both extra- and intracellular spaces and Z is limited by the combined resistance of R_i and R_e in parallel.

An example of the resulting Bode plots for such an equivalent circuit is given in Fig. 3.6b with R_i = 100 Ω, R_e = 100 Ω, and C_m = 1 μF. As stated above, at very low frequencies or direct current

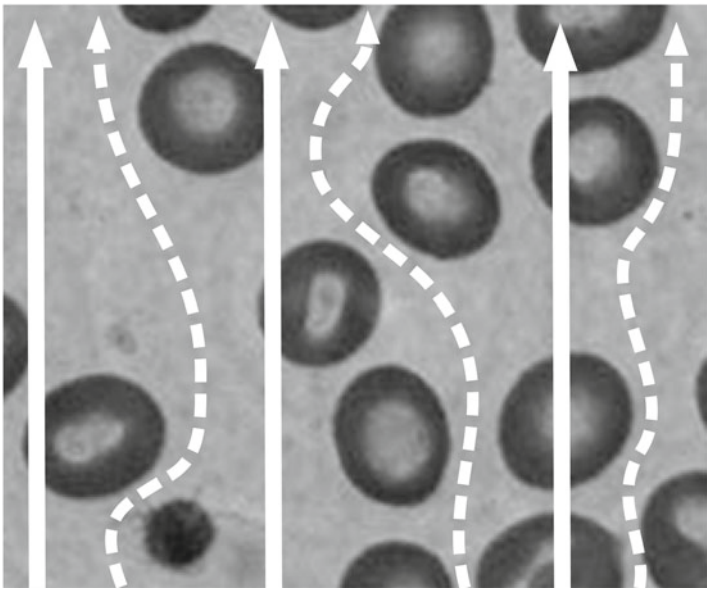

Fig. 3.7 Current flow at low and high frequencies. At low frequencies or direct current (*dashed line*) capacitance obstructs the current from penetrating the cells. At high frequencies (*solid line*), capacitance is short-circuited and the current can flow through both extra- and intracellular compartments

sources the current is blocked by the capacitive properties of the cell membrane and is only able to flow through R_e. Thus, for frequency converging towards zero, the phase is zero degree and Z is purely resistive. Hence, at zero frequency Z is equal to R and termed R_0. Accordingly, for the equivalent electrical circuit in Fig. 3.6a, it can be stated that

$$R_0 = R_e\ [\Omega]. \tag{3.7}$$

In the above example R_e is therefore equal to 1 kΩ. With increasing frequency, the cell membrane is gradually short-circuited until finally Z equals R_e and R_i in parallel. Thus, Z at infinite frequency is also purely resistive and termed R_∞. It can be calculated as

$$\frac{1}{R_\infty} = \frac{1}{R_e} + \frac{1}{R_i}\ [\Omega]. \tag{3.8}$$

3.3.2.2 Bode Plot Versus Cole Plot

The same information revealed by Bode plots can be displayed by plotting X_c vs. R on a complex plane. Such a plot's impedance, at least for the equivalent circuit in Fig. 3.6a, is given by

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)}\ [\Omega]. \tag{3.9}$$

where τ is the relaxation time of the system. It is a constant, which takes into account that polarization, the field-induced disturbance of the charge distribution in a region, does not occur instantaneously. Instead, there is a momentary delay in polarization after the application of an electric field. If the frequency is low enough that all charges are given the required time to change their position, polarization is maximal. In contrast, at a higher frequency there will be less time for the charges to

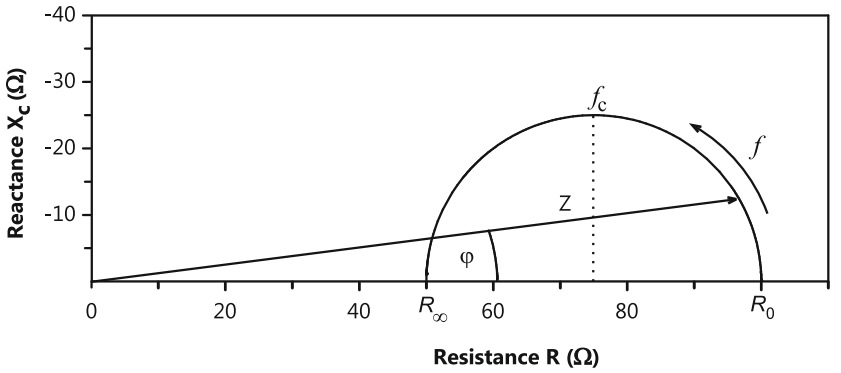

Fig. 3.8 Complex impedance plot for R-RC circuit indicated in Fig. 3.6. Reactance (X_c) is plotted vs. resistance (R) as a function of frequency. R_0 indicates resistance at 0 frequency and is expected to represent the extracellular space only. R_∞ is a measure of the total resistance offered by the extracellular and intracellular space. At very low frequencies, the impedance of cell membranes is high and thus blocks the conduction through the intracellular space. Hence, the measured impedance is purely resistive (R_0). As frequency increases, the current penetrates the cell membranes and X_c also increases. Once frequency has reached a certain threshold, i.e. the characteristic frequency (f_c), where X_c is at a maximum, X_c decreases when frequency is further increased as cell membranes "lose" their capacitive characteristics. As a result, at high frequencies Z is again purely resistive (R_∞). Furthermore, because the conducting volume increases with higher frequencies (an increasing amount of intracellular fluid is conducting the current) Z decreases. The impedance locus corresponds to data of the R-RC circuit indicated in Fig. 3.6 (R_e = 100 Ω; R_i = 100 Ω and C_m = 1 μF). Z, impedance; R_0, resistance at zero frequency; R_∞, resistance at infinite frequency; f_c, characteristic frequency

orient themselves. Hence, as frequency increases polarization and permittivity will decrease. The time period till the system relaxes toward a new equilibrium is characterized by the time constant τ. Generally, it is defined as:

$$\tau = RC\,[\mathrm{s}]. \tag{3.10}$$

and for the circuit in Fig. 3.6a it is given by:

$$\tau = \left(R_i + R_e\right)C_m\,[\mathrm{s}]. \tag{3.11}$$

To plot X_c vs. R, they need to be rationalized as follows:

$$R = R_\infty + \frac{R_0 - R_\infty}{1+\omega^2\tau^2}\,[\Omega]. \tag{3.12}$$

$$X_c = -\frac{\omega\tau\left(R_0 - R_\infty\right)}{1+\omega^2\tau^2}\,[\Omega]. \tag{3.13}$$

Plotting X_c vs. R yields a locus corresponding to a semi-circle with a center on the real axis at $(R_0 + R_\infty)/2$, and with a radius of $(R_0 - R_\infty)/2$, a high-frequency intercept at R_∞ and a low-frequency intercept at R_0 (Fig. 3.8). φ can be expressed mathematically as the inverse tangent of the quotient of X_c and R.

For convenience, it has been commonly adopted that the diagram is plotted in the first quadrant of the complex plane. Complex impedance plots have been referred to by a variety of names, such as 'Argand diagram', 'Wessel diagram', 'Nyquist plot' or 'Cole plot'. Though there is some criticism about the appropriateness (McAdams and Jossinet 1995), the terms 'Nyquist plot' and 'Cole plot' are now frequently used to refer to complex impedance plots in the field of bioimpedance research. The circle of the impedance plot indicates Z for frequencies between zero and infinity. As frequency increases, the tip of the impedance vector moves anti-clockwise around the locus and indicates the decrease of Z. Furthermore, at any given frequency, phase can be expressed by the angle between the

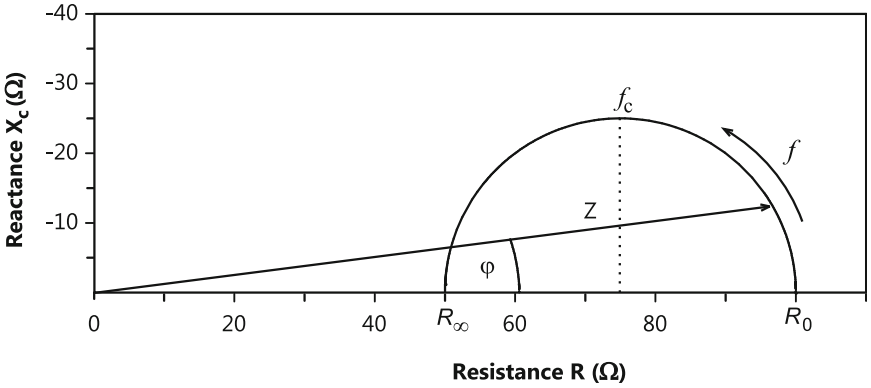

Fig. 3.9 Complex impedance plot of real whole-body measurement of a human subject (*white circles*) and its and its equivalent R-RC circuit (*continuous line*). X_c is plotted versus R for a range of frequencies between 4 and 1,024 kHz of a sample of an adult, healthy man (*white circles*). The *dotted line* shows the corresponding curve fit and extrapolation of R_0 and R_∞. R_e = 652 Ω, R_i = 1,164 Ω, R_Ω = 418 Ω, and C_m = 2.67 nF. The *solid line* indicates the impedance locus, which would have been expected according to the Fricke model with its center at 535 Ω (=$(R_0 + R_\infty)/2$ = (652 + 418)/2 = 535) and a radius of 117 Ω (= $(R_0 - R_\infty)/2$ = (652 − 418)/2 = 117). In comparison to the locus expected from the equivalent circuit corresponding to the Fricke and Morse model, the center of the locus obtained for experimental data is suppressed below the *x*-axis. The angle to the suppressed center is given by φ. *Z*, impedance; R_0, resistance at zero frequency (= extracellular resistance R_e); R_∞, resistance at infinite frequency (= sum of extracellular and intracellular resistance, i.e. $1/R_\infty = 1/R_e + 1/R_i$); f_c, characteristic frequency

impedance vector and the real axis, and R and X_c are obtained by the coordinates of the locus. Finally, f_c is termed the characteristic frequency ($f_c = 1/(2\pi\tau)$) and indicates the frequency at the peak of the locus, where X_c is at a maximum. Thus, the same information given by two Bode plots can be visualized in a single graph. The biggest advantage of complex impedance plots in bioimpedance research and applications is to mathematically derive R_0 and R_∞. They are two quantities providing important diagnostic information, but they cannot be measured directly because of practical constraints and the occurrence of multiple dispersions. For these reasons, a number of bioimpedance applications employ fitting algorithms to measured data between a few kHz and 1 MHz and extrapolate R_0 and R_∞.

3.3.2.3 Drawbacks of the Fricke and Morse Model

Though the Fricke-Morse model had been shown to be useful for describing the electrical properties of suspensions of red blood cells and some homogeneous tissues, it was also apparent from the first studies that the model was not accurately representing the complex behavior of other living tissues (Cole 1972). When experimental data for living tissue is plotted in a complex impedance plane, it can be observed that the center of the semi-circle is located below the real axis. A typical example for a complex impedance plot of real living tissue and its electrical equivalent R-RC circuit is given in Fig. 3.9.

Measurements were taken at 496 logarithmically spaced frequencies between 4 and 1,024 kHz. The dotted line indicates fitted data for *Z*. R_e was assumed to equal R_0, whereas R_i was calculated as:

$$R_i = \frac{R_0 R_\infty}{R_0 - R_\infty} [\Omega]. \tag{3.14}$$

Whereas the center of the equivalent R-RC circuit is located on the real axis at 535 Ω and a radius of 117 Ω, experimental data yields an arc with a corresponding semicircle that has a suppressed center and increased radius compared to its equivalent R-RC circuit. It could be speculated that the

equivalent circuit model proposed by Fricke and Morse has blatant simplifications. For instance, that the intracellular medium is usually treated as a pure ionic conductor. However, a number of additional cellular structures such as mitochondria, the nucleus, the endoplasmatic reticulum, lyosomes, and the Golgi apparatus actually confine the idea of the intracellular compartment as a purely conductive medium. Accordingly, the cytoplasm is actually a mixture of capacitive and conductive properties and it is only for reasons of simplicity that it is treated as pure electrolyte. Similarly, it should also be noted that a number of transmembrane protein complexes protrude through the lipid bilayer (see also Fig. 3.4). Electrically, these structural channels (or pores) represent shunt pathways in parallel with the lipid bilayer. Though important for the subject of bioelectricity, the membrane conductance is usually very low, and can be ignored in bioimpedance measurements.

Instead, the theoretical explanation of the discrepancy between the expected and observed impedance locus often includes the concept of a distribution of relaxation times. For an ideal dielectric, the real part of complex permittivity is assumed to be constant and the imaginary part equal to zero. A biological system, which could be characterized by a single relaxation time should be composed of identical structural elements, which do not exhibit any interactive effects. Real biological tissue is, however, structurally diverse, and individual elements such as particles in a concentrated suspension can also lead to a distribution of relaxation times in the bulk properties, even though the dilute suspensions of the same material might exhibit a single time constant (Foster and Schwan 1989).

3.3.2.4 Cole-Cole Model

In order to account mathematically for the 'depressed semicircle' observed for biological tissue, Cole and Cole (1941) extended the expression for describing bioimpedance data in the complex impedance plane according to the Fricke-Morse model (Eq. 3.9) by the parameter α.

$$Z = R_{\infty} + \frac{R_0 - R_{\infty}}{1 + \left(j\omega\tau_0\right)^{\alpha}} [\Omega] \tag{3.15}$$

where τ_0 is the mean or characteristic time constant and α is a dimensionless numerical distribution parameter related to the width of the particular distribution, having a value between 0 and 1. Geometrically, the effect of the parameter α is that the locus appears as an arc with its center below the real axis.

Since the Cole model is a mathematical model, it cannot be correctly represented by an equivalent electrical circuit. An analogue representation that is nonetheless used to symbolize the distribution of time constants is given in Fig. 3.10.

As stated above, one of the most commonly cited reasons for the α parameter is the heterogeneity of cell sizes and shapes in biological tissue (Ackmann and Seitz 1984; Foster and Schwan 1989). In this regard, it should be noted that α is empirically derived and a clear explanation of its physical meaning is still lacking today. Cole and Cole (1941) already emphasized the descriptive nature of α by stating that in the absence of any satisfactory explanation, the distribution function implied by α is nothing more than a means of expressing the experimental results. Due to the lack of a clear physical meaning for α, the Cole model has also been criticized for being a descriptive rather than an explanatory model (Moissl et al. 2006). Descriptive models characterize tissue electrically by means of both known and electric components and algorithms. These models primarily describe the observed phenomena without providing sound explanations related to the underlying anatomical structures. In contrast, explanatory models try to employ basic concepts of electrical theory to mimic similar properties in biological materials. However, the major drawback of explanatory models is their simplification of the material under study, jeopardizing a correct representation of the true tissue properties.

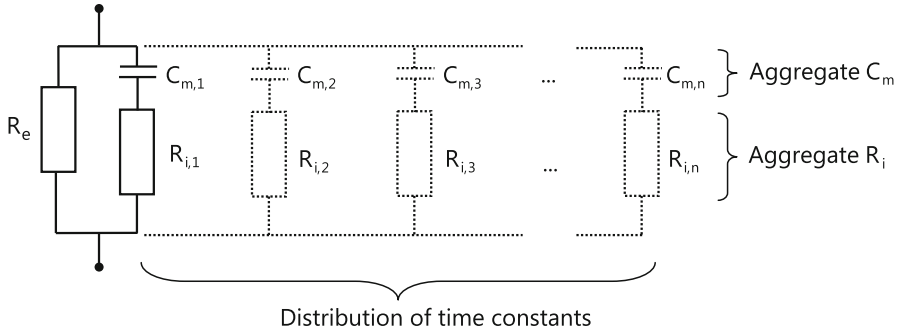

Fig. 3.10 Equivalent electrical circuit analogous to Cole model. The Cole-Cole model is a mathematical model and its electrical properties cannot be correctly represented by common electrical equivalent circuits. The distribution of time constants is therefore indicated by an infinite number of RC branches in parallel. An alternative way to physically realize the frequency-dependent capacitance is a so-called constant phase element. C_m, membrane capacitance; R_i, intracellular resistance of a single branch; R_e, extracellular resistance

Finally, various authors also noted characteristic deviations in actual whole-body impedance spectra from the theoretically expected arc at frequencies higher than 500 kHz (Van Marken Lichtenbelt et al. 1994; Stroud et al. 1995; Scharfetter et al. 1997b). Predominantly, this effect can be attributed to stray capacitance in the environment due to the presence of other electronic equipment as well as the interaction between electrode impedance and lead positioning or it might also have physiological meaning (Bolton et al. 1998). Accordingly, while the discrepancy of observed data from the expected Cole-Cole model might be simply due to a phase shift associated with the propagation delay of the signal along the measurement site, Scharfetter et al. 1997b) also suggested that the deviation might be explained by a difference in beta-dispersion center frequencies between blood and muscle. Given that muscle tissue and blood can be assumed to lie in parallel, two impedance spectra might be detected that do not fit a single Cole-Cole arc Scharfetter et al. 1997b). Irrespective of the underlying mechanism of the deviation, in settings where various electrical equipment are used, such as in intensive care units, artifactual instrument errors might be erroneously interpreted as abnormal fluid balances. In addition to improvements regarding instrument design such as active screening of the voltage sensing leads with preamplifiers at the electrode ends (Bolton et al. 1998), it has also been suggested to extend the classical Cole model (Eq. 3.15) by a correction factor (De Lorenzo et al. 1997; Bolton et al. 1998; Scharfetter et al. 1998). In addition, given that the frequency range up to 500 kHz seems to be high enough for most applications such as volume rendering, it has been recommended that data obtained in the high-frequency domain and/or limit bioimpedance measurements to frequencies lower than 500 kHz for these purposes be interpreted carefully (Scharfetter et al. 1998).

3.4 Principles of Bioimpedance Measurements

3.4.1 Terminology

The applied current lies between 200 and 800 μA, depending on the instrumentation employed. The frequency of the current varies according to the underlying biophysical principle between a few kHz and 1 MHz. Using phase-sensitive devices Z can be separated into its real and imaginary parts, i.e. R and X_c. For these types of analyses, the terms single and multi-frequency BIA as well as bioimpedance spectroscopy (BIS) are commonly used. Single-frequency BIA refers to the measurement technology

of performing measurements at a single frequency. In accordance, multi-frequency BIA implies a technique employing data collection at more than one frequency. Finally, in order to clearly distinguish multi-frequency BIA from BIA based on Cole plots or other models for fitting impedance data over the entire frequency range (between 1 kHz and 1 MHz), the term BIS has also been frequently used to refer to the latter. For reasons of clarity, this terminology is also followed in the present work.

3.4.2 Safety

Geddes and Baker (1989) provide a summary of the impact of alternating current sources on biological tissue. Alternating currents at power line frequencies (50–60 Hz) stimulate nerve and muscle cells with a threshold of perception of a few mA. Higher currents induce pain and involuntary muscle contractions. Yet, at substantially higher frequencies the large tissue capacitance raises the threshold of perception. Using tactile electrodes, the threshold of perception increases from 100 μA at 10 Hz to 2 mA at 1 kHz, to over 10 mA at 10 kHz (Settle et al. 1980). Consequently, the currents in the microampere range employed in bioimpedance monitoring present no hazard to the subject. Though no interference is anticipated for patients with cardiac pacemakers or defibrillators, the possibility cannot be categorically eliminated and for these reasons patients with implanted cardiac pacemakers or catheters filled with conductive fluid leading into the heart are usually excluded from bioimpedance measurements. In addition, according to the *NHANES Body Composition Procedures Manual* (2000) subjects with artificial joints, pins, plates, or other types of metal objects in their body should also be excluded from the measurement. Similarly, the effects of bioimpedance measurements in pregnancy have not been well researched and some manufacturers have recommended excluding pregnant women.

3.4.3 The Four-Terminal Technique

3.4.3.1 Electrical Properties of the Skin

The measurement of bioimpedance requires an interface between instrumentation and the human body or segment under study. The transfer between the ion-related transport of electric charges in the human body and the electron-based transport in the measurement equipment is achieved by the application of electrodes to the skin surface. In order to obtain a measurement of deep-tissue impedance the upper layers of the skin (epidermis and dermis) need to be bridged. Due to its multi-layered structure, skin demonstrates capacitive effects. Since skin is also penetrated by channels formed by sweat pores and hair follicles there is also a direct conductive connection between the upper layer of the skin (stratum corneum) and the subcutaneous tissue layers. The electrical properties of the skin can therefore be modeled by a capacitor in parallel with a resistor.

3.4.3.2 Needle Electrodes Versus Surface Electrodes

To minimize the effects of skin impedance on deep-tissue impedance measurements needle electrodes penetrating the upper layers of the skin were frequently used in the past. Due to subject discomfort and poor reliability this technique failed to gain large-scale acceptance. In order to minimize the effect of contact impedance related to surface electrodes, the following procedures can be taken into account. First of all, the respective skin areas are cleaned with alcohol to remove oil and dead tissue particles

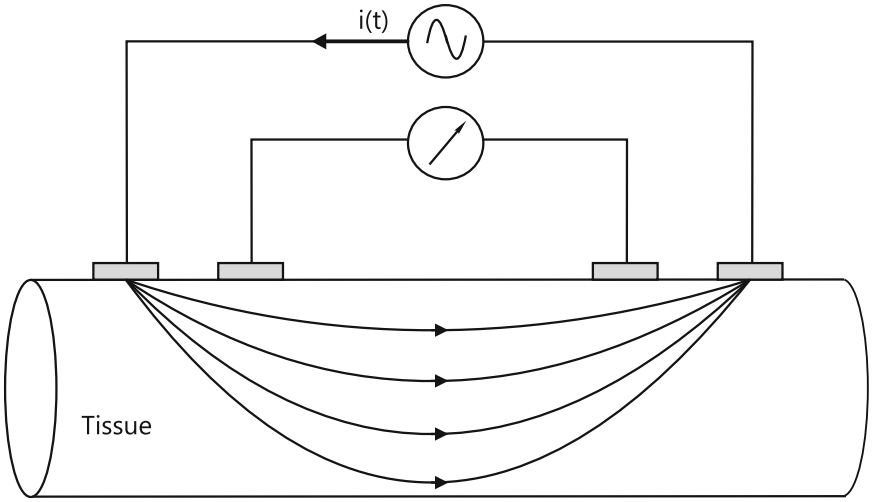

Fig. 3.11 Schematic presentation of tetrapolar electrode configuration and non-uniformity of current lines distribution for spot electrodes. Present bioimpedance technology usually employs a tetrapolar electrode arrangement. The current is introduced via the outer (distal) electrodes, while the voltage is picked up by the inner (proximal) electrodes. Using spot electrodes the current distribution is not uniform with current lines being most densely distributed in close proximity to the current injecting electrodes

which may negatively affect the conductive properties of the skin. Extensive alcohol treatment of the skin could, however, cause dehydration of the upper skin layers and induce contraindicative effects. Consequently, cleaning of the electrode sites should be restricted to a few seconds and given enough time to dry. Additionally, silver/silver-chloride (Ag/Ag-Cl) electrodes coated with an electrolytic gel reduce the polarization of the electrode to a minimum. The electrolyte fills the pores and wrinkles of the skin, and produces an optimal surface contact. The electrolyte also diffuses through the outer layers of the skin and improves their conduction, thus lowering the skin-electrode contact impedance. Since human electrolytes correspond approximately to a 0.9% sodium chloride solution, this would also be expected to be the ideal electrolyte for bridging the skin-electrode interface. Yet, in order to achieve lower contact impedances, gels containing 4% sodium chloride are commonly used for bioimpedance measurements (Fercher 1992). In spite of these measures, contact impedance remains relatively unstable. It depends on additional factors such as the pressure employed to apply the electrodes, skin thickness and skin secretions. For these reasons, the standard for performing bioimpedance measurements is the use of a four-terminal electrode set up, commonly referred to as a tetrapolar electrode arrangement. With this electrode configuration the current enters into the skin via two outer injecting electrodes (current electrodes), while the voltage signal is picked up by a second pair of two inner electrodes (voltage electrodes). Because of a high input impedance of the voltmeter, the voltage-sensing electrodes draw no or negligible current. Accordingly, polarization effects as well as the skin-electrode contact impedance are minimized and a measurement of deep-tissue impedance can be obtained. This electrode configuration is almost immune to movement artifacts or to changes in the interface impedance. For instance, Cornish et al. (1998) found that changes in skin temperature and hydration have no significant effect on bioimpedance measurements employing the four-terminal technique. Finally, it should be noted that the spacing between the two electrode pairs should theoretically be as large as possible. If the current electrodes are located further away from the voltage-sensing electrodes, the latter detect a signal in a region with a more uniform current distribution. In contrast, if the inner electrode pair is closely placed to the outer electrode pair, the current distribution will be less uniform since the current density is higher near the outer electrodes (Fig. 3.11).

3.4.3.3 The Human Body: An Isotropic Conductor?

It should be noted that the current flow may be constricted near the electrodes if the electrodes are small, yielding an additional constrictional resistance. Furthermore, the distribution of current lines depicted in Fig. 3.11 represents a simplified ideal, which is only true for isotropic conductors. An isotropic conductor exhibits the same electrical properties regardless of the measurement direction. However, human tissue and body fluids can be highly anisotropic. Figure 3.5 indicates that skeletal muscle can exhibit a 1.5-fold increase in conductivity when measured in transverse compared to longitudinal direction. The assumption of a unidirectional array of muscle fibers might roughly be acceptable for the limbs. Hence, they might be approximated by the cylindrical model of the human body with the different tissue compartments arranged in parallel. In the trunk, however, muscles lie perpendicular to the current distribution and conductivity is altered. Additionally, organs and adipose tissue depots are diversely arranged. They limit the development of homogeneous electric fields, which can be highly variable between and within subjects. This has been empirically confirmed by studies reporting a two- to fourfold difference between trunk and limb resistivity and a three- to four times higher coefficient of variation of trunk resistivity compared to limb resistivity (Baumgartner et al. 1990; Chumlea and Baumgartner 1990). Thus, the individual composition and distribution of intra-abdominal adipose fat depots and the dielectric properties of organs such as the lung as well as the orientation of muscle fibers jeopardize the assumption of a homogeneous current distribution. This problem has not been solved satisfactorily. Though the use of band electrodes would improve the development of uniform current distribution, the viability of the approach in terms of economic attractiveness, subject comfort, and simplicity of use would be lowered besides introducing other technical difficulties such as the reliability of electrode positioning. For these reasons the determination of trunk impedances should be interpreted with care when a parallel resistance lumped parameter model is used to represent the human body.

3.4.4 The Basic Biophysical Model

The total impedance of the human body against an alternating current is composed of several partial impedances related to different tissue types and fluid compartments. Assuming that the different types of tissue are aligned in parallel, that these tissues are an electrical source-free region, that they are mainly isotropic and conductive in character and that any magnetic fields can be neglected, the human body can be regarded as a complex conductor consisting of discrete conductive paths arranged in parallel. These parallel paths might include skeletal muscle, bone, fat, blood, neural, connective, skin and other tissues. The total resistance of the body can then be assumed to be the sum of the resistances of each of these discrete conductive paths. Figure 3.12 provides a simplified model describing the relation of the cross-sectional area A (m^2) and resistivities ρ ($\Omega \cdot m$) of these individual tissue components to their length l (m) and total resistance R_{tot} (Ω). Based on a rearrangement of Eq. 3.2, the term l/R_{tot} is directly related to the sum of the quotients of each discrete cross-sectional and its resistivity. Accordingly, total resistivity ρ_{tot} can also be expressed as the ratio of total cross-sectional area A_{tot} of the conductor and the sum of the quotients of the individual areas A and their respective resistivities ρ.

Given that an applied current always follows the path of the least resistance, R_{tot} is mainly a reflection of the extracellular fluid, blood, muscle and other highly conductive tissues since fat and cortical bone have a conductivity which is more than 20 times higher than that of muscle in longitudinal direction (see also Fig. 3.5). The measurement of R_{tot} can therefore provide structural information about body fluids and fat-free mass. Basically, the determination of conducting volume is based on

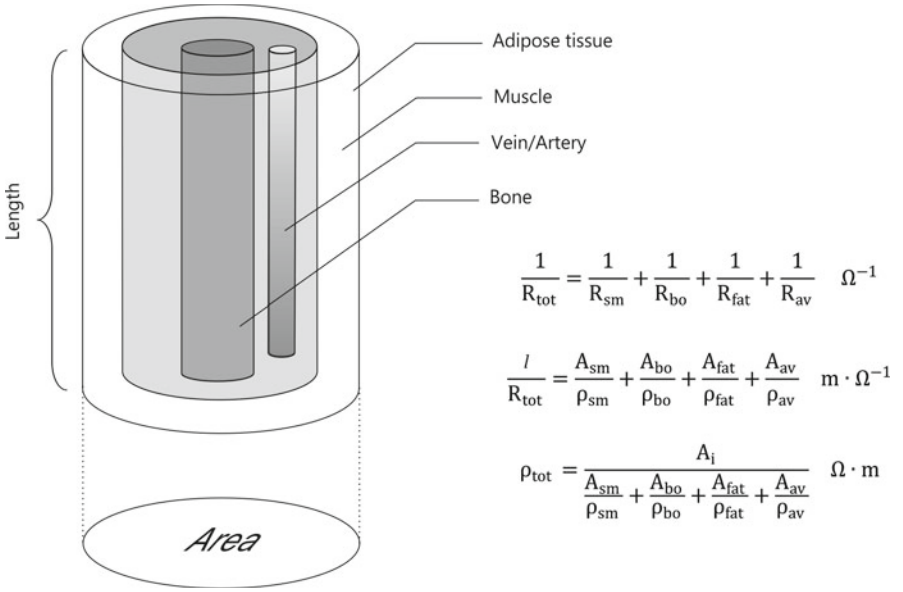

Fig. 3.12 A parallel resistance lumped parameter model of a body segment. The model assumes body segments to correspond to concentric cylinders of different tissues arranged in parallel when exposed to an electric current. Total resistance (R_{tot}) can be expressed as the sum of individual resistors arranged in parallel. Furthermore, R_{tot} is inversely related to the sum of the quotients of each discrete cross-sectional and its resistivity, whereas the latter is also directly proportional to length. Consequently, the total resistivity (ρ_{tot}) can also be expressed as the ratio of total cross-sectional area (A_{tot}) of the conductor and the sum of the quotients of the individual areas and their respective resistivities. l, conductor length; R, resistance; A, cross-sectional area; ρ, resistivity; the subscripts tot, sm, bo, fat, bl, neu, con, sk denote total tissue, skeletal muscle, bone, fat, blood, neural, connective, and skin tissue, respectively

the physical and geometrical constraints of resistance (Eq. 3.2) and the relationship between volume, length and cross-sectional area. Since volume V (m^3) is the product of length l (m) and cross-sectional area A (m^2), the latter can be defined as:

$$A = \frac{V}{l}\,[\mathrm{m}^2]. \tag{3.16}$$

Substituting Eq. 3.16 into Eq. 3.2 and simple algebraic rearrangement gives:

$$V = \rho\frac{l^2}{R}\,[\mathrm{m}^3]. \tag{3.17}$$

where the quotient of l^2 and R is frequently termed the resistance index (l^2/R) and can be considered as the fundamental quantity of structural bioimpedance applications (note that the dimensions are frequently expressed in centimeter instead of meter). Alternatively, R is sometimes used instead of Z, yielding the impedance index l^2/Z. Hence, if ρ is known, l and R (or Z) can be measured and subsequently used for the determination of conducting volume, i.e. the human body or body segment. These relationships, however, assume that the human body is an isotropic conductor (equivalent electrical properties regardless of the measurement direction) with homogeneous length and cross-sectional area and that the proportion of a specific tissue area is consistent along the limb. Since these assumptions are a grave simplification of the human body, alternative bioimpedance models have been proposed. These models include restricting measurements to body segments or even cross-sectional areas, modeling the limbs as truncated cones, or taking into account that

tissues other than intracellular and extracellular fluid also draw some of the current (Brown et al. 1988; Van Kreel et al. 1998; Fuller et al. 1999; Biggs et al. 2001; Stahn et al. 2007).

3.4.4.1 Descriptive Versus Explanatory Models

Most applications rarely derive ρ in the laboratory in vitro or empirically in vivo. Instead, ρ is usually determined by regression analysis, first using an established gold standard as a reference for the quantity of interest, which is then correlated to l^2/R (for a comparison of regression-based techniques and biophysical approaches based on causal relationships see Stahn et al. 2007). Frequently, the final prediction algorithms also include additional predictors such as age, body mass or gender to compensate for the violation of assumptions underlying the above-mentioned model. Some approaches have also employed artificial neural networks to relate the impedance index to the target quantity (Mohamed et al. 2003).

A number of terms have been used to indicate the distinction between these two approaches: empirical vs. structural models, statistical vs. causal relationships, indirect vs. doubly indirect, or descriptive vs. explanatory models. Irrespective of terminology, the major difference between descriptive and explanatory approaches is that the latter are based on well-established assumptions that do not require further development by statistical modeling. This distinction also highlights the major drawback of the use of regression analysis to derive prediction formulas. The relationships underlying a statistical model may be highly sample-specific. Consequently, the prediction equation becomes less stable in subjects differing from the sample underlying the original validation study. This drawback can be most problematic in multiple regression analysis. Certainly, it may seem quite tempting to include additional covariates to compensate for some of the violations underlying the respective biophysical model. However, though prediction accuracy might be improved, the resulting equations tend to become less generalizable since the underpinning relation between the dependent variable and the additional predictors may be highly sample-specific. Examples of bioimpedance applications based on either approach are provided and discussed in detail in the following chapters on bioimpedance of this book.

3.4.5 Whole-Body Versus Segmental Measurements

3.4.5.1 Distal Electrode Arrangement

Most BIA models employ a so-called whole-body approach in which the body is modeled as a single cylinder and electrodes are placed at the wrist and ankle of one side of the body (Figs. 3.13 and 3.14). This electrode configuration is referred to as distal bioimpedance measurement.

Based on the fundamental biophysical model underlying BIA (Eq. 3.17), impedance can be used to obtain an estimate of total body fluid volumes. Usually, conductive length is replaced by height because it is easier to obtain than the actual length of the conductor (sum of arm, trunk and leg length), and has been shown to only marginally lower the predictive potential of the index (Chumlea et al. 1988). The side of the body being measured does not have a significant effect on impedance in healthy adults (Baumgartner 1996). Contralateral electrode placement between the right wrist and left ankle or vice versa affect results only minimally (< 1.7%, Lukaski et al. 1985). For reasons of consistency and standardization, measurements at the right side of the body are usually considered as the norm (US Department of Health and Human Services. National Center for Health

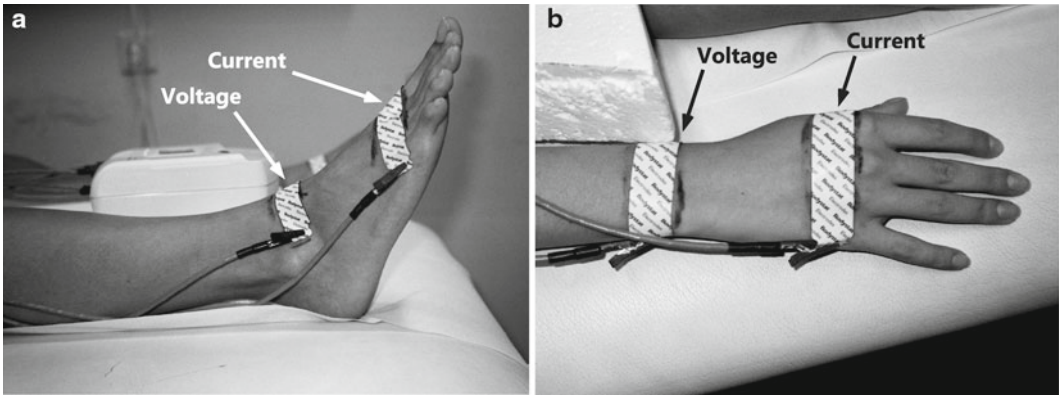

Fig. 3.13 Typical electrode arrangement. The figure displays a typical electrode configuration for a whole-body measurement. The outer (current or source) electrodes introduce the current, while the inner (voltage or sensing) electrode pair picks up the voltage. The source electrodes are placed in the middle on the dorsal surface of the right hand and foot just below the metacarpal-phalangeal and metatarsal joints, respectively. The sensing electrodes are positioned midline between the styloid processes of the ulna and radius on the dorsal surface of the wrist and midline between the medial and lateral malleoli on the dorsal surface of the right ankle. Further details of electrode configurations are given by Stahn et al. (2006) and Stahn et al. (2008)

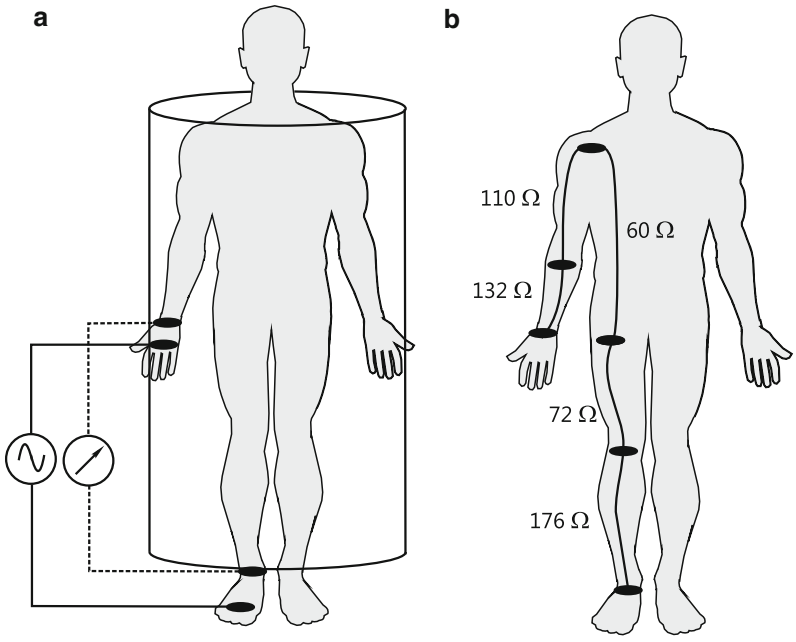

Fig. 3.14 (**a**) Whole-body bioimpedance measurement modeling the body as a single cylinder. Schematically illustrates that the conventional whole-body measurement configuration assumes that the human body can be modeled as a single isotropic cylinder with a homogeneous cross-sectional area. Consequently, assuming that bone, fat, connective tissue and skin draw negligible current, the resistance index (I^2/R) can be used to provide an estimate of different fluid volume compartments. (**b**) Body segment resistance distribution. Reveals the discrepancy between segment mass and segment resistance. Although the trunk contributes ≈50% of total body mass, due to its large area it only contributes marginally to total resistance (≈15%)

Statistics 2000). Yet, it should be noted that patients having experienced stroke, trauma or other conditions concomitant with atrophy of a single body side might exhibit significant discrepancies between body sides.

Limitations of Whole-Body (Distal) Measurements

As outlined in subsection 4.4, the distal measurement configuration is based on the assumption that the human body is an isotropic (equivalent electrical properties regardless of the measurement direction) conductor with homogeneous length and cross-sectional area. Obviously this assumption is incorrect since the human body is a complex of truncated cones, cylinders and ellipsoids. In particular, the cross-sectional area of the trunk is ≈5–10 times larger than those of the arm and leg (Organ et al. 1994). Given that the cross-sectional area of a conductor is inversely related to R, the trunk contributes ≈ 15% of distal whole-body resistance (R_{wb}), although it contains ≈ 50% of the body mass (Clarys and Marfell Jones 1986). The discrepancy between the relations of body segment masses to total body mass and segment resistances to R_{wb} are illustrated in Fig. 3.14b. Due to this disparity even large variations of trunk resistance might not be reflected in R_{wb}. Additionally, the change of electrode positions at the foot and hand can cause a change in R_{wb} exceeding that of the trunk. The trunk-limb relationship might therefore explain why some studies could not confirm the diagnostic potential of l^2/R (Diaz et al. 1989; Eckerson et al. 1992).

3.4.5.2 Proximal Electrode Arrangement

One approach to circumvent the strong influence of limb resistance on whole-body measurements is to employ a proximal electrode arrangement as suggested by Scheltinga et al. (1991). This configuration places the electrode pairs at the level of the elbow and knee, respectively, and is therefore referred to as proximal compared to a distal electrode positioning at the ankle and wrist. The current source electrodes can also alternatively remain in their distal position to avoid artifacts related to constrictional resistance (Deurenberg et al. 1995). Thus, the relative impact of the limbs on whole-body values is reduced. Scheltinga et al. (1991) found that the proximal approach accounted for 50% of the whole-body technique and that changes in fluid status were more accurately reflected by the proximal electrode arrangement. A clear superiority of the proximal compared to distal electrode placement is, however, questionable. Whereas some investigators could substantiate the advantage of the technique (Lukaski 1993; Gudivaka et al. 1994), other researchers did not confirm a significant improvement (Danford et al. 1992; Deurenberg et al. 1995; Turner and Bouffard 1998).

3.4.5.3 Segmental Electrode Arrangement

A more sophisticated approach to eliminating the disparity between body segments is to model the human body as five cylinders, i.e. two arms, two legs and a trunk with varying cross-sectional areas. Total conductive volume (V_{tot}) can then be expressed as

$$V_{tot} = 2\rho_{arm}\frac{l_{arm}^2}{R_{arm}} + 2\rho_{leg}\frac{l_{leg}^2}{R_{leg}} + \rho_{trunk}\frac{l_{trunk}^2}{R_{trunk}}\,[\mathrm{m}^3]. \tag{3.18}$$

where ρ_{arm}, ρ_{leg}, ρ_{trunk}, l_{arm}, l_{leg}, l_{trunk}, R_{arm}, R_{leg} and R_{trunk} refer to resistivity (Ω·m), length (m) and resistance (Ω) of arm, leg and trunk segments, respectively. Certainly, further refinement of this approach is possible. For instance, the limbs could be further differentiated in their lower and upper

parts, respectively. Some of such developments are therefore further discussed in subsection 4.5.3.5. There are several ways to relate segmental data to total conductive volume. Basically, resistivity of the three sections can be assumed to be either constant or different. Hence, in structural bioimpedance modeling some models either rely on a single resistivity for all body segments or assume resistivity to be segment-specific. Similarly, in empirically derived segmental bioimpedance models the sum of the (weighed) resistance indices can be regressed against a dependent variable that is used as a reference. Alternatively, multiple regression analysis can also be used to predict a dependent variable from the three respective body segments.

The Role of Uniform Current Distribution for Segmental Measurements

The potential of segmental measurements was first mentioned by Settle and his coworkers in 1980 and it was almost a decade later that Chumlea et al. (1988) first published a segmental approach for determining fat mass and fat-free mass. For this purpose, current source and voltage-sensing electrodes were placed at the shoulder and wrist, ankle and hip, and hip and sterna notch for determining R_{arm}, R_{leg} and R_{trunk}, respectively. Theoretically, the sum of ipsilateral R_{arm}, R_{leg} and R_{trunk} should be equal to R_{wb} measured between the ankle and wrist. Data by Chumlea et al. (1988) however exceeded R_{wb} by roughly 16%. Such a discrepancy was too large to be purely attributed to experimental error. Organ et al. (1994) showed that this phenomenon could be explained by the fact that data from dissimilar measurement configurations were compared. They further explained that the sum of R_{arm}, R_{leg} and R_{trunk} would only be equal to R_{wb} when the same current source and magnitude are achieved. The placement of the current source electrodes next to the voltage-sensing electrodes caused a larger potential difference of each segment, respectively. Similarly, as already suggested for the proximal electrode placement, current injection should therefore be maintained via the ankle and wrist. Nonetheless, such segmental measurements still suffer from two major drawbacks. Firstly, subject comfort is reduced since at least partial undressing is necessary for correct electrode placement. More importantly, however, reliability is put at risk since at least for less experienced personnel the correct location of specific landmarks at the shoulder, hip and chest is likely to be more prone to errors than the positioning of electrodes at the wrist and ankle.

Effective and Reliable Electrode Placement for Segmental Measurements

In order to avoid difficulties underlying segmental measurements requiring electrode placements at the limbs and trunk, first Patterson et al. (1988) and Patterson (1989), and later Organ et al. (1994), as well as Cornish et al. (1999, 2000) presented a segmental measurement technique which only requires the application of two additional electrodes at the equivalent positions of the hand and foot at the contralateral side of the body. This technique will now be explained in detail.

Assuming that the current between the ipsilateral wrist and ankle flows in a longitudinal direction, the equipotential lines should be perpendicular to the current distribution lines in narrow sections.[1] For this reason, it should be possible to obtain the same voltage signal at any specific anterior, posterior and lateral level. That means that there is a virtual connection between the left wrist and the right shoulder, allowing the determination of the segmental resistance of the right arm by measuring the voltage between the right and left wrist (Fig. 3.15).

[1] Equipotential lines indicate points with identical potentials. If an electrical charge is moved along an equipotential line, it experiences no electric force and hence no work is performed. Since there is no force driving the charges, there is no current flow between two points with the same potential.

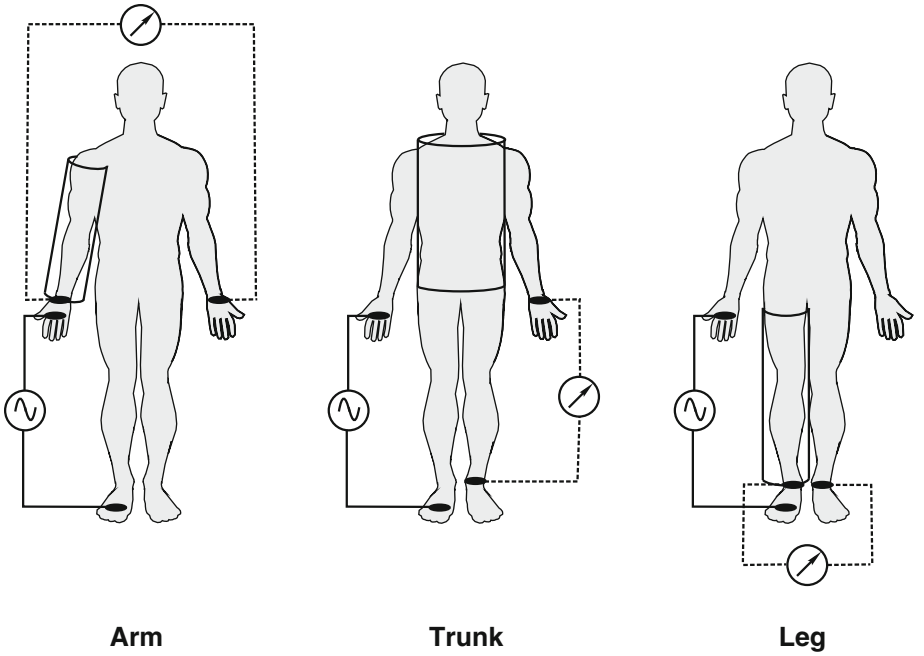

Fig. 3.15 Segmental bioimpedance measurements for right arm, trunk and right leg. This is an electrode configuration for segmental measurements that is based on the conventional whole-body measurement with two electrodes attached to the right hand and foot, respectively. In addition, only two extra detector electrodes are needed. These electrodes are placed at the equivalent positions (with regard to the detector electrodes of the right side of the body) of the left side of the body to determine segmental resistance of the arms, legs, and trunk, respectively. This measurement configuration neither requires the current injection electrodes to be moved nor to locate additional electrode sites other than those for the whole-body approach. To obtain separate resistance measurements of the right arm, leg and trunk the crocodile clips for measuring the potential difference are connected to the electrodes of the left and right wrists and ankles as indicated

In accordance, R_{leg} (right side) can be measured by sensing the voltage potential between the right and left ankle. R_{trunk} then only requires the determination of the voltage between the left wrist and left foot. Alternatively, the suggestion of Cornish et al. (2000) was to sense voltage between the contralateral wrist and ankle to first obtain the sum of R_{trunk} and R_{arm} (R_{trunk} and R_{leg}) and then compute R_{trunk} by subtracting R_{arm} (i.e. R_{leg}) from the sum of R_{trunk} and R_{arm} (i.e. R_{trunk} and R_{leg}). The ideal assumption of a current flowing only in a longitudinal direction is certainly not entirely valid. In regions where the electric field is not aligned in parallel with the longitudinal body axis, the equipotential lines are not linear and complex to determine. This difficulty increases in regions where the current has to pass regions with marked changes in cross-sectional area and where the poorly conducting tissues such as bone (e.g., shoulder and hip joints) complicate the development of a homogeneous electrical field. Despite these constraints, Cornish et al. (1999) empirically showed that the distal extremity of both the upper and lower limb is at the same equipotential as all parts of the upper and lower limb respectively. The variation in Z relative to the standard electrode site along the proposed equipotential lines was less than 1% and the standard deviation of relative Z did not exceed 2%. It should be noted that this deviation comprises both a technical measurement error as well as biological variations. Due to orthostatic effects substantial fluid shifts occur while lying supine, which might have confounded constant measurement conditions during that study. Thus, the observed discrepancies of 2% might simply be caused by a technical and biological variation.

Potential and Limitations of Segmental Measurements

The largest uncertainty underpinning the segmental approach can be traced to the volume estimation of the trunk. Given the anatomical complexity of the trunk, the assumption of isotropy is far from being fulfilled. Furthermore, given the disparity between segmental resistances and masses, small errors in R_{trunk} can lead to substantial artifacts in volume estimations of the trunk. In addition, the full potential of segmental measurements can only be achieved when the corresponding segmental lengths are also determined. This introduces additional measurement error, and if the electrode setup as suggested by Organ et al. (1994) is employed, the reference points for segmental lengths need to be determined without knowledge of the true conductive length.

Nonetheless, the segmental approach seems to be promising. Similar to the proximal electrode arrangement, it seems to be less prone to errors related to fluid shifts within body segments. For instance, Zhu et al. (1998a) demonstrated that in contrast to the whole-body approach the segmental technique is independent of the body position. In a study by Thomas et al. (2003) 13 impedance measurements were performed over a 60-min period while lying supine. While the whole-body impedance index linearly and significantly decreased by 6.6% after termination of testing, no significant changes were observed for the segmental approach. Some authors also suggested that the poorer performance of BIA in obese subjects might be related to the single-cylinder assumption underpinning the whole-body approach (Swan and McConnell 1999). Furthermore, a segmental approach would also be useful in the monitoring of body fat distribution and for classifying different types of obesity (gynoid vs. android obesity). In summary, a number of studies monitoring different fluid compartments during surgery and hemodialysis found the segmental technique to be a promising extension of the whole-body approach (Patterson et al. 1988; Patterson 1989; Bracco et al. 1996, 1998, 2000; Tatara and Tsuzaki 1998; Zhu et al. 1998b, 2000; Biggs et al. 2001).

Commercially Available Segmental Bioimpedance Systems

It is worth noting that the segmental approach also led to the commercial availability of a number of instruments, which combine a scale with a bioimpedance monitor. These instruments use tactile electrodes at the feet and allow bioimpedance measurements of the lower extremities. Similarly, some manufacturers also introduced hand-held devices to measure the bioimpedance of the upper extremities. As long as these two types of devices are not combined, the techniques are generally prone to errors associated with body fluid and tissue distribution since they both assume the upper or lower body to be representative of the total body. For instance, leg-to-leg instruments will hardly detect any changes in upper-body composition or reflect fat mass in android obesity, whereas hand-to-hand devices might not accurately measure fat in subjects with gynoid obesity. Thus, unless such approaches consider differences in fat mass distribution or limit the analysis of the target quantity to the segments measured, these methods should be carefully applied to assess individual body composition levels. A refinement of the technique that overcomes these drawbacks is a segmental eight-tactile electrode system, which is based on the segmental principle suggested by Organ et al. (1994), allowing the separate determination of the trunk and limbs, respectively. Recent validation studies have confirmed the validity of the approach, at least in healthy populations (Jaffrin and Morel 2009). Given its speed and ease of use it might promote the acceptability of BIA in the clinical, research and particularly epidemiological settings.

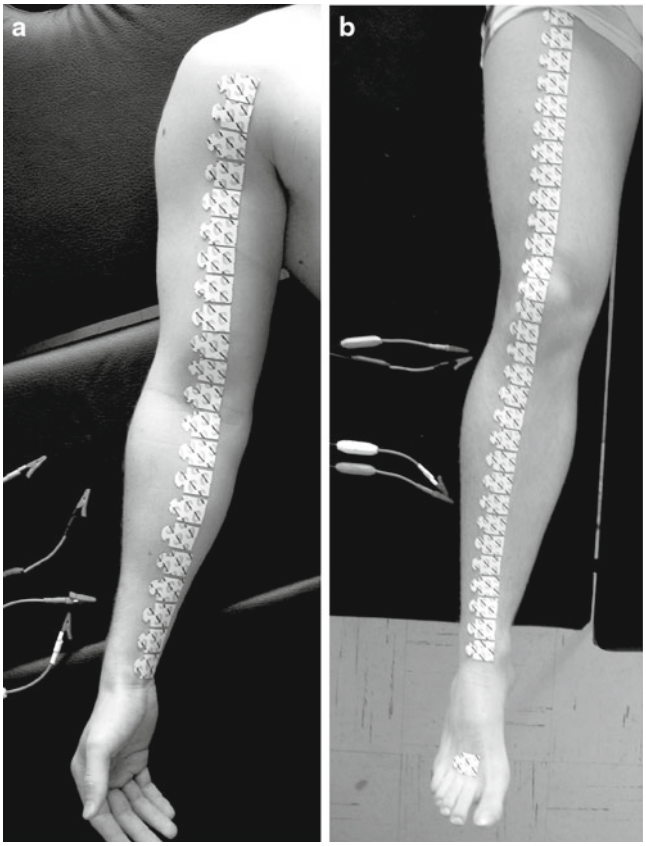

Fig. 3.16 Electrode configuration for the determination of limb resistance profiles. This figure displays the electrode configurations for the determination of limb resistance profiles of the arm (**a**) and leg (**b**), respectively

Directions for Future Research

Finally, ongoing research is trying to improve the segmental approach. For instance, Van Kreel et al. (1998) postulated that modeling the body segments as a combination of truncated cones and cylinders would more strictly reflect the geometrical properties of the human body. Though promising, this approach failed to improve the prediction of total body water as compared to whole-body measurements. A field of emerging interest is to restrict body composition analysis by bioimpedance measurements to specific body segments instead of using various segmental measurements to model whole-body composition. Limiting analyses to the extremities apparently avoids difficulties associated with assuming isotropy in the trunk. Furthermore, if measurements are reduced to small limb segments the assumption of representing the conducting volumes as cylinders will apparently gain significance. A further step is to perform local bioimpedance measurements to estimate skeletal muscle cross-sectional area. This type of measurement configuration has also been employed to provide diagnostic information on neuromuscular diseases (Tarulli et al. 2005), on induced muscle damage after prolonged physical exercise (Elleby et al. 1990) as well as on subcutaneous fat layers (Elia and Ward 1999; Scharfetter et al. 2001). Another approach combining the determination of individual measurements to cross-sectional areas and full segmental limb measurements is based on multiple measurements along the limbs (Fig. 3.16).

The basic idea of this approach is obtain a resistance profile of the limb, and approximate these data by a fitting algorithm so that it is possible to derive the resistance at any possible site along the limb (Fig. 3.17).

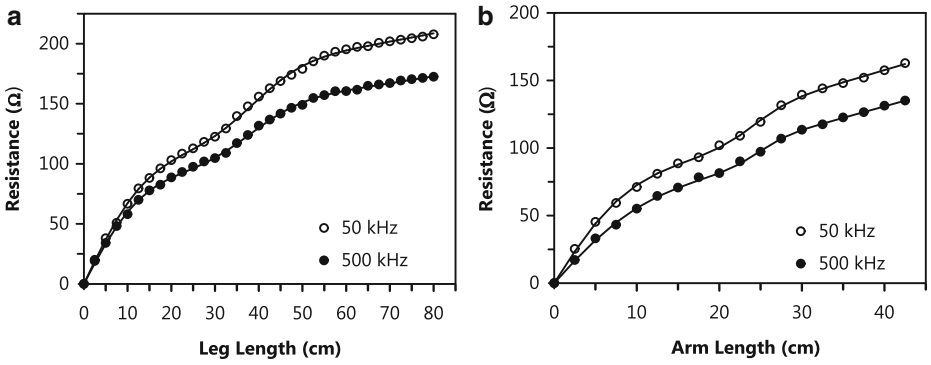

Fig. 3.17 Measured (*circles*) and curve-fitted (*continuous lines*) resistance profile of limbs. This figure illustrates typical resistance profiles of the leg (**a**) and arm (**b**) determined at 50 kHz (*white circles*) and 500 kHz (*black circles*) of a single subject. *Continuous lines* indicate curve-fitted data by two cumulative Gaussian functions plus a *straight line*. The goodness of fit for the model as determined by the coefficient of determination is 0.999 based on data published in Stahn et al. (2007)

Accordingly, assuming that the injected current is flowing in longitudinal direction only and that the resistivity of the tissue of interest is much smaller than that of other tissues, an estimate of the cross-sectional area (A) at a specific site (x) can be obtained from:

$$A(x) = \frac{\rho}{dR/dx}\,[\mathrm{cm}^2]. \tag{3.19}$$

where ρ (Ω·cm) is resistivity, and R (Ω) is the resistance of any specific site. Finally, the total limb volume can be computed as the integral over x of the estimated cross-sectional area. An example for an individual subject where skeletal muscle volume was determined for the leg and arm using this approach is given in Fig. 3.18.

The agreement between MRI-measured skeletal muscle mass and BIA is excellent in healthy populations. Furthermore, at least for the leg this approach is clearly superior to conventional segmental BIA for estimating skeletal muscle mass. The total error can be reduced by as much as 50% when compared to conventional segmental measurements. Furthermore, irrespective of the prediction accuracy the approach is promising as it does not imply the need of sample-specific regression equations. Yet, further validation of the technique is required to assess its accuracy in a variety of populations and to quantify the variability of specific resistivity and its impact on the estimation of skeletal muscle volume. Though the approach could also become more efficient by employing measurements at fewer electrode sites, it should be noted that measurement and its analysis are more sophisticated and time-consuming than conventional segmental BIA. Thus, in spite of the fact that the approach might serve several promising clinical applications and provide useful research opportunities, the trade-off between the gain in accuracy and the setback in efficiency should be carefully considered prior to the implementation of the technique.

3.5 Potential Errors in Bioimpedance Measurements

Consideration of Eq. 3.2 presents some of the major interferences on bioimpedance measurements: the length of the conductor, its volume and temperature-dependent resistivity, which is primarily determined by protein and ion concentrations (see also subsection 3.1). Moreover, since tissue is

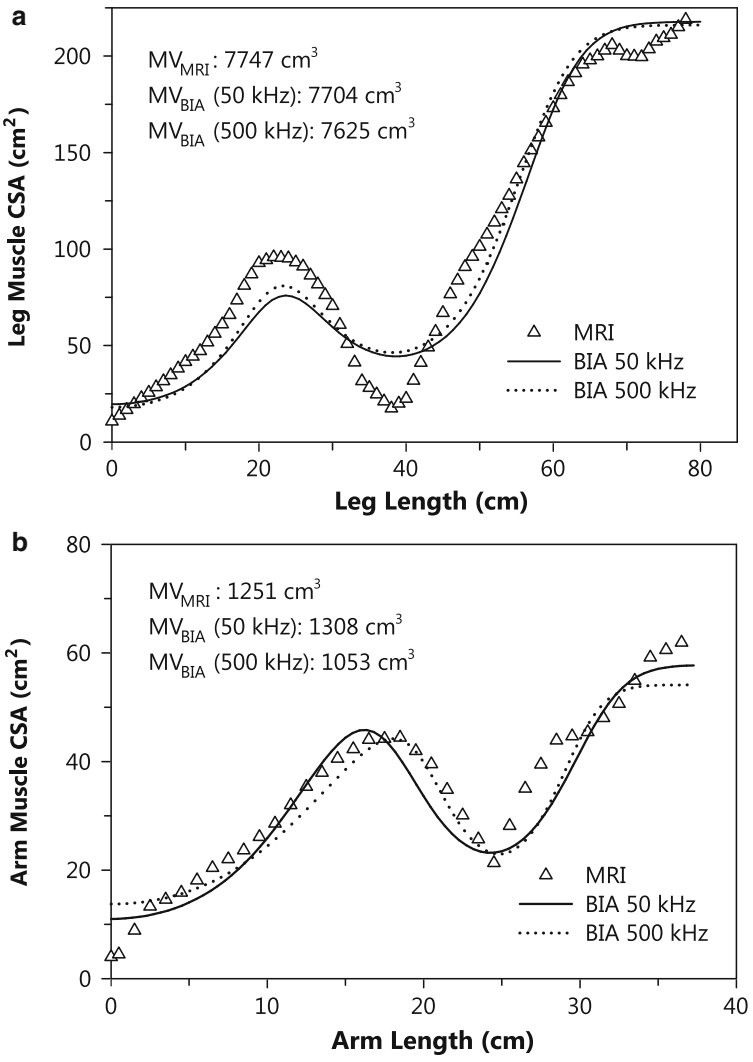

Fig. 3.18 MRI-measured (*triangles*) and BIA-estimated (*continuous and dotted lines*) muscle volume derived from limb resistance profiles. This figure shows the agreement between MRI-measured and BIA-estimated muscle volume derived from resistance profiles of the leg (**a**) and arm (**b**) of a single subject. MRI data is represented by *triangles*. *Continuous and dotted lines* refer to estimates of muscle volume based on bioimpedance measurements at 50 and 500 kHz, respectively. Leg muscle volume was 7,747, 7,404 and 7,625 cm^3 as determined by MRI, BIA at 50 kHz and BIA at 500 kHz, respectively. Arm muscle volume was 1,251, 1,308 and 1,053 cm^3 as determined by MRI, BIA at 50 kHz and BIA at 500 kHz, respectively (Based on data published in Stahn et al. (2007))

characterized by both capacitive and resistive properties, measurements are also dependent on the dielectric constants of the respective tissues. Any changes in one or more of these variables can therefore yield a change in bioimpedance.

3.5.1 Resistance Versus Impedance

It should be noted that some bioimpedance monitors do not allow distinguishing of the real and imaginary parts. Consequently, they consider the imaginary part of bioimpedance to be negligible and substitute Z for R. Though some authors report the fraction of X_c to be as low as $< 4\%$, individual

proportion can exceed 15% in young trained subjects (own unpublished observations). At either zero frequency (or very low) or infinite (or very high) frequencies, this difference is negligible since in this case Z converges toward R_0 and R_∞, respectively. At frequencies near the characteristic frequency f_c (30–100 kHz), however, a substantial amount of Z can be related to the capacitive properties of the tissue and results obtained by phase-insensitive instrumentation should therefore be interpreted with care. Consequently, the choice of Z or R should always be in accordance with the requirements of the regression equations employed.

3.5.2 Conductor Length

The length of the conductor is determined by the distance between the voltage-sensing electrodes or simply standing height, when a conventional whole-body approach is employed. Based on our own unpublished observations in 182 (96 men and 86 women) subjects, aged between 17 and 70 years with a body mass index ranging between 17 and 44 $kg \cdot m^{-2}$, height approximates about 94% of actual conductive length (sum of arm, leg, and trunk length). For the Reference Man (170 cm, 70 kg), and assuming R_e and R_i to be 500 and 100 Ω, respectively, this leads to an underestimation of 1.63 and 2.17 L for extra- and intracellular water by Hanai's mixture theory. Similarly, using a regression equation for total body water derived in representative sample (Sun et al. 2003) introduces an error of 3.18 L. These errors are, however, rather theoretical as such systematic bias can be corrected for by regression weights and/or resistivity values. Nonetheless, if the ratio of standing height to conductive length varies markedly between individuals, the conventional resistance index l^2/R can be prone to significant artifact error.

In accordance with that, measurement errors pertaining to height or body segments can confound the computation of l^2/R. Measurements of body lengths should therefore be performed by an experienced anthropometrist to the nearest millimeter. Moreover, due to the small diameter of the wrists and ankles in comparison to the remaining body parts, a deviation of the voltage-sensing electrodes of one centimeter can already induce changes in Z of nearly up to 5%, with distal electrode shifts causing substantially larger errors than proximal shifts (Elsen et al. 1987; Gualdi-Russo and Toselli 2002). While such a variation might still be acceptable for whole-body measurements, it should be noted that for segmental measurements (e.g., upper arm or thigh), this error can be inflated to 10% as a result of the shorter conductive length. This underlines the importance of choosing easily accessible and reproducible electrode sites, particularly when several measurements are performed such as during segmental analyses.

3.5.3 Spatial Geometry and Postural Changes

The subject's position during the performance of the measurement is a further important factor, which deserves clarification. Though a number of commercially available instruments combing a scale with a bioimpedance monitor employ lower-limb measurements in a standing position, the typical measurement procedure in most health or laboratory settings is characterized by having the subject lie in a supine position. On the one hand, this methodology is related to clinical conditions. On the other hand, this practice can be traced to the advantage of allowing subjects to remain in a comfortable, relaxed position. The major differences between whole-body impedance

while lying in a supine position and remaining in a standing position are related to local fluid shifts due to orthostatic effects. While a continuous increase in whole-body impedance can be observed for supine measurements (Roos et al. 1992; Shirreffs and Maughan 1994; Scharfetter et al. 1997b; Evans et al. 1998; Zhu et al. 1998a), whole-body impedance decreases while standing (Zhu et al. 1998a). Postural changes from standing to supine position result in rapid transfer of ≈0.5 L of blood from the extremities to the trunk (Kirsch et al. 1979). This fluid shift is most pronounced within the first 20–30 s after postural changes, after which it gradually slows down and nearly reaches a plateau after 30 min (Linnarsson et al. 1985; Shirreffs and Maughan 1994). Concomitant with this fluid shift is a reduction of filtration pressure in the extremities, causing plasma volume to increase, which, in turn, is compensated by changes in heart rate, blood pressure, and stroke volume. Treating the human body as a single cylinder with homogeneous cross-sectional area, measurements of whole-body impedance are insensitive to any fluid volumes changes. Consequently, decreases in extracellular water of up to 4.9% have been reported after 30 min of lying in a supine position (Zhu et al. 1998a). Since postural effects on bioimpedance measurements are most pronounced during the initial minutes after changing from standing to supine position (Scharfetter et al. 1997b; Shirreffs and Maughan 1994; Zhu et al. 1998a), a 10-min resting period prior to determination of bioimpedance measurements has been recommended. This period can be understood as a compromise between maintaining the efficiency of the technique and considering some primary physiological interference. Though an extended resting period would physiologically be favorable, this would undermine the quick character of the technique. However, as long as testing conditions remain identical, any fluid shifts associated with postural changes might not actually put the accuracy of the outcome variable at risk since the underlying model was derived exactly under these conditions. With regard to the effect of orthostatic fluid shifts on bioimpedance measurements it is worth noting that various prediction equations might suffer from systematic bias when applied in the clinical setting. Given that most regression equations have been developed in subjects who were measured within 10 min after lying down, these equations might cause substantial error when applied to persons who are restricted to bedrest for several hours or days (Kyle et al. 2004). At least theoretically though, a rather sound remedy for avoiding measurement artifacts due to peripheral fluid volume shifts induced by postural changes is to employ a segmental measurement technique (Zhu et al. 1998a) or placing the voltage sensing electrodes at more proximal positions such as at the elbow and knee (Scheltinga et al. 1991). A final aspect that needs to be taken into consideration with regard to body positioning is the placement of the limbs in relation to the trunk. A flexion in the elbow and knee joints as well as a change in the arm-trunk and leg-trunk angle can alter whole-body impedance by up to 10%. The smallest bias for arm-trunk angles is found at 10 ± 5 degrees, and for leg-trunk angles at 15 ± 5 degrees (Lozano et al. 1995). The cause for this phenomenon is not well understood. It can be speculated that any alteration of the joint angle induces a change in the electrical field as limb joints change shape. While it may seem obvious that limb extension should be limited, it is equally important that the limbs are not too closely positioned to the body to avoid capacitive couplings.

3.5.4 Ion Concentration

Given that conductivity is predominantly determined by the amount of ions (see subsection 3.1), any changes in ion concentrations can affect measurements of bioimpedance and the derived estimates of body composition. According to Scharfetter et al. (1995) a 5-mmol change in ion

concentration is associated with changes in extracellular water and intracellular water by about 2% and 5%, respectively. Consequently, assuming an extracellular and intracellular compartment of 17 and 25 L for the Reference Man, these changes correspond to errors of 0.34 and 1.2 L, respectively. While for the extracellular space such deviations might be tolerated, it should be noted that the relative error for estimations of intracellular water reaches 4.8%. The larger error for intracellular water is not unexpected. On the one hand, intracellular water can be derived as the difference of total body water and extracellular water, thus propagating the errors of extracellular and total body water measurements. On the other hand, if the volume calculations are based on Hanai's mixture theory (see Chap. 23, Selected Applications of Bioelectrical Impedance Analysis: Body Fluids, Blood Volume, Body Cell Mass and Fat Mass) both intra- and extracellular resistivities are required for the calculation, again propagating the errors underlying each parameter. Thus, the uncertainty of the volume estimations for intracellular water are generally higher than for extracellular water.

3.5.5 Tissue Temperature

Another major interference on bioimpedance measurements can be attributed to temperature. As temperature increases the viscosity of a solvent decreases. In turn, ion mobility increases, also causing conductivity to increase. According to Pethig (1979) the temperature coefficient of biological tissue is similar to that of electrolyte solutions and is about $-2\%\cdot°C^{-1}$ for conductivity and +0.5%/°C for permittivity at frequencies up to 50 kHz. These measurements, however, pertain to in-vitro measurements, and in-vivo studies employing skin temperature measurements have shown that impedance changes by $-0.39\%\cdot°C^{-1}$ to $-1.0\%\cdot°C^{-1}$ (Scharfetter 1999). The exact causes for the temperature dependence are still unclear. Increased perfusion, higher sweat gland activities, increased ion activities in the electrode coating, an increase of conductive volume (vasodilatation) and extra- and intracellular fluid shifts are some aspects that are discussed with regard to the increase of conductivity with increasing tissue and body fluid temperature (Caton et al. 1988; Gudivaka et al. 1996; Liang et al. 2000; Buono et al. 2004).

3.5.6 Sigman Effect and Hematocrit

The relationship between hematocrit (*Hct*) and conductivity has been well researched. Generally, it has been found that with increasing *Hct*, conductivity decreases. (Fricke and Morse 1925). Another aspect also related to the temperature dependence pertains to the Sigman effect. Basically the Sigman effect refers to the observation that conductivity changes as a function of blood velocity. Due to the observation that the Sigman effect is less prominent at lower *Hct* values (Valentinuzzi et al. 1996), it can be speculated that the increase of conductivity with increasing blood velocity is also related to blood cells. Though a full explanation of the Sigman effect has not been provided, it is assumed that with increased blood flow velocity erythrocytes orient themselves in parallel with the direction of the blood flow and present a reduced obstruction to the current flow compared to resting conditions. However, modification of the arterial lumen as well as cell clustering around the axial region of vessels might also play a role and the clear distinction of the separate contributions of these three events still needs to be investigated.

3.5.7 Ventilation

Since inspiration and expiration inflate and deflate lung volume, altering its dielectric properties, even changes in ventilation might theoretically affect bioimpedance. In fact, some researchers have suggested using transthoracic bioimpedance measurements for lung function monitoring (Valentinuzzi et al. 1996). In practice, the interference can be neglected as the reported dependence of *Z* on ventilation during conventional bioimpedance modeling seems to be negligible (Elsen et al. 1987; Baumgartner et al. 1988; Evans et al. 1998). Only for maximal inspiration and expiration does *Z* seem to be significantly affected by ventilation (Baumgartner et al. 1988; Gualdi-Russo and Toselli 2002).

3.5.8 Daily Activities, Nutrition and Menstrual Cycle

Besides the above-mentioned aspects, a number of investigators have reported additional significant exogenous factors influencing bioimpedance related to individual subject characteristics. Generally, any physiological change pertaining to one of the above-mentioned aspects can lead to variations in bioimpedance. Physical exercise, for instance, can substantially alter fluid volumes and electrolytes, thus also affecting *Z* (for review, see Stahn et al. 2006). Additionally, even the concomitant reduction in glycogen might influence the measurement. The numerous effects may also counteract and offset each other, causing *Z* to remain unchanged. Due to different adaptation processes following regular physical activity, the mechanisms involved in acute bouts of physical exercise may further contribute to within- and between-subject variability. Though small bouts of physical activity at a low intensity might not considerably alter bioimpedance monitoring, potential influences cannot be discounted. To reduce potential bias, physical activity should therefore be avoided at least 24 h prior to measurements.

Likewise, nutrition can play a role in bioimpedance monitoring. Its effect seems to be less prominent though. While electrolytic fluids have shown to both increase and decrease *Z* as a function of their ion concentrations (Roos et al. 1992; Asselin et al. 1998; Gudivaka et al. 1999), the effects related to the consumption of water seem to be less clear. Minimal changes in *R* or *Z* have been reported after consumption of 0.5–1 L of water or an electrolyte/carbohydrate drink (Rising et al. 1991; Evans et al. 1988; Dixon et al. 2006). However, Gomez et al. (1993) found a significant increase in resistance of 10 Ω after a period of four hours. Similarly, Gualdi-Russo and Toselli (2002) observed a significant increase of up to 17 Ω in Z 30 min after ingestion of 100 mL of Gatorade. Fogelholm et al. (1993) studied the effects of meals, high and low in electrolytes, on *Z*. Though average changes in *Z* were relatively marginal (+3 Ω to −5 Ω compared to median *Z* of 482 Ω), some individuals showed marked changes as compared to the fasting state (up to 20 Ω). These results were confirmed by Slinde and Rossander-Hulthén (2001), Gallagher et al. (1998) and Deurenberg (1988). However, some investigators did not detect a substantial influence of meals on bioimpedance (e.g., Chumlea et al. 1987). These contrasting results are likely to be explained by different methods and protocols and do not alleviate the impact of meal as a potential source of error in individuals. Certainly, the acute effects of nutrition on bioimpedance and their statistical significance occur to be a matter of sample size, study protocol, and methods (e.g., high/low electrolyte meal, total calories consumed, body size and composition, and time point of measurement). Thus, in individuals, nutrition, and particularly meals high in electrolyte content remain a potential source of error. For these reasons, it has recommended to perform bioimpedance measurements in a fasting state and to control hydration by limiting the amount and type of fluid consumption prior to the measurement (Fogelholm et al. 1993; Gallagher et al. 1998).

Table 3.2 Key features for standardization of bioelectrical impedance measurements

1.	Performance of repeated measurements at same time of the day.
2.	No large meals 2–4 h prior to testing.
3.	No coffee consumption >8 h prior to testing.
4.	No alcohol consumption >8 h (>24–48 h) prior to testing.
5.	Consumption of liquids limited to 1% of body mass 2 h prior to testing.
6.	No heavy physical activity >8 h (>12 h) prior to testing.
7.	No diuretic medications seven days prior to testing.
8.	Voiding immediately prior to testing.
9.	Removal of metallic jewelry prior to measurement.
10.	Fixed resting period (usually 5–10 min) in supine position prior to testing. Exact procedures should follow the manufacturer's specifications and/or the instructions provided by the literature underlying the prediction model employed.
11.	Constant body segment flexion (arm-trunk angles: 10° ± 5°; leg-trunk angles: 15° ± 5°). Supporting material (e.g., styrofoam blocks) can be used to maintain this body position. A piece of thin acrylic may be needed to be placed between the legs and/or the arm and trunk if be separated, respectively.
12.	Standard preparation of electrode skin surface (hair removal, cleaning with alcohol solution). No skin lesion at the site of electrodes.
13.	Use of electrodes that meet the manufacturer's requirements. Store electrodes appropriately (heat protection to maintain gel integrity).
14.	Position electrodes according to manufacturer's specifications or the instructions provided by the literature underlying the prediction model employed. Separation of current source and voltage-sensing electrodes by at least 5 cm.
15.	Maintaining thermoneutral conditions (constant ambient temperature and humidity).
16.	Calibration check of technical instrumentation prior to testing.
17.	Isolation of metallic objects and other electronic devices by a distance of at least 50 cm.
18.	Measurement of height or body segment length at least to the nearest 0.5 cm.
19.	Measurement of weight at least to the nearest 0.1 kg.
20.	Use only prediction models (equations) that have also been validated for the bioimpedance analyzer used or calibrate the instrument appropriately.

This table provides a list of general recommendations that should be considered for standardizing bioimpedance measurements in the clinical as well as the research setting. Further details regarding the standardization under specific clinical and disease conditions are provided by Kyle et al. (2004)

Finally, in female subjects total body water tends to increase after ovulation due to increased plasma progesterone levels. In spite of some contradicting results, neither the time of measurement during the menstrual cycle nor the administration of oral contraceptive seems to substantially confound bioimpedance measurements (Chumlea et al. 1987; Deurenberg et al. 1988; Gleichauf and Roe 1989; McKee and Cameron 1996; Gualdi-Russo and Toselli 2002). Nonetheless, in women experiencing large weight gains (2–4 kg) during the menstrual cycle, careful interpretation of bioimpedance data is necessary since a substantial amount of the increase in body mass can be related to total body water (Bunt et al. 1989).

In summary, measurement conditions (ambient temperature and posture), physiological state (physical activity or other events altering core and skin temperature, blood flow, ventilation, fluid distribution within different compartments and between different body segments), prandial and hydration state, and technical reliability of the operator (electrode placement and anthropometric measurements) may affect the reproducibility of in-vivo bioimpedance measurements. It is therefore imperative to perform bioimpedance measurements under highly standardized conditions, which are summarized in Table 3.2.

3.6 Reliability

One of the biggest challenges of bioimpedance monitoring is to distinctly relate changes in Z to physiological events. As outlined in the previous section any change in Z can be related to changes in tissue resistivity, changes in tissue geometry, or a combination of both. In many practical settings both parameters change simultaneously making it difficult to associate changes in Z with its underlying physiological phenomena (Lozano-Nieto 2000). This difficulty is a constant of the reliability and validity of bioimpedance applications. Validity will be discussed in detail with regard to specific applications in the following chapters on applications of bioelectrical impedance analysis. The following section will therefore exclusively focus on the reliability of bioimpedance measurements.

For the determination of the overall reliability of bioimpedance measurements, it needs to be taken into account that the latter are also dependent on technical measurement error. Depending on the test circuit (simple or complex impedance measurements), reliability of single-frequency bioimpedance measurements have measurement errors in the range of 1% to 2% (Segal et al. 1985; Roche et al. 1986; Van Loan and Mayclin 1987; Steijart et al. 1994) and reliability coefficients for repeated measurements exceeding 0.99 (Graves et al. 1989). Ward et al. (1997) studied the reliability of multi-frequency measurements. The relative differences between measured and expected Z were small (average between 0.7% and 1.3% for different machines from the same manufacturer) and somewhat larger for phase angle (average between 2.4% and 7.2%). Extrapolated R_0 was within 3% of theoretical values over a range of 50 Ω to 800 Ω. Extrapolated R_∞ was fitted equally well between 100 Ω and 530 Ω. For lower Z, particularly below 50 Ω, measurement accuracy decreased remarkably. However, usually values obtained for whole-body Z in vivo are of the order of several hundred ohms. Similar technical errors were reported by Oldham (1996) when he tested six bioimpedance analyzers. Yet, he also noted that in some instruments errors can get as large as 20% for values similar to those normally encountered in the human body and concluded that the state-of-the-art error for bioimpedance measurements appears to be within ±1% and ±2%. Substantial differences between the technical accuracy of commercially available bioimpedance systems were also reported by other investigators (Deurenberg et al. 1989; Graves et al. 1989; Smye et al. 1993; Bolton et al. 1998).The overall reliability of bioimpedance measurements is therefore a combination of the electronic precision and accuracy of instrumentation used, the technical operator reliability, the standardization of measurement conditions and individual subject characteristics. A number of studies confirmed that bioimpedance measurements can be performed with high within-day and between-day reliability when experienced investigators employ strictly standardized measurement protocols. Table 3.3 provides a summary of different reliability studies of bioimpedance. The average coefficient of variation for within-day and between-day variability is approximately 1–2% and 2–3%, respectively, and underlines the acceptable reproducibility of the method under standardized conditions. Nonetheless, it should be noted that the statistics reported rely on averages and the repeatability for individual measurements can be substantially lower. This pertains in particular to measurements at very low frequencies (1–5 kHz), to segmental measurements of the trunk as well to measurements of X_c. There is a clear need for future studies to investigate the reliability of segmental bioimpedance measurements as well as to provide data for R and X_c at a range of frequencies, including extrapolation of R_∞ and R_0. In addition to reporting average statistics, such studies should include the documentation of the range of deviations for individual measurements. This could be achieved by using Bland-Altman plots and reporting limits of agreement.

Table 3.3 Summary of reliability of in-vivo whole-body bioimpedance measurements (M, men; W, women)

Authors	Instrumentation	Variables	Methods	Reliability Statistics	Reliability
Deurenberg et al. (1988)	RJL BIA 101	R (50 kHz)	Four different days within a period of 3–4 weeks	Coefficient of variation	2.8%
Elsen et al. (1987)	RJL BIA 103	R (50 kHz)	Consecutive duplicate measurements with and without marked electrode sites	Correlation coefficient	0.998 (with) 0.989 (without)
			Four 5-min intervals with and without blanket	Mean relative changes	–0.02% to –0.6% (with) 0.4–2% (without)
Fornetti et al. (1999)	RJL BIA-101 A	R, X_c (50 kHz)	Consecutive duplicate measurements (replacement of electrodes not indicated)	Intraclass correlation coefficient form repeated measures ANOVA	0.957–0.980
Graves et al. (1989)	Valhalla Scientific model 1990-A, RJL BIA-101, Med-Fitness model 1000, Bioelectrical Sciences model 200Z	R (50 kHz)	Consecutive duplicate measurements with electrodes kept in place	Reliability coefficient (not further specified)	>0.99
Jackson et al. (1988)	RJL BIA 103B	R (50 kHz)	Two different testers on two different days within a 7-day period	Generalizability coefficient for all conditions	0.957 (M) 0.967 (W)
Kushner and Schoeller (1986)	RJL BIA 101	R (50 kHz)	Six 20-min intervals[a] Six 1-week intervals[b]	Coefficient of variation	1.3% (0.3–1.9%)[a]
Kyle et al (2003)	Xitron 4000B	R (50 kHz)	1 week 1 month	Not indicated	0.999 (1 week) 0.997 (1 month)
Lukaski et al. (1985)	RJL system	R (50 kHz)	Five consecutive days	Coefficient of variation	2%
Monnier et al. (1997)	Human IM-Scan	Z (1, 5, 10, 50, 100 kHz)	Single 10-min interval	Coefficient of variation	0.8–4.2% (0.6–7.6%)
Schell and Gross (1987)	RJL BIA 103	R (50 kHz)	Ten consecutive days	Coefficient of variation	2.0%
Stahn et al. (2006)	Bodystat Quadscan 4000	Z (5, 50, 100, 200 kHz)	Two 60-min intervals	Intraclass correlation coefficient form 2-way mixed ANOVA	0.998–0.999 for wb 0.997–0.999 for arm 0.942–0.981 for trunk 0.997–0.998 for leg

(continued)

Table 3.3 (continued)

Authors	Instrumentation	Variables	Methods	Reliability Statistics	Reliability
Turner and Bouffard (1998)	RJL Spectrum lightweight Instrument	R^e, X_c^f (50 kHz)	Two consecutive days (24 h) on two different occasions and three trials	Generalizability coefficients	0.87–0.98 for R (M) 0.67–0.91 for X_c (M) 0.84–0.96 for R (W) 0.54–0.98 for X_c (W)
Van Loan and Mayclin (1987)	RJL BIA 101	R (50 kHz)	Eight consecutive days	Coefficient of variation	2.9% (1.31–6.95%)

This table provides a summary of various reliability studies on bioimpedance measurements. The studies included measurement intervals as low as a few minutes and as long as 6 weeks. Reported data covered a range of reliability statistics including correlation coefficients, mean relative changes, coefficient of variations, intraclass correlation coefficients, as well as generalizability coefficients. It is noteworthy that most studies were conducted at a frequency of 50 kHz and report only data for whole-body measurements. Data for segmental measurements are provided by Stahn et al. (2006). As indicated in the table measurements of the trunk seem to be less reliable than measurements of the arm and leg. Furthermore, measurements at low frequencies (≤5 kHz) are less reliable than measurements at higher frequencies (≥50 kHz). This seems to be particularly important for measurements at 1 kHz, for which Monnier et al. (1997) reported a coefficient of variation of 4.2% for repeated measurements after 10 min, with a confidence interval ranging between 2.9% and 7.6%. This also highlights that in spite of excellent reliability statistics for average data, individual deviations can be much higher

Summary Points

- Bioimpedance measurements refer to all methods based on the characterization of the passive electrical properties of biological tissue. This is achieved by the introduction of a constant, alternating current below the threshold of perception, and the measurement of the resulting voltage potential.
- The technique has unique advantages in so far as it is non-invasive, it is inexpensive, it can be operated at low costs, it only needs minimal operator training, it enables continuous online monitoring, it is quick, and is easily portable.
- Most applications of bioimpedance monitoring have focused on body composition analysis and have become popular under the term bioelectrical impedance analysis (BIA).
- The fundamental parameters obtained from this measurement are impedance, phase, resistance, and reactance. All can be used to provide diagnostic information about the physiologic properties and events of the human body.
- A basic understanding of impedance, phase, reactance, and resistance is recommended to correctly understand and interpret bioimpedance measurements. Dependent on whether the bioimpedance monitor is phase-sensitive or not, resistance and reactance can be differentiated from impedance. Hence, resistance and impedance should not be used interchangeably.
- Human cells can be modeled by a resistor in parallel with a capacitor and resistor in series. The intra- and extracellular fluid compartments are expected to be pure electrolytes and modeled by resistors, whereas the cell membrane is represented by a capacitor. Hence, the passive electrical passive properties of tissue exhibit a frequency-dependent response.
- Low-frequency currents are more or less blocked by the cell membrane, and bioimpedance measurements are therefore a reflection of the extracellular fluid compartment only. In contrast, high-frequency currents increasingly short-circuit the cell membrane, and bioimpedance are indicative of both extra- and intracellular fluid.
- The upper and lower limits of the frequencies employed are biophysically limited. Even the lowest (i.e. highest) possible frequencies can only be considered approximates of the extracellular (i.e. the combination of the extra- and intracellular) space.
- Bioimpedance spectroscopy (BIS) is technique to estimate resistance at zero and infinite frequency. Employing a phase-sensitive device, resistance and reactance are obtained at several frequencies (15–500) between a few kHz and 1 MHz. Using Cole-Cole modeling, these data can be used to extrapolate resistance at 0 kHz and at infinite frequency.
- The passive electrical passive properties of tissue are also highly tissue-specific, with fat and bone having a high resistance per unit length and area, and muscles, and the vascular compartments having a relatively low resistance.
- To obtain a deep-tissue bioimpedance measurement, the upper layers of the skin need to be bridged. Presently, a tetrapolar electrode arrangement is used for this purpose. Two outer electrodes introduce the current, while two inner electrodes pick up the voltage using a high input impedance voltmeter.
- Assuming that fat draws negligible current, and the human body or body parts can be geometrically approximated by cylinders, the basic biophysical model is based on the fact that resistance is proportional to length and inversely proportional to area.
- Conventional BIA involves whole-body measurements between the right wrist and right ankle. For convenience, conductive body length is usually replaced by height.
- The use of the basic biophysical model for this measurement is based on the assumption that the human body is an isotropic conductor with homogenous cross-sectional area. Importantly, given

the geometrical and electrical complexity of the human body, the limbs make up most of whole-body bioimpedance measurements.
- To minimize the impact of the distal limbs, a proximal electrode configuration between the elbow and knee has been proposed. Alternatively, the body can be separated in segments such as arms, legs, and trunk, for which bioimpedances are determined separately.
- More recent developments also focus on local measurements to determine abdominal adipose tissue, muscle cross-sectional area at various points along the limbs, or even skinfold thickness.
- Given the anatomical complexity of the trunk, the assumption of isotropy is far from fulfilled, and segmental measurements of the limbs seem at present to be most promising.
- The reliability of bioimpedance measurements is excellent. However, there are a number of endogenous and exogenous factors that can substantially bias data collection. Electrode placement, body position and posture, temperature, blood chemistry, ovulation, nutrition, hydration, physical activities can substantially impact the reliability of bioimpedance measurements. Each measurement should therefore closely follow specific standardization procedures.

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Chapter 4
An Anthropometric Analysis of Seated and Standing People

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Abstract Thermal radiative exchanges of the human body with surrounding surfaces play an essential role in describing the thermal conditions of people in a given environment. Moreover, they could be induced by, among other causes, the presence of high intensity radiant sources, like lighting spots or infrared heating panels. This implies that a suitable set of radiation data related to human body anthropometry is required. This set of data mainly comprises the body surface area, the clothing area factor, the effective radiation area factor, and projected area factors. Several analytical or experimental methods may be utilized in order to compute these parameters. A detailed description of the most common of these will be illustrated in this study, pointing out their main features and their ease of application or otherwise. Thereafter, with reference to a field experiment conducted by means of purpose-built experimental apparatus, a detailed analysis concerning the determination of the values of clothing area factor, effective radiation area factor and projected area factors of a sample of standing and seated, and male and female subjects of the population of southern Italy will be described. In addition, the results of a study to determine differences in anthropometric parameters with regard to different gender and nationalities will be reported. The study will conclude by analyzing a specific case-study.

Abbreviations

Mathematical symbol	Description	Unit of measurement
A_b	Total surface area of naked person	m^2
A_{cl}	External surface area of clothed person	m^2
A_p	Projected area of body	m^2
$A_{p,cl}$	Projected area of clothed person	m^2
$A_{p,n}$	Projected area of naked body	m^2
A_r	Effective radiating area of body	m^2
$A_{r,cl}$	Effective radiating area of clothed person	m^2
$A_{r,n}$	Effective radiating area of naked body	m^2
C	Convective heat loss	W
C_{res}	Respiratory convective heat loss	W

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_4,

Abbreviations (continued)

Mathematical symbol	Description	Unit of measurement
d	Distance	m
E_{d}	Diffusion heat loss	W
E_{res}	Respiratory evaporative heat loss	W
E_{sw}	Evaporation of sweat heat loss	W
f_{cl}	Clothing area factor	–
f_{p}	Projected area factor	–
$F_{\mathrm{p}\rightarrow i}$	View factors between the subject and i-th surface	–
f_{r}	Effective radiating area factor	–
h	Height of subject	cm
h_{c}	Convective heat exchange coefficient	W/m^2°C
I_{cl}	Thermal insulation of clothing	m^2°C/W
K	Conduction heat loss	W
M	Metabolic power	W
p_{a}	Water vapor partial pressure	Pa
q_{ir}	Intensity of radiation emitted by a high intensity heat source	W/m^2
Q_{res}	Thermal loss by respiration	W
Q_{sk}	Thermal loss through skin surface	W
R	Radiation heat loss	W
R_{hi}	High intensity radiation heat exchange	W
R_{lt}	Low temperature radiation heat exchange	W
ΔS	Variation in human body internal energy over unit of time	W
t_{a}	Air temperature	°C
t_{cl}	Clothed surface temperature	°C
t_i	Temperature of i-th surface of the enclosure	°C
$\overline{t}_{\mathrm{r}}$	Mean radiant temperature	°C
$\overline{t}_{\mathrm{r,I}}$	Mean radiant temperature of irradiated subject	°C
t_{sk}	Skin temperature	°C
v_{ar}	Relative air velocity	m/s
w	Weight of subject	kg
W	Mechanical power	W
α	Azimuth angle	°
α_{ir}	Relative absorptance of skin	–
β	Altitude angle	°
ε	Emissivity of human body	–
σ	Stefan–Boltzmann constant	W/m^{2}K^4

4.1 Introduction

The thermal sensation of a subject in a confined environment is related to the need of a human organism to realize a homeothermic state at body core level by means of physiological mechanisms, thus maintaining the balance between internal heat production and dispersion toward the environment. This variation, in units of time, ΔS of internal energy for a subject placed in a confined environment is equal to the difference between metabolic heat production, M, (excluding

Table 4.1 Dependence parameters appearing in the thermal balance equation

Terms appearing in the thermal balance equation		Dependence parameters							
		M (W)	I_{cl} (m²°C/W)	t_a (°C)	v_{ar} (m/s)	$\overline{t}_r$ (°C)	p_a (Pa)	t_{sk} (°C)	E_{sw} (W)
Metabolic power	M	✓							
Mechanical power	W	✓							
Respiratory convective heat loss	C_{res}	✓		✓					
Respiratory evaporative heat loss	E_{res}	✓					✓		
Convective heat loss	C		✓	✓	✓				
Radiation heat loss	R		✓			✓			
Diffusion heat loss	E_d		✓					✓	
Evaporation of sweat heat loss	E_{sw}								✓

This table reports the relation between terms appearing in the thermal balance and some physical physiological independent parameters

the so-called mechanical power, W) and thermal loss due to respiration, Q_{res}, and through the skin surface, Q_{sk}:

$$\Delta S = (M - W) - (Q_{res} + Q_{sk}) \tag{4.1}$$

Metabolic heat production depends on the activity performed by the subject and, in turn, part of metabolic heat production is converted into mechanical power. Respiration heat losses occur during respiration, when the subject inhales a certain amount of air. Since this air generally has a different temperature and humidity level compared with that of the body core, a portion of the body's internal heat is transferred to the external environment by means of convective (C_{res}) and evaporative (E_{res}) exchanges. Respiration heat losses depend on metabolic heat production, M, temperature, t_a, and air humidity in the environment; the latter is normally expressed by means of water vapor partial pressure, p_a.

Heat exchanges through the external surface of the human body occur because the thermo-hygrometric conditions of the skin are generally different from those of the surrounding environment. This induces thermal exchanges between the subject and the environment, which are termed *dry heat loss* (that is, by convection, C, radiation, R, and conduction, K) and *latent heat loss* (due to vapor diffusion through the skin, E_d, and evaporation of the sweat, E_{sw}).

Convective heat exchanges depend on the relative air velocity, v_{ar}, the clothed surface temperature, t_{cl} (defined as the mean temperature of the clothed surface, including uncovered parts), and the air temperature, t_a. Radiation heat exchanges depend on the clothed surface temperature, t_{cl}, and the mean radiant temperature of the surrounding environment, $\overline{t}_r$ (defined as "the uniform temperature of an imaginary black enclosure in which an occupant would exchange the same amount of radiant heat as in the actual non-uniform enclosure," as reported in the ISO Standard 13731) (ISO 2001). Both these heat exchanges depend on the thermal insulation of clothing, I_{cl}. In addition, the clothed surface temperature, t_{cl}, is a dependent variable that can be expressed as a function of the other parameters. Conductive heat exchange, caused by contact with objects, is usually ignored due to its low value.

Latent heat loss due to vapor diffusion through the skin is caused by migration of the vapor through the surface layer of the skin; it depends on the skin temperature, t_{sk}, and the evaporative thermal insulation of clothing. Latent heat loss due to evaporation of the sweat, E_{sw}, is assumed to be an independent parameter. Accordingly, the thermal balance equation will be:

$$\Delta S = (M - W) - (C_{res} + E_{res} + C + R + E_d + E_{sw}) \tag{4.2}$$

where each term may be expressed as a function of some physical and physiological independent parameters, as reported in Table 4.1.

Table 4.2 Typical contributions (absolute and percentual) of the components of a thermal balance equation

	Winter		Summer	
Heat loss	W/m^2	%	W/m^2	%
Respiratory convective	0.7	1	1.3	2
Respiratory evaporative	4.6	8	5.2	8
Convective	19.6	32	22.8	33
Radiation	22.2	36	24.4	35
Diffusion	11.0	18	12.5	18
Evaporation of the sweat	2.9	5	2.9	4
Total	61.0	100	69.2	100

This table reports contributions of each terms appearing in the thermal balance equation (excluding metabolic and mechanical powers) in a typical thermo-hygrometric condition of a subject performing a sedentary activity inside a thermal uniform environment and normally clothed for the time of year (i.e., air velocity of 0.1 m/s, humidity ratio 50%, air temperature of 20°C in winter and 26°C in summer). It highlights that the heat exchanged by radiation represents one of the major factors of the human body thermal balance

Appling balance (4.2) to a typical thermo-hygrometric condition of a subject performing a sedentary activity inside a thermal-uniform environment and normally clothed for the time of year (i.e., air velocity of 0.1 m/s, humidity ratio 50%, air temperature of 20°C in winter and 26°C in summer), the results in Table 4.2 are generated. They highlight that, of the main contributions of the human body thermal balance, heat exchange by radiation represents one of the major factors meriting further research.

4.2 Dry Heat Exchanges Between a Confined Environment and the Human Body

Many human activities take place in a confined environment in which the temperature of the surrounding surfaces and air are normally different from the temperature of the external surfaces of the human body. This involves convective and radiative thermal exchanges between the external surface of the clothed body, the air, and the surrounding surfaces of the environment.

4.2.1 Convective Exchanges

The convective heat exchange occurring within a confined environment, due to a difference between the air temperature and the temperature of the external part of the clothed body, may be expressed by the following equation:

$$C = A_{cl} h_c \left(t_{cl} - t_a \right) \tag{4.3}$$

where A_{cl} is the external surface area of a clothed person, h_c the convective heat exchange coefficient, t_{cl} and t_a the clothed surface temperature and air temperature, respectively. The external surface area of a clothed person in (4.3), i.e., the external surface area of the clothed body including unclothed parts (IS0 2001), may be calculated as:

$$A_{cl} = f_{cl} A_b \tag{4.4}$$

where f_{cl} is the clothing area factor and A_b the total surface area of a naked person.

4.2.2 Radiative Exchanges

The radiation heat exchange occurring from the subject to the environment may be evaluated by means of the following equation (considering the human subject as a small body in a large cavity):

$$R = \sigma \varepsilon A_r \left[(t_{cl} + 273)^4 - (\overline{t}_r + 273)^4 \right] \tag{4.5}$$

where A_r is the effective radiating area of the body, $\sigma = 5.67 \times 10^{-8}$ Wm^{-2} K^{-4} (the Stefan–Boltzmann constant), ε the emissivity of the human body (usually equal to 0.97, that is, a mean value between the emissivity of the most common type of clothing 0.95 and the human skin 1.00) (Fanger 1970), t_{cl} the clothed surface temperature and $\overline{t}_r$ the mean radiant temperature.

Equation 4.5 may be utilized in moderate environments, in which surface temperatures of walls are quite low and generally close to that of the air. Therefore, the presence of high intensity heat sources, characterized by a small area, high temperature, and a high directional radiant emission, causes a further radiative exchange toward the human body. It can be evaluated by:

$$R_{hi} = \alpha_{ir} A_p q_{ir} \tag{4.6}$$

where α_{ir} is the relative absorptance of the skin, A_p the projected area of the body, and q_{ir} the intensity of the radiation emitted by the source that directly hits the subject. Thus, the total thermal radiation leaving the body can be expressed as:

$$R = R_{lt} - R_{hi} = \sigma \varepsilon A_r \left[(t_{cl} + 273)^4 - (\overline{t}_r + 273)^4 \right] - \alpha_{ir} A_p q_{ir} \tag{4.7}$$

In (4.7), the effective radiating area of the body takes into account that the human body is not totally convex: the surface of a body that exchanges radiant energy with the environment through a solid angle of 4π is smaller than the actual surface area of the body if the body is not everywhere convex, e.g., the human body (ISO 2001). The effective radiating area of the body can be calculated by means of the following expression:

$$A_r = f_r f_{cl} A_b \tag{4.8}$$

where f_r is the effective radiating area factor, f_{cl} the clothing area factor, and A_b the total surface area of a naked person. However, the projected area of the body, A_p, is the surface of the profile of the human body projected onto a plane perpendicular to the direction of the radiant source. It may be determined, once the projected area factor f_p and the effective radiating area of the body A_r are known, by:

$$A_p = f_p A_r \tag{4.9}$$

or

$$A_p = f_p f_r f_{cl} A_b \tag{4.10}$$

Equation 4.7 may also be written as:

$$R = \sigma \varepsilon A_r \left[(t_{cl} + 273)^4 - (\overline{t}_{r,I} + 273)^4 \right] \tag{4.11}$$

where $\overline{t}_{r,I}$ represents the mean radiant temperature of an irradiated subject. It is expressed by:

$$\overline{t}_{r,I} = \sqrt[4]{\left(\overline{t}_r + 273\right)^4 + \frac{\alpha_{ir} q_{ir} A_p}{\varepsilon \sigma A_r}} - 273 \tag{4.12}$$

$\overline{t}_r$ being the mean radiant temperature of an non-irradiated subject, exposed only to a low temperature thermal exchange with the internal surface of the environment. Thus, the mean radiant temperature may be calculated as a function of the temperatures of the N surrounding surfaces of the enclosure, t_i, and the view factors (or *angle factors*) between the subject and the same surfaces, $F_{p \to i}$:

$$\overline{t}_r = \sqrt[4]{\sum_{i=1}^{N} \left(t_i + 273\right)^4 F_{p \to i}} - 273 \tag{4.13}$$

The view factors are defined as the fraction of the diffuse radiant energy emitted by a surface, which is received directly by another surface. They can be evaluated using diagrams where they are reported as a function of the relative position of people with surrounding surfaces (Fanger 1970; ISO 1998).

Excluding the use of these diagrams, the angle factor can be computed by means of a relationship, depending on the projected area factor:

$$F_{P \to i} = \frac{1}{\pi} \int_{x/y=0}^{x/y=a/c} \int_{z/y=0}^{z/y=b/c} \frac{f_p}{\sqrt{\left[1 + \left(x/y\right)^2 + \left(z/y\right)^2\right]^3}} d\left(x/y\right) d\left(z/y\right) \tag{4.14}$$

where a, b, and c are geometrical parameters singling out the position of the subject with respect to the internal surfaces of the envelope (Fanger 1970) and f_p is the projected area factor.

4.3 Methodologies for the Determination of Various Relevant Anthropometric Parameters

In order to determine the comfort conditions of people living in a confined moderate environment, the methods currently available in the literature require the use of various anthropometric parameters. Some of these parameters have been assessed using field and laboratory measurements, and the values obtained have been subsequently applied to mathematical models. However, other parameters seem to depend strongly on the specific anthropometric features of people, like gender, ethnic group, age, and so on. Now follows a discussion relating to the most important parameters involved in the evaluation of the thermal comfort conditions of people. We will deal in greater detail with the total surface area of a naked person, the clothing area factor, the effective radiating area factor, and the projected area factors by describing a field experiment conducted by the authors of this chapter.

4.3.1 Determining the Body Surface Area of a Naked Person

Since the heat production of a subject is proportional to the surface area of the human body, it is necessary to determine this anthropometric parameter, using a mathematical equation to determine surface area, in order to avoid the direct complex measurement of the shape of the human body. Early publications on this subject include the Meeh (1879) and Howland and Dana (1913) equations,

based only on the weight of the subject, and the Miwa and Stolzer (1898) equation, founded on several anthropometric parameters. Further equations can be found in literature that only depends on height and weight of the subject, easily measurable parameters.

Of these relationships, the most frequently used is that proposed by D. DuBois and E.F. DuBois (1916):

$$A_b = 0.20247\left(\frac{h}{100}\right)^{0.725} w^{0.425} \tag{4.15}$$

where h (cm) is the height and w (kg) the weight of the subject.

This procedure for determining human body surface, utilized by D. DuBois and E.F. DuBois, is based on the use of sheets of gummed hemp, which wrapped onto the subjects and subsequently cut out in pieces and placed onto a horizontal plane. The hemp pieces were then photographed, cut out again, weighed and converted into square meters, as the known value of the photographic paper weight.

Following the publication of the DuBois formula, other expressions have been published, including the following:

– Boyd's formula (1935):

$$A_b = 0.0003207\, h^{0.3} \left(1000w\right)^{0.7285 - 0.0188 \log_{10}(1000w)} \tag{4.16}$$

– Gehan and George's formula (1970):

$$A_b = 0.0235\, h^{0.42246} w^{0.51456} \tag{4.17}$$

– Haycock et al.'s formula (1978):

$$A_b = 0.024265\, h^{0.3964} w^{0.5378} \tag{4.18}$$

– and Mosteller's formula (1987):

$$A_b = \sqrt{\frac{hw}{3600}} \tag{4.19}$$

Comparing the results obtained by these different formulas reveals a similarity among them (Calvino et al. 2006), with a standard deviation lower than 6%. The DuBois formula is currently adopted in anthropometric evaluation.

4.3.2 Determining the Clothing Area Factor

The clothing area factor is the ratio between the external surface area of a clothed person and the surface area of a naked body:

$$f_{cl} = \frac{A_{cl}}{A_b} \tag{4.20}$$

Since the outer surface of a clothed person is always greater than the surface of a naked body, the clothing area factor is always greater than unity. It may be computed by one of three methods: (1) starting with the values of the effective radiating area of the clothed and naked person; (2) by means of a limited number of values of the projected area of the clothed and naked body; and (3) as a function of the thermal resistance of the clothing.

With reference to (1), the clothing area factor is determined thus:

$$f_{\mathrm{cl}} = \frac{A_{r,\mathrm{cl}}}{A_{r,n}} \tag{4.21}$$

where $A_{\mathrm{r,cl}}$ is the effective radiating area of the clothed body and $A_{\mathrm{r,n}}$ the effective radiating area of the naked body.

Method (2) compares the projected area of a clothed subject with the projected area of the same naked subject, as measured for six directions: altitude angles of 0° and 60°, and, for each altitude, azimuth angles of 0°, 45°, and 90°. Then the clothing area factor for the *i*-th direction is determined according to the equation:

$$f_{\mathrm{cl},i} = \frac{A_{\mathrm{p,cl},i}}{A_{\mathrm{p,n},i}} \tag{4.22}$$

and the clothing area factor is estimated as:

$$f_{\mathrm{cl}} = \frac{\sum_{i=1}^{6} f_{\mathrm{cl},i}}{6} \tag{4.23}$$

Referring to method (3) and given that the surface area of the clothing increases with the clothing thickness (usually related to its insulation), the clothing area factor is estimated by means of the following equation (ISO 1995):

$$f_{\mathrm{cl}} = 1.00 + 1.97 I_{\mathrm{cl}} \tag{4.24}$$

in which I_{cl}, expressed in $\mathrm{m^2{}^{\circ}C/W}$, is the clothing insulation of the person.

4.3.3 Determining the Effective Radiating Area Factor

The ratio between the effective radiating area of a clothed body, $A_{r,\mathrm{cl}}$, and the external surface area of a clothed body, A_{cl}, is defined as the effective radiating area factor:

$$f_{\mathrm{r}} = \frac{A_{\mathrm{r,cl}}}{A_{\mathrm{cl}}} \tag{4.25}$$

Using (4.20) and (4.21), we can express:

$$f_{\mathrm{r}} = \frac{A_{\mathrm{r},n}}{A_{\mathrm{b}}} \tag{4.26}$$

The computation of the effective radiating area of the human body (clothed or naked) was originally provided by Underwood and Ward (1966). By means of a method involving the use of photographs, they measured the projected areas of 25 male and female subjects. They then utilized these values of the projected areas with which to propose an empirical equation for the calculation of the effective area for a naked subject in a seated posture. Thereafter, an experimental method was proposed by Fanger (1970), the aim of which was to evaluate the projected area of seated and standing people. This photographic method involved 20 subjects (10 male and 10 female), naked and clothed, in seated and standing postures.

Other authors have also proposed different methods for assessing data concerning the radiative parameters of the human body. For example, Rizzo et al. (1991) have proposed two algorithms for the automatic computation of projected area factors for seated and standing persons by utilizing the original experimental data provided by Fanger. Jones and Ogawa (1992) have subsequently elaborated values of the projected area for the whole body and for single bodies.

The dependence of the projected area on the effective area is given by the following equation:

$$A_{\mathrm{r}} = \frac{4}{\pi} \int_{\alpha=0}^{\pi} \int_{\beta=0}^{\pi/2} A_{\mathrm{p}} \cos\beta d\alpha d\beta \tag{4.27}$$

where α and β are the azimuth and the zenith angles of the beam projected by the radiant source onto the barycenter of the human body respectively (Fanger 1970).

A numerical solution has been proposed by Alfano et al. (1997):

$$A_{\mathrm{r}} = \frac{4}{\pi} \Delta\alpha\Delta\beta \sum_{i=1}^{N+1} \sum_{j=1}^{M+1} A_{\mathrm{p},ij} \cos\beta_j \tag{4.28}$$

where N and M are the number of steps adopted for the azimuth and zenith angles respectively.

Unfortunately, this relationship is not viable when the discrete steps Δα and Δβ are too wide (Calvino et al. 2001), as is the case of several experimental works found in the literature. The application of the trapezoid rule for the solution of (4.27) leads to a more accurate result (Scheid 1968):

$$\int_{X_o}^{X_N} y(x)dx \cong \frac{1}{2}\Delta X \left(y_0 + 2\sum_{i=1}^{N-1} y_i + y_N \right) \tag{4.29}$$

When applied to the calculation of the effective radiating area, this equation provides the following expression, which is a function of the measured values of the projected areas, $A_{\mathrm{p},ij}$:

$$A_r = \frac{\Delta\alpha\Delta\beta}{\pi} \left\{ A_{p,0,0} + A_{p,N,0} + 2\sum_{i=1}^{N-1} A_{p,i,0} + 2\sum_{j=1}^{M-1} \left[\left(A_{p,0,j} + A_{p,N,j} + 2\sum_{i=1}^{N-1} A_{p,i,j} \right) \cos\beta_j \right] \right\} \tag{4.30}$$

Moreover, referring to (4.20), the external surface area of the same clothed person may be obtained as a function of the naked body surface area and the clothing area factor:

$$A_{\mathrm{cl}} = f_{\mathrm{cl}} A_{\mathrm{b}} \tag{4.31}$$

The terms used in (4.25) are absolutely determinate, given the evaluation of the f_{r} parameter.

4.3.4 Practical Methods and Techniques for the Projected Area Factors

The projected area factor in a given direction is defined as the ratio between the area of a human body projected onto a plane perpendicular to the direction, A_{p}, and the effective radiating area of the body, A_{r}:

$$f_{\mathrm{p}} = \frac{A_{\mathrm{p}}}{A_{\mathrm{r}}} \tag{4.32}$$

Regarding its determination, two kinds of methods are currently available: experimental methods, based on actual measured values of the project area of the human body, and numerical simulation methods, based on the reconstruction of the 3D human body numerical model.

4.3.4.1 Experimental Methods

Several experimental methods have been assessed over recent years in an attempt to measure the projected areas of standing and seated people, by means of photographic methods (Guibert and Taylor 1952; Underwood and Ward 1966; Fanger 1970; Calvino et al. 2005; Calvino et al. 2009). These consist of photographing the subject from many directions, with each photograph providing the project area of the body for a given viewing angle. When the project area of the body is known for an adequately large number of angles, all radiation data for the body can be calculated (Fanger 1970). Fanger applied this method to a Scandinavian panel of ten men and ten women. The apparatus employed six mirrors in fixed positions, at steps of 15°, and a movable mirror (see Fig. 4.1). The body (subject) is placed on a platform that can be pivoted around a vertical axis and elevated. By turning the movable mirror, the subject can be photographed with a fixed camera from six different angles (altitude β) on a vertical plane (six mirrors). By rotating the platform 15° at a time, a total of 13 horizontal angles (azimuth α) can be investigated. In total, 78 exposures (i.e., 13 × 6) within a quarter sphere are obtained, the measurement of which is sufficient due to the right/left symmetry of the body, and because the projected area from any two opposite directions is the same. Projected areas, $A_p(\alpha, \beta)$, were then obtained by means of double planimeter.

Once the values of the projected areas, A_p, are obtained, it is possible to deduce the effective radiating area, A_r, and the projected area factor, $f_p(\alpha,\beta)$, as a function of the azimuth and zenith angles. The last parameter is defined as the ratio between the projected area, $A_p(\alpha,\beta)$, and the effective radiating area of the human body, as described in (4.32).

The data of the projected area factor provided by Fanger are reported in Fig. 4.2 (Fanger 1970), for standing and seated postures; these data are currently used in ergonomic evaluations.

In order to take more pictures of subjects at smaller angle steps and verify Fanger's original data for non-Scandinavian people, we have designed and constructed a photographic platform at the Dipartimento dell'Energia of the Università degli Studi di Palermo (Calvino et al. 2005). A procedure for managing the digital images of the human body has been assessed, taking into account the measurement of people's projected areas in standing and seated postures at various azimuth and zenith angles.

This experimental apparatus can be classified as a *single viewpoint method* (Roebuck et al. 1975). It is composed (see Fig. 4.3) of an anthropometer, scales, mechanical equipment, optical apparatus, and a system for producing images.

The optical apparatus comprises a digital camera which is linked to a PC, the aim of which is to generate images and process them with appropriate software. The camera has been selected due to its compatibility with the computer, its graphical resolution, and is capacity to be remotely controlled. The digital camera comprises the camera's objective and the optical sensor; the former is required to reach a compromise between the minimization of the optical distortion of the image and the length of the jib (Calvino et al. 2005). After the images are produced, they are suitably edited to remove objects unrelated with the shape of people being measured. In order to remove any undesired color intensity, which could lower the contrast level of the image, the images are subjected to a filtering process. They are then converted into a gray scale to enhance the manageability of the elaboration process. Finally, the images are converted from the gray to a black and white scale, as shown in Fig. 4.4.

The final step is the computation of the projected area of the subject and this is accomplished by simply counting the black pixels. To convert the values of these data from the number of pixels to surface area (m^2), they are multiplied by the proper conversion factor obtained by the measurement of a sample image, which refers to an object of known dimensions. Starting from the statistical analysis of the anthropometric characteristics of a given group of people, it is now possible to address measurements of projected areas pertaining to subjects statistically representative of this group.

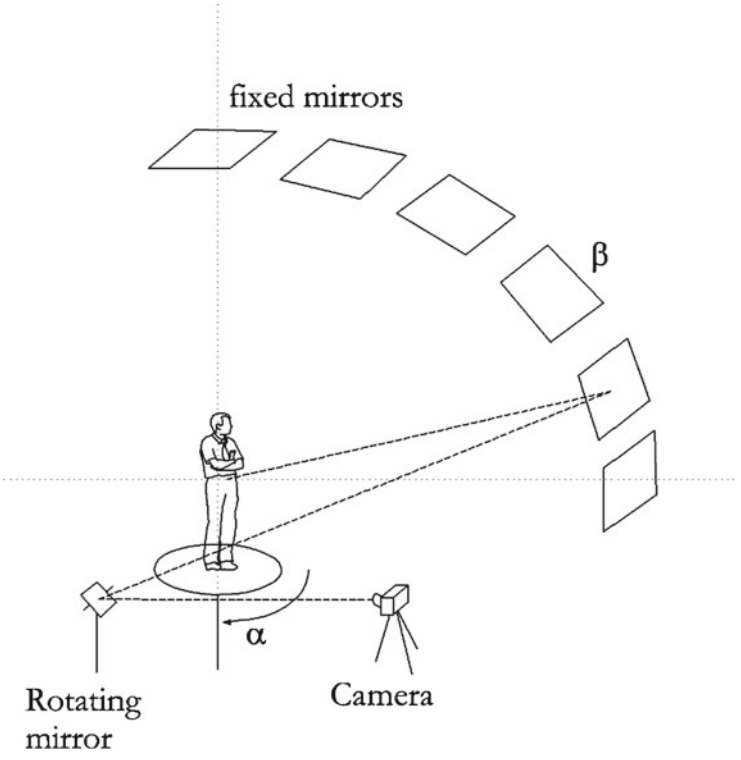

Fig. 4.1 Description of the photographic method utilized by Fanger. The experimental method assessed by Fanger consists of photographing the subject from several directions; the apparatus employed six mirrors in fixed positions, at steps of 15°, and a movable mirror. The subject is placed onto a platform, which can be pivoted around a vertical axis as well as being elevated

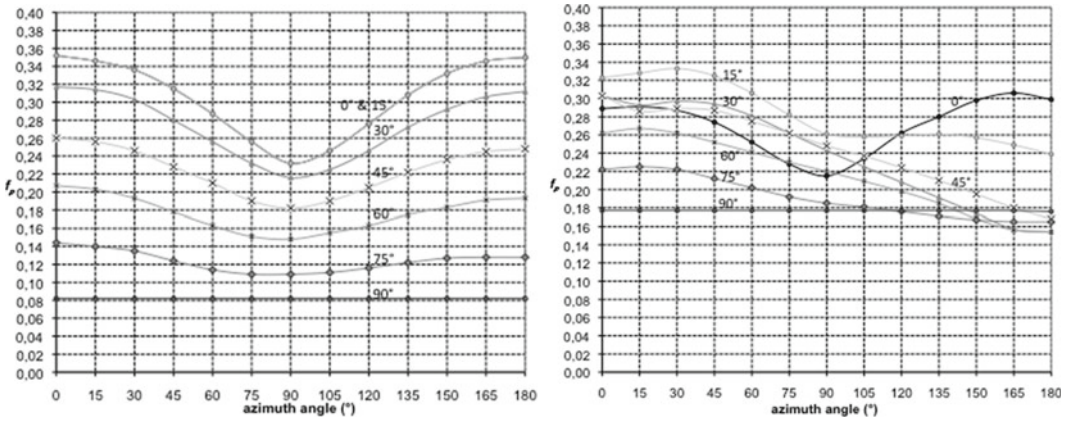

Fig. 4.2 Projected area factors for standing (*left*) and seated (*right*) people. By the values of the projected areas, obtained with experimental methods, it is possible to deduce the projected area factor. The results reported, provided by Fanger for standing and seated postures, are currently used in ergonomic evaluations

Calvino et al. (2009) have selected the subjects whose weight and height values fall within the 10th and the 90th percentiles, with respect to statistical data for the southern Italian population. Table 4.3 shows these limit values for male and female subjects.

The mean values of the projected area factors, f_p, for standing and seated people have been evaluated; they are shown in Fig. 4.5.

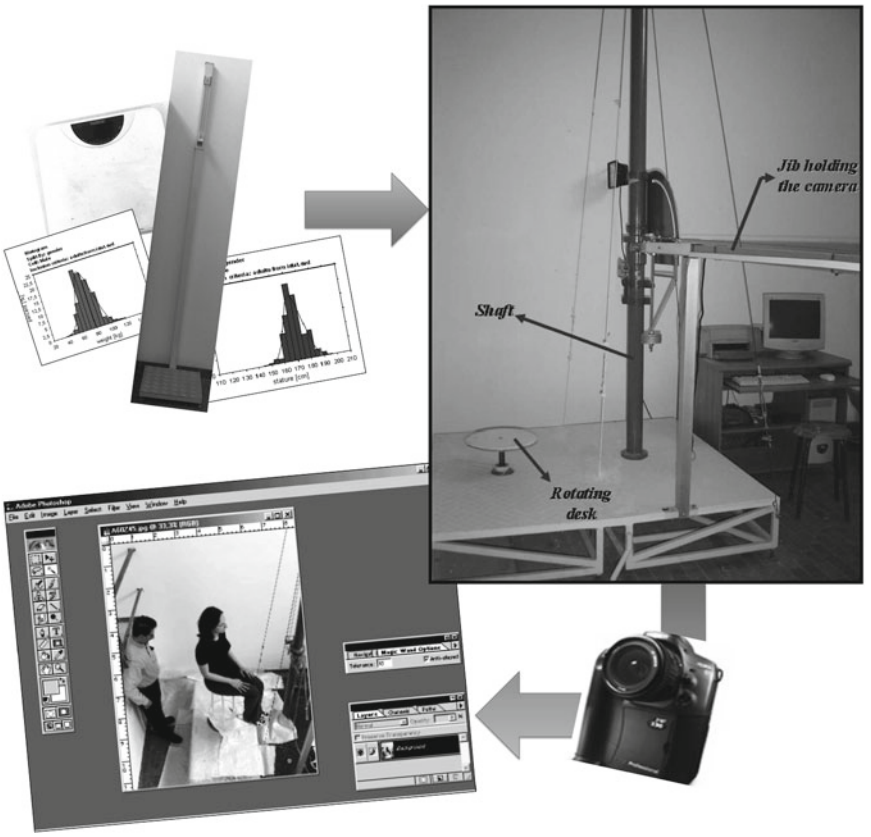

Fig. 4.3 Experimental apparatus. The experimental apparatus realized at the Dipartimento dell'Energia of the Palermo University is composed of an anthropometer, scales, mechanical equipment, optical apparatus, and a system for producing images

4.3.4.2 Numerical Simulation Methods

One of the first researchers to propose a new numerical simulation method for predicting the effective radiating area and the project area of the human body for any posture was Tanabe (Tanabe et al. 2000). This method is based on the solar gain simulation, as proposed by Ozeki et al. (1992, 1997), according to which body shape was obtained by means of commercially available software and divided into 4,396 quadrilateral surface elements, for both standing and seated postures. To derive the project area of the human body, they utilized the parallel ray method introduced by Fanger (1970): "this project area is equal to the surface area of the human body where parallel rays reach directly and which is projected onto a plane perpendicular to the parallel rays" (Tanabe et al. 2000). The projected area is evaluated by utilizing both surface elements A_i and incident angles θ_i of the parallel rays to the surface elements. Thus, the projected area A_p of the human body is obtained by means of the following equation:

$$A_p = \sum_i \gamma_i A_i \cos\theta_i \tag{4.33}$$

where γ_i indicates whether a parallel ray reaches the surface element ($\gamma_i = 1$) or not ($\gamma_i = 0$). The algorithm utilized for calculating the project area of a human body is shown in Fig. 4.6.

Tanabe et al. (2000) applied the algorithm, in Fig. 4.6, to 91 directions of the ray (13 × 7), 13 values of the azimuth angle and seven values of the zenith angle. They utilized (4.27) to evaluate the

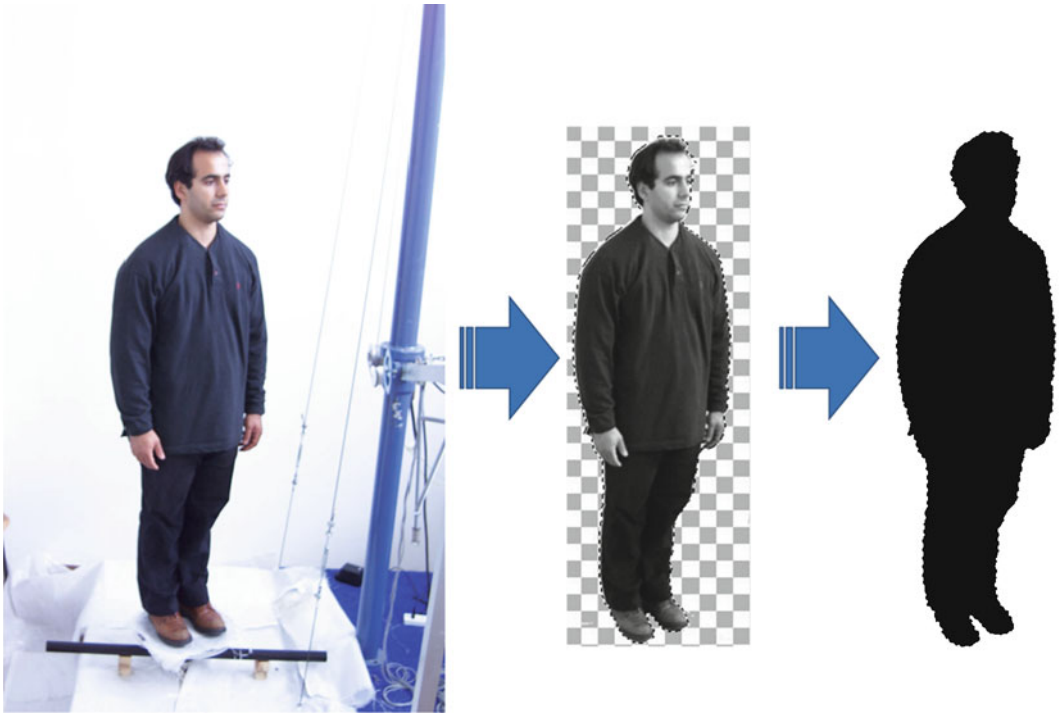

Fig. 4.4 Starting from the actual image, the *gray* and *black-and-white* scales. The images are suitably edited to remove objects unrelated and any undesired color intensity; then they are converted into a *grey* scale and finally to a *black and white* scale

Table 4.3 Weight and height values, corresponding to 10th and 90th percentiles for male (subscript M) and female (subscript F) subjects of the southern Italian population

Percentiles (%)	$Weight_M$ (kg)	$Weight_F$ (kg)	$Height_M$ (cm)	$Height_F$ (cm)
10	62	50	161	153
90	90	79	180	169

This table reports the limit values (10th and 90th percentiles) of weight and height for male and female subjects, with respect to statistical data for the southern Italian population, within which Calvino et al. (2009) have selected the subjects

effective radiation area. Finally, they divided the obtained projected area by the effective radiating area to evaluate the project area factor (see Fig. 4.7).

Another study that utilized a numerical simulation method is that of Lo Curcio (2009), who also utilized commercially available software (Poser®) to obtain a body-shape digital model and to photograph it from several viewing angles with a virtual camera; he thus simulated the photographic method utilized by Fanger. The algorithm utilized for calculating the projected area of a human body is shown in Fig. 4.8.

Lo Curcio applied this algorithm to 12 body shape models (six male and six female) from Italy, Australia and Britain, China, Japan, Germany, and the United States (see Fig. 4.9).

The main anthropometric characteristics of these body shape models are reported in Table 4.4.

Figure 4.10 shows the projected area factors of standing (left) and seated (right) people, referring to the Italian male sample, obtained by Lo Curcio (2009).

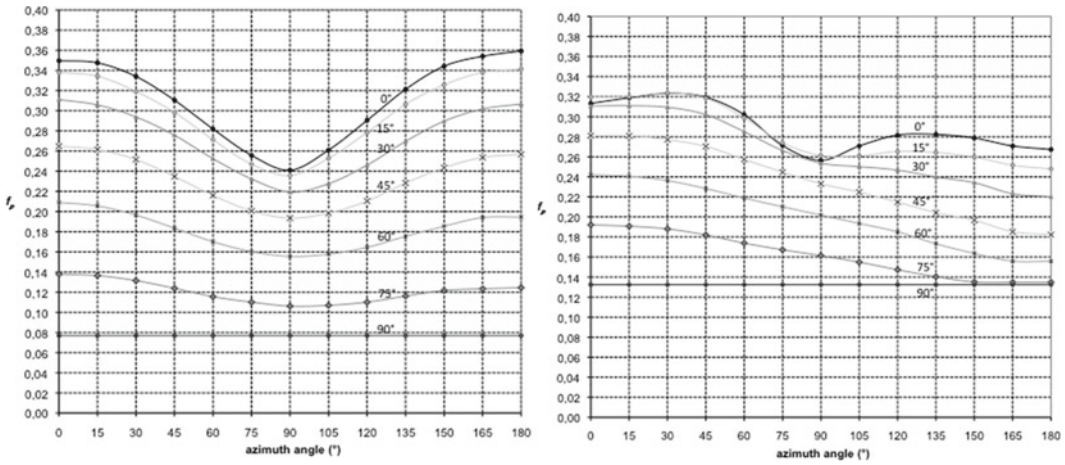

Fig. 4.5 Projected area factors of standing (*left*) and seated (*right*) people referring to the southern Italian population (Calvino et al. 2009). Calvino and his co-workers, have evaluated the mean values of the projected area factors, for standing and seated people, selecting the subjects whose weight and height values fall within the 10th and the 90th percentiles, with respect to statistical data for the southern Italian population

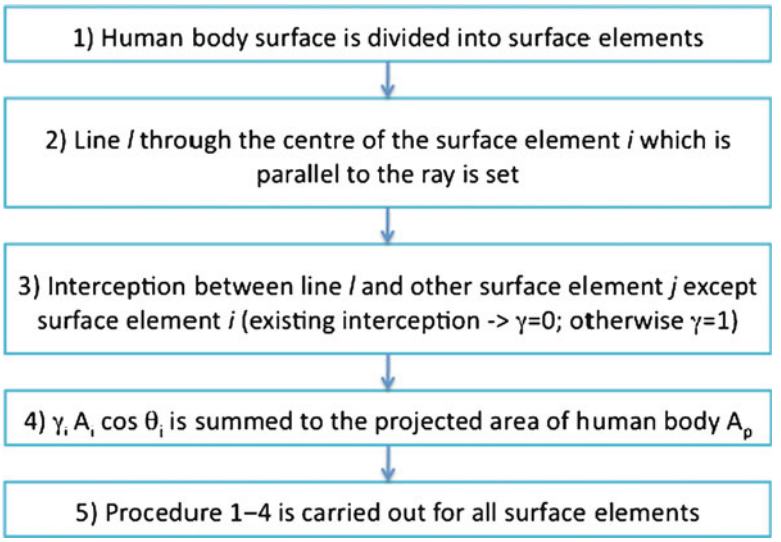

Fig. 4.6 Algorithm for calculating project area of the human body (Tanabe et al. 2000). The Tanabe numerical simulation method for predicting the effective radiating area and the project area of the human body (Tanabe et al. 2000) is based on the solar gain simulation, according to which body shape, obtained by means of commercially available software, is divided into quadrilateral surface elements

4.4 Anthropometric Parameters in the Literature

A comparison of the results of the studies considered in this chapter (Fanger 1970; Tanabe et al. 2000; Calvino et al. 2009; Lo Curcio 2009) reveals a high agreement of the data of the projected area factor in a standing posture; the same cannot be said of data relating to the projected area factor in a

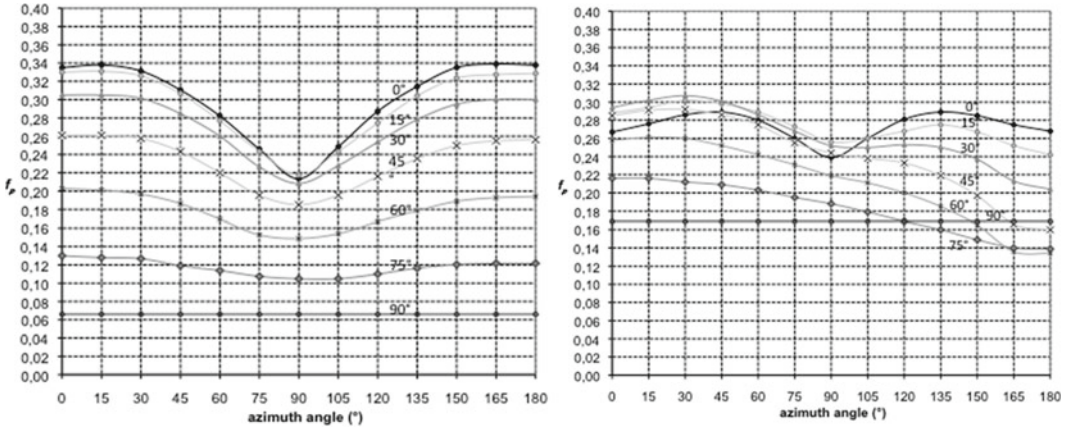

Fig. 4.7 Projected area factors of standing (*left*) and seated (*right*) people, referring to the Tanabe's samples (Tanabe et al. 2000). Tanabe and his co-workers applied their numerical simulation method to 91 directions of the ray, obtaining the mean values of the projected area factors, for standing and seated people

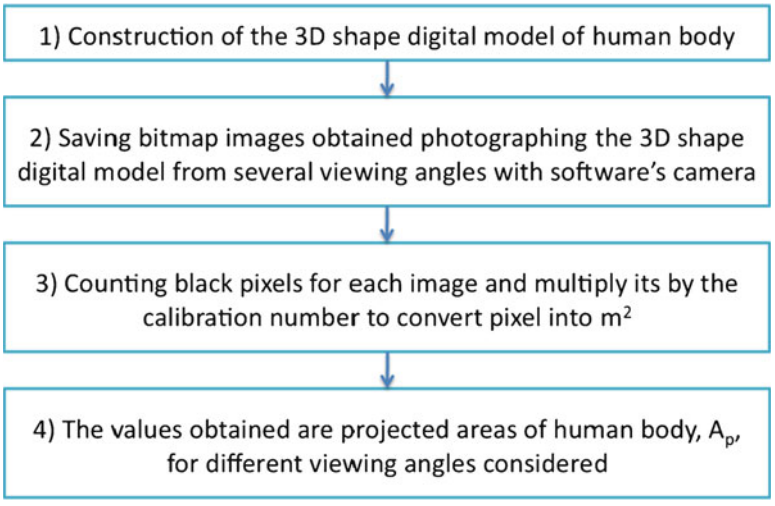

Fig. 4.8 Algorithm for calculating project area of the human body (Lo Curcio 2009). The Lo Curcio numerical simulation method utilizes commercially available software (Poser®) to obtain a body-shape digital model and to photograph it from several viewing angles with a virtual camera; the images are then processed to deduce the projected areas

seated posture. Data for the projected area factors (Fig. 4.2) are available in graphical form (Fanger 1970); nevertheless we can also recall a polynomial algorithm, proposed by Rizzo et al. (1991), for an easy computation of the mean projected area factors for standing and seated people:

$$f_p(\alpha,\beta) = \sum_{i=0}^{4}\sum_{j=0}^{3} A_{ij}\alpha^i\beta^j \tag{4.34}$$

where α and β are azimuth and zenith angles respectively, and A_{ij} are proper coefficients depending on the posture of those involved (see Table 4.5).

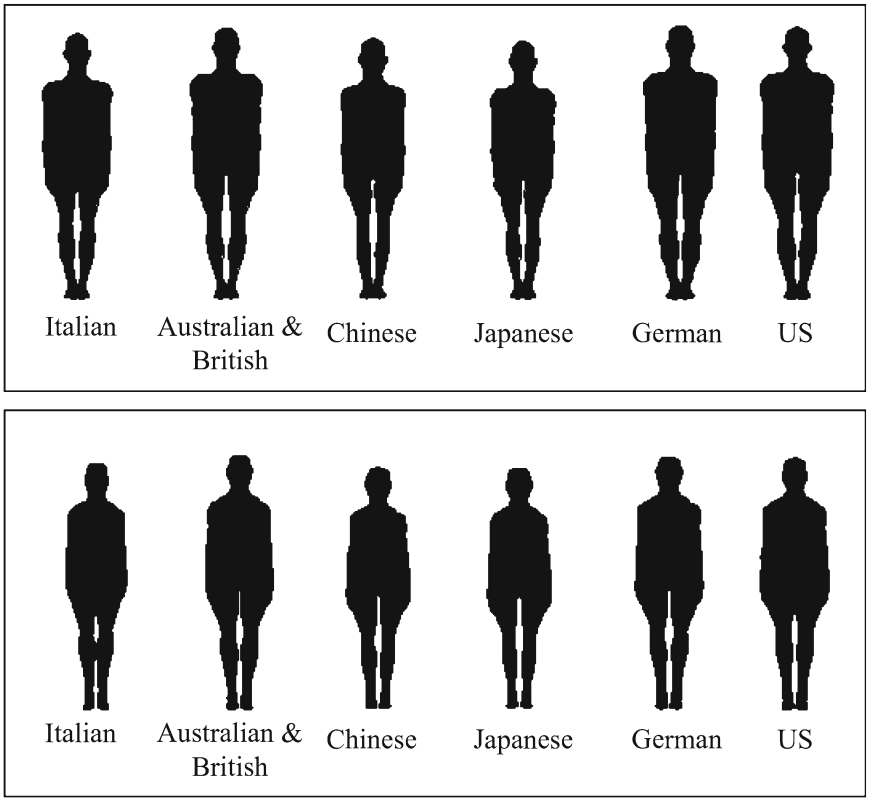

Fig. 4.9 Digital shape model of human body in standing posture of male (*up*) and female (*down*) samples. Lo Curcio applied his algorithm to six male and six female digital body shape models, representative of Italian, Australian and British, Chinese, Japanese, German, and United States ethnic groups

Table 4.4 The main anthropometric characteristics of the body shape of models analyzed by the Lo Curcio's study

	ISO 7250 (1995)	Anthropometric measurements	Italian	Australian & British	Chinese	Japanese	German	US
Male subjects	4.01.02	Stature (mm)	1,714	1,759	1,686	1,685	1,771	1,769
	4.01.04	Shoulder height (mm)	1,405	1,451	1,388	1,368	1,463	1,459
	4.01.05	Elbow height (mm)	1,082	1,109	946	1,061	1,116	1,115
	4.01.07	Crotch height (mm)	834	818	784	790	824	826
	4.01.08	Knee height (mm)	454	468	432	430	475	475
	4.02.09	Shoulder breadth (mm)	459	472	439	448	475	482
	4.02.14	Knee-cap height (mm)	530	508	473	474	511	511
Female subjects	4.01.02	Stature (mm)	1,590	1,632	1,569	1,565	1,655	1,630
	4.01.04	Shoulder height (mm)	1,304	1,339	1,275	1,278	1,358	1,337
	4.01.05	Elbow height (mm)	1,000	1,028	1,027	987	1,043	1,027
	4.01.07	Crotch height (mm)	757	744	723	700	755	743
	4.01.08	Knee height (mm)	431	431	395	395	437	430
	4.02.09	Shoulder breadth (mm)	406	449	394	411	448	457
	4.02.14	Knee-cap height (mm)	483	471	460	458	478	470

This table reports the main anthropometric characteristics of the Lo Curcio's body shape models utilized to evaluated the influence of gender and nationality on the projected area factors and the effective radiating area

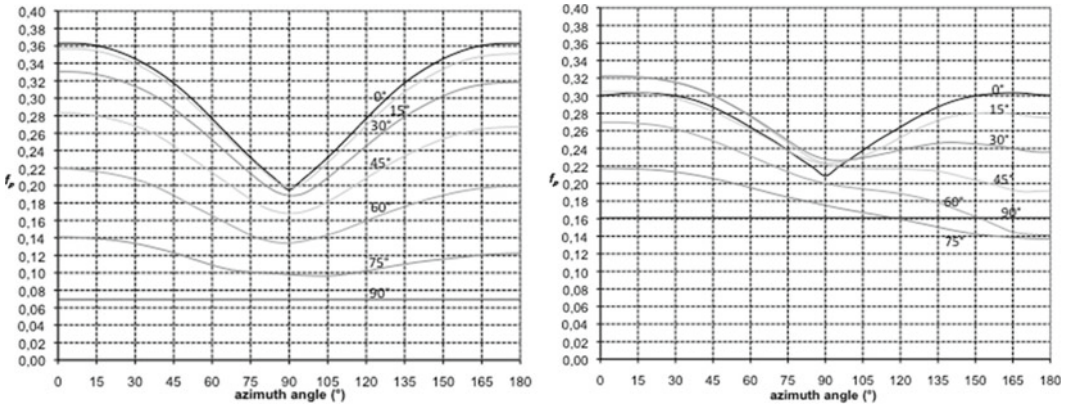

Fig. 4.10 Projected area factors of standing (*left*) and seated (*right*) people, referring to the Italian male sample (Lo Curcio 2009). Lo Curcio has evaluated the mean values of the projected area factors, for standing and seated subjects, male and female, starting from the statistical analysis of the anthropometric characteristics of several ethnic groups; in the figure are reported the results obtained for the Italian, male sample

Table 4.5 Coefficients *Aij* for standing and seated subjects

			i-th index				
	A_{ij}		0	1	2	3	4
Seated posture	*j*th index	0	+2.884 E-01	+2.225 E-03	−9.292 E-05	+9.027 E-07	−2.517 E-09
		1	+2.225 E-03	−7.653 E-05	+4.021 E-06	−4.632 E-08	+1.380 E-10
		2	−5.472 E-05	+7.286 E-07	−6.215 E-08	+7.690 E-10	−2.341 E-12
		3	+1.802 E-07	−1.457 E-09	+3.152 E-10	−4.015 E-12	+1.231 E-14
Standing posture	*j*th index	0	+3.453 E-01	+1.945 E-03	−1.023 E-04	+1.003 E-06	−2.747 E-09
		1	+6.930 E-04	+1.122 E-05	−1.502 E-07	+4.040 E-10	+8.461 E-13
		2	−7.319 E-05	−1.288 E-06	+3.676 E-08	−3.036 E-10	+7.489 E-13
		3	+3.675 E-07	+1.030 E-08	−2.517 E-10	+1.969 E-12	−4.715 E-15

This table reports coefficients A_{ij} of a polynomial algorithm, proposed by Rizzo et al. (1991), for an easy computation of the mean projected area factors for standing and seated people ($f_p(\alpha,\beta)=\sum_{i=0}^{4}\sum_{j=0}^{3}A_{ij}\alpha^i\beta^j$ where α and β are azimuth and zenith angles respectively)

4.4.1 Comparison with Fanger's Data of Projected Area Factors

In this section, we will compare the trends for the projected area factor relating to the standing and seated postures of Lo Curcio's (2009) study with those of Fanger (1970). The analysis reveals that there is a strong agreement between the data of the two studies as regards the standing posture. In particular, the mean excursion of differences is contained in the range (−0.020, +0.020), for male and female subjects, with the exception of the 90° azimuth angle, for which the differences reach values equal to −0.040 for female subjects and −0.030 for male subjects. This consideration highlights an underestimation of the projected area factors in Lo Curcio's study with respect to Fanger's study for positions close to the azimuth angle of 90°. This is probably due to the absence of hair in Lo Curcio's digital model study. However, the analysis of data relating to the seated posture reveals a significant agreement between the two studies, with the exception of the 30° zenith angle, for which the difference reaches a value of 0.080 (for an azimuth angle of 180°). This latter observation indicates a significant disagreement only for a zenith angle of 30° for the seated posture, which has also been demonstrated by the studies of Tanabe et al. (2000) and Calvino et al. (2009).

Table 4.6 The effective radiating area and the effective radiating area factor for standing and seated postures

		Literature reference				
Posture	Parameters	Rizzo et al.	Tanabe et al.	Fanger et al.	Horikoshi et al.	Miyazaki et al.
Standing	A_r (m^2)	1.424	1.276	1.262	1.312	1.317
	f_r (–)	0.806	0.744	0.725 ± 0.013	0.803 ± 0.005	0.834
Seated	A_r (m^2)	1.300	1.176	1.211	1.214	1.224
	f_r (–)	0.735	0.691	0.696 ± 0.017	0.740 ± 0.012	0.775

This table reports the effective radiating area and effective radiating area factor for standing and seated postures, as available in the current literature

Table 4.7 The effective radiating area and effective radiating area factor for standing and seated postures (male subjects) (Lo Curcio 2009)

		Australian					
Posture	Parameters	British	Italian	Chinese	Japanese	German	US
Standing	A_r (m^2)	1.388	1.253	1.210	1.197	1.449	1.460
	f_r (–)	0.771	0.784	0.790	0.788	0.777	0.774
Seated	A_r (m^2)	1.326	1.196	1.153	1.145	1.361	1.381
	f_r (–)	0.737	0.748	0.752	0.753	0.730	0.732

This table reports the effective radiating area and effective radiating area factor for standing and seated postures for male subjects as a function of posture and nationality, obtained by Lo Curcio (2009). This results regard subject characterized by the main anthropometric characteristics reported in Table 4.4

4.4.2 Influence of Gender and Nationality on Projected Area Factors

A comparison of the available data relating to project area factors pertaining to people of different gender and nationality reveals a high level of agreement. Indeed, the observed excursions of differences of project area factors are very low; the mean ranges of excursions are:

- (–0.017, +0.017) varying the nationality, for standing posture (reference: Italian sample);
- (–0.018, +0.014) varying the nationality, for seated posture (reference: Italian sample);
- (–0.011, +0.017) varying the gender, for standing posture;
- (–0.023, +0.028) varying the gender, for seated posture.

The projected area factor thus does not depend significantly on the different anthropometric characteristics existing between the various ethnic groups worldwide. Furthermore, passing from standing to seated posture, the range of excursion of the projected area factor remains almost unvaried with changing nationality, while it shows a slight increase with varying gender. As a general consideration, these changes are mainly highlighted in the sitting posture and are probably due to the geometric differences between male and female subjects.

4.4.3 Comparison of Available Effective Radiating Area Values

We will proceed in this section, to compare values of effective radiating area, as available in the current literature. A comparative summary of the effective radiating area and effective radiating area factor for standing and seated postures are reported in Tables 4.6–4.8.

Table 4.8 The effective radiating area and effective radiating area factor for standing and seated postures (female subject) (Lo Curcio 2009)

Posture	Parameters	Australian British	Italian	Chinese	Japanese	German	US
Standing	A_r (m^2)	1.254	1.107	1.074	1.082	1.263	1.261
	f_r (–)	0.802	0.810	0.824	0.822	0.809	0.794
Seated	A_r (m^2)	1.181	1.020	0.991	1.013	1.168	1.182
	f_r (–)	0.756	0.747	0.760	0.769	0.748	0.744

This table reports the effective radiating area and effective radiating area factor for standing and seated postures for female subjects as a function of posture and nationality, obtained by Lo Curcio (2009). This results regard subject characterized by the main anthropometric features reported in Table 4.4

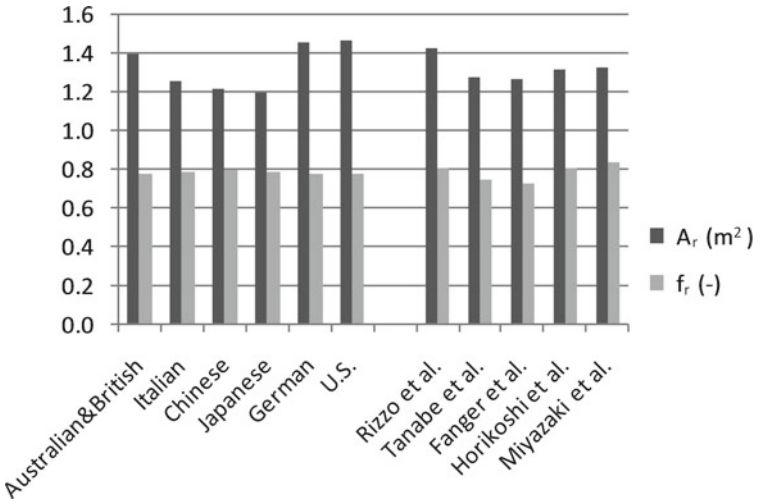

Fig. 4.11 The effective radiating area and the effective radiating area factor versus nationality (only male subjects) and literature studies (standing posture). The graph of the effective radiating area and the effective radiating area factor for male subjects in standing posture shows a correlation of the data from Lo Curcio's study and data currently available in literature

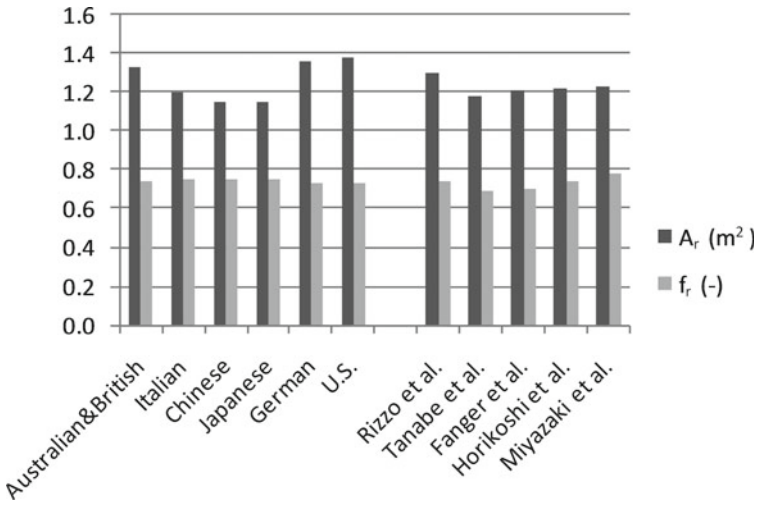

Fig. 4.12 The effective radiating area and the effective radiating area factor versus nationality (only male subjects) and literature studies (seated posture). The graph of the effective radiating area and the effective radiating area factor for male subjects in seated posture shows a correlation of the data from Lo Curcio's study and data currently available in literature

In order to enhance data comparison, we report only graphs of the effective radiating area and the effective radiating area factor as a function of gender, posture and nationality (see Figs. 4.11–4.14).

These graphs show a correlation of the data from Lo Curcio's study, for male subjects, using data currently available in literature.

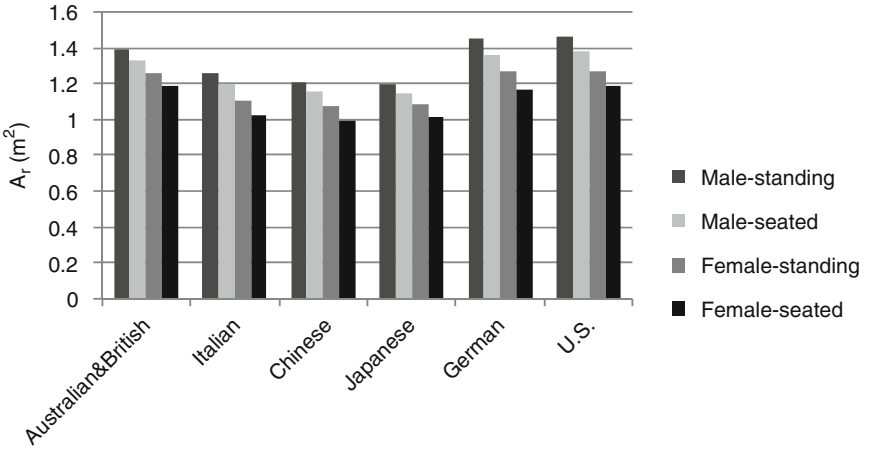

Fig. 4.13 The effective radiating area versus gender, posture, and nationality. The graph of the effective radiating area for male and female subjects, in seated or standing posture, shows a correlation of the data from the different people analyzed in the Lo Curcio's study

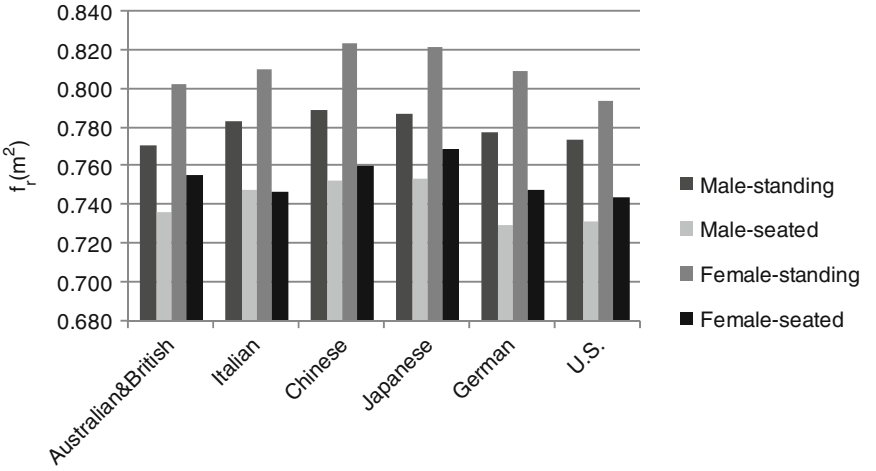

Fig. 4.14 The effective radiating area factor versus gender, posture and nationality. The graph of the effective radiating area factors for male and female subjects, in seated or standing posture, shows a correlation of the data from the different people analyzed in the Lo Curcio's study

4.5 Applications to Other Areas of Health and Disease

Although the previous description refers to standing and seated postures, the analysis of the anthropometric parameters can be extended to other situations, where people are mainly in a lying posture, as in hospitals. The utility of the relationship for the calculation of the radiative exchanges of an irradiated subject placed in a given enclosure and the importance of the knowledge of anthropometric parameters will now be illustrated by means of a numerical example.

Consider a naked resting subject, lying on the back, placed in a moderate thermal uniform environment with air temperature and mean radiant temperature of 26°C and a low speed of air

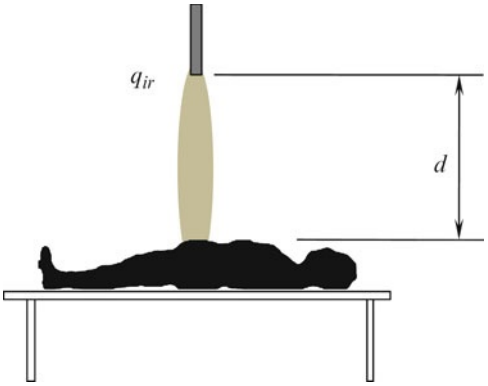

Fig. 4.15 Sketch of subject about to undergo surgery. The case for a patient about to undergo surgery may be considered as a naked resting subject, lying on his back, placed in a moderate thermal uniform environment, with a lamp placed in front of him

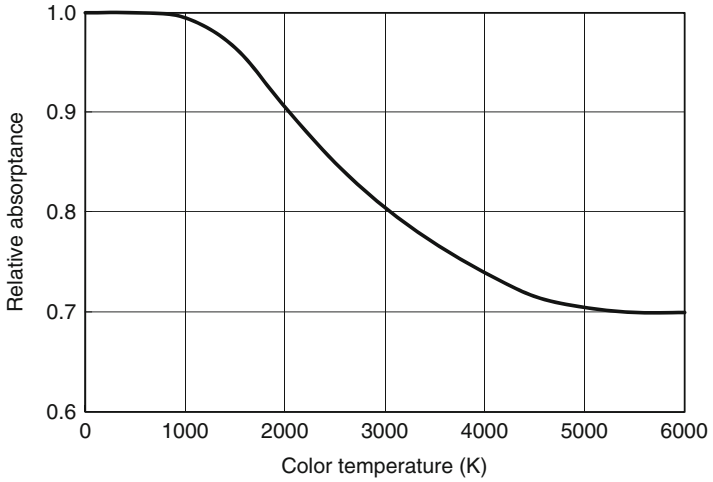

Fig. 4.16 Relative absorptance of skin at various color temperatures (ASHRAE 1989). The relative absorptance of skin depends on the color temperature of the emitting source

(i.e., less than 0.15 m/s). A lamp with a color temperature of 3,000 K is positioned in this environment whose intensity of the emitted radiation at the distance of 1 m, $q_{ir,1m}$, is equal to 150 W/m^2. The lamp, a high intensity heat source, is placed in front of the subject at a distance varying from 1 to 4 m; this may be the case for a patient about to undergo surgery (see, e.g., Fig. 4.15).

The positions of the human body and the lamp enable us to adopt the view factor values for standing people and, consequently, the pertinent equation for the radiative human body thermal balance.

In order to evaluate the total thermal radiation leaving the body for unit of body area, (4.35) is used, dividing (4.7) by the naked body surface area:

$$\frac{R}{A_b} = \sigma \varepsilon f_r \left[\left(t_{cl} + 273 \right)^4 - \left(\overline{t}_r + 273 \right)^4 \right] - \alpha_{ir} f_p q_{ir} \tag{4.35}$$

In (4.34), the clothed surface temperature, t_{cl}, may be obtained by means of a balance of the dry component of the energy exchanged between the external surface of the body and the environment (Fanger 1970). Emissivity, ε, and the effective radiating area factor, f_r, have been assumed equal to 0.97 and 0.696, respectively; the projected area factor, f_p, has been set at the value of 0.35 (valid for a standing subject with altitude and azimuth angles of 0°); and the relative absorptance of skin, α_{ir}, has been assumed to be equal to 0.8, with reference to Fig. 4.16.

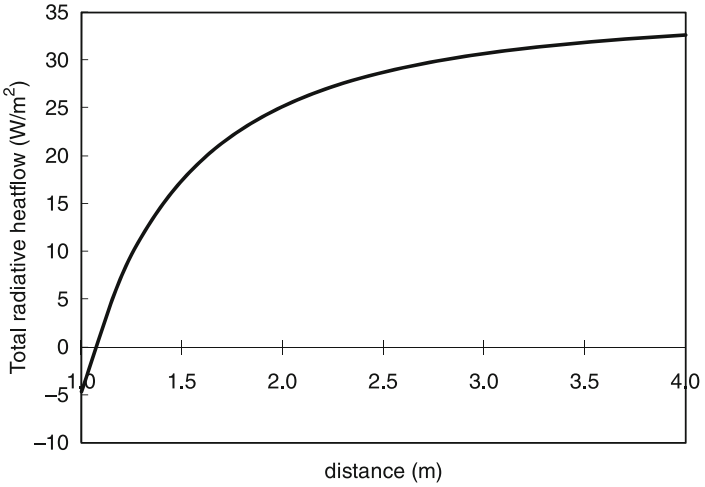

Fig. 4.17 Total thermal radiation as a function of the distance between the body and the high intensity heat source. The figure shows as, when a lamp is near to the subject, the total radiative heat flow is a gain, whereas, when a lamp is further away, the radiative heat flow is a dispersion

Moreover, the dependence of the radiant flow on the distance of the lamp has been evaluated by the following equation:

$$q_{\mathrm{ir}}(d) = \frac{q_{\mathrm{ir},1m}}{d^2} \tag{4.36}$$

Finally, the behavior of the radiative heat flow leaving the body of the irradiated subject is reported in Fig. 4.17, as a function of the distance between the subject and the lamp.

In Fig. 4.17, the total radiative heat flow by the subject toward the environment is assumed as positive, while the total radiative heat flow reaching the human body from the environment is assumed as negative. When the lamp is near the subject, the total radiative heat flow is a gain; when the lamp is further away, this radiative heat flow is considered dispersion.

These considerations definitely confirm the crucial importance of the knowledge of human body radiative parameters (particularly, the projected and the effective radiating area factor) in order to evaluate radiative heat flows and the thermal sensation of a subject. Similar considerations can be made for clothed persons by taking into account the importance of other human body radiative parameters, which the clothing area factor will markedly increase.

Summary Points

- The thermal sensation of a subject in a confined environment is related to the need of the human body to arrive at a homeothermic state at body core level.
- In order to evaluate the thermal condition of a subject in a confined environment, a suitable set of radiation data referring to the human body anthropometry is required.
- The main parameters facilitating the evaluation of the convective and radiative exchanges between the human body and the environment are:
  - The body surface area;
  - The clothing area factors;
  - The effective radiation area factor;
  - The projected area factors.

- A detailed description of the practical methods and techniques for determining the relevant human body anthropometry parameters has been described by pointing out the main features and the ease or otherwise of their suitable application.
- The results of a new study concerning the determination of the differences of peoples of various gender and nationalities on the radiation anthropometric parameters has been outlined.

Key Points of Homeothermic State

- The thermal comfort of people in confined, thermally moderated environments is considered to be of paramount importance today in order to guarantee optimal working and living conditions to the occupants of any given building. The conditions for ensuring indoor comfort involve a relevant consumption of energy, required by HVAC systems in winter (heating) and summer (cooling). Thus, suitably addressing the thermal conditions of buildings could result in a significant primary energy saving.
- In order to evaluate the thermal body (thermo-hygrometry) comfort conditions at a design level, specific algorithms, which obtain human body thermal balance in a given indoor environment, are required. This calls for knowledge of various important anthropometric parameters, particularly in relation to the radiative heat exchange of the human body, which represents one of major factors in the thermal balance of human body.
- Algorithms, practical methods and techniques for obtaining such parameters (the body surface area, the clothing area factor, the effective radiating area factor and the project area factors) have been reported in this chapter.
- The potential of these parameters to address new areas of health and disease, particularly in hospitals and buildings where people assume predominantly supine postures, has also been analyzed.

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Chapter 5
Optical and Electromagnetic Shape-Capturing Systems for Limb Anthropometrics

Mark D. Geil

Abstract The allied health disciplines of prosthetics and orthotics require specialized knowledge of anthropometrics and have consequently developed instrumentation and systems to capture shapes of specific body segments. This instrumentation has found application for digital shape capture and subsequent model modification for intact and residual limbs as well as for the head and torso. Two primary technologies have emerged. Optical scanners are largely non-contact and use combinations of digital cameras, lasers, and lights to capture the surface geometry of a limb. Electromagnetic field-based systems are contact scanners that require the entire surface of the limb segment to be traced using a stylus. The accuracy of both systems has been established versus known measures and conventional hand-tool anthropometrics. Furthermore, the use of systems for routine collection of anthropometrics for all patients has been proposed even in cases when the instrumentation is not used as part of the process of fabrication of a prosthesis or an orthosis. Additional utility is possible with the use of the digital caliper function of magnetic field scanners. In particular, the collection of body segment parameters that is a necessary part of clinical gait analysis is significantly more efficient with the digitizer. An additional practical application of the systems is centralized fabrication of prosthetic and orthotic components. In conclusion, specialized equipment for limb digitization has benefitted the disciplines of prosthetics and orthotics and could have ancillary benefits in other fields as well.

Abbreviations

CAD/CAM	Computer aided design/Computer aided manufacturing
CNC	Computer numerical control
CAPOD	Computer aided prosthetic and orthotic design
BSP	Body segment parameter

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_5,

5.1 Introduction

While anthropometry is already important in health care disciplines that monitor growth or changes in limb shape and size, its importance increases when a device must be fabricated to provide a customized, intimate fit with the limb. In particular, the allied health disciplines of prosthetics and orthotics require detailed information about human extremities, including residual limbs following amputation and congenitally malformed limbs (Table 5.1). Such information must contain three-dimensional data including not only overall limb volume, contours, and dimensions, but also the location of certain skeletal and soft-tissue landmarks. In addition, specific conditions require anthropometric data for the head and torso.

Historically, prosthetists and orthotists have found ways to capture anatomical shapes using simple tools and a minimum of measurements. Casting has been and still is used to produce a three-dimensional negative impression of an anatomical segment, from which a positive plaster model can be produced, modified, and used for the fabrication of an orthosis or a prosthetic socket (Fig. 5.1).

Table 5.1 Key features of prosthetics and orthotics

Prosthetics	Orthotics
Prostheses are devices that replace a missing body part	Orthoses, or braces, are devices that augment an existing body part
Prostheses are fabricated and fit by a prosthetist	Orthoses are fabricated and fit by an orthotist
Limb prostheses replace arms or legs, and may include joints including knees or elbow	Limb orthoses may be used to control range of motion, modify shape, or transfer forces
Limb loss may occur as a result of congenital deformity or dysfunction, trauma, or disease	Limb orthoses may be necessary when muscle function is compromised, resulting in either too much or too little tone

These key facts provide an introduction to the related allied health care disciplines of prosthetics and orthotics

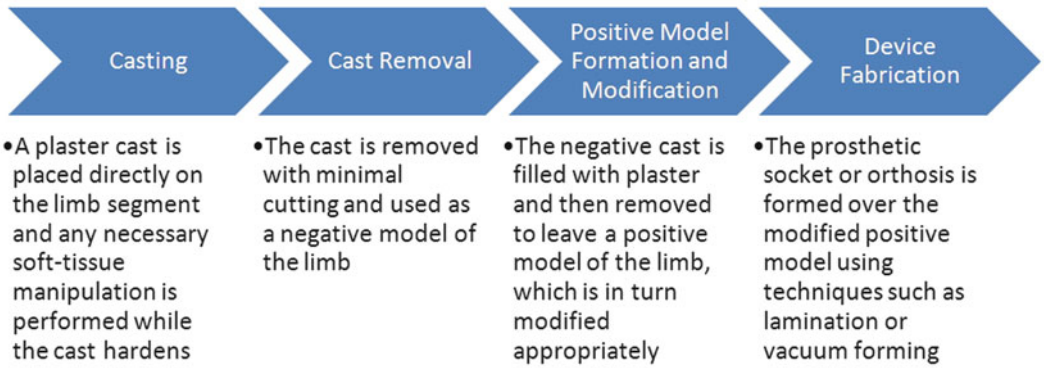

Fig. 5.1 Fabrication flow chart. Fabrication process in prosthetics and orthotics using traditional limb capture techniques

In the process of seeking enhancements to this traditional process, technologies in computer aided design and manufacturing (CAD/CAM) were modified for clinical use in prosthetics and orthotics (Boone and Burgess 1989; Houston et al. 1992). CAD/CAM rectification is intended to accomplish several tasks: capturing the three-dimensional anatomical shape, allowing software-based modification of that shape, and producing output data suitable for automated manufacture. Ancillary benefits of the process are related to anthropometrics research; most notably, the process generates a digital model of the shape from which any required anthropometric dimension can be obtained.

Although development continues in all aspects of CAD/CAM in prosthetics and orthotics, technologies for digital capture of anatomical shapes have outpaced technologies for automated fabrication of orthoses or prosthetic sockets. Consequently, practical application of CAD/CAM often entails automated manufacture of a positive model upon which the final step in Fig. 5.1 must still be performed, as opposed to direct automated manufacture of a finished socket or orthosis (Smith and Burgess 2001).

This chapter will focus on technologies and techniques for digital shape capture of the human extremities, with a focus on digitization of the residual lower limb of an individual with limb loss for the purpose of prosthetic socket fabrication.

5.2 Limb Anthropometrics

Specific anthropometric measurements are important in prosthetics and orthotics because of the clinical needs of individual patients. Very specific limb dimensions might be important for needs as diverse as increased force application for skeletal control or pressure relief for comfort. Common clinical needs necessitating specific anthropometric measurements are detailed in Table 5.2.

These clinical needs require detailed and accurate understanding of measures associated with the complete limb, such as residual limb volume, alongside specific measures of one anatomical aspect with respect to another, such as the linear distance from the distal end of the residual limb to the center of the patella.

With a goal of clinical efficiency, prosthetists and orthotists have developed means to fabricate devices that meet the varied clinical needs of patients without quantifying specific anthropometric data. Before digitization was available, techniques were developed to transfer anatomical landmarks to the positive model and then modify the model to add or reduce volume based on clinical experience. These techniques persist such that a large percentage of facilities do not routinely record a wide array of anthropometric measurements. This practice impedes post-hoc research in prosthetics and orthotics, and CAD/CAM techniques have been proposed for routine data collection, even when conventional fabrication techniques are used (Geil 2007).

Table 5.2 Anthropometric examples

Category	Clinical need	Example of required anthropometrics
Prosthetic socket	Comfort, pressure relief over skeletal prominences	Height of fibular head over cross-sectional limb circumference
Prosthetic socket	Suspension and weightbearing control	Location of patellar tendon relative to patella and distal aspect of the residual limb
Spinal Orthosis	Prevention of curve progression in scoliosis	Spinal curvature and height of specific vertebrae

Examples of anthropometric requirements that might be required to address specific clinical needs in prosthetics and orthotics

5.3 Technologies for Digital Shape Capture

Technologies designed specifically for use in prosthetics and orthotics have developed into two primary platforms: magnetic field and optical. Electromagnetic field-based digitization involves tracing the contour of the limb, while optical digitization requires little to no contact with the limb. Each approach has advantages and disadvantages in terms of ease of use, accuracy, repeatability and clinical utility. Both arrive at similar sets of anthropometric outcomes.

5.3.1 Magnetic Field-Based Digitization

Magnetic-field based systems for the digital capture of human limb shapes typically use three components: a magnetic field emitter, a stylus, and a reference field sensor (Fig. 5.2). The reference sensor is attached to the limb to provide a local coordinate system. Limb anthropometrics are initially defined with respect to this limb coordinate system to allow for the possibility of limb movement. The stylus is then used to identify overall limb space and orientation (anterior, posterior, medial, and lateral aspects). To capture limb volume and contours, the limb surface is traced with the stylus. Finally, anatomical landmarks of interest are identified with the stylus.

5.3.2 Optical Digitization

Optical scanners use different combinations of cameras, light-emitting diodes, and eye-safe lasers to capture the shape of the limb (Fig. 5.3). These systems usually perform the shape capture process in less time than magnetic field contact scanners. Digital camera-based optical scanners usually involve the application of a material to the limb. In some cases, a white sleeve is placed over the limb,

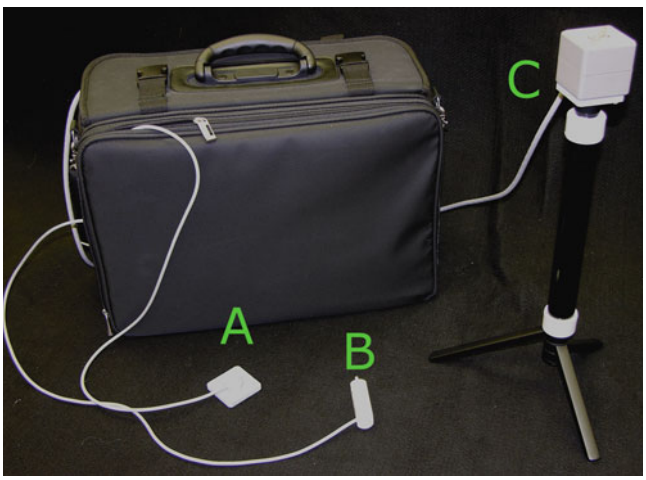

Fig. 5.2 Magnetic field-based instrumentation. Instrumentation for digital shape capture based on magnetic field-based sensors. Components are labeled as follows: (**a**) reference field sensor; (**b**) stylus; (**c**) magnetic field emitter

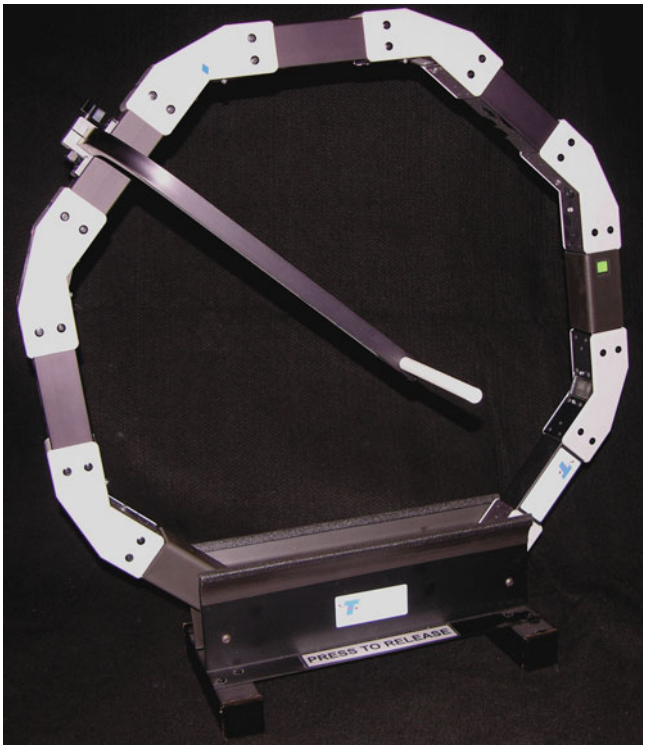

Fig. 5.3 Optical instrumentation. Optical instrumentation for limb anthropometry. The ring shown emits parallel bands of light on a limb and cameras record the distance between lines

and the scanner system uses lasers or light emitting diodes to project a fixed array of stripes or a grid onto the sleeve. In some cases, reflective markers placed on the surface identify contours.

In both scenarios, human limbs are most often mathematically modeled as closed cylinders, and the same software can be used to observe or modify models obtained through either method. Clinically, an important distinction between the methods is that non-contact methods are usually faster, but they do not allow the clinician the opportunity to manipulate soft tissue during the shape capture process.

5.4 Anthropometric Outcomes

Completed digital models of the limbs enable the collection of multiple anthropometric measures. Digital models are produced in file formats appropriate for computer numerical control (CNC) milling machines or rapid prototyping machines, and these files afford the measurement of linear dimensions, circumferences, and volume in any direction. Discipline-specific front–end software used for model modification displays a limited set of measurements; nonetheless, readily available outcomes are still vast. Standard measurements include (Fig. 5.4):

- Circumference at any level perpendicular to the long axis of the limb
- Anterior–Posterior diameter at any level perpendicular to the long axis
- Medial–Lateral diameter at any level perpendicular to the long axis
- Linear distance from any point on the model surface to the distal end parallel to the long axis

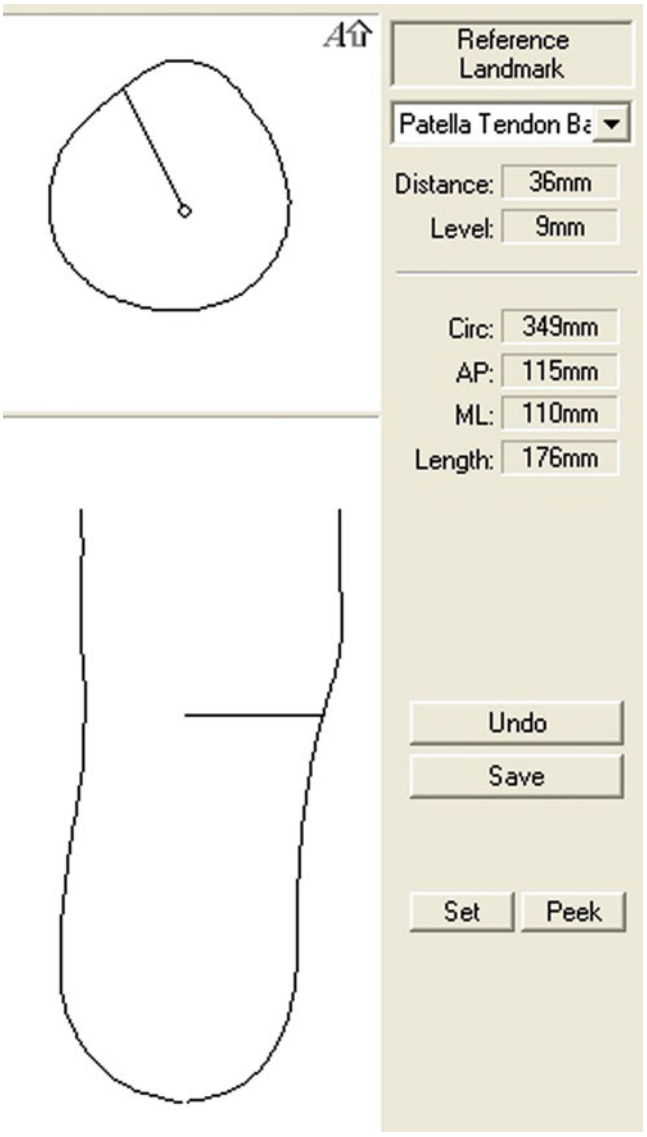

Fig. 5.4 Measurements within software. Basic anthropometric measurements reported for a model of the residual limb of an individual with transtibial amputation on Omega Tracer software (version 11.0, Ohio Willow Wood, Mt. Sterling, Ohio, USA)

Another important clinical outcome is limb volume, since closeness of fit is essential for component function. While clinicians do not routinely quantify volume, temporal fluctuations in volume for a given patient are important. In prosthetics, socks are used to fill space between the prosthetic socket and the residual limb, and the number of sock ply has developed as an indirect measure of volume.

Perhaps one reason that volume has not been routinely measured is the difficulty in measurement and the equipment required. Magnetic resonance imaging and related medical imaging techniques can be used to assess volume, but the process and equipment are expensive. Water displacement has been used as a primary tool and to validate other tools (Fernie and Holliday 1982; Smith et al. 1995),

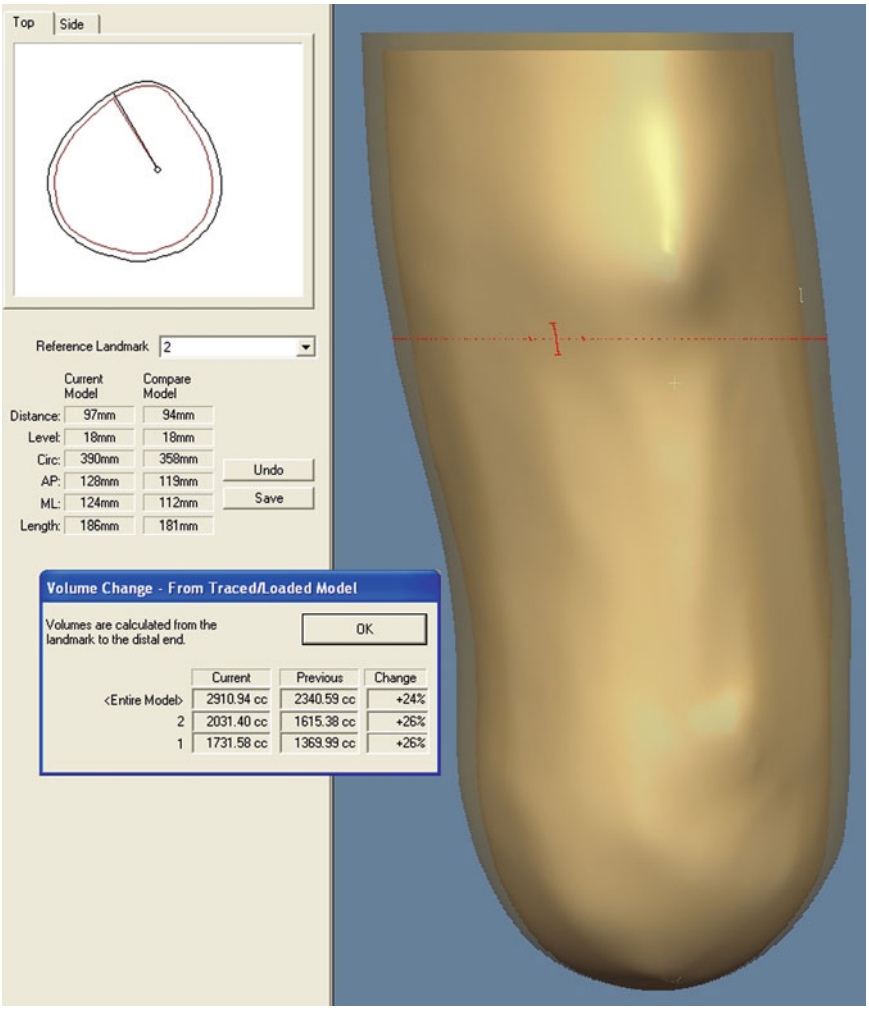

Fig. 5.5 Volume comparison in software. Comparison of volume for two residual limb scans on Omega Tracer software (version 11.0, Ohio Willow Wood, Mt. Sterling, Ohio, USA). Volume difference is displayed visually and reported numerically

but it is cumbersome. Electrical bioimpedance has been used to assess residual limb volume within the prosthetic socket in individuals with amputation (Sanders et al. 2007); like all of these techniques, it requires specialized equipment.

Because limb volume fluctuation within an individual is of such importance, a useful feature of software customized for digital shape capture in prosthetics and orthotics is the ability to visualize volume fluctuation and to add or remove volume in a model (Fig. 5.5).

In some cases, the volume measurement is not the most essential outcome, but it is related to the essential outcome. Prosthetic sockets must employ some type of suspension to remain affixed to the residual limb. Designs have evolved through history, and newer sockets have been developed with a different suspension philosophy than their predecessors. Socket designs that originally reduced volume at certain anatomical landmarks to apply active pressure have been augmented or replaced by total surface bearing sockets that employ an additional gel liner interface, hydrostatic sockets intended to equalize pressure over the entire residual limb, and sub-atmospheric pressure suspension

systems which employ vacuum to maintain suspension. With these approaches, accurate measure of the contours and shape of the limb are paramount. The fact that digitized limb models permit the calculation of the curvature of the surface of the limb at any point (Vannah et al. 2000) may become more important as socket designs continue to necessitate very close fit.

5.5 Accuracy of Digital Shape Capture

The accuracy of models that result from digital shape capture can be assessed using anthropometry. Comparisons must be made between the model and a known standard. For the sake of simplicity, Lilja et al. measured accuracy using a cylinder (Lilja and Oberg 1995). For measures of volume using a Swedish Computer-Aided-Prosthetic and Orthotic-Design (CAPOD) System, a consistent systematic error of 2.5% was identified. Because general volume modifications are easily accomplished within software, such a general error is not a major clinical concern. The same study identified random error of 0.5%, which is comfortably small for most clinical applications. Johansson and Oberg compared two CAD systems for precision and accuracy and found results similar to Lilja et al. for the CAPOD system and larger random errors for the ShapeMaker system, but still less than 1.3% (Johansson and Oberg 1998).

Geil focused on common clinical anthropometric measurements to assess the precision, accuracy, and reliability of two types of systems: a contact and non-contact scanner (Geil 2007). This research also investigated operator experience, comparing a group of experienced practitioners to a group of prosthetics students. In general, measurement results were consistent across systems and operators, and the mean difference in measurement between the systems was less than 1 cm. A specific source of error was identified in the use of the optical non-contact scanner to determine limb diameter. If the scanner was held at an angle to the line perpendicular to the long axis of the limb, and this deviation was not corrected in the model, diameters were overestimated as the hypotenuse of a triangle formed based on the angle of deviation (Fig. 5.6).

Geil's work suggests that modern CAD/CAM systems can be of clinical value for the purpose of routine collection of anthropometrics, even if they are not used for limb modeling, rectification, or device fabrication.

5.6 Applications to Other Areas of Health and Disease

Clinical gait analysis is an important procedure that provides insight into movement disorders that is not otherwise available through observation. Human walking is dynamic and complex, and specialized equipment is required to record human motion, model the segments of the human body, and reconstruct the motion paths in three dimensions for subsequent analysis (Perry 1992).

In its relatively young history, a reasonably standard approach to modeling of the human body has emerged. In general, three-dimensional kinematics are recorded with a minimum of three markers per segment. The lower extremities are modeled by rigid segments for the foot, lower leg or shank, upper leg or thigh, and pelvis. Shared markers near joint axes of rotation minimize the total number of markers required. These markers must be combined with information about the geometry of each segment in order to accurately model joint centers, segment centers of mass, segment lengths, and segment moments of inertia. Specific anthropometric data called body segment parameters (BSPs) provide this geometric information (Vaughan et al. 1992).

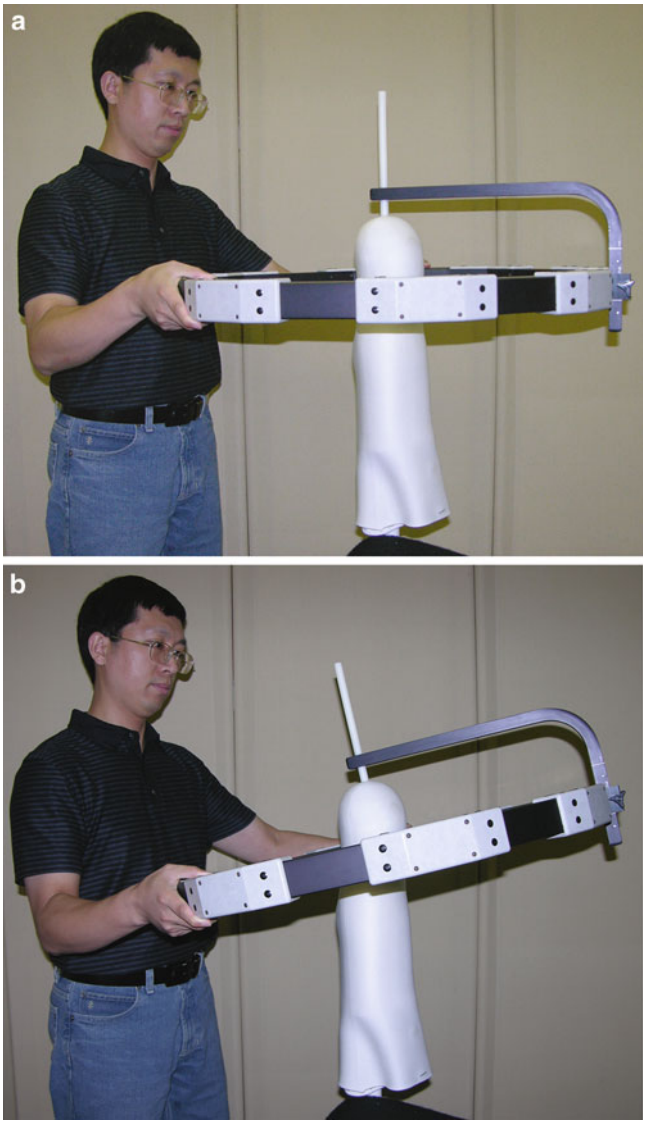

Fig. 5.6 Source of error in shape capture. Optical scanner positioned on a model of a residual limb, illustrating alignment of scanner perpendicular to the long axis of limb (**a**) and oblique to the long axis of limb (**b**). If not subsequently corrected in software, the angle in (**b**) will introduce errors in limb diameter and circumference measurements

In practice, BSPs are collected at the beginning of a gait analysis session. The number of measurements required depends on the model used and can be fairly large. A largely untapped utility present in contact scanners for digital shape capture in prosthetics and orthotics has application in clinical gait analysis. Because magnetic field-based systems employ two independent sensors in the same magnetic field (one to establish the limb coordinate system and one for contact scanning), the linear distance between the two sensors can be readily determined. In this technique, the two sensors function as ends of digital calipers (Fig. 5.7). In our laboratory, we have utilized the digital caliper mode to streamline collection of BSPs in clinical gait analysis.

This approach provides significant time savings, in particular due to the fact that once the calipers are in place for a given measurement, the operator simply pushes a button on one of the sensors and

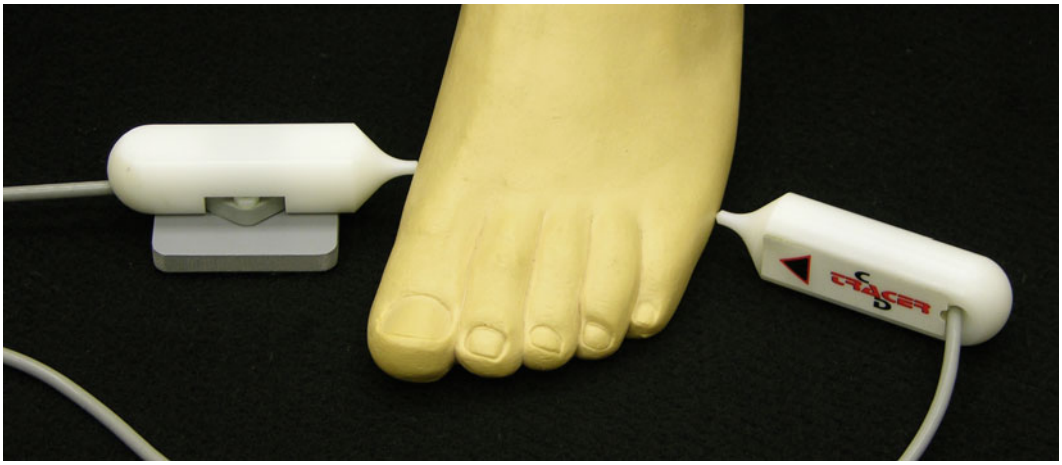

Fig. 5.7 Digital calipers. Configuration of a magnetic field contact scanner as digital calipers. The model reference sensor is used as an additional stylus. The system provides real-time feedback of the distance between the two sensors, and the dimension can be recorded by the system (following software modification) by clicking the button marked with the black triangle on the stylus

the measurement is recorded. This avoids problems associated with standard calipers, including inadequate throat size, the need to remove the caliper from the limb to read the gauge, and the possibility of misreading the gauge.

When the digital caliper technique was used in our laboratory by two investigators to measure a standard set of ten lower limb BSPs and compared to measurement using traditional calipers and tape measures for ten subjects, the digital caliper technique was more efficient. The mean time to complete the measurements using digital calipers was 1 min, 30 s. The mean time to complete the measurements using traditional measurement tools was 4 min, 5 s. The difference is statistically significant ($p < 0.0001$). Research to compare the accuracy of the two techniques is ongoing.

5.7 Practical Methods and Techniques

One of the advantages of digital shape capture of limb anthropometrics is the portability of digital files. With the traditional method described in Fig. 5.1, the only complete record of limb shape and volume is the physical positive model. If the limb shape has been digitized, complete shape information is contained in a single computer file.

This portability has expanded the practicality of central fabrication in prosthetics and orthotics (Smith and Burgess 2001). In this model, practitioners see patients at a different facility from the one in which components are fabricated. There are multiple potential benefits to a central fabrication approach. Facility overhead is reduced, enabling the establishment of smaller offices in more locations, possibly reducing expense. However, the model does require close communication between practitioner and fabricator. In particular, anthropometric definitions must be clearly defined. A variable such as “residual limb length” is highly dependent on measurement technique. Even if the proximal location from which length is measured is clearly specified, results can vary widely. If the length is measured on the limb or on a positive model, one practitioner might align the caliper parallel to the long axis of the limb. Another might keep the caliper close to the surface

of the limb. Still another might use a tape measure. If the same measurement is determined from a digitized model using anthropometric software, it is important to understand the technique employed by the software.

The portability of shape capture equipment has also found application in the developing world, where patient care is challenged by distance. With fewer fabrication facilities and increased difficulty for patients to reach those facilities, portable anthropometric measurement can be the only feasible patient care solution. Because digital shape capture devices can be carried by the practitioner to remote locations and because they produce computer files that can be easily transferred to distant fabrication facilities, they provide a practical solution to challenging patient care.

Summary Points

- Tools for digital capture of limb shapes have developed specifically for clinical use in prosthetics and orthotics
- Prosthetists and orthotists have need for measurements of limb length, circumferences at certain levels, and anterior–posterior and medial–lateral limb diameters
- Limb volume is important but not routinely quantified
- Two primary technologies are used for digital shape capture: optical scanners and electromagnetic field scanners
- Accuracy of these devices has been independently assessed in the literature
- Magnetic field-based systems have a potential application in clinical gait analysis for the routine recording of body segment parameters
- Digitization of the limbs has advanced the concept of centralized fabrication of prosthetic and orthotic components

Table 5.3 Key features of limb digitzation systems

Time for capture	Digitization occurs in real time. Optical systems can capture a limb shape in less than 1 s. Contact scanners require contact with the entire limb surface area, which can take 2–3 min.
Landmarks and modification	Optical systems automatically identify landmarks, which are in some cases special marks affixed to the limb prior to digitization. Contact systems allow marker identification using the stylus. Modification can occur on the limb with contact scanners and in post-processing with both systems.
Patient involvement	The limb must be held relatively still and extended with both technologies. A reference sensor in magnetic field systems permits some patient movement within the magnetic field. Most systems can be used with the limb in a variety of orientations.
Portability	Both systems are portable enough to take to remote locations and can be carried by one person along with a laptop computer. This portability has permitted the use of limb digitizers in developing countries to treat patients who do not have local facilities and cannot travel.

This table lists the key features of limb digitization systems, including their practical use in the clinic

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Chapter 6
The Composite Index of Anthropometric Failure (CIAF): An Alternative Indicator for Malnutrition in Young Children

Shailen Nandy and Peter Svedberg

Abstract Malnutrition is a serious problem in many developing countries. It is one of the main causes of child morbidity and contributes significantly to premature mortality. This chapter discusses the design and use of an alternative indicator of malnutrition – the composite index of anthropometric failure (CIAF). It argues the three most commonly used anthropometric indicators of stunting, wasting and underweight, while providing valuable information about distinct biological processes, are individually unable to provide a comprehensive picture of the overall burden of malnutrition among young children in a population. They are frequently used to predict health and mortality risk, but provide quite limited information on the relationship between malnutrition and disease. The CIAF, however, can also be used to predict morbidity risk, and in its disaggregated form provides a more useful picture of the relationship between ill health and malnutrition. It can also be used to examine the relationship between different forms of malnutrition and poverty.

Using the new World Health Organization (WHO) reference population norms and recent anthropometric data on 45,377 Indian children aged under 5 years, the prevalence of stunting, wasting and underweight are calculated and compared to prevalence estimates by the CIAF. Age adjusted logistic regression is used to see how well different indicators predict morbidity risk. Analysis of variance is used to see the relationship between groups of anthropometric failure and poverty. This chapter also provides information on how reliable, nationally representative anthropometric data from household surveys can be freely accessed by researchers to pursue their own study.

Abbreviations

ARI	Acute Respiratory Infection
CIAF	Composite Index of Anthropometric Failure
DHS	Demographic and Health Survey
HTA	Height for Age
LSMS	Living Standards Measurement Study
MDGs	Millennium Development Goals
MICS	Multiple Indicator Cluster Surveys
NCHS	National Center for Health Statistics

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_6,

NFHS	National Family Health Survey
PAPFAM	Pan Arab Project for Family Health
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WTA	Weight for Age
WTHT	Weight for Height

6.1 Introduction

Other chapters in this Handbook detail the use of assorted anthropometric indicators to reflect malnutrition in young children, and set out how new, more appropriate, international growth norms for children have been developed by the WHO. This short chapter aims to:

1. Present the CIAF as a policy-relevant alternative means of assessing the prevalence of child malnutrition
2. Demonstrate how and why the CIAF is a more comprehensive indicator of malnutrition *than conventional indicators*
3. Show how the CIAF can be used to reflect the relationship between malnutrition, morbidity and poverty; and
4. Provide guidance on how to obtain reliable, nationally representative, anthropometric data on children and adults collected in household surveys around the world can be accessed at no cost and used in research

6.2 What Is the Composite Index of Anthropometric Failure (CIAF)?

The CIAF was first proposed by Swedish development economist, Professor Peter Svedberg (Svedberg 2000). The conventional indicators of malnutrition reflect different aspects of anthropometric failure. Stunting (low height for age (HTA)), which reflects retarded skeletal growth, is used as an indicator of chronic malnutrition. Wasting (low weight for height (WTHT)), which means loss of fat and lean tissue, is a measure of more acute malnutrition. Underweight (low weight for age (WTA)), finally, can be caused by stunting or wasting, or combinations thereof. Each indicator provides valuable information about quite distinct biological processes (World Health Organization 1995), which in turn require different clinical responses.

Malnutrition is a function both of food deprivation and disease. Both are often consequences of poverty, and as such, all anthropometric indicators only serve as proxies for evaluating the prevalence of malnutrition among children. As proxies, they may over- and underestimate malnutrition in different dimensions. They miss, for example, the possibility that children can be malnourished by being too physically inactive for a healthy life, even if they are not stunted or underweight. In addition, anthropometric failure can sometimes be the outcome of disease unrelated to nutrition (e.g. Crohn's disease, Celiac disease). Hence, while anthropometric failure is most often caused by a combination of ill health and inadequate diet, anthropometric indicators alone cannot tell us what the main cause is at the level of individuals.

The three conventional indicators cannot provide a single figure of the overall estimate of malnutrition among children in a population; although such information should be useful to policy makers

and planners, whose task it often is to allocate resources and design programmes and interventions to reduce malnutrition in a given region or country (Nandy and Miranda 2008).

Svedberg argues that stunting, wasting and underweight are not independent entities, and that while underweight is often used to reflect the extent of both chronic and acute malnutrition, it cannot distinguish between them. Underweight is also limited by the fact that it does not identify the sum of those children who are stunted and/or wasted, and so provides an underestimate of the extent of anthropometric failure in a population. What is needed instead is a means of identifying all undernourished children, be they stunted and/or wasted and/or underweight. The solution is the CIAF.

6.3 Constructing the CIAF

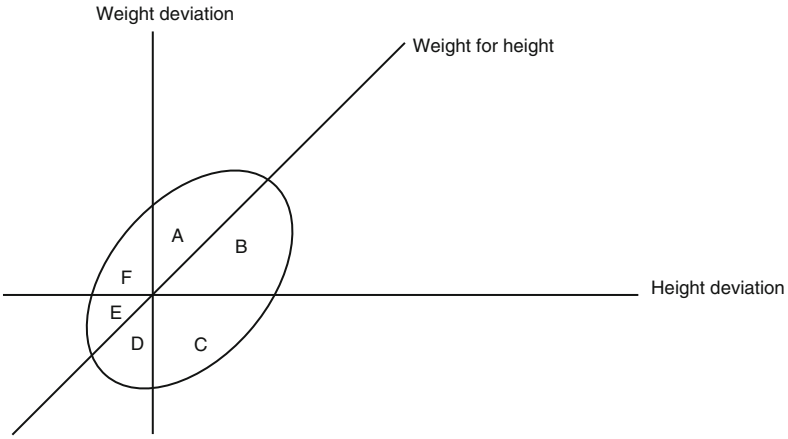
Svedberg modelled the distribution of different combinations of anthropometric failure in a population using Fig. 6.1. The vertical axis shows the deviation from the WTA norm, the horizontal axis shows deviation from the HTA norm and the diagonal line gives the combinations of weights for heights, which comply with the norm.

Thus, underweight (i.e. low WTA) would include children in sections (Groups) C, D and E, but misses those children in Groups B and F; stunting (i.e. low HTA) would include children in sections (Groups) D, E and F, but misses those children in Groups B and C; and wasting (i.e. low WTHT) would include children in sections (Groups) B, C and D, but misses those in Groups E and F. Svedberg (2000: 196) reasoned

> If one considers a child who is either stunted, wasted, or underweight… to be in a non−acceptable state, the only anthropometric indicator capable of giving an all−inclusive estimate is: CIAF=(1−a)/(a+b+c+d+e+f)=(1−a)/1=1−a, which we call the Composite Index of Anthropometric Failure.

Table 6.1 shows the groups of anthropometric failure in more detail.

The overall prevalence of malnutrition is then ascertained by summing all of the groups together, but excluding the children in Group A (i.e. those not experiencing any form of anthropometric failure). In operationalising the CIAF for the first time, an additional group, Group Y, containing children who are only underweight, was identified and added to Svedberg's model (Nandy et al. 2005).



Source: Svedberg (2000). By Permission of Oxford University Press, Inc.

Fig. 6.1 The total prevalence of anthropometric failure (Svedberg 2000. By permission of Oxford University Press, Inc.)

Table 6.1 Groups of anthropometric failure among children[a]

Group	Description	Wasting	Stunting	Underweight
A	**No failure**: Children whose height and weight are above the age-specific norm and who do not suffer from any anthropometric failure	No	No	No
B	**Wasting only**: Children with acceptable weight and height for their age, but who have subnormal weight for height (WTHT)	Yes	No	No
C	**Wasting and underweight**: Children with above-norm heights, but whose weight for age (WTA) and WTHT are too low	Yes	No	Yes
D	**Wasting, stunting and underweight**: Children who suffer from anthropometric failure on all three measures	Yes	Yes	Yes
E	**Stunting and underweight**: Children with low WTA and low height for age (HTA), but who have acceptable weight for their height	No	Yes	Yes
F	**Stunting only**: Children with low HTA but who have acceptable weight, both for their age and for their short height	No	Yes	No
Y	**Underweight only**: Children who are only underweight – whose WTA is acceptable	No	No	Yes

[a]Another theoretical combination would be the children who were "wasted and stunted" but not underweight. This combination is not physically possible since a child cannot have a low WTHT and low HTA and not be underweight

Table 6.2 Malnutrition among Indian children under 5, NFHS 2005 ($N = 45{,}377$) (Calculated from NFHS-3)

Indicator of malnutrition	Prevalence rate (%) (with 95% CIs)	Estimated number of Indian children under 5
Stunting	**48.3** (47.5–49.1)	61,739,475
Wasting	**20.1** (19.5–20.7)	25,692,825
Underweight	**42.8** (42.0–43.7)	54,709,100
CIAF	**61.8** (60.9–62.6)	78,995,850

Let us now provide an illustration of how the prevalence of malnutrition as estimated by the CIAF classification differs from estimates based on the three conventional indicators. Using anthropometric data on 45,377 Indian children aged under 5 years collected in the 2005 National Family Health Survey (NFHS-3) (IIPS and Macro International 2007), the prevalence of stunting, wasting and underweight were calculated. Estimates of malnutrition were made based on the new WHO international reference population (World Health Organization Multicentre Growth Reference Study Group 2006). Table 6.2 shows the rates of stunting, wasting and underweight obtained and the estimated number of children affected. It also shows the prevalence of malnutrition when the CIAF is used as an aggregate indicator of malnutrition.

Among the children for whom valid anthropometric data were collected, 48% were stunted, 43% were underweight and 20% experienced wasting. The CIAF provides a much higher prevalence of malnutrition, of 62%. This difference is considerable in terms of the numbers of children affected. According to the United Nations estimates, there were around 127,825,000 children aged under 5 in India in 2005 (UNPOP 2008). This means, applying the percentages in Table 6.2, 62 million children were stunted, 26 million were wasted, and 55 million were underweight. However, according to the CIAF, there were closer to 80 million children in one or more states of anthropometric failure. This difference of nearly 18 million children has clear cost and policy implications for planners and for international targets like the Millennium Development Goals (MDGs). Table 6.3 provides estimates of malnutrition for several other countries based on conventional measures as well as the CIAF,

Table 6.3 Prevalence rates of malnutrition among children under 5 in seven countries (Calculated from National Demographic and Health Surveys)

Country and year of DHS	Underweight (%)	Stunting (%)	Wasting (%)	CIAF (%)
Bangladesh (2008)	**41.1**	43.4	17.6	**56.1**
Nepal (2006)	**38.8**	49.6	12.9	**57.9**
Nigeria (2008)	**23.4**	40.8	14.0	**51.6**
Liberia (2007)	**18.4**	38.1	7.6	**44.0**
Ghana (2008)	**14.0**	27.5	9.0	**35.6**
Egypt (2008)	**6.1**	29.0	7.4	**36.0**
Dominican Republic (2007)	**3.2**	10.0	2.3	**12.5**

using the new WHO reference population norms. It shows clearly the magnitude of difference when underweight is used to estimate the overall prevalence of malnutrition (chronic=stunting and acute=wasting) as compared to the CIAF. In populous countries like Bangladesh, Egypt and Nigeria, these differences can amount to many millions of children.

6.4 Using the CIAF as a Disaggregated Measure

Given the known relationship between malnutrition and morbidity and mortality (Eveleth and Tanner 1990; Schroeder and Brown 1994; Rice et al. 2000; Caulfield et al. 2004), the conventional indicators are often used as predictors of risk. However, Svedberg reasoned that a more disaggregated classification of malnutrition, which set out specific failures as well as combinations of failures, might have greater predictive power than the conventional indicators. He suggested that the children who were simultaneously stunted, wasted and underweight were likely to be at a greatest risk of mortality. This theory can be tested, when suitable data become available. In the present case, the NFHS 2005 data only allow for the theory to be tested with regards to morbidity.

Table 6.4 shows the distribution of children in the sample across distinct groups of anthropometric failure. Over one third of children (38%) experience no failures at all. Around one quarter of all children are both stunted and wasted (Group E), and around one in seven (15%) were only stunted. One in eleven children (9%) experienced a triple failure (Group D), around 11.4 million children. These are the children predicted to be at a greatest risk of ill health.

6.5 Indicators of Morbidity

Three health conditions are used here to gauge the relationship between the various CIAF classes and morbidity: the prevalence of diarrhoea, dysentery and acute respiratory infection (ARI) (WHO/CDR 1994). Each condition, either alone or associated with malnutrition, is a common cause of death among children under 5 in developing countries (Tomkins and Watson 1989; Smith et al. 1991; Cunha 2000). Information about children's health is ascertained in the NFHS 2005/2006 from the mother or main caregiver. Respondents are asked if, during the previous 24 h or 2 weeks, the child has had diarrhoea, and if so, was there any blood in the stool. Children with diarrhoea were then classed as having diarrhoea and those who had had blood in the stool were classed as having dysentery.

Table 6.4 Groups of anthropometric failure among Indian children, under 5, NFHS 2005 (N = 45,377) (Calculated from NFHS-3)

Group	%
A – No failure	38.2
B – Wasting only	4.3
C – Wasting and underweight	6.9
D – Wasting, stunting and underweight	8.9
E – Stunting and underweight	24.8
F – Stunting only	14.6
Y – Underweight only	2.3
Total	**100.0**

Children who were reported to have a cough with/without a fever and who had breathing difficulties (short, rapid breaths) and who showed symptoms of a chest infection were considered to have an ARI.

6.6 Predicting Risk

According to the NFHS 2005, around 9% of children under 5 experienced diarrhoea in the 2 weeks preceding the survey, of whom about 11% had symptoms of dysentery (i.e. just under 1% of all children sampled). The prevalence of ARI among children under 5 years was 6%.

Table 6.5 shows how the CIAF and groups of anthropometric failure can be used alongside conventional indicators of malnutrition to assess morbidity risk. In this instance, age-adjusted logistic regressions have been used to show the different risks associated with different forms of malnutrition, as well as with the disaggregated CIAF.

If the relationship between malnutrition and diarrhoea is considered first, it is clear that the odds ratios for children experiencing stunting, wasting and underweight are all roughly equal, with no statistically significant difference between them. The aggregate CIAF performs as well as each of the individual measures. With regards to dysentery, stunting and underweight provide similar indications of risk, as does the CIAF. Wasting, however, as a single indicator, appears to be a relatively poor predictor of dysentery.

The value of the CIAF is in the way it can be used as a disaggregated measure. When children with no failures (i.e. Group A) are set as the referent, against which each of the other groups are compared, a more nuanced pattern can be observed. As Svedberg predicted, children who experience a triple failure (i.e. those who are stunted, wasted and underweight, in Group D) are at greatest risk of suffering from diarrhoea and dysentery – around 50% and 80%, respectively, more likely than children with no failures. As one might expect, the risks of diarrhoea and dysentery are greater for children with multiple anthropometric failures (i.e. in Groups D and E), and especially so when stunting is among the failures (Group F).

The picture with regards ARI is less clear. In this instance, underweight is the only statistically significant (but weak) predictor among the single indicators. The disaggregated CIAF groups of anthropometric failure show there to be no strong predictors, in contrast to the findings of a study, which conducted an identical analysis on an earlier round of the NFHS (Nandy et al. 2005). In 2005, there were only marginal differences in the prevalence of ARI for children of different background characteristics (e.g. maternal education, standard of living, etc.). This lack of variation suggests that in India, respiratory infections affect children irrespective of their socioeconomic background (IIPS and Macro International 2007), which in turn may explain the low predictive power of the indicators.

Table 6.5 Predicting morbidity risk Indian children, under 5, NFHS 2005 ($N = 45{,}377$)

	Diarrhoea[a]		Dysentery		Acute respiratory infection	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Indicator						
Stunting	**1.18**[b]	(1.10–1.26)	**1.56**[b]	(1.28–1.90)	1.04	(0.96–1.12)
Wasting	**1.23**[b]	(1.14–1.32)	1.12	(0.89–1.41)	1.00	(0.91–1.10)
Underweight	**1.24**[b]	(1.16–1.32)	**1.52**[b]	(1.25–1.84)	**1.12**[c]	(1.03–1.21)
Composite Index of Anthropometric Failure (CIAF)	**1.19**[b]	(1.11–1.27)	**1.56**[b]	(1.26–1.92)	1.01	(0.93–1.09)
Groups of anthropometric failure						
A – No failure (referent)	1.00		1.00		1.00	
B – Wasting only	1.12	(0.96–1.29)	0.97	(0.56–1.68)	**0.81**[c]	(0.66–1.00)
C – Wasting and underweight	**1.22**[c]	(1.08–1.38)	1.33	(0.89–1.99)	1.02	(0.87–1.19)
D – Wasting, stunting and underweight	**1.48**[b]	(1.34–1.65)	**1.80**[b]	(1.30–2.51)	1.10	(0.96–1.26)
E – Stunting and underweight	**1.24**[b]	(1.13–1.35)	**1.76**[b]	(1.36–2.26)	1.08	(0.98–1.19)
F – Stunting only	1.02	(0.92–1.13)	**1.42**[c]	(1.05–1.93)	0.90	(0.79–1.02)
Y – Underweight only	0.84	(0.66–1.06)	1.49	(0.80–2.78)	1.06	(0.82–1.37)

[a]Includes children with dysentery
[b]$P < 0.001$
[c]$P < 0.05$

Further work on data from other countries, or a pooled analysis, might provide more conclusive answer as to the relationship between ARI and malnutrition.

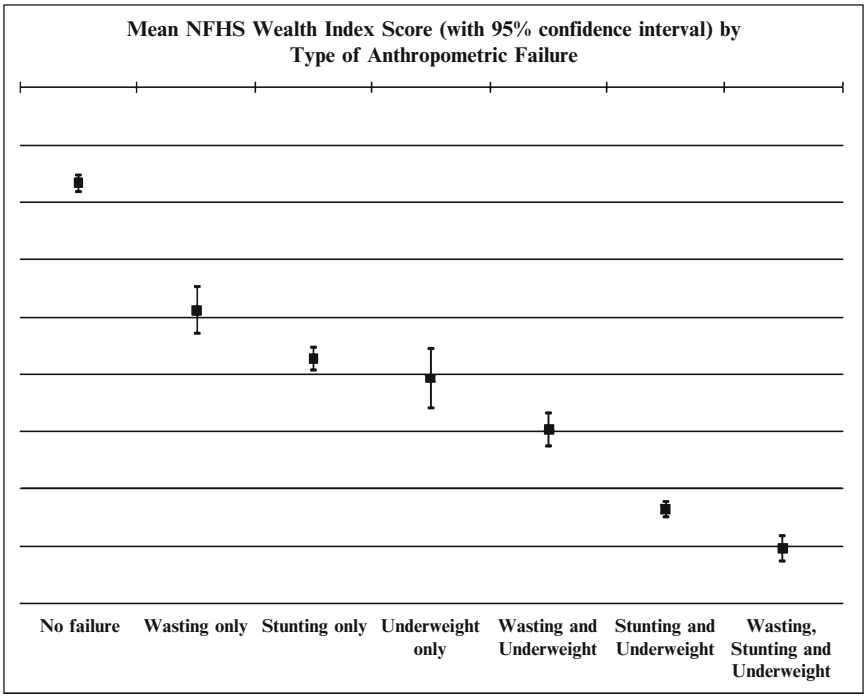
6.7 Anthropometric Failure and Poverty

The NFHS 2005 contains a wealth index based on household ownership of different assets (e.g. land, type of house) and durable goods (e.g. car, television, radio), which can be used to reflect socioeconomic disadvantage, deprivation and poverty. Such asset indices commonly serve as proxies for household wealth and economic status (Montgomery et al. 2000; Filmer and Pritchett 2001; Falkingham and Namazie 2002; Howe et al. 2008) in the absence of data on income or expenditure.

Svedberg reasoned correctly that children experiencing multiple anthropometric failures would be at greatest risk of ill health. Can a similar conclusion be reached with regards to poverty? Figure 6.2 shows the results of an analysis of variance (ANOVA) of the mean wealth index scores for each subgroup of anthropometric failure. Children with no failure have significantly higher (i.e. better) wealth scores than children with any form of anthropometric failure.

Two other things are apparent: first, children with a single failure (i.e. who experience wasting only, stunting only or underweight only) have significantly higher scores than children who experience multiple failures, and second, children who experience a triple failure are on average likely to live in the poorest households. These findings confirm similar analyses of the previous round of the NFHS (Nandy et al. 2005) and support those of other studies on malnutrition and poverty (ACC/SCN 1997; Wagstaff and Watanabe 2000).

Svedberg has in recent work built on his model of anthropometric failure, to include overweight and obesity (Svedberg 2007). Recent survey data from Mexico has revealed the existence of sizeable



Source: Calculated from NFHS-3

Fig. 6.2 Malnutrition and poverty in India (Calculated from NFHS-3)

proportions of children (5–10%) who are stunted *and* overweight/obese (Fernald and Neufeld 2007), whose distribution is similar to those identified above (i.e. greater prevalence among poorer socio-economic groups). The simultaneous prevalence of overweight/obesity and stunting has also been observed in other countries undergoing nutritional transition, such as Russia, Brazil and South Africa. There are genuine concerns about the potential negative impacts on health of obesity, and how these might manifest when combined with chronic malnutrition, for example, increased risk of chronic disease in later life.

6.8 Sources of Anthropometric Data

There is now an unprecedented amount of household survey data available to researchers. International organisations like the WHO, World Bank and UNICEF conduct surveys using standardised questionnaires and sampling methodologies, many of which can be accessed for free, or at low cost, over the Internet (Box 6.1). These surveys provide information used by international agencies to monitor international development targets, such as the MDGs, and summarised in many of their flagship reports (e.g. UNICEF's *State of the World's Children Reports*, the UN Development Programme's *Human Development Reports*, etc.). Researchers interested in conducting their own analyses can access most of these data at little or no cost.

One of the best sources of primary household-survey data are the demographic and health surveys (DHS) (Vaessen 1996). Survey data are provided for free and are available online to those who want them. Surveys were first conducted during the 1980s, and by mid 2009 about 270 DHS surveys have

Box 6.1 Household survey data available on the Internet

- Demographic and Health Surveys: www.measuredhs.com
- DHS STATcompiler: www.statcompiler.com
- UNICEF's Multiple Indicator Cluster Surveys: www.childinfo.org/mics.html
- World Bank Living Standard Measurement Study: http://iresearch.worldbank.org/lsms/lsmssurveyFinder.htm
- World Health Organization World Health Surveys: www.who.int/healthinfo/survey/en/index.html
- Pan Arab Project for Family Health: papfaminfo@papafam.org
- China Health and Nutrition Survey: www.cpc.unc.edu/projects/china/data/data.html
- World Health Organization Database on Child Growth and Malnutrition: www.who.int/nutgrowthdb/en/

been published, providing a unique data base for cross-country investigations. Many countries have been surveyed repeatedly, allowing for analyses of changes of time. The DHS also provides access to useful tools like the STATCOMPILER, which can be used to make comparisons between countries of a range of different nutrition-related indicators.

UNICEF used the DHS format to develop its own survey programme, the Multiple Indicator Cluster Surveys (MICS). Three rounds of MICS have been conducted, the most recent in 2005/2006. Similar to the MICS and DHS are the surveys conducted by the Pan Arab Project for Family Health (PAPFAM), which cover the countries of North Africa and the Middle East. Two rounds of surveys have been conducted, with a third ongoing. The World Bank, as part of its Living Standards Measurement Study (LSMS), has conducted surveys in more than 30 countries. As well as collecting data on health and nutritional status, detailed information about household expenditure and consumption are recorded. The WHO runs its own survey programme, the World Health Surveys, in over 70 countries. Many of these surveys, and also some recent DHS, include detailed information about respondent location (GPS co-ordinates), making it possible to map malnutrition, morbidity and mortality more precisely. Another source of anthropometric data for researchers is the China Health and Nutrition Survey, a collaborative project between the Carolina Population Centre at the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety at the Chinese Centre for Disease Control and Prevention. This is a longitudinal survey of 4,400 households in nine of China's provinces. Data from seven rounds can be accessed from the website shown in Box 6.1.

The World Health Organization Database on Child Growth and Malnutrition provides a standardised compilation of child growth and malnutrition data from nutrition surveys conducted around the world since 1960. Data on children's nutritional status are provided using both the "old" NCHS and the new, WHO multi-country reference population data.

6.9 Conclusions

This chapter has shown how and why the CIAF is an important new policy-relevant anthropometric indicator of malnutrition. It showed how conventional indicators "miss" large numbers of malnourished children, and that the CIAF is the only indicator to provide a single figure, aggregate estimate

of the overall burden of malnutrition among children in a population. The disaggregated CIAF allows for more nuanced assessments of the relationship between malnutrition, morbidity and poverty, and is increasingly being used in the assessments of child poverty and malnutrition (Gordon et al. 2003; Baschieri and Falkingham 2007; Seetharaman et al. 2007). Given the ready availability of anthropometric data from household surveys, it is likely to be used much more frequently in future research.

Efforts to reduce malnutrition will depend heavily on reducing poverty and raising people's living standards. This will require improving the quality of their homes, and their access to basic services, such as clean water and effective sanitation, as well as food of sufficient quality and quantity. Access to affordable qualified health care to prevent the debilitating effects of diseases like dysentery and pneumonia are essential if children's nutritional status is to improve. The CIAF provides researchers and planners with another tool to assess change and see if progress is being made.

Summary Points

- The conventional indicators of malnutrition – stunting, wasting and underweight – each individually "miss" large numbers of malnourished children.
- The CIAF provides an aggregate measure to estimate the overall burden of malnutrition among young children.
- In its disaggregated form, the CIAF can be used to predict the varying risks of morbidity for different types of anthropometric failure.
- The CIAF can be used to show the relationship between poverty and multiple anthropometric failures.
- Anthropometric data from hundreds of household surveys are available on the Internet and can be downloaded and used by independent researchers.

Key Features

- The CIAF can provide policy-relevant information on the pattern of child malnutrition in any country.
- The CIAF can be used to illustrate the complex relationship between morbidity risk and malnutrition.
- The CIAF can be easily computed using freely available, individual-level household survey data from over 70 countries.

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Chapter 7
The Human Body Shape Index (HBSI): An Anthropometric Measure Based on an Age-Related Model of Human Growth

Maria K. Lebiedowska and Steven J. Stanhope

Abstract Body shape during age-related human growth is customarily described using either the body mass index (BMI) or the Ponderal Index (PI). These indices describe the human body shape (HBS) with different proportions between body mass (M) and body height (H). Both indices are affected by age during childhood. The establishment and maintenance of age- and sex-specific databases is time consuming and an expensive process. The lack of a general model for abnormal HBS makes the comparison of different populations (both in respect to time and location) very difficult. Efforts to evaluate the epidemic status of childhood obesity would benefit from the development of new tools and the refining of existing simple, reliable tools to evaluate and monitor HBS. An age invariant, sex-specific human body shape index (HBSI) has been recently introduced as an alternative to age-specific BMI and PI models. The HBSI was based on a mathematical model of human growth of Polish children (5–18 year old) between years 1985 and 1990. The sample was characterized by ideal fat composition (judged by 95th percentile of BMI values). To model growth, the best fit between individual body height (h) and body mass (m) was calculated separately between sexes with the function $M = c_p H^{\chi}$. The models of growth were $M = 13.11\ H^{2.84}$ ($R^2 = 0.9$) and $M = 13.64\ H^{2.68}$ ($R^2 = 0.91$) in girls and boys respectively. The HBSIs were calculated as ($HBSI_p = M/H^{\chi}$), where $HBSI_B = 13.74 \pm 1.72$ (in boys), $HBSI_G = 13.21 \pm 1.73$ (in girls) and $HBSI = 13.47 \pm 1.74$ (for both sexes). While the sensitivity and specificity of HBSI in the classification of the pathological changes in human body shape has not been explored, HBSI may be beneficial over other age-specific indices in the comparative analysis of HBS in children originating from different populations (location, diversity, and time periods) over long periods of growth.

Abbreviations

HBS	Human body shape
M_G, M_B, M	Body mass in girls, boys and pooled together treated as a physical variable (respectively)
H_G, H_B, H	Body height in girls, boys and pooled together treated as a physical variable (respectively)

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_7,

h, m	Body height (m) and body mass (kg) in the individual subjects
BMI	Body mass index (BMI = m/h^2)
PI, RI	Ponderal /Rohrer index (PI, RI = m/h^3)
$HBSI_G$, $HBSI_B$, HBSI	Human body shape index in girls, boys (respectively) and pooled together
S.D.	Standard deviation
N	Number of subjects

7.1 Introduction

7.1.1 The Shape of the Living Organisms and the Environment

One of the basic features of life is an active interaction of an organism with the environment. From the systemic point of view, in order to survive in the environment living organisms (systems) need to maintain a state of the homeostasis. Homeostasis is an ability of a system to effectively act within the domain of environmental changes. The wider the range of the adaptation to environmental changes, the larger the chances the system will survive. An ability of a system to control position in space and time is determined by the system's structure and biomechanical interaction between the living organism and the environment. In humans, gravity and body structure combine to limit some activities but facilitate others. For example: walking and not floating is possible in the earth's gravitational field. However the reverse is true in the space. Any activity in a gravitational field requires more energy expenditure with increasing mass of an object. Potential energy is used to maintain the body in a certain position in relation to the gravitational field and kinetic energy moves the body in that field. The organisms living on earth exhibit very large variation in body size (for example elephant vs. ant) with a comparatively small variation in the body density (1–2 g/cm^3), because water is the substantial component of any earthly body. Body mass is usually associated with the size of the body. While the body density varies little, shapes vary greatly. The shapes of earthly organisms usually exhibit some form of symmetry (axial or rotational). The proportions between the dimensions in a three-dimensional space are an estimate of a body's distribution. In humans, mass is non-uniform and distributed mainly along the long axis of the body. The distribution of human body mass is the elementary determinant homeostasis. It affects all aspects of interaction with the environment which are necessary for basic human functions.

7.1.2 The Human Body Shape

Human body size and shape change during ontogenetic and phylogenetic development. Throughout a lifespan, the human body also undergoes physiological and pathological processes that affect its size and shape. Human body shape (HBS), mass distribution and its changes are subjects of interest in various scientific disciplines such as anthropometry, biomechanics, nutrition, and ergonomics. The monitoring and prediction of changes in mass and its distribution is important in an individual subject and in monitoring population trends. For the sake of this chapter, growth is defined as an age-related increase in body height and mass.

Prenatal development is characterized by the most dramatic and qualitative changes in HBS. During the first year of a child's life, rapid growth and change in mass distribution take place. Body proportions undergo rapid change, especially in the areas of the head and trunk. The body proportions continue to

change until a relatively robust adult-like body structure emerges by the age of 5–7 years. The next stage (7–18 years) is characterized mainly by quantitative changes, with an almost proportional increase in body size and mass in three dimensions (except for a short time of puberty). When the final body height is achieved (18–21 years) increases in body size and mass may occur only in two dimensions. Body height usually remains unchanged until the later stages of aging. Other factors such as demographics and life style also affect HBS. Changes in HBS other than due to age-related growth may be early signs of development or acceleration of disease. In the face of an epidemic of childhood obesity (Wang et al. 2008) and associated obesity-related health problems, monitoring of changes in HBS that are not related to age-related growth continues to be an important medical and social challenge.

This chapter addresses the challenge of developing an age invariant, sex-specific human body shape index (HBSI) as an alternative to indices based on age grouping body mass. Algorithms to establish a mathematical model of growth in children (5–18 years old) and the application of the growth model to establish an age-independent body mass index (HBSI) will also be introduced. A primary goal of this work is to model changes in HBS due to age-related growth as a means for enhanced monitoring of the incidence of overweight and obesity in children.

The chapter is broadening the previously published paper (Lebiedowska et al. 2008).

7.2 Quantitative Evaluation of Human Body Shape (HBS)

7.2.1 Standard Methods of Evaluation of HBS

There are different ways to quantify HBS, the most basic being to monitor indices based on commonly accessible data: body mass (m) and body height (h).These two anthropometric measures are very important in routine clinical practice; they are widely accessible and routinely monitored during clinical examination. The most popular body mass index (BMI), or Quételet's index, is defined in adults as BMI = m/h^2 (Ricardo and Araujo 2002). BMI has become an accepted tool to quantify obesity with established ranges for obesity (www.cdc.gov). Its associations with other measures of obesity in adults had been confirmed (Dahlström et al. 1985). BMI is fully justified in adults because of the matured stature, and an increase in body mass, and therefore dimensions, can occur only in the horizontal plane. However in children, growth occurs in three dimensions. Ponderal (PI) or Rohrer index (RI) index, (PI = m/h^3) accounts for three-dimensional growth of the human body (Sheldon et al. 1940). PI, or its inverse, has often been used to quantify obesity in young children 0–3 years old (Davies and Beverley 1979), but it is seldom used in older children (Alley et al. 1968; Agarwal et al. 2001; Ricardo and Araujo 2002; Mei et al. 2002).

In children, the applications of BMI and PI are more complex than in adults. BMI increases and PI decreases during growth, with much more substantial changes in BMI than PI (Alley et al. 1968; Rolland-Cachera et al. 1982; Garn et al. 1986; Cole et al. 1995; Agarwal et al. 2001; Ricardo and Araujo 2002). In children the changes of BMI and PI with body height require the application of age charts and the application of percentile or z-score analysis. Standardized, smoothed (Flegal 1999) percentile growth charts are routinely generated from data obtained from samples of population of children in different age groups (Alley et al. 1968; Pietrobelli et al. 1998; Cole et al. 2000; Ricardo and Araujo 2002). Percentiles describe what percentage of the sampled population exhibits the same value of the index as an individual. A z-score is calculated as the ratio between the difference of a data point obtained in an individual and the mean value in an age group, divided by the standard deviation (S.D.) of the age group. Both a z-score and percentile analysis relate the individual HBS to

the data obtained from a control/non-disabled population. The growth charts require data collection in the age groups and neither *z*-scores nor percentile calculations allow for a direct comparison of different populations (Cole et al. 2000). Neither percentile nor *z*-score analyses define absolute physiological thresholds for classification of abnormal HBS including obesity. As a result the application of BMI growth charts may lead to an underestimation of obesity in children and a more precise classification criteria of obesity is necessary (de Onis 2004; Wang 2004).

7.2.2 Mathematical Modeling of Human Growth

Until human growth is completed and final body height is reached (18–21 age), a monotonic increase in body height is related to a three-dimensional increase in body dimensions and mass distribution. Since human growth consists of the different periods during which the body shape undergoes qualitative and quantitative changes we focus on age-related human growth between 5–18 years. In children 5–18 years old, growth appears to follow the rule of allometry (or geometrically similar growth) (Günter 1975), because the proportions between body part dimensions may be considered somewhat invariant.

7.3 Practical Methods and Techniques

7.3.1 The Mathematical Model of the Human Growth

To establish mathematical models of human growth we identified body height as the primary age-related growth factor. Body height increases monotonically during growth as opposed to body mass, which fluctuates. To model growth, the best fit between individual body height (h) and body mass (m) was calculated separately in boys (B) and girls (G) with the function $M_p = c\ H^{\chi}$, where: p = <B,G>, c, χ = sex-specific constant, H and M = body height and mass treated as physical variables (Benn 1971). The body height is expressed in meters (m) and body mass in kilograms (kg). There are several ways to obtain the approximation.

1. The exponent χ can be identified by calculation of the best mathematical fit of the function between body mass, and body height $M = c\ H^{\chi}$.
2. Due to the mathematical properties of the logarithmic function the exponent χ can also be calculated as a slope of the linear regression function between the $\log(M) = a + \chi \log(H)$. Any statistical package or Excel or curve fitting software can be used to calculate one of the above mathematical approximations.

7.3.2 Establishing an Age-Related Growth Model

Sex-specific growth models have been developed based on a set of data collected in 847 Polish children (444 girls and 403 boys, aged 5–18 years) obtained between 1985 and 1990 (Lebiedowska et al. 2008) (Table 7.1). The sample of Polish children contained a homogeneous sample of children with generally ideal body fat composition, as judged by 95th percentile of BMI (<24.4 in girls and <23.5 in the boys). No obesity/overweight or underweight was reported in the sample.

Table 7.1 Demographics of the sample Polish children 5–18 years old (between 1985 and 1990)

	Girls (N = 444)			Boys (N = 403)		
		m (kg)	h (m)		m (kg)	h (m)
Age (years)	N	Mean ± S.D.	Mean ± S.D.	N	Mean ± S.D.	Mean ± S.D.
5	26	18.88 ± 2.19	1.12 ± 0.04	29	20.81 ± 2.75	1.14 ± 0.05
6	43	22.57 ± 4.64	1.19 ± 0.06	30	22.37 ± 3.48	1.2 ± 0.06
7	37	24.78 ± 3.55	1.25 ± 0.05	33	25.15 ± 3.6	1.26 ± 0.06
8	23	26.79 ± 5.13	1.28 ± 0.06	34	29.96 ± 6.83	1.33 ± 0.07
9	42	28.68 ± 4.97	1.34 ± 0.06	35	30.23 ± 4.73	1.35 ± 0.05
10	33	34.59 ± 8.3	1.39 ± 0.08	37	34.72 ± 6.83	1.42 ± 0.07
11	30	39.18 ± 8.3	1.49 ± 0.08	31	37.67 ± 6.17	1.46 ± 0.08
12	36	42.25 ± 7.71	1.55 ± 0.08	34	42.71 ± 10.9	1.52 ± 0.1
13	31	48.84 ± 9.14	1.578 ± 0.07	36	48.48 ± 11.3	1.6 ± 0.09
14	38	52.73 ± 6.25	1.63 ± 0.06	38	56.74 ± 9.5	1.68 ± 0.07
15	21	52.97 ± 6.1	1.63 ± 0.04	10	51.61 ± 9.7	1.657 ± 0.07
16	36	56.88 ± 7.26	1.64 ± 0.06	20	65.3 ± 8.47	1.76 ± 0.06
17	37	58.16 ± 8.27	1.63 ± 0.06	29	65.72 ± 7.99	1.78 ± 0.07
18	11	61.35 ± 10.05	1.67 ± 0.08	7	67.97 ± 10.69	1.79 ± 0.08

Reprinted from Lebiedowska et al. (2008). With permission
This table lists the demographics of the children included into the study. N: number of subjects, m: body mass, h: body height, S.D.: standard deviation

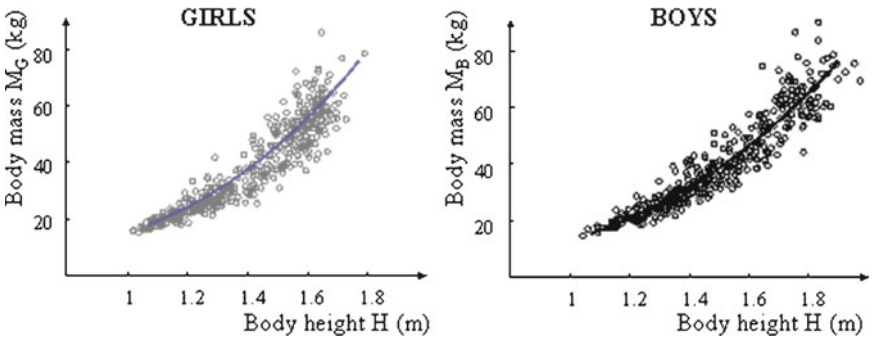


Fig. 7.1 Mathematical models of growth based on the exponential fit between body mass (M) and body height (H) in 847 (444 girls, and 403 boys) Polish children 5–18 years old. The growth models in girls $M_G = 13.11\ H^{2.84}$ ($R^2 = 0.9$) (*left*) and in boys $M_B = 13.64\ H^{2.64}$ ($R^2 = 0.91$) (*right*) (Modified from Lebiedowska et al. (2008). With permission)

1. The mathematical approximations of the body mass (m) against body height (h) obtained from individual subjects were calculated separately for boys and girls with the function $M_p = c\ H^{\chi}$ (Fig. 7.1).
2. The same model was calculated using a logarithmic function where the exponent χ was equal to the slope of the linear regression function between the log (M) = $a + \chi \log(H)$ (Fig. 7.2).

Both mathematical methods generated the following models of growth: $M_G = 13.1\ H^{2.84}$ ($R^2 = 0.9$) for girls and $M_B = 13.1\ H^{2.84}$ ($R^2 = 0.91$) for boys and $M = 13.1\ H^{2.76}$ ($R^2 = 0.89$) for both sexes.

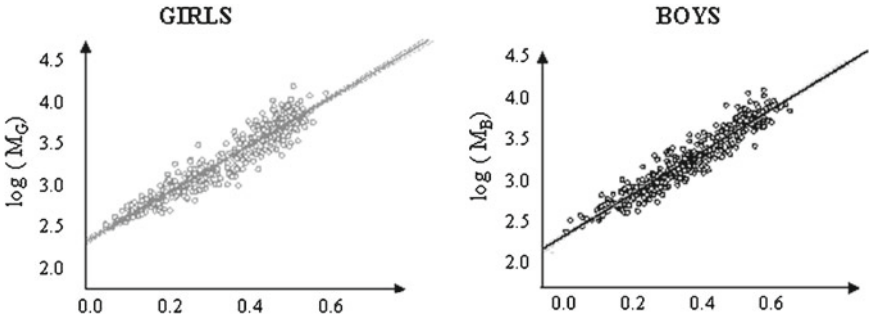


Fig. 7.2 Mathematical models of growth based on the linear fit of log(*H*)-log(*M*) function in 847 (444 girls, and 403 boys) Polish children 5–18 years old. The linear regression line in girls (*left*) $\log(M_G) = 2.57 + \mathbf{2.84} \log(H_G)$; $r = 0.95$) and in boys (*right*) $\log(M_B) = 2.61 + \mathbf{2.68} \log(H_B)$; $r = 0.95$ (*right*)

7.3.3 Physical and Physiological Interpretation of Age-Related Growth Models

Assuming that body density does not change, human growth follows the rule of allometry or geometrically similar growth, if the proportions between the sizes of body parts are invariant. In prefect geometrical similar growth, an increase in body mass according to the third power of body height would be expected. In other words, if $\chi \rightarrow 3$ the assumption about the geometrically similar growth is more reliable. The difference between the exponent χ and number 3 describes the discrepancy between the experimental and geometrically similar model of growth. Growth in Polish children 5–18 years old followed the geometrical model with 10.6% accuracy in boys and 5.3% accuracy in girls (as judged from the differences between the experimentally obtained value of χ and number 3). The larger exponents obtained in girls, in part, reflects the fact that the final average body height reached by males is larger than in females (http://www.cdc.gov). However, gender-specific changes in body proportions may play a role. The group of Polish children contained a homogeneous sample of children with generally ideal body fat composition, as judged by 95th percentile of BMI (<24.4 in girls and <23.5 in the boys). Similar exponents reported in a population of English children (Rosenthal et al. 1994) suggest similar growth in English and Polish children between years 1985 and 1992. Due to the lack of the generally accepted "golden standards" for human growth at this time, we treat these experimentally established models of growth as a reflection of ideal age-related growth. It is important to model age-related growth in order to separate healthy age-related growth from changes in HBS related to changes in percentage body fat.

It should be emphasized that the described growth models may be beneficial to the description of HBS growth-related changes over a longer period of time, when body height is the most important factor affecting growth. To analyze the shorter periods of growth, or to characterize the diverse populations other models may be more suitable.

7.3.4 General Guidelines for the Establishment of Age-Independent Indices Based on Growth Models

To calculate an individual HBSI, the following procedure should be followed:

1. Body mass data obtained from individual subjects should be divided by the body height to the sex-specific exponent χ ($\chi = 2.84$ for girls and $\chi = 2.64$ for boys).

2. Correlations between HBSI and body height should be calculated. If there are no statistically significant correlations, the correlation between the index and the calendar age should be calculated. If the correlation with the calendar age is not statistically significant the mean and S.D. of the index may be considered as HBSI of the population from which the sample comes.
3. To determine if it is necessary to introduce age corrections, the data should be divided into age groups and the mean of HBSI of the age groups should be calculated. A one-factor ANOVA test can be used to determine the effect of age on the HBSI. If the groups' mean is significantly different, an age correction for each group should be introduced as the ratio between the mean of each group and the first age group.

7.3.5 Application of Normalization Algorithms in the Establishment of Age-Independent, Sex-Specific, Human Body Shape Indices

The sex-specific human body shape indices ($HBSI_p$) were calculated using a sample population of Polish children using body mass and body height of individual subjects as $HBSI_p = m/h^x$. Polled HBSI for girls and boys were calculated using the mean power of body height across sexes. Mean and S.D.s, correlations and the slopes of linear regression lines between HBSI and H are displayed in Table 7.2.

The HBSI were compared for 4 age categories (5–9, 9–12, 12–15 and 15–18 years old). To determine the degree to which the mean indices were affected by age, indices for each age were compared using ANOVA test with Bonferroni adjustment. The HBSI were statistically different in girls (Table 7.3) but not in boys (Table 7.4).

The largest difference occurred between age groups 9–12 and 15–18 years (1.28 or 0.75 S.D.s, $p = 0.003$). Based on the analysis, appropriate age corrections had been introduced in girls (Table 7.4).

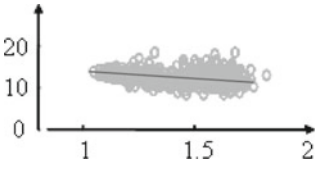
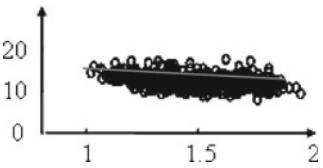
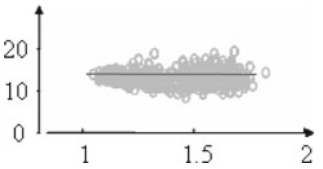
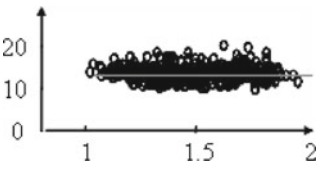
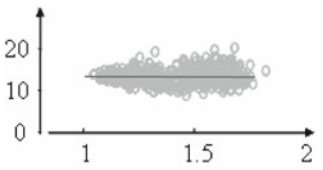
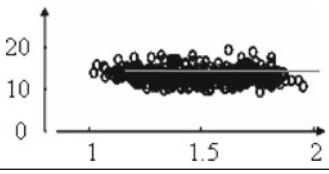
7.3.6 The Physical and Physiological Interpretation of the HBSI

HBSI exhibited very low and statistically not significant correlations between indices and body height and next calendar age with the slopes of the regression lines approaching 0. The fact that HBSI could be considered independent of body height sanctions the characterization of a population of children 5–18 years old with one mean and one S.D. The Polish data model is designed to reflect the normal age-related changes in HBS. It seems that at least in some applications, BMI in children 5–18 years old may be replaced as a HBS measure with the HBSI which is coherent with the biomechanics of human growth. The HBSI may also replace multiple indices with two sex-specific, age-invariant indices.

HBSI may be very useful in some applications requiring comparison of HBS changes over time, coming from different populations. In the case of one sex or single subject analysis the application of gender-specific HBSI should be considered. In the case of a single population of children of both genders, the pooled HBSI could be beneficial to healthcare professionals.

PI based on the ideally geometrically similar growth ($\chi = 3$) decreases slightly with the body height and age, introducing more variability over the age groups (Lebiedowska et al. 2008). Due to larger variability of PI over HBSI, PI may introduce a slightly larger error over HBSI in the classification of

Table 7.2 PI, HBSI of Polish children (5–18 years old; between years 1985 and 1990) as a function of body height (horizontal line)

	Girls $N = 444$		Boys $N = 403$	
	Regression equation	Mean ± S.D.	Regression equation	Mean ± S.D.
PI = m/h^3 (kg/m^3)	15.81–2.28 H $r = -0.15$, $p = 0.002$	12.47 ± 1.64	17.32–3.46 H $r = 0–0.34$, $p < 0.001$	12.21 ± 1.62
				
$HBSI_G$ (kg/m$^{2.84}$)	12.93 + 0.19 H $r = 0.02$, $p = 0.66$	13.21 ± 1.73	–	
				
$HBSI_B$(kg/m$^{2.68}$)	–		13.51 + 0.15 H $r = 0.02$, $p = 0.7$	13.74 ± 1.72
				
HBSI (kg/m$^{2.76}$)	12.18 + 0.98 H $r = 0.1$, $p = 0.03$	13.6 ± 1.79	14.2– 0.59 H $r = 0–0.08$, $p = 0.13$	13.34 ± 1.67
				

Modified from Lebiedowska et al. (2008). With permission
This table illustrates that *HBSI*: Human Body shape Index, but not *PI*: Ponderal Index can be considered as independent on the body height (*H*) (horizontal line in all graphs)

abnormal HBS. PI may still be useful, especially in the analysis of different populations, irrespective of location and time (Seltzer 1966; Nahum 1966; Huber 1969; Hattori and Hirohara 2002; Rolland-Cachera et al. 1982; Ricardo and Araujo 2002).

As the HBSI described above were based on growth models treated as the "gold standard" of human growth, they carry over the advantages and the limitations already mentioned. HBSI may be useful to describe HBS growth-related changes over a larger period of time, when increase in body height is the most important factor affecting growth. To analyze shorter periods of growth (for example during puberty) other indices, may be more suitable.

Table 7.3 $HBSI_B$ in age groups in boys

Age group (years old)	*N*	Mean ± STD
5–9	124	13.80 ± 1.55
9–12	103	13.51 ± 1.65
12–15	107	13.69 ± 1.93
15–8	69	14.03 ± 1.75

Reprinted from Lebiedowska et al. (2008). With permission
This table shows the lack of statistically significant differences ($p = 0.253$) between mean $HBSI_G$ in age groups

Table 7.4 $HBSI_G$ in age groups in girls

Age group (years old)	*N*	Mean ± STD	$HBSI_G$ age correction
5–9	129	13.42 ± 1.37[a,b]	0.98
9–12	105	12.65 ± 1.76[c]	0.96
12–15	105	12.69 ± 1.83[d]	0.96
15–18	105	13.93 ± 1.67	1.05

Reprinted from Lebiedowska et al. (2008). With permission
This table shows the differences between the mean $HBSI_G$ in age groups
[a]5–9 and 9–12 years old, $p = 0.003$
[b]5–9 and 15–18 years old, $p = 0.006$
[c]9–12 and 15–18 years old, $p = 0.001$
[d]12–15 and 15–18 years old, $p = 0.001$
The appropriate age corrections for girls have been calculated (last column)

7.3.7 Application of HBSI for the Establishment of Standard Thresholds for Detection of Overweight and Obesity in Children

Out of the full spectrum of the HBS two extremes are especially important from the humanitarian, social and economic point of view. Malnutrition causes 53% of all deaths in children younger than 5 years (Bryce et al. 2005), whereas obesity has been announced as a major public health crisis in the USA (Cole et al. 2000; Wang et al. 2008). The limitation of BMI to detect obesity in children based on the growth charts was reported by Piers et al. 2000 and de Onis, 2004. The differences in the estimates of the prevalence of obesity in children and adolescents vary from 11–24%, despite using the same set of the data (Troiano and Flegal 1999). The lack of uniform, absolute thresholds for obesity classification in children must play a role in the diffusion of the estimates. Future studies should compare the sensitivity and specificity of HBSI versus other indices in the classification of the obesity/malnutrition in children (Field et al. 2003). The model of growth which was used to establish the HBSI was based on the sample of population of Polish children (5–18 years old; between years 1985 and 1990), characterized by ideal fat composition as judged by 95th percentile of BMI values. In addition, a similar model of growth (during a comparable period of time) was reported in English children (Rosenthal et al. 1994). The lack of any other "golden standard" suggests that the model based on the population of Polish children may serve as a model of natural growth. The absolute thresholds for HBS based on the model are displayed in Table 7.5.

The thresholds are based on the sex- and age-specific percentiles values: "underweight" (<5th percentiles), "normal" (5th–85th percentiles), "at risk of overweight" (85th–95th percentiles) and "overweight" (≥95th percentiles). Since these thresholds for overweight and obesity were established

Table 7.5 Thresholds for overweight and obesity based on a model of growth of Polish children (5–18 years old) between years 1985 and 1990.

Sex		Ranges of indices in Polish children population	
		Girls ($N = 444$)	Boys ($N = 403$)
$HBSI_G$ (kg/m$^{2.84}$)	Underweight	<10.67	–
	Normal	10.67–14.97	
	At risk of overweight	14.97–16.4	
	Overweight	≥16.4	
$HBSI_B$ (kg/m$^{2.68}$)	Underweight	–	>11.27
	Normal		11.27–15.36
	At risk of overweight		15.36–17.19
	Overweight		≥17.19
HBSI (kg/m$^{2.76}$)	Underweight	>10.96	>10.97
	Normal	10.96–15.39	10.97–14.93
	At risk of overweight	15.39 – 16.85	14.93–16.57
	Overweight	≥16.85	≥16.57

Modified from Lebiedowska et al. (2008). With permission
This table displays the ranges of sex-independent (HBSI) and sex-specific ($HBSI_B$, $HBSI_G$) body shape indices for: underweight (<5th percentiles), normal (5th percentiles–85th percentiles), at risk of overweight (≥85th percentiles and ≥95th percentiles) and overweight (≥95th percentiles) conditions
N: number of children, *B*,*G*: boys and girls respectively

Table 7.6 The key features of Human Body Shape Index (HBSI)

Human BODY Shape Index HBSI	Girls	Boys	Girls and boys
HBSI	$HBSI_G = m/h^{2.84}$	$HBSI_B = m/h^{2.68}$	$HBSI_G = m/h^{2.76}$
Mean (±S.D.)	13.21 ± 1.73	13.74 ± 1.72	13.47 ± 1.74
Units	kg m$^{-2.84}$	kg m$^{-2.68}$	kg m$^{-2.76}$

This table lists equations to calculate HBSI: Human Body Shape Index from body mass, m (kg) and body height $h(m)$ (first row). The reference values (mean and standard deviations: S.D.) of HBSI of Polish children (5–18 years old; between years 1985 and 1990) are listed in the second row, and the appropriate units in the third row

using sample distributions, the development of physiologically based thresholds for overweight and obesity should be explored. There exists a discrepancy between the definitions for abnormal HBS in children and adults. It is well established that increased BMIs in adults (for overweight BMI ≥ 25 and for obesity BMI ≥ 30) are associated with the changes in other anthropometric, biochemical and instrumental measure of obesity (Dahlström et al. 1985; Wang et al. 2004). The projection of well established adult thresholds into the pediatric population may lead to the development of physiologically based thresholds. It seems however, that the thresholds may be sex specific.

7.4 Application of the Growth Models to Other Areas

The algorithms presented for the development of growth models and the establishment of age-independent HBSI were originally developed to separate the influence of growth and rehabilitation treatment in children. The normalization techniques has been successfully applied to children aged

5–18 years and the age independent, normalized databases of various biomechanical parameters (maximum knee extension and flexion isometric movement of force, lower-leg moment of inertia, passive stiffness and damping of the knee joint (Lebiedowska et al. 1996). The approach presented in this chapter can be easily applied in ergonomics (Lebiedowska 2006), sport and other research disciplines where human growth affects the outcome measures.

Summary Points

- The growth of Polish children 1985–1990 was close to the geometrically similar growth (10.6% accuracy in boys and 5.3% accuracy in girls).
- The lack of any other "golden standard" suggests that the model based on the population of Polish children 1985–1990 may serve as a model of natural growth.
- The age independent, sex-specific index (HBSI) was based on the mathematical model of Polish children's growth.
- HBSI characterizes the shape of children 5–18 years old with one sex specific, age-independent mean and one standard deviation.
- HBSI allows for comparison of the changes in the human body shape during growth in individuals and between different populations (time, location).
- Comparison of sensitivity and specificity of HBSI and standard BMI to detect overweight and obesity in children should be explored.

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Chapter 8
Reproducibility of DXA Measurements of Bone Mineral and Body Composition: Application to Routine Clinical Measurements

Colin E. Webber

Abstract Measurements of bone mass and body composition using X-ray based dual photon absorptiometry (DXA) are used extensively to investigate patients suspected to be suffering from conditions that affect the skeleton or soft tissues. Commonly, such measurements seek to establish whether or not a change has occurred since a previous measurement. The ability to detect change is determined by perhaps the most important characteristic of a DXA system; that is the precision of the measurement. In this chapter, the results of precision assessments made in various groups of subjects using equipment housed in a routine, diagnostic Department of Nuclear Medicine are reviewed and compared to published values.

In phantoms, the precision or reproducibility of a bone mineral density (BMD) measurement is better than 0.005 g cm^{-2} even if the number of measurements from which the precision is derived is accumulated over an extended time period. In children, same-day precision for spine BMD, whole body BMD and proximal femur BMD worsens to values of 0.007, 0.009, and 0.011 g cm^{-2}, respectively. For adults, the same-day precision of spine BMD decreases further to 0.010 g cm^{-2} while femur BMD precision is virtually unchanged. Long-term precision for spine BMD and femur BMD decreases again to 0.029 and 0.023 g cm^{-2} while for the radius, long-term precision is 0.012 g cm^{-2}. The precision attained by routine clinical laboratories for the measurement of BMD can be comparable to that obtained by research laboratories.

The same-day precision of DXA measurements of body composition in children is about 20 g for whole body bone mineral content (WBBMC), 250 g for lean tissue mass (LBM) and 190 g for fat mass (FM). In adults, same-day precision for WBBMC is similar to that measured in children while for LBM and FM, same-day precision worsens to about 350 and 280 g, respectively. Extending the time interval between pairs of measurements to more than 1 day makes the reproducibility of soft tissue composition assessments much worse as the effect of daily fluctuations in dietary balances will be included in the reproducibility evaluation. The presence of obesity means that the precision of measurements in all body composition compartments deteriorates.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_8,

Abbreviations

BMD	Bone Mineral Density
BMI	Body Mass Index
CV	Coefficient of Variation
DOF	Degrees of Freedom
DXA	X-Ray based Dual Photon Absorptiometry
FM	Fat mass
ICC	Intra-class Correlation Coefficient
LBM	Lean Body Mass
LSC	Least Significant Change
SD	Standard deviation
WBBMC	Whole Body Bone Mineral Content

8.1 Introduction

When several measurements are made of a given variable, the extent of dispersion of the results about a mean value is determined by the reproducibility or precision of the technique. In turn, precision determines the magnitude of the smallest difference that can be detected reliably between successive measurements of the same variable. If the difference between repeat measurements of the same variable for a range of subjects is small and shows little variation, then the reproducibility, or precision, is good. The better the reproducibility, the greater is the chance of correctly identifying the extent and direction of a change between two measurements.

DXA is an X-ray based technique that can be used to measure the mass of each constituent in an object that consists of two radiologically distinct materials. Since people can be considered as a mixture of bone mineral and soft tissues, DXA can be applied to the measurement of bone mineral and body composition. The technique depends upon differences in the relative attenuation of X-rays by the two materials at two different energies. The key features of DXA are listed in Table 8.1.

When DXA measurements are used for the assessment of fracture risk in patients suspected of suffering from osteoporosis, scans are performed at fracture-prone sites such as the spine or hip. DXA measurements of body composition require a scan of the whole body. Typical examples of a lumbar spine scan and a whole body scan are shown in Figs. 8.1 and 8.2. Figure 8.2 clearly demonstrates the discrimination between fat and lean constituents of soft tissues.

The reproducibility of a bone mass or body composition measurement technique is important since it establishes the time interval that must elapse before a likely change in response to disease progression or in response to a putative treatment intervention can be detected. Precision for a technique such as DXA depends, in part, upon the measurement context. For example, it is to be expected that the reproducibility of BMD measured for an inanimate object such as a model spine embedded in a plastic block will be better than when reproducibility is measured for a living subject. In turn, the reproducibility derived from measurements repeated on the same day in a person will be expected to be better than that derived from measurements repeated over an extended period of time in the same person. These different reproducibilities are termed phantom in vitro precision, same-day in vivo precision and long-term in vivo precision, respectively. The term “short-term precision” should be applied to reproducibility measurements separated by a period of a few months while the term “long-term precision” should be applied to reproducibility measurements separated

Table 8.1 Key features of X-ray based dual energy absorptiometry (DXA or DEXA)

Bone mineral attenuates low-energy X-rays to a much greater extent than soft tissues.
Bone mineral and soft tissues attenuate medium-energy X-rays to a similar extent.
Attenuation measurements for low- and medium-energy X-rays transmitted through people allow an evaluation of the mass of mineral and soft tissue in the path of the X-rays.
DXA measurements of bone mineral can be applied to fracture-prone sites such as the spine and hip in patients suspected to be suffering from osteoporosis.
A DXA scan of the whole body allows the evaluation of total mineral mass in the skeleton and total soft tissue mass in the body.
The differences in density and composition between lean and fat mean that the relative attenuation of low and medium energy X-rays, when measured at locations where no bone mineral is present, is dependent on soft tissue composition.
DXA allows non-invasive, in vivo measurements of bone mass and body composition.

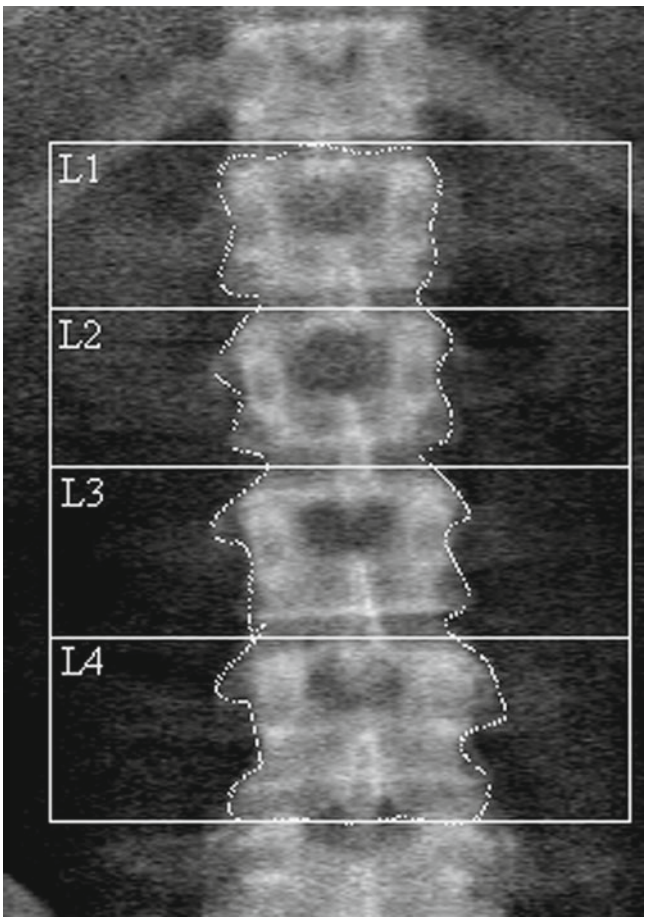

Fig. 8.1 A typical DXA scan of the lumbar spine. Analysis software places regions of interest over the projected vertebrae from L1 to L4. The result is expressed as an areal density (g cm^{-2}); that is, the mass of bone mineral detected (BMD) within the region of interest divided by the area of bone mineral measured

by a period of a year or more. The first purpose of this chapter is to review the mathematical means of assessment and expression of reproducibility for DXA measurements of bone mass and body composition. This is followed by the reporting of results of same-day and long-term reproducibility for in vitro phantom BMD measurements. Same-day in vivo precision is then established for children who are either above or below age 10. Next, same-day and long-term in vivo precision is

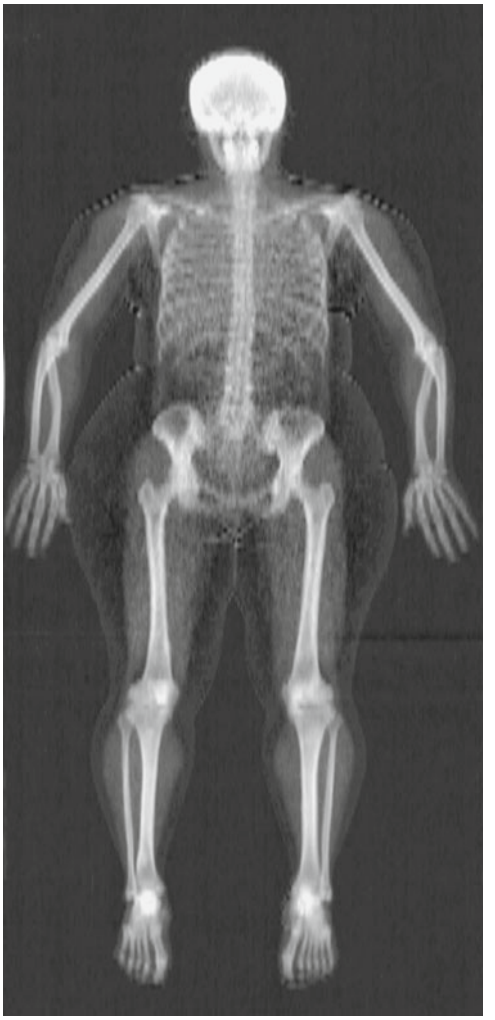

Fig. 8.2 A whole body DXA scan. The primary software analysis divides the body mass into contributions from bone mineral and soft tissue. A secondary analysis separates the soft tissue into lean and fat components

evaluated in adults. Finally, same-day in vivo precision is also measured for WBBMC, LBM, and FM. Most of these precision assessments are made using equipment within a routine, clinical Department of Nuclear Medicine.

The second purpose of this chapter is to compare the reproducibility attainable during routine clinical DXA measurements of bone and body composition with values of precision reported in the literature. While there are many reported bone mass precision measurements, considerably less information is available concerning the reproducibility of DXA-based body composition measurements. If the precision measured in a routine clinical service setting is similar to accepted published values then equipment and personnel normally dedicated to clinical practice should be able to participate in research protocols. Clinical trials that are designed to search for small changes in bone mass or body composition frequently require the participation of multiple sites to recruit sufficient subjects to detect an anticipated change with a given statistical confidence. If the precision of routine clinical DXA systems is equivalent to that of research DXA systems, then the opportunities for trial recruitment may be expanded.

8.2 Definitions of Precision

8.2.1 Phantom Precision

The reference article that defines BMD reproducibility and describes methods for precision assessment was published by Glüer et al. (1995). If numerous (n) measurements of BMD (x) are made for a phantom without repositioning between measurements, the precision of the measurement will be reflected in the *standard deviation* (SD) of the frequency distribution given by the familiar expression:

$$\text{Phantom Precision} = \left(\sum \frac{(x-\mu)^2}{(n-1)} \right)^{0.5} \tag{8.1}$$

where μ is the mean of the BMD measurements.

When the BMD for the same phantom is measured numerous times over a period of about 1 year with repositioning between each measurement, it is to be expected that the frequency distribution will broaden and the SD will increase reflecting the additional variance introduced from time-dependent changes in machine performance and phantom positioning.

8.2.2 In Vivo Same-Day Precision

When an additional source of variance, such as that originating from a patient, is introduced, the SD increases further. The SD derived from multiple in vivo measurements in a single subject would be greater than that established for a phantom. However, it is unreasonable to collect multiple measurements from a single subject because even though the radiation dose from a DXA measurement of bone mineral or body composition is acceptably low, good radiation safety practice demands that individual exposures are minimized. In addition, reproducibility is likely to differ between subjects and it is preferable to establish precision in a representative group of volunteers. A solution that satisfies both requirements is to replace many measurements in one person with a pair of measurements in many subjects. If two measurements are made in one subject the SD will be according to (8.1),

$$\left\{ \frac{\left[x_1 - \left(\frac{x_1 + x_2}{2} \right) \right]^2}{2-1} + \frac{\left[x_2 - \left(\frac{x_1 + x_2}{2} \right) \right]^2}{2-1} \right\}^{0.5} \tag{8.2}$$

which, provided sufficient care is taken with the algebra, reduces to

$$\text{Subject Same} - \text{Day Precision} = \left\{ \frac{(x_1 - x_2)}{2^{0.5}} \right\} \tag{8.3}$$

This expression shows that when two measurements are taken in one subject, the SD for that subject depends upon the difference between the two measurements. The reproducibility for the

BMD measurement technique is then obtained from an appropriate combination of the individual subject precisions obtained from a representative sample of volunteers (m subjects). That is:

$$\text{Technique Same} - \text{Day Precision} = \left\{ \frac{\sum (x_1 - x_2)^2}{2m} \right\}^{0.5} \tag{8.4}$$

Equation (8.4) is equivalent to expression 4b in the formulation by Glüer et al. (1995).

8.2.3 In Vivo Long-Term Precision

The difference between two BMD measurements separated by a considerable length of time will include contributions from both measurement uncertainty and bone mass change due to aging or disease. The measurement uncertainty not only reflects those factors that contribute to same-day uncertainty but also includes the influence of time-dependent changes in both patient and instrument such as, changes in body weight and soft tissue composition and modifications to measurement procedures or protocols, respectively. In addition there may be a contribution when different technologists perform the first and second measurements, a scenario that is likely in a clinical department offering routine diagnostic measurements of bone mass and body composition.

The assumption can be made that age-dependent changes in bone mass within a particular patient can be described accurately by fitting the measured BMD values to a mathematical expression that adequately represents the time-dependent changes for that patient. The measurement precision is then related to the extent of the deviations of the observed BMD values from the derived equation and is represented by the standard error of the estimate. The change required from (8.3) for the estimation of precision is that the differences between paired measurements are replaced by the differences between the measured and a predicted BMD, $\hat{\mathbf{x}}$, at each time point. The expression for subject long-term precision also has to be modified to account for the parameters estimated from the fitting process. If a linear change of bone mass is assumed then precision will be given by:

$$\text{Subject Long} - \text{Term Precision} = \left(\sum \frac{(x - \hat{\mathbf{x}})^2}{(n-2)} \right)^{0.5} \tag{8.5}$$

where the summation is performed across all n BMD measurements. The number of degrees of freedom (DOF) has been reduced by 2 because the slope and intercept of the fitted line has been calculated from the measured BMD values. If a more complicated expression, such as a second-order polynomial, is used to fit the measured BMD data, then the denominator of (8.5) may have to be modified accordingly. The intercept and the coefficients of the linear and quadratic terms would have to be fitted so that the denominator of (8.5) would become (n–3).

Once precision has been established in a sufficient number of representative subjects, long-term precision for the technique can be calculated using (8.6).

$$\text{Technique Long} - \text{Term Precision} = \left\{ \sum \frac{(x - \hat{\mathbf{x}})^2}{(\text{DOF} - 2)} \right\}^{0.5} \tag{8.6}$$

where the summation is performed across all subjects. Equation (8.6) is equivalent to expression 12 in the formulation by Glüer et al. (1995). If the time interval over which measurements are obtained for a subject is relatively short (<5 years) then the expected changes in BMD will likely be well represented by a linear expression. Longer time intervals may require fitting the observed

BMD values with a second-order polynomial expression that assumes no specific mechanism of age-dependent BMD decline.

When a variable is normally distributed, such as lumbar spine BMD at a given age in normal adults, the 95% confidence range extends from 1.96 SDs below the mean expected-for-age value to 1.96 SDs above the mean expected-for-age value. This range closely corresponds to a *Z*-score range from −2 to +2. When a variable such as the absolute difference between two successive, individual BMD measurements is considered, the difference always has to be finite and cannot take on a negative value. The normal distribution is inappropriate when describing differences between pairs of BMD measurements and is replaced by the Chi Square distribution. The upper and lower 95% confidence intervals are selected from tables depending on the total number of DOF involved.

8.2.4 Derived Terms

Despite the simplicity of using the SD as the expression of precision, other mathematical constructs have been devised. For example, the SD is often expressed as a *coefficient of variation* (CV) which is simply the SD expressed as a percentage of the mean value. The CV is not recommended as a means of expression of bone mass or body composition reproducibility. This is because the CV will increase in populations such as children or subjects with disease who will have low mean values for the measured variable. However, the increased CV does not necessarily indicate a poorer precision.

Another form of expression for reproducibility is the *intra-class correlation coefficient* (ICC). The ICC is applicable when reproducibility is measured in groups of samples extracted from a single population and measures the proportion of the total variance that can be attributed to the population rather than to the measurement technique. As technique reproducibility improves, the value of the ICC approaches 1.

There are a number of terms that are derived from the precision measured in a group of subjects. The uncertainty in the BMD difference between two groups of subjects is $(SD^2 + SD^2)^{½}$. The upper limit of the 95% confidence interval for this uncertainty is $1.96 \times 2^{½} \times SD$. It is argued that if the difference between two successive measurements exceeds this value, then a statistically significant change has taken place. This upper limit is termed the *least significant change* (LSC). The LSC is also referred to as the *smallest detectable difference* (SDD).

8.3 BMD Precision

In this section, the results of precision measurements that have been derived from a densitometer operating in a busy, routine, clinical environment will be presented. This machine is located within a Department of Nuclear Medicine in an acute care hospital and provides DXA measurements of bone mass and body composition for referred inpatients and outpatients. The densitometer is operated typically by a number (~8) of experienced staff and, commonly, one or two trainees participating in a rigorous in-house DXA training program. It is essential for such a DXA service to know the reproducibility that is achievable by staff in representative groups of patients attending for diagnostic tests. In Sects. 8.3.1–8.3.4, precision results are presented for phantoms, children and for same-day and long-term precision in adults. In Sect. 8.3.5, the measured precision is compared with published values.

Table 8.2 In vitro precision for DXA measurements of spine BMD in a phantom

Phantom	Precision (g cm^{-2})
L1–L4 spine, same-day	0.0024
L1–L4 spine, long-term	0.0038

Precision deteriorates when the time scale is extended

Table 8.3 Same-day, in vivo precision for DXA measurements of BMD in children

Children	Same-day precision (g cm^{-2})
L1–L4 spine	0.0068
Total femur (left hip)	0.0110
Whole body	0.0087

Precision in children differs between sites and is considerably worse than precision measured in a phantom

8.3.1 Phantom BMD Precision

When a standard lumbar spine phantom was measured without repositioning on 33 occasions over a period of 75 min using a Hologic Discovery A densitometer, the mean and SD was 1.0224 ± 0.0024 g cm^{-2}. When the same quality control phantom was measured on 156 occasions over a period of 236 days with no more than a single measurement performed on any 1 day, the mean and SD was 1.0230 ± 0.0038 g cm^{-2}. The mean BMD values are not statistically different from each other but the SD for the extended phantom measurements is greater by a factor of 1.6. These values for the phantom reproducibility are shown in Table 8.2.

8.3.2 In Vivo Same-Day BMD Precision in Children

The densitometer responsible for the results shown in Table 8.2 has also been used to determine same-day precision in a number of groups of patients. Since many referrals involve children from McMaster Children's Hospital, we established reproducibility of bone mass and body composition measurements in children (Leonard et al. 2009). Thirty-two children were allocated to either a group aged less than ten (nine girls and six boys) or a group aged ten and above (nine girls and eight boys). Repeat BMD measurements for the lumbar spine (L1–L4), for the total region of the proximal femur and for the whole body were made with repositioning between the two studies.

Table 8.3 shows the results of precision measurements in children. There was a marginally poorer precision for lumbar spine BMD measurements in younger children (0.0083 vs. 0.0052 g cm^{-2}) with no significant differences between the groups for proximal femur BMD (0.0126 vs. 0.0094 g cm^{-2}) or for whole body BMD (0.0087 vs. 0.0086 g cm^{-2}). The results that are shown in Table 8.3 represent averages for the whole group of 32 children. It might be expected that reproducibility would be worse in younger children because of a poorer ability to co-operate during positioning for the DXA scan. On the other hand, reproducibility might be expected to be better in younger children since the number of transmitted X-rays will be greater than in older children so that statistical uncertainties of measured count rates will be less. It is clear that short-term in vivo precision in children is worse than both short-term and long-term precision in a phantom.

Table 8.4 Same-day, in vivo precision for DXA measurements of BMD in adults

Adults	
L1–L4 spine	0.0103
Total femur (left hip)	0.0117
Total femur (both hips)	0.0077

Precision for spine BMD is poorer in adults than children. Precision for hip BMD is the same for children and adults

8.3.3 In Vivo Same-Day BMD Precision in Adults

Same-day precision was measured for groups of 30 adults recruited from routine referrals by each of eight experienced technologists again using the same densitometer as in Sect. 8.3.1 (Nelson et al. 2009). Each technologist performed repeat scans of the lumbar spine and the proximal femur with repositioning between each scan. The results averaged over all 8 technologists are shown in Table 8.4. Same-day precision for lumbar spine BMD was better in children than in adults (0.0068 vs. 0.0103 g cm^{-2}) whereas there was no difference between children and adults for the total region of the left femur (0.0110 vs. 0.0117 g cm^{-2}). This result for the spine is likely explained by the fact that the greater transmission of X-rays through children means that there is less uncertainty in measured count rates, while for the proximal femur, errors arising from patient positioning dominate the uncertainty and are approximately the same for children and adults. Unfortunately, we have not yet established the precision of routine WBBMD measurements in adults so that we only have the value for children shown in Table 8.3 (0.0087 g cm^{-2}).

Precision was measured by each of eight technologists in order to determine the extent, if any, of differences between technologists in spine and hip BMD reproducibility. It was found that lumbar spine reproducibility ranged from a low of 0.008 g cm^{-2} to a high of 0.011 g cm^{-2}, values that were statistically not different from each other. In sharp contrast, for the total region of the left proximal femur, reproducibility ranged from a low of 0.006 g cm^{-2} to a high of 0.016 g cm^{-2}, values that were statistically different from each other. Even when the total regions of both hips were considered together, reproducibility varied from a low of 0.004 g cm^{-2} to a high of 0.011 g cm^{-2}, again values that were statistically different from each other.

8.3.4 In Vivo Long-Term BMD Precision in Adults

The measurement of long-term precision in patients presents a considerable challenge. As outlined in Sect. 8.2.3, the time interval between measurements must be sufficiently long to ensure that both the technologist and the patient are not influenced by recall of positioning strategies from the first measurement. In addition, the time interval must be long enough so that the factors that determine long-term precision have sufficient opportunity to be expressed. In addition, since the factors that do influence precision are more likely to exert their influence over extended periods of time, it is likely that long-term precision will increase as the duration of the period of assessment increases. For any reasonable estimate of long-term precision, the time interval required should be at least 1 year or, preferably, longer. During such long time intervals, there is every chance that BMD will change through normal, age-dependent bone mass adjustments (either positive or negative) and there must be an adjustment for such time-dependent changes. Long-term precision is determined from the

Table 8.5 Long-term, in vivo precision for DXA measurements of BMD

Adults	Long-term precision (g cm^{-2}) Linear bone change	Long-term precision (g cm^{-2}) Polynomial bone change
L1–L4 spine	0.0463	0.0295
Total femur	0.0224	0.0231
1/3 radius	0.0135	0.0116
UD radius	0.0128	0.0101

Long-term precision at the spine depends upon the model assumed for temporal changes in BMD

extent of the deviations between measured BMD values and the corresponding values predicted from a line fitted to all BMD measurements as expressed in (8.5).

Spine BMD was measured in a group of 13 postmenopausal women who attended the same Department of Nuclear Medicine that performed the same-day precision measurements as mentioned above. The women had originally belonged to a control group for a prospective study of the impact of low and medium dose hormone replacement therapy upon bone mass (Beaumont et al. 1996). Since the completion of the study, the women had been followed with frequent DXA measurements. None of the 13 women took any medication known to affect bone metabolism during the extended follow-up periods. The average age for the 13 women at the time of the first measurement was 54.9 ± 2.1 years and the average duration of follow-up was 18.6 years. There were a total of 217 lumbar spine BMD measurements with a total follow-up period of 241.6 person–years. The long follow-up periods meant that many different technologists performed the measurements and a variety of different densitometers was used. There was initially a Norland 2600 machine using a ^{153}Gd source that was followed, in turn, by a QDR 1000, a 4500A and a Discovery A X-ray based system from Hologic. Serial BMD measurements of the non-dominant radius and the total region of the left proximal femur were also performed for shorter follow-up periods in the same 13 women using only the X-ray based densitometers.

Table 8.5 shows that when it was assumed that age-dependent changes in BMD followed a linear pattern, long-term precision was 0.046 g cm^{-2} at the spine, 0.022 g cm^{-2} for the total region of the proximal femur and 0.013 g cm^{-2} for the radius. However, simple observation of the BMD changes over time showed that an assumption of linear change was inadequate. When it was assumed that the temporal changes in BMD were better modeled using a second-order polynomial expression, the long-term precision for spine BMD was improved to 0.029 g cm^{-2}. Long-term precision for the proximal femur and the radius was unchanged at 0.023 and 0.011 g cm^{-2}, respectively.

Long-term precision for the spine is almost three times worse than same-day precision, while long-term precision for the femur is twice the same-day precision. The site with the best long-term precision is clearly the radius. This suggests that the radius could be the most suitable site for the detection of BMD changes. However, it is not clear if important changes in BMD are expressed at the radius to the same extent as at the spine and femur.

8.3.5 Comparison with Published Precision Data

When 57 published papers concerning the reproducibility of BMD measurements were reviewed (Wilson and Smith 2009), median values for same-day, in vivo coefficients of variation for the spine and

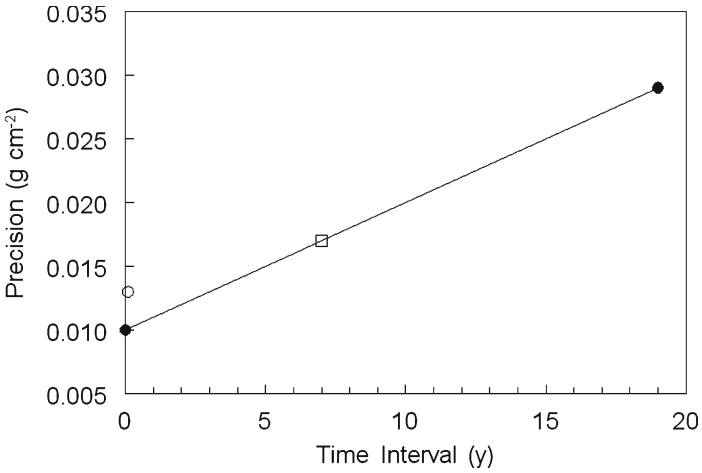

Fig. 8.3 Dependence of long-term precision upon the duration of the time interval for the collection of BMD measurements: results obtained from a routine, clinical department (●); from Leslie (2008) (○) and Patel et al. (2000) (□)

total region of the femur were found to be 1.10% and 1.20%, respectively. Unfortunately, reproducibility was only reported as a CV but if it is assumed that the mean spine and hip BMD was 1.0 g cm^{-2}, then same-day precision is 0.011 g cm^{-2} for the spine and 0.012 g cm^{-2} for the total region of the hip. These results correspond almost exactly to the same-day precision given in Table 8.4 for the spine and hip suggesting that it is possible for routine, clinical BMD clinics to achieve precision standards normally associated with research laboratories.

Short-term precision has been derived from spine BMD measurements that were separated by periods of between 3 and 49 days (Leslie 2008). Short-term precision was found to be 0.020 g cm^{-2} which was significantly worse than the same-day precision of 0.013 g cm^{-2}.

Long-term precision was measured by Patel et al. (2000) in 40 postmenopausal women each followed for up to 7 years. Again, precision was only reported as the CV which for the spine was 1.65% and for the total region of the hip was 1.57%. Assuming once more that the mean spine and hip BMD was 1.0 g cm^{-2}, the long-term precision is 0.017 g cm^{-2} for the spine and 0.016 g cm^{-2} for the total region of the hip. These values are better than those given in Table 8.5 (0.029 and 0.023 g cm^{-2}) which were derived over follow-up periods of almost 20 years. The results of same-day, short-term and long-term precision measurements for the spine are shown together in Fig. 8.3 and demonstrate a dependence of precision upon the time interval over which BMD measurements are performed. Measurement precision declines as the follow-up period is extended. This observation leads to the notion that there is an optimum time for the allowed interval between BMD measurements in a patient; that interval is determined by the balance between a longer interval to be sure a detectable BMD change will occur and a shorter interval to exploit the better long-term in vivo precision.

Patel et al. (2000) observed that a body mass index (BMI) greater than 28 kg m^{-2} had a negative impact on precision as did a large change in BMI during the follow-up period. Nelson et al. (2009) also showed that even though reproducibility for the lumbar spine did not differ between technologists, precision did worsen as the BMI of a patient increased. Again in contrast, there was no detectable dependency of proximal femur BMD precision upon BMI.

8.4 Body Composition Precision

In this section, the only body composition precision results obtained from the same densitometer used in Sects. 8.3.1–8.3.4 are those reported for children in Sect. 8.4.2. The other precision values reviewed in this section have been extracted from the literature.

8.4.1 Precision of Body Composition Measurements in Phantoms

Louis et al. (2006) scanned a Hologic whole body phantom on 18 occasions over a 5-month period and found a precision of 23 g for WBBMBC, 135 g for LBM and 171 g for FM (Table 8.6). A similar precision for WBBMC was found by Ellis et al. (2004) who reported a SD of 21 g for repeated measurements of a commercial phantom.

8.4.2 Same-Day In Vivo Precision of Body Composition Measurements in Children

The reproducibility achieved in a routine Nuclear Medicine Department for body composition measurements is listed in Table 8.7 for groups of younger and older children (Leonard et al. 2009). For adolescents, the reproducibility for WBBMC, LBM and FM was 18, 251, and 189 g, respectively with better precision obtained for younger children.

Other published reports have determined same-day precision in children. Wosje et al. (2006) measured reproducibility in 34 children using a Hologic 4500A densitometer. They reported values for WBBMC, LBM and FM precision of 0.02, 0.17, and 0.15 kg, respectively, results that are consistent with those given in Table 8.7. Margulies et al. (2005) used a Lunar Prodigy to measure precision in 49 children aged between 5 and 17 years. Reproducibility was reported as 48 g, 0.4 kg, and 0.3 kg, respectively. These results demonstrate a considerably poorer precision probably because a variety of scan modes ("thick," "standard," and "thin") were used in the analysis of DXA scans.

8.4.3 Same-Day and Short-Term In Vivo Precision of Body Composition Measurements in Adults

When reproducibility was assessed in 20 adults with immediate repositioning, SDs of 15, 348, and 278 g were obtained for WBBMC, LBM and FM, respectively (Jensen et al. 1997). Same-day precision for WBBMC is the same in adults and children whereas the precision for both LBM and FM is approximately 100 g worse in adults than in children. As shown in Table 8.8, when the time interval between pairs of total body DXA scans is extended to between 1 and 7 days the corresponding SDs increase to 24, 470, and 314 g (Jensen et al. 1997). When body composition reproducibility was determined from whole body scans obtained on each of four consecutive days, the SDs for WBBMC, LBM, and FM were 29, 532, and 389 g, respectively (Kiebzak et al. 2000). Short-term precision for LBM worsened by about 150 g while for FM, short-term precision was about 70 g worse than same-day reproducibility. These comparisons reflect the added variance introduced by day-to-day fluctuations in food and, particularly in the case of LBM, fluid balances.

Table 8.6 In vitro precision for DXA measurements of body composition in a phantom (Louis et al. 2006)

Phantom	Precision (g)
WBBMC	23
LBM	135
FM	171

Table 8.7 Same-day, in vivo precision for DXA measurements of body composition in children

Children	Same-day precision (g) age < 10 years	Same-day precision (g) 10 > age > 18
WBBMC	13	18
LBM	201	251
FM	172	189

Precision of body composition measurements is poorer in teenagers and adolescents than in younger children

Table 8.8 In vivo precision for DXA measurements of body composition in adults

Precision Number of subjects (*N*)	WBBMC (g)	LBM (g)	FM (g)	References
Same-day				
N = 20	15	348	278	Jensen et al. (1997)
Short-term				
N = 35	24	470	314	Jensen et al. (1997)
N = 20	29	532	389	Kiebzak et al. (2000)
Obese				
N = 9, *same-day*	40	530	590	Cordero-MacIntyre et al. (2002)
N = 20, *short-term*	30	1,679	1,559	Cordero-MacIntyre et al. (2002)

Precision of body composition measurements in adults is worse than in children particularly when measurements are recorded on different days and in the presence of obesity

Thomsen et al. (1998) found that same-day precision in eight subjects was 39, 503, and 395 g for WBBMC, LBM, and FM precision, respectively. When the same authors measured same-day precision eight times in a single subject, the corresponding values were 6, 96, and 97 g, respectively demonstrating that there are large differences in precision between subjects.

8.4.4 *In Vivo Precision of Body Composition Measurements in the Presence of Obesity*

As stated above, Wosje et al. (2006) observed that the same-day precision for 34 non-obese children was 0.17 kg for LBM and 0.15 kg for FM. At the same time, they found in 32 obese children, same-day precision was 0.47 and 0.50 kg for LBM and FM, respectively. That is, precision worsened for LBM and FM by factors of 2.8 and 3.3, respectively. The reproducibility for WBBMC was unaffected by the presence of obesity in children. In nine obese postmenopausal women, same-day reproducibility was 40, 530, and 590 g for WBBMC, LBM, and FM (Cordero-MacIntyre et al. 2002). As shown in Table 8.8, short-term reproducibility, when measured by the same researchers using the

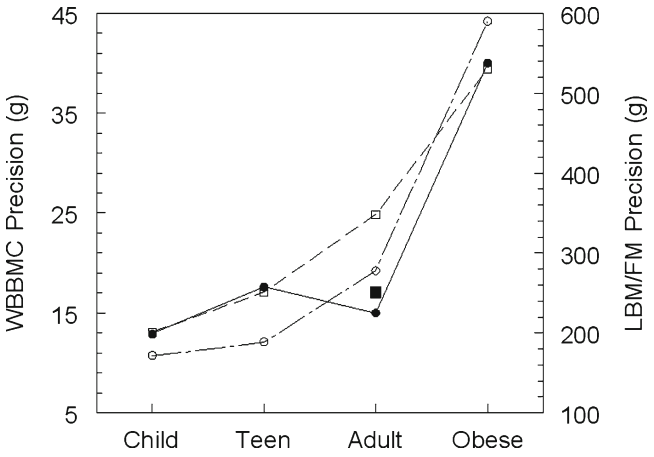

Fig. 8.4 Same-day Precision for measurements of WBBMC (●——●), LBM (□---□) and FM (○——○) in various groups of subjects. Also included is the precision of FM (■) in patients with AIDS (Cavalcanti et al. 2005)

same equipment in 20 obese postmenopausal women after an interval of 3 months, worsened for LBM and FM to 1,679 and 1,559 g, respectively (Cordero-MacIntyre et al. 2002). That is, precision for LBM and FM deteriorated by factors of 3.2 and 2.6, respectively, when short-term reproducibility was compared to same-day reproducibility. There is little relevance in measuring long-term precision of LBM and FM measurements because the time-dependent changes in soft tissue composition can be large over periods of time of 1 year or longer.

The impact of obesity upon reproducibility of body composition measurements is illustrated in Fig. 8.4 which shows results extracted from Tables 8.7 and 8.8 as well as the results of same-day precision measurements of FM in a group of 30 HIV positive subjects (Cavalcanti et al. 2005). WBBMC precision is similar for children and adults at about 15 g but deteriorates dramatically by a factor of about 3 with obesity. The precision of LBM and FM measurements is best in young children and is equal to about 200 g. Reproducibility worsens steadily for adolescents, adults and obese subjects; again, precision for LBM and FM is about a factor of 3 worse in the presence of obesity.

Summary Points

- Precision or reproducibility reflects the ability of a technique to produce the same result when the same variable is measured and establishes the smallest difference between successive measurements that can be considered to be significant.
- In vivo same-day precision is based upon the differences between two measurements of BMD performed in each of a representative group of subjects with repositioning between the two BMD measurements.
- In vivo long-term precision is based upon the individual differences between the measured BMD values recorded over an extended time period and the corresponding predicted BMD values derived from a mathematical fit to the complete series of BMD measurements.
- Precision is best expressed as a SD and not as a coefficient of variation.
- Same-day and long-term BMD precision for a spine phantom is better than 0.005 g cm^{-2}.
- Same-day precision for spine BMD in children is 0.007 g cm^{-2} deteriorating to 0.010 g cm^{-2} in adults.
- Same-day precision for BMD of the total region of the left hip in children is 0.011 and 0.012 g cm^{-2} in adults.
- Long-term BMD precision increases as the measurement time period is extended.

- Long-term precision over a period of close to two decades is 0.029 g cm^{-2} for BMD at the spine and 0.023 g cm^{-2} for the total region of the left hip.
- Same-day precision for WBBMC is better than 20 g in children and adults.
- Same-day precision for LBM is about 200 g in young children, worsens to 250 g in adolescents and to about 350 g in adults.
- Same-day precision for FM is about 170 g in young children, worsens to 190 g in adolescents and to about 280 g in adults.
- Short-term precision in adults deteriorates to about 470 g for LBM and to about 350 g for FM in comparison to same-day precision.
- In the presence of obesity, same-day precision for both LBM and FM in children deteriorates to about 500 g.
- In the presence of obesity, short-term precision for both LBM and FM in adults deteriorates to about 1,600 g.

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Chapter 9
Self-Reported Anthropometry: Body Mass Index and Body Composition

Savvas P. Tokmakidis, Antonios D. Christodoulos, and Helen T. Douda

Abstract Obesity is a threat in our society, associated with several health-related problems. Monitoring body weight and height is the most commonly used, fast and easy method to evaluate overweight and obesity, assess related health risks and develop appropriate prevention strategies. Self-reported anthropometry frequently replaces actual measurements, mainly in population studies due to financial reasons. The purpose of this chapter is to examine the validity of self-reported body measures as a diagnostic method for the evaluation of overweight and obesity in different populations. Self-reported data for anthropometric indices derive from personal interviews, telephone interviews or mail questionnaires. Numerous studies have found that self-reported and actual measures are highly correlated; however, this approach may be misleading, given that sources of bias cannot be assessed by the correlation coefficient of the Pearson's r statistic. Reviews of validity studies show that height is mostly over-reported and weight under-reported. These misreports are reflected in the calculation of body mass index (BMI) and the subsequent assessment of overweight and obesity prevalence, which are all constantly underestimated. A number of factors have been reported to affect the extent of the bias between self-reported and measured anthropometrics, including – inter alia – age and gender distribution of the study population, weight status, race/ethnicity, socioeconomic status, cultural differences and variations in study protocols. Taken together, these findings suggest that, based on self-reported data, specific sub-groups would be incorrectly classified, which would lead to an inaccurate assessment of the obesity-related morbidity risk of a population, with important implications for health planning. Self-reported anthropometry could be more usable if appropriate correction factors were used in epidemiological studies, by taking actual measures from an independent sub-sample of the same population, by collecting specific socio-demographic characteristics and/or by lowering the BMI threshold for overweight and obesity.

Abbreviations

BMI	Body mass index
DM	Directly measured
F	Females
M	Males

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_9,

NR Not reported
OB Obesity
OW Overweight
ROC Receiver operation characteristic techniques
SES Socio-economic status
SR Self-reported

9.1 Introduction

The prevalence and severity of overweight and obesity has increased in all sectors of the population over the last decades, becoming a worldwide epidemic (Wang and Lobstein 2006). Numerous research studies to date clearly demonstrate that obesity in childhood and adult life increases several metabolic risk factors related to cardiovascular disease (Poirier et al. 2006). The World Health Organization has declared obesity as one of the greatest challenges and chronic disease risk factors in this century. Therefore, identification and accurate monitoring of overweight or obesity prevalence are essential and can provide useful guidance to public health professionals in order to estimate the extent of the problem, assess secular trends and develop effective intervention strategies.

Obesity is the result of excess body fat. However, the accurate measurement of body fat mass requires sophisticated and often costly methods with limited applicability in the clinical setting. Thus, several measures of body weight standardized for height have been used as a proxy index of adipose tissue. The most commonly used screening tool for overweight and obesity is the body mass index (BMI), defined as body weight divided by height squared ($kg \cdot m^{-2}$). Given its strong association with adiposity measurements derived from dual energy X-ray absorptiometry (0.83–0.98), BMI seems to be an appropriate measurement for the indirect assessment of adiposity (Lindsay et al. 2001; Weerarathna et al. 2008).

Straightforward measurements of weight and height in large population samples and on a regular basis are not always technically feasible, due to financial limitations and time requirements. Thus, health research frequently uses self-reported data for height and weight as an alternative to actual anthropometric measures (Spencer et al. 2002; Lissau et al. 2004). The BMI derived from these reports is subsequently used to screen for overweight and obesity (Engstrom et al. 2003).

However, concern has been raised about the accuracy and validity of self-reported height and weight, given that existing research evidence has shown inconsistent outcomes. Some researchers suggest that self-reported anthropometry is valid and has an advantage compared to the directly measured body dimensions (see Table 9.1), since it is convenient, time-saving, requires no equipment and is easy to apply to large populations (Bolton-Smith et al. 2000; Stommel and Schoenborn 2009). In contrast, others consistently noted systematic bias in self-reported data (Gorber et al. 2007;

Table 9.1 Advantages and disadvantages of self-reported anthropometry

Advantages	Disadvantages
• Convenient • Time-saving • Low cost • Requires minimum equipment • Easy to apply to large-scale population studies	• Systematic and random bias, affected by age, gender, ethnicity, body composition and health status • Consistent underestimation of overweight and obesity prevalence • Misjudgement of obesity-related health risks

This table lists the pros and cons of using self-reported anthropometry instead of direct measurement of height and weight in order to assess BMI and estimate obesity

McAdams et al. 2007). The latter insist that these data could lead to erroneous estimating rates of overweight and obesity. Furthermore, the validity of self-reported anthropometry appears to vary in gender, age, race or ethnicity. In addition, weight status itself, i.e. being overweight or obese, may also affect the reported anthropometric values. In this context, the goal of the present chapter is to discuss these issues and examine the validity of self-reported body measures as a diagnostic method for the evaluation of overweight and obesity in different populations.

9.2 Differences in the Procedure of Self-Reported and Directly Measured Data

Self-reported data for anthropometric indices derive from personal interviews, telephone interviews or mail questionnaires. Subjects are generally randomly selected from a population and are asked to provide their height and weight, in addition to other demographic data (age, gender, education level, socio-economic class, health status, etc.). The interval between collection of self-reported and direct measurements in validity studies ranges from the same day to a few months, or is not reported (Boström and Diderichsen 1997; Sherry et al. 2007). The elapsed time between measures should be controlled and taken into account in analyses, given that changes in weight can occur over short time-periods (Gorber et al. 2007). Bias in self-reported weight and height is larger in telephone interviews than in in-person interviews (Ezzati et al. 2006).

Measured data for anthropometry are more reliable. In population studies, however, errors affecting the outcome of the data can also occur when researchers do not use standard procedures and consistent guidelines. Studies comparing self-reported versus measured data should be based on reproducible and appropriate procedures. Measurement methods, including the calibration of the equipment and details of the procedure should be reported. Measurement conditions such as the order of measurement, who is taking the measurements, what equipment is being used, as well as what clothes or shoes are worn should be provided. This is of importance when the measurements are determined to the nearest 0.1 cm and 0.5 kg. For instance, during measurements of adolescents, light clothing might be acceptable, but measuring height in growing subjects with shoes on is likely to cause errors (weight of shoes and height of soles and heels, especially among youth with regard to current fashion trends).

9.3 Correlations Between Self-Reported and Measured Anthropometry

Numerous validity studies have used correlation analyses to interpret associations between self-reported and measured anthropometric indices. Regardless of significant or trivial mean differences in height, weight and/or BMI, the vast majority of the existing literature on the validity of self-reported data reported high correlations between self-reports and actual measures (see Table 9.2). However, the use of correlation coefficients as an index of validity has been frequently criticized. This approach may be misleading, since this statistic has been designed to investigate bivariate relationships and to assess only the closeness to a linear relation between two methods and not agreement or whether the methods can be used interchangeably. Furthermore, sources of systematic bias cannot be assessed via Pearson's *r* coefficient of correlation.

This means that correlation coefficient analysis is insensitive to any possible differences in the means and variances of raw data. Consequently, the high correlations observed between self-reported

Table 9.2 Differences between self-reported and directly measured anthropometry, differences in the prevalence of obesity and correlation coefficient between the self-reported and measured values obtained from various studies

			Correlation coefficient (*r*)			Differences in means (SR-DM)			Differences in prevalence (%)			
References	Sample	Age (year)	Height	Weight	BMI	Height (cm)	Weight (kg)	BMI (kg/m^2)	SR OW	DM OW	SR OB	DM OB
De Vriendt et al. (2009)	982	10–18	0.95	0.96	0.90				11.2	13.2	1.2	2.0
	475 F					0.38	–0.60	–0.32				
	507 M					–0.47	–0.67	–0.12				
Fonseca et al. (2009)	462								17.5	18	8	9.1
	233 F	14.0 ± 1.8	0.84	0.96	0.89	1.0 (4.8)	–1.3 (3.2)	–0.79 (1.6)	16.3	20.2	6	7.3
	229 M	14.0 ± 2.0	0.93	0.95	0.81	0.39 (5.2)	–0.68 (4.8)	–0.29 (2.2)	18.8	15.7	10	10.9
Lim et al. (2009)	383 F	34.1 ± 7.9	0.94	0.97	0.95	1.33 (1.84)	–0.62 (2.14)	–0.62			12	16.7
	358 M	37.4 ± 8.4	0.94	0.95	0.91	1.54 (2.23)	–0.93 (3.47)	–0.77			29.1	36.9
Stommel and Schoenborn (2009)	15.161	18–85	NR	NR	NR	0.95 (0.04)	–0.75 (0.05)	–0.59 (0.02)	34.2	33.6	28.1	31.6
	Underweight					0.50	2.14	0.64				
	Normal weight					0.58	0.53	0.02				
	Overweight					1.11	–0.6	–0.56				
	Obese					1.16	–2.02	–1.56				
	Extreme obese					1.24	–4.31	–2.12				
Dekkers et al. (2008)	1.298	43.9 ± 8.6	0.99	0.99	0.99	0.7	–1.4	–0.7	69.7	66.3	26.8	33.7
	4344 F		0.98	0.99	0.99	0.7	–1.2	–0.7	64.7	62.9	30.2	37.1
	864 M		0.99	0.99	0.98	0.7	–1.5	–0.7	72.2	68.1	25.1	31.9
Shields et al. (2008)	4.567	12 to >80	NR	NR	NR	0.7	–2.1	1.1	32	33.8	15.2	22.6
	2.108 F					0.5	–2.5	1.2	25	28.2	15	21
	2.429 M					1.0	–1.8	0.9	38.8	39.4	15.4	24.2
	Females											
	435	12–24				1.7	0.3	0.8				
	735	25–44				2.3	–0.2	0.9				
	673	45–64				3.1	–0.4	1.4				
	426	65–79				2.7	–1.6	1.6				
	160	80 or older				1.8	–3.3	1.9				
	Males											
	435	12–24				1.2	–0.3	0.6				
	684	25–44				1.5	–0.7	0.8				
	589	45–64				2.4	–1.1	0.9				

	325	65–79				2.5	–2.3	1.6				
	75	80 or older				1.0	–2.6	1.1				
Elgar et al. (2005)	415	15–17				0.43	–0.52	–0.29	13.9	18.7	2.8	4.4
	225 F		0.76	0.95	0.88	0.31	–0.61	–0.28	13.1	17.6	3.6	5.4
	190 M		0.87	0.94	0.88	0.58	–0.43	–0.29	14.8	19.9	2	3.3
Brener et al. (2003)	2,032 (957 F/1075M)	Grades 9–12	0.93	0.93	0.93	2.7	–3.5	–2.6	14.8	21.4	14.9	26
Spencer et al. (2002)	4.808	35–76	All >0.90						34.6	39.9	10.7	14.8
	2,938 F		NR	NR	NR	0.60 (2.68)	–1.40 (2.45)	–0.72 (1.27)	28.9	33.1	11.3	14.7
	1,870 M		NR	NR	NR	1.23 (2.57)	–1.85 (2.92)	–0.96 (1.24)	43.6	50.8	9.7	14.9
Bolton-Smith et al. (2000)	971 F		NR	NR	NR	1.7 (2.37)	0.95 (2.64)	–0.17 (1.34)	27.3	33.1	16.9	18.9
	865 M		NR	NR	NR	1.3 (2.50)	0.63 (3.45)	–0.19 (1.40)	30.8	37.2	17	19.7
	Females								34.6	41.7	17.1	20.5
	244	25–34				0.9	2.1	–0.3				
	237	35–44				0.6	2	–0.4				
	245	45–54				0.8	1.7	–0.3				
	245	55–64				1.4	0.9	0.2				
	Males								27.3	33.1	16.9	18.9
	189	25–34				0.5	1.6	–0.3				
	216	35–44				0.6	1.9	–0.4				
	228	45–54				0.4	1.0	–0.2				
	232	55–64				0.5	0.7	–0.0				
Goodman et al. (2000)	11,495	Grades 7–12	0.94	0.95	0.92				NR	NR	8.1	9.7
	5,690 F		NR	NR	NR		1.02	–0.27	NR	NR	NR	NR
	5,805 M		NR	NR	NR		–0.19	–0.03	NR	NR	NR	NR
Boström and Diderichsen (1997)	1,764 F					–0.79	–1.64	–0.85	19.3	30	6.7	12.1
	1,444 M					–0.60	–0.74	–0.40	23.3	32.3	3.8	6.2

This table presents correlation coefficients between self-reported and measured anthropometrics, differences between self-reported and directly measured mean for height, weight and BMI, as well as differences between reported and observed prevalence of overweight and obesity, obtained from published studies
SR self-reported, *DM* directly measured, *M* males, *F* females, *OW* overweight, *OB* obesity, *NR* not reported

and measured anthropometric indices do not imply validity. However, based solely on high correlation coefficients, several studies suggest that self-reported height and weight should be considered as valid proxy measures for actual values, especially in analyses that use these values as continuous variables (Davis and Gergen 1994; Brener et al. 2003).

9.4 Differences Between Self-Reported and Actual Anthropometric Measures

A review of relevant studies revealed significant differences between self-reported and actual anthropometric measures (see Table 9.2). Height is mostly over-reported (Spencer et al. 2002; Brener et al. 2003; Shields et al. 2008; Stommel and Schoenborn 2009; Fonseca et al. 2009), but also under-reported (Dekkers et al. 2008; De Vriendt et al. 2009). The magnitude of the discrepancies between self-reported and measured height is relatively small (from -0.5 cm to ~2 cm), with the exception of one study (Brener et al. 2003), which reported differences of ~6.9 cm in US adolescents. It seems, therefore, that young individuals have a tendency to overestimate their body height to a greater extent compared to older age groups.

On the other hand, weight is systematically under-reported in most studies and the degree of under-reporting ranges from 0.5 to 4.5 kg in children, adolescents and adults. The mean errors in self-reported height and weight are relatively small; however, in most studies the standard deviations of the differences are large, implying significant between-subject variability in the accuracy of self-reported height and weight.

These misreports are reflected in the calculation of BMI, which is constantly underestimated, with distortions in weight influencing this underestimation to a greater degree than distortions in height. The magnitude of the discrepancies between self-reported and measured BMI ranges from no difference to ~2 $kg \cdot m^{-2}$, whereas standard deviations are smaller in comparison to the individual values of height and weight. In contrast to this trend, Bolton-Smith et al. (2000) found that BMI was overestimated in a Scottish population aged 25–64 years by a mean difference 0.2 ± 1.4 $kg \cdot m^{-2}$ in men and 0.2 ± 1.3 in women.

9.5 Factors Affecting the Bias

The magnitude of the observed differences between self-reported and actual anthropometric measures varies between studies. An array of factors may be associated with the inaccuracy of self-reported height and weight, including – inter alia – population characteristics such as age distribution, gender, ethnicity, weight status, socio-economic status, cultural norms, perceived body image or size, motivation and variations in study protocols (Bolton-Smith et al. 2000; Spencer et al. 2002; Dekkers et al. 2008). The main findings of relevant studies that investigated factors possibly affecting the accuracy of self-reported anthropometrics are presented below.

9.5.1 Gender Differences

Although self-reported BMI understates measured BMI for both genders, the patterns of accuracy in self-reported anthropometric measures appear to be influenced by gender, with females tending to underreport their weight to a greater degree than males (Ezzati et al. 2006; Shields et al. 2008;

Stommel and Schoenborn 2009); consequently, self-reported BMI is most often lower for females, compared to males, leading to the false conclusion that prevention programs should be targeted more at males. The bias towards greater under-reporting among females tends to disappear with older age (Stommel and Schoenborn 2009). Other surveys found no significant gender differences in the degree of inaccuracy in self-reported anthropometrics (Bolton-Smith et al. 2000; Tokmakidis et al. 2007; Fonseca et al. 2009). According to some authors, females report their weight and height more accurately than males and the resulting discrepancy in BMI is then smaller in females (Spencer et al. 2002). The greater discrepancy often observed in females may be associated with a socially desirable response, a reflection of the greater emphasis that women give on thinness and the perceived pressure to conform to cultural norms for social desirability (Brener et al. 2003).

9.5.2 Age Differences

Several studies have examined the possible associations between age and the accuracy of self-reports in height, weight and BMI, with conflicting results. Investigating the accuracy of self-reported height and weight in Belgian adolescents, De Vriendt et al. (2009) observed that age did not affect the extent of the bias in BMI values. Data on children and adolescents from our laboratory (Tokmakidis et al. 2007) revealed that high school students (aged 12.5 ± 0.3) tended to overestimate their height and under-report their weight to a greater degree than elementary school pupils (aged 11.4 ± 0.4). As a result, the understating of BMI was greater for high school compared to elementary school pupils (mean difference is measured vs. reported BMI: 1.61 ± 1.4 $kg \cdot m^{-2}$ vs. 0.79 ± 1.8 $kg \cdot m^{-2}$, respectively, $p < .001$).

Results from another data set in the United States, adolescents (Himes et al. 2005) indicated an increasing overestimation of height by males with age and less underestimation of weight in subsequent age groups in both genders. The greater biases in weight were observed at ages 12–14, possibly implicating enhanced body dissatisfaction or poor body image at early adolescence. Assessment of sexual maturation in self-report studies could be helpful in understanding deviations of self-reported anthropometrics from corresponding measured values in adolescence, given that maturity status may alter adolescents' body image perceptions.

Another contributing reason to the observed discrepancy in self-reported dimensions in the youth could be, at least partially, the large physical changes characterizing adolescence. Adolescents who undergo such rapid body changes without being regularly weighed and measured are less likely to be aware of their actual height and weight.

Data on Swedish adults 18–84 years (Bostrom and Diderichsen 1997) revealed that overestimation of height increased, whereas underestimation of weight decreased with age in both genders. Stommel and Schoenborn (2009) analyzed data from the National Health and Nutrition Examination Survey and found the larger underestimates of measured BMI among the youngest and oldest individuals (Fig. 9.1). Shields et al. (2008) reported that age was strongly associated with over-reporting of height and weakly related to BMI underestimation in the Canadian Community Health Study. In an adult Scottish population study (Bolton-Smith et al. 2000) there was no systematic trend by age, however the oldest individuals (55–64 years old) tended to underestimate their height the least and their weight the most. In contrast to the aforementioned studies, Dekkers et al. (2008) found that in Dutch overweight employees, the self-reported bias of body dimensions was not greater in older individuals than in younger individuals.

Over-reporting of height in older individuals may be associated with the height loss that commonly occurs among older subjects, as a result of the aging process, such as osteoporosis and/or loss of

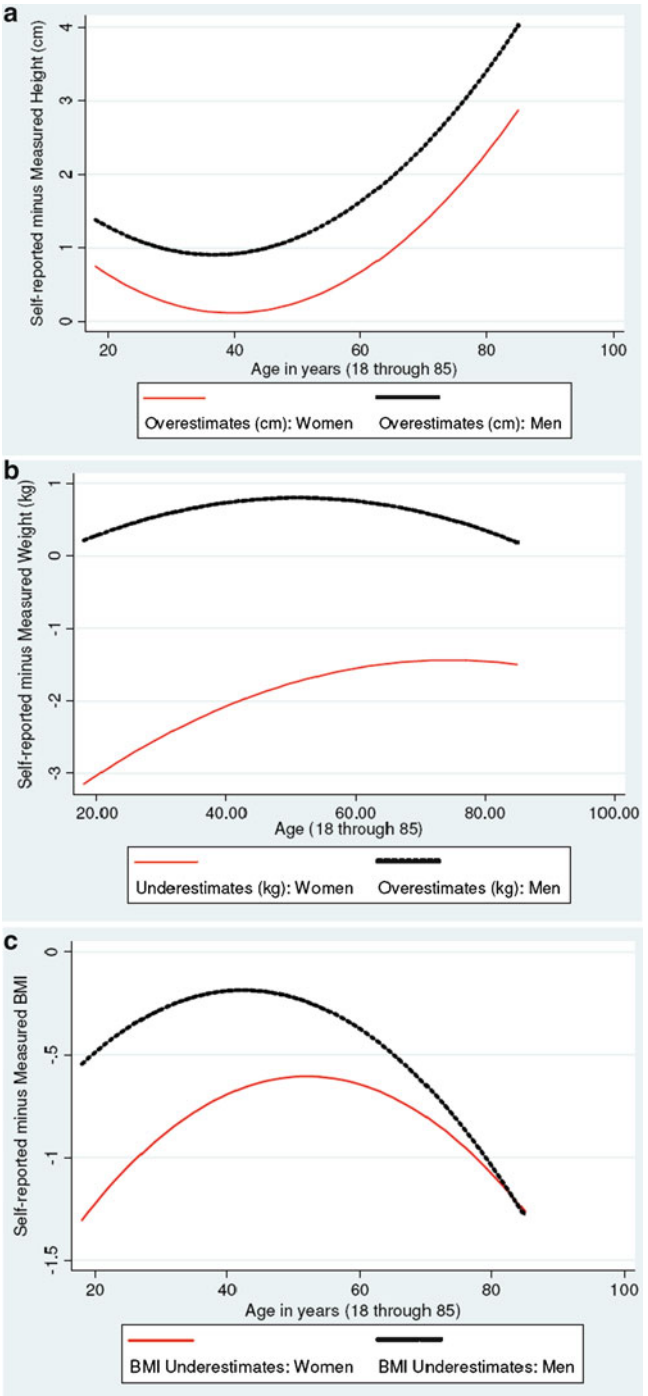

Fig. 9.1 Association of age and gender with discrepancies between self-reported and measured anthropometric indices. This Figure illustrates how age and gender are associated with the discrepancies between self-reported and measured height (**a**), weight (**b**) and BMI (**c**): Fitted values. (Reprinted from BMC Public Health, Stommel and Schoenborn (2009), p. 6, BioMed Central Ltd)

muscle tone. Stature declines with age in older individuals by up to 2 cm per decade after age 30 and this loss may not be perceived by the individuals, so they may report their height as it was in previous age periods (Shields et al. 2008). Moreover, access to routine health care or other issues related to the populations studied may account for the observed discrepancies.

Table 9.3 Differences in BMI values ($kg \cdot m^{-2}$) by BMI categories based on measured height and weight in selected studies

		BMI categories based on measured height and weight			
References	Sample	Underweight <18.5	Normal weight 18.5–24.99	Overweight 25.0–29.99	Obesity ≥30.0
Stommel and Schoenborn (2009)	15.161	0.64	0.02	–0.56	–1.16 (Class I-II)[a] –2.12 (Class III)[a]
Danubio et al. (2008)	F	0.2	–0.9	–0.7	–1.1
	M	–1.8	–0.6	–0.2	–1.4
Shields et al. (2008)	2.108 F	0.2	–0.5	–1.4	–2.1 (Class I)[a] –3.0 (Class II)[a] –5.0 (Class III)[a]
	2.429 M	2.6	–0.1	–1.0	–1.9 (Class I)[a] –2.7 (Class II)[a] –4.0 (Class III)[a]
McAdams et al. (2007)	F	NR[b]	–0.54[b]	–1.23	–1.86
	M	NR[b]	–0.07[b]	–0.75	–2.01
Spencer et al. (2002)	2,938 F	0.19	–0.44	–0.96	–1.35
	1,870 M	0.61	–0.60	–1.02	–1.66

This table focuses on the mean differences in BMI values across BMI categories based on actual measurements of height and weight. Positive values represent overestimates, negative values represent underestimates.
[a]Obesity Class I: 30.0 ≤ BMI ≤ 34.99; Obesity Class II: 35.0 ≤ BMI ≤ 39.99; Obesity Class III: BMI ≤ 40.0 (clinical obesity)
[b]BMI <25 $kg \cdot m^{-2}$ was classified as normal weight in this study

9.5.3 Weight Status

It seems that the magnitude of the discrepancy between self-reported and actual anthropometric measures is strongly affected by the actual body size, with heavier people mostly understating their weight (Spencer et al. 2002; Shields et al. 2008; De Vriendt et al. 2009; Stommel and Schoenborn 2009) and underweight individuals overestimating (Stommel and Schoenborn 2009), but also underestimating (De Vriendt et al. 2009) their weight.

Overall, the extent of underestimation of BMI increases with increasing weight and BMI category (Table 9.3). We found a significant effect of BMI status in the accuracy of self-reported parameters in Greek students, with a higher BMI resulting in trivial discrepancies in height, but in considerable biases in weight and BMI. The same pattern was observed when differences were computed for elementary and high school students separately (Fig. 9.2). Similarly, Himes et al. (2005) found out that the errors in self-reports became increasingly negative as weight and BMI categories increased, with steeper slopes in females (Fig. 9.3). These patterns of underestimation suggest that the greatest impact of the bias in self-reported BMI will be to systematically underestimate overweight and obesity prevalence, defined by the upper percentiles.

The bias towards greater under-reporting among the higher BMI categories is a notable consistent finding in the literature, indicating a general negative scaling pattern of errors in self-reported height, weight, and BMI relative to the measured dimensions. It is possible that some overweight and obese individuals avoid weighing themselves and consequently report their body dimensions less accurately. This could also be explained by the social sensitivity generally associated with body image (Bolton-Smith et al. 2000; Gorber et al. 2007; Stommel and Schoenborn 2009). Although it is clearly an objective, measurable phenomenon (i.e. BMI), obesity is also considered a subjective, emotional

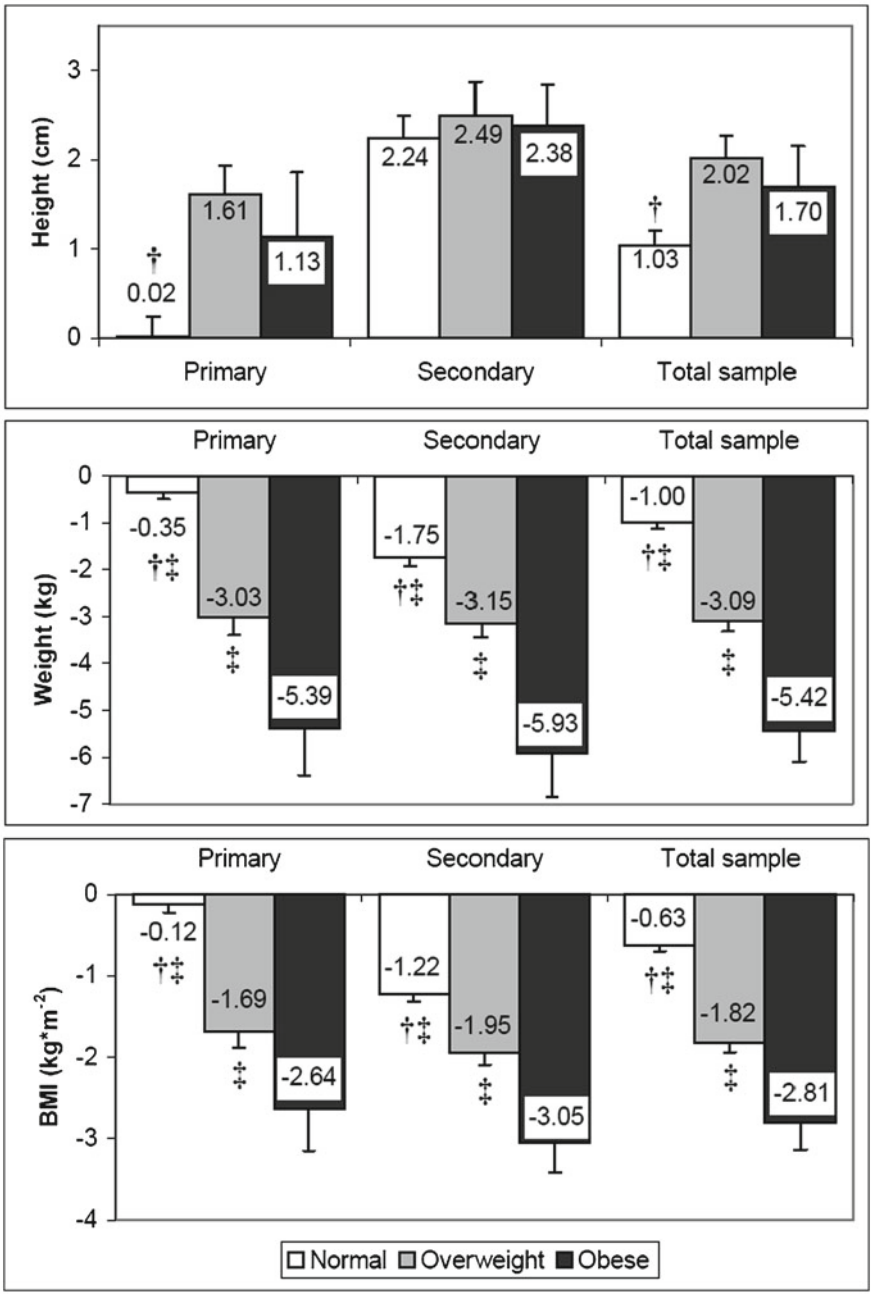

Fig. 9.2 The effect of BMI status in the accuracy of self-reported anthropometric parameters in Greek school children. This Figure illustrates the differences between self-reported and measured values of height, weight and BMI across BMI categories in Greek primary and high school students. Values significantly different: † vs. overweight (*p*-values between.004 and.001); ‡ vs. obese (*p*-values between.02 and.001) (Reprinted from Tokmakidis et al. (2007), p. 309, with permission from Elsevier)

experience of one's body and body image, and has been significantly associated with internal states such as low self-esteem (Goodman et al. 2000). Since a lower self-esteem is associated with greater bias in self-reported weight (Elgar et al. 2005), discrepancies in self-reported anthropometric values

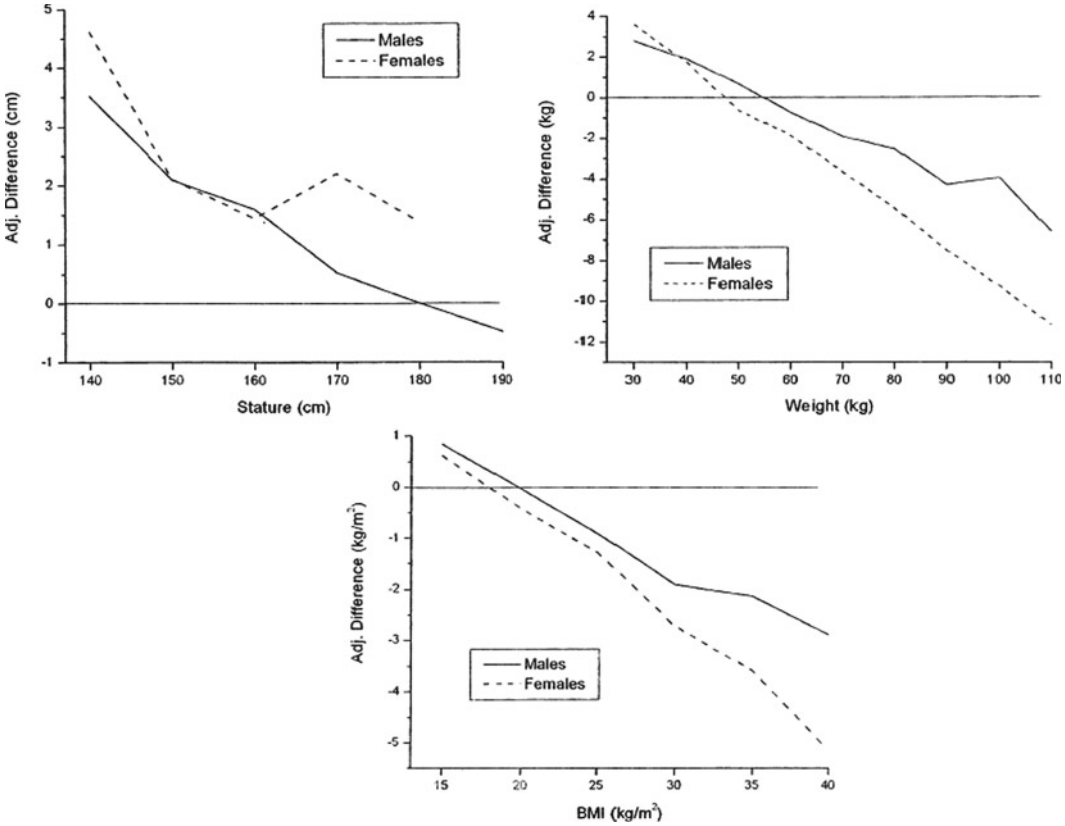

Fig. 9.3 Patterns of bias in self-reported anthropometric values relative to categories of the measured dimension by gender. This figure presents mean differences for self-reported minus measured dimensions, plotted separately for males and females relative to categories of the measured dimension (Reprinted from Himes et al. (2005), p. 275, with permission from Elsevier)

possibly reflect discrepant perceptions of body image among individuals, implying one's unwillingness or inability to acknowledge his or her obesity because of denial and/or social stigma.

9.5.4 Socio-Economic Status

Many investigators have pointed out social and economic status differences, indicated by several parameters, such as income, occupation, education, wealth and/or place of residence, as important determinants that appear to influence the prevalence of overweight and obesity. The extent of misreporting anthropometric indices seems to be greater in individuals with higher BMI values. Therefore, it is conceivable that social class differences could bias height, weight and BMI values based on self-reports (Table 9.4).

There is a limited number of studies examining the association of social and economic status indices with the accuracy of self-reported anthropometrics, with inconsistent findings. Both effects and no-effects have been reported. Himes et al. (2005) found that male adolescents in the highest

Table 9.4 Key features of socio-economic status

1. SES differences could have an influence on self-reported anthropometry
2. SES is a measure of an individual's or family's social and economic position in the community, relative to others
3. SES is determined based on a combination of variables including income, occupation, education, wealth and/or place of residence
4. SES is typically broken into three categories: high SES, middle SES, and low SES, which describe the three areas a family or an individual may fall into
5. Existing data on SES conditions and the accuracy of self-reported height, weight and BMI are inconsistent

This table lists the key facts of socio-economic status including definition, assessment methods, and categorization (American Psychological Association, 2007)

SES socio-economic status

socio-economic groups overestimated their height relatively more than males with lower socio-economic scores. However, data on British and the US adolescents revealed no association between social class or parental education and the accuracy of reported height, weight or BMI (Crawley and Portides 1995; Goodman et al. 2000).

Data from studies on adults implicate that less educated subjects, male non-manual workers and female manual workers underestimate actual weight respectively more than those with higher education, male manual workers and female non-manual workers (Boström and Diderichsen 1997; Dekkers et al. 2008). Further, women with a higher family income are more aware of their current weight and thus report their weight more accurately than women with a lower family income (Jalkanen et al. 1987).

9.5.5 Race and Ethnicity

The accuracy of self-reported anthropometric indices may differ among various ethnic populations, due to differences in body size, cultural norms and/or different sensitivities about being overweight (Dekkers et al. 2008; Stommel and Schoenborn 2009). Hence, a number of studies have investigated this issue.

Data analyses on US adolescents showed that race and ethnicity was not related to the bias between self-reported and measured BMI (Goodman et al. 2000; Brener et al. 2003). Himes et al. (2005) came to similar findings in a population of Minnesota adolescents, still, they further reported significant main effects of ethnicity for height and weight in males, with Asian males tending to overestimate height and underestimate weight more than black or Hispanic males.

Thai men and women showed results consistent with findings in Western populations, since they misreported their height and weight in ways similar to their counterparts in developed countries (Lim et al. 2009). On the other hand, Japanese showed extremely small height and weight discrepancies, compared to other studies, probably due to the practice of annual health checkups in Japan and the greater awareness of their body size (Wada et al. 2005). Findings from the National Health and Nutrition Examination Surveys II and III indicate a non-significant effect of race (white/black), but important, consistent ethnic differences between Mexican Americans and other groups, independent of other variables (Gillum and Sempos 2005). It is not unknown if these differences are due to cultural differences in awareness of body size, different cultural norms or differing views of body image (Himes et al. 2005) and further research is needed to clarify these issues.

9.5.6 Other Factors Affecting the Bias

A limited number of studies have included various factors that may be related to the accuracy of self-reported anthropometrics, such as smoking status, physical activity, health status, end digit preference, diet restraint, weight history and medication for cardiovascular risk factors. However, their findings are disparate and should be interpreted with caution.

The reasons for misreporting are multiple and complex. Hence, it becomes clear that apart from the aforementioned factors, several other factors could probably operate independently or simultaneously and affect the bias between self-reported and measured anthropometric values. For instance, clothes may account for some of the apparent underestimation in self-reported weight, since weighing at home is likely to be done in minimal clothing. Yet, weighing scales, even within clinics and hospitals, are significantly inaccurate (Bolton-Smith et al. 2000). Further research into the characteristics of over- and under-reporters will help to understand the reasons for misreporting, get more insight into this issue and improve the accuracy of self-reported anthropometric indices.

Self-reported data present a trend of bias towards the ideally expected value (wishful thinking). In industrialized societies, where the ideal of tallness and the desire to be slim prevail, people may tend to report values of height and weight that are close to their ideal values rather than to their actual measures. Short stature is socially undesirable, leading short individuals to report higher values of body height. On the other hand, the increasing prevalence of overweight and obesity in the recent years does not seem to have made excess weight more acceptable; thus, feeling the pressure to conform to "desirable" standards, individuals in the upper BMI categories tend to hide and under-report their weight. Individuals with body composition close to ideal fall within the appropriate confidence interval values.

9.6 Differences in Estimated Prevalence of Overweight and Obesity

The errors in self-reported height and weight are compounded in the derived BMI variable and this is particularly important when BMI values are used to classify subjects into standard categories of BMI (underweight, normal weight, overweight and obese). The substantial deviations of the self-reported from the actual BMI values, particularly at the high and low ends of the BMI scale, are large enough to result in misclassifications and underestimates of possible weight problems.

The majority of the reviewed studies found that the prevalence estimates of overweight and obesity were substantially lower with self-reported rather than measured data, with wide variability in the extent of underestimation (see Table 9.2 and Fig. 9.4). In the Canadian Community Health Study (Shields et al. 2008), the prevalence of overweight and obesity based on self-reports was respectively 2% and 7.4% lower than the estimate based on actual measurements, with particularly pronounced differences among older people (>65 years old). The obesity prevalence based on self-reported values was 15% and 13% lower for elderly men and women, respectively.

In a study from our laboratory (Tokmakidis et al. 2007), prevalence estimates in Greek students were 23.1% for overweight and 4.3% for obesity, but according to measured data the corresponding rates were 28.8% and 9.5%, respectively. Hence, the self-report screen missed 41.5% of overweight and 57.8% of obesity cases, leading to an underestimation of overweight and obesity by 3.7% and 5.8% respectively for elementary school and 8.4% and 4.4% respectively for high school students. The magnitude of underestimation for the total sample was comparable with that reported for overweight (4.8%) and higher than that reported for obesity (1.6%) in Welsh adolescents (Elgar et al. 2005). These differences imply that self-reported data might not be as valid as data obtained from actual measurements, calling into question the use of self-reports as a screen for overweight and obesity.

9.7 Implications for Health and Disease

Misclassification of overweight and obese subjects belonging to a lower BMI category would lead to erroneous estimating rates of overweight and obesity (Fig. 9.4). This means that, if self-reported data were used, overweight and obese individuals under-reporting their weight would be less likely to engage in weight control practices and receive appropriate interventions and education, given that they would be classified and would also continue to perceive themselves as having normal weight.

Children and adolescents having a wrong body image perception or being unaware of their weight problem may not be stimulated to take appropriate preventive steps and adopt healthy behaviors, in terms of a balanced diet and enhanced participation in physical activities, in order to limit further weight gain. For instance, based on self-reported data obtained from a nationwide sample of Greek school-aged children, Karayiannis et al. (2000) concluded that the prevalence of childhood overweight (15.3%) and obesity (1.8%) was lower in Greece compared to most other western countries, contradicting the corresponding prevalence estimates for overweight (21.6–30.3%) and obesity (5.6–9.5%) reported by studies based on actual measures from children and adolescents from several Greek regions (Fig. 9.5).

It is notable that the prevalence estimates of overweight and obesity observed in the aforementioned study, which was conducted in 1997–1998, were even lower than the percentages that were observed in a study carried out 15 years earlier in Crete. According to the study's conclusion, a significant proportion of overweight and obese children, who should be targeted for nutritional and physical activity advice, would be missed for intervention purposes. This is especially relevant in the light of evidence that obesity, as well as several obesity-related risk factors, tend to track from childhood and adolescence into adult life.

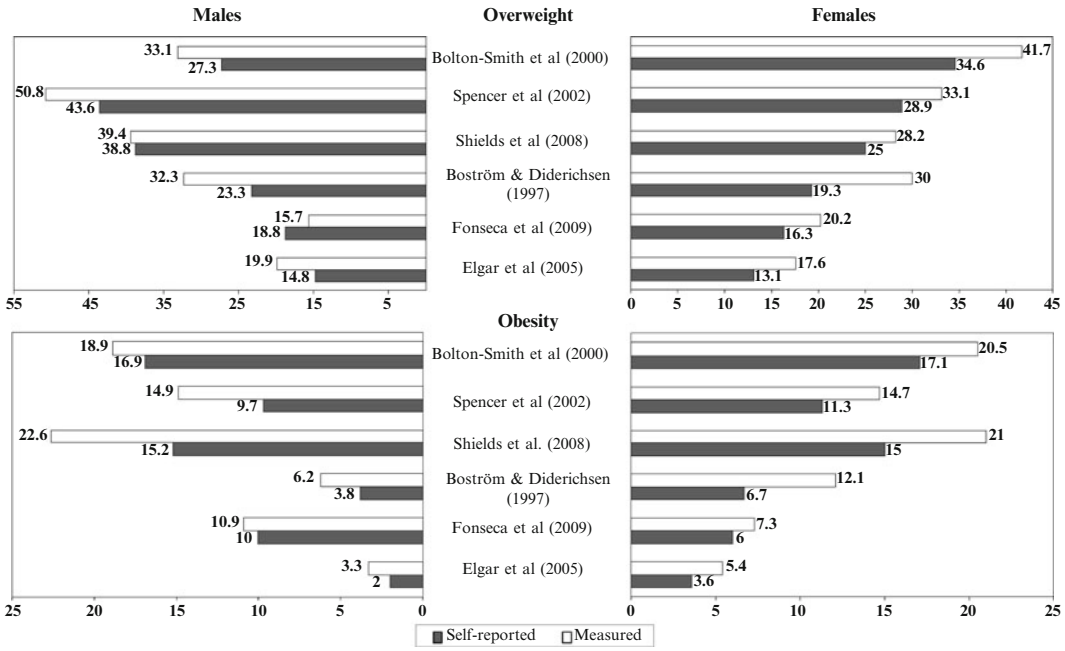

Fig. 9.4 Differences in prevalence estimates of overweight and obesity by collection method and gender in published studies. This figure illustrates differences in prevalence estimates of overweight/obesity between self-reported and measured anthropometry by gender in relative studies

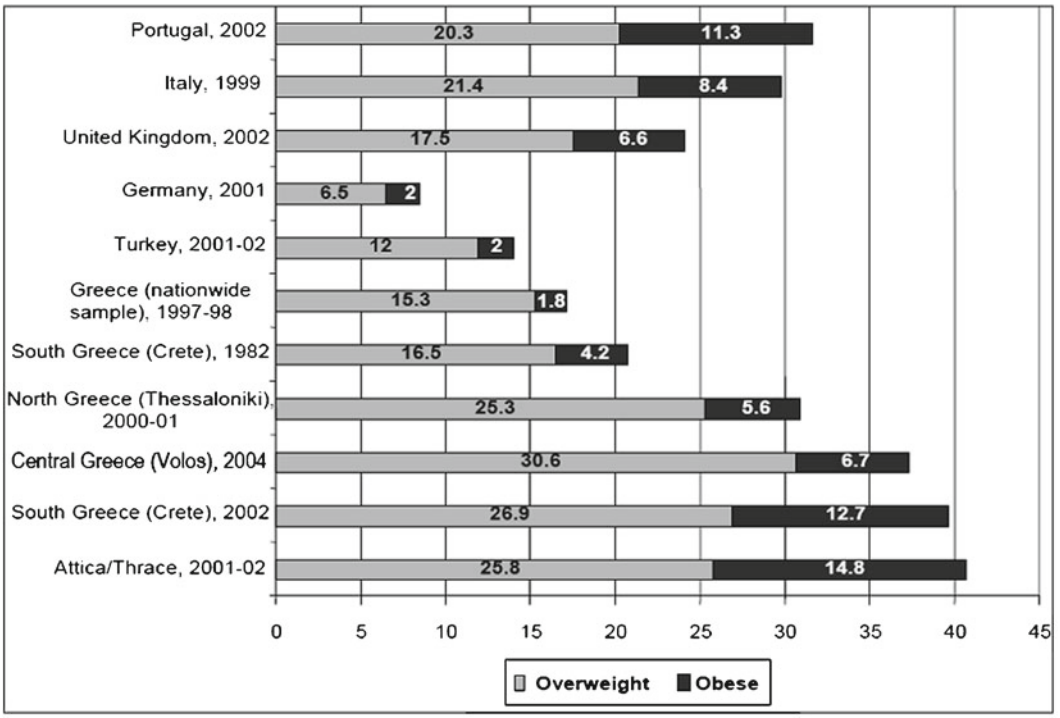

Fig. 9.5 Prevalence of childhood overweight and obesity in several districts of Greece and other European countries, according to published data. This Figure presents prevalence rates of childhood overweight and obesity in several districts of Greece and other European countries, according to published data (With kind permission from Springer Science+Business Media, Tokmakidis et al. 2006, p. 871)

Concerning the relationship of self-reported BMI to obesity-related health disorders, research evidence provides conflicting conclusions. It is often suggested that underestimating obesity prevalence may result in diminished associations between obesity and health outcomes. This is in contrast with another data set, which supports that misclassification of self-reported BMI leads to exaggerated associations between overweight and obesity and concomitant morbidity (Shields et al. 2008). Finally, data from the National Health and Nutrition Examination Study III showed that self-reported anthropometric data can provide sufficiently accurate information in epidemiological studies, in which the primary outcomes are disease biomarkers or obesity-related diseases (McAdams et al. 2007). Consequently, caution is necessary when assessing the association of obesity-related health conditions with self-reported anthropometrics.

9.8 Suggestions to Reduce the Bias

Over-reporting of height and under-reporting of weight increases with rising levels of BMI. There are data indicating that the reporting bias for weight has increased in the last years and the greater overall bias may reflect the increasing prevalence of overweight and obesity worldwide (Shields et al. 2008). In this context, it is important to measure the magnitude of the bias periodically, in order to examine if it changes over time.

Developing correction factors that could be applied to eliminate or at least decrease the magnitude of the biases in BMI associated with self-reported anthropometric values, is an attractive idea (Gorber et al. 2007). Hence, to improve the accuracy of BMI estimates, it has been suggested that future large-scale studies should take measured data from at least a random sub-sample of the cohort, in order to examine the size and direction of any bias as well as to identify the sources of this bias (Elgar et al. 2005; Ezzati et al. 2006; Danubio et al. 2008). Identified sources of bias can be entered into adequate models as explanatory variables along with reported values and the derived predictive equations can then be applied to the whole cohort to minimize the bias (Spencer et al. 2002).

Moreover, some researchers support that self-reported BMI scores could be further adjusted, based on a few, easily collected demographic data such as gender, age, race and ethnicity, marital status and household income (Stommel and Schoenborn 2009). By using the adjusted measures, overall estimates of the population overweight and obesity prevalence are substantially improved, whereas it seems that the adjusted self-reported scores deliver risk estimates that are close to those obtained on the basis of the actual BMI values, particularly if parametric prediction models are used.

Another simple method to obtain more accurate estimates of obesity prevalence from self-reports is the "reduced BMI threshold", which proposes the lowering of BMI cutoff-points for the overweight and obese categories, using receiver operation characteristic (ROC) techniques (Lim et al. 2009). Reduced BMI thresholds should be computed from ancillary data collected on a limited representative sample, if the method is going to be used in populations with different characteristics.

A practical and convenient approach, however, is to provide the appropriate information to the target population. Giving guidelines to the subjects, for instance, to get their body height and weight measurement prior to the participation in the survey and have a proper preparation for the report could reduce the error bias of self-reported data (De Vriendt et al. 2009).

9.9 Summary

The literature review showed that, overall, self-reported data provides useful information. Individuals are quite capable of reporting their height and weight. However, self-report should be used carefully when determining BMI-categories, given that systematic errors related to several population characteristics could lead to an underestimation of overweight and obesity. These biases in reporting may have important implications for appropriate health planning, especially if diagnostic, preventive or therapeutic decisions have to be taken. Identifying sources of misreporting and correcting for bias may improve health surveys of obesity and overweight problems. Given the time required as well as the high costs of actual data collection, self-reported body weight and height remains an important screening tool for population-based estimates of obesity-related risks.

Summary Points

- The utility of self-reported data depends on the purpose for which they are used
- Despite limitations and systematic biases, self-reported anthropometry remains a useful screening tool, when epidemic or large scale population studies require prompt proxy results
- Actual measurements should be preferred instead of self-reported data, when accuracy is the prerequisite
- The accuracy of self-reported-anthropometry depends on the study population
- Adults provide better self-reported figures than children and adolescents

- Overweight and obese individuals tend to misreport their body dimensions more than normal weight subjects
- Awareness of current body size as well as frequency of body measurements provide better self-reported values
- Identifying reasons of misreporting, understanding their potential interactions and developing correction factors may improve the accuracy of self-reported anthropometrics

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Chapter 10
Body Composition Analysis Using Radionuclides

Themistoklis Tzotzas, Georgios Karanikas, and Gerasimos E. Krassas

Abstract Body composition studies were first recorded around the time of the Renaissance, and advances by the mid-twentieth century facilitated growth in the study of physiology, metabolism and different diseases. They are divided into two main groups, i.e. radionuclide and non-radionuclide methods. Simple methods based on body mass index (BMI), skinfolds and circumference measurements along with bioelectrical impedance analysis (BIA) technique are useful tools in everyday clinical practice, while more sophisticated non-radionuclide methods include underwater weighing (UWW), air-displacement plethysmography (ADP) and dual energy X-ray absorptiometry (DXA). In radionuclide methods, total body water (TBW) and total body potassium (TBK) are the two main traditional methods which were considered the 'reference' standard for body fat measurement. Computed tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography (PET) scan and neutron activation analysis (NAA) are new methods which provide a detailed description of different tissues. Imaging methods (CT and MRI), in particular, opened a new era in body composition research by offering the possibility of qualitative and quantitative measurements of various tissues such as bone, skeletal mass, hepatic tissue and adipose tissue. CT and MRI estimates of visceral and ectopic adipose tissue using a single slice at L4–L5 level or multiple slices are considered the reference methods for assessing regional fat distributions. PET scan using specific radiopharmaceuticals can visualize active metabolic tissues like brown adipose tissue, which is found primarily in infants and has been considered to be essentially nonexistent and of no physiological relevance in adults. Additionally, this method can follow and provide direct depot-specific measurements of substrates uptake (e.g. insulin – stimulated glucose uptake) in various tissues and organs during insulin resistant states. Therefore, functional imaging with PET scan provides a tool for a better understanding of the physiology of obesity, type 2 diabetes mellitus and related metabolic disorders.

This chapter provides an overview of the present status, mainly of radionuclide methods in everyday clinical practice for patients with obesity and related metabolic diseases, as well as in human research.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_10,

Abbreviations

ADP	Air-displacement plethysmography
AT	Adipose tissue
BAT	Brown adipose tissue
BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
C/O	Carbon/oxygen
CT	Computed tomography
CV	Coefficient of variation
DXA	Dual energy X-ray absorptiometry
F-18-FDG	Fluorine-18-fluoro-2-deoxy-D-glucose
FFM	Free-fat mass
HD	Hydrodensitometry
^{40}K	Potassium-40
MRI	Magnetic resonance imaging
MIBG	^{123}I-meta-iodo-benzyl-guanidine
MRS	Magnetic resonance spectroscopy
NAA	Neutron activation analysis
PET	Positron emission tomography
PET-CT	Positron-emission tomography and computed tomography
SAT	Subcutaneous adipose tissue
TBW	Total body water
TBK	Total body potassium
TBCa	Total body calcium
TBN	Total body nitrogen
T2DM	Type 2 diabetes mellitus
UWW	Underwater weighing
VAT	Visceral adipose tissue
WC	Waist circumference
WHR	Waist to hip ratio

10.1 Introduction

Body composition studies were first recorded around the time of the Renaissance, and advances by the mid-twentieth century facilitated growth in the study of physiology, metabolism and different diseases including obesity (Fig. 10.1). Simple and practical methods were available to early investigators, such as anthropometry techniques based on skinfold and circumference measurements. From measurements of weight and length, the BMI [weight (kg)/height (m^2)] can be calculated, which is currently the most commonly used clinical index of under- and over-nutrition, and may be used to roughly predict body composition.

The discovery and continuous development of X-ray technology gave completely new insights into the composition of the human body – information which was available exclusively to the post-mortem investigator earlier.

In the beginning, body composition methods partitioned body weight into two compartments, fat and lean body mass, now referred to as free-fat mass (FFM) and various components (Wang et al. 1999)

Fig. 10.1 In the seventieth century Paduan physician Santorio Sanctorius (1561–1636), spent many years eating, sleeping and working in a 'statical' chair connected to the arm of a calibrated scale. He paved the way for the contemporary discipline of metabolism. (Reproduced from Heymsfield (2008). With permission)

Table 10.1 Levels of body composition and measurement methods to determine various components (adapted from Mattson and Thomas 2006)

Atomic	Molecular	Tissue/organ	Whole body
N, Ca, P, S, K, Na, Cl ….	Minerals (bone, soft tissue) CHO	Bone	Lower limbs
H	Protein	Visceral organs	
C	Lipid	Bone Skeletal muscle	Trunk
O	Water		Upper limbs
		Adipose tissue	Neck
			Head
	Methods		
TBK, TBN	TBK, DXA	CT, MRI, PET scan	Skinfold, BIA

A brief overview of the most often used compartment models according to the base for the description of the body in terms of atoms, molecules, etc. and the measurement methods to determine the size of various components are indicated

CHO carbohydrates, *TBK* total body potassium, *TBN* total body nitrogen, *DXA* dual-energy-X-ray photon absorptiometry, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* scan positron emission tomography scan, *BIA* bioelectrical impedance analysis

(Table 10.1, Fig. 10.2). Among these methods whole body K counting and UWW, were considered the 'reference standards' of their era for body fat measurement (Heymsfield 2008). These methods, however, were based on assumptions such as the constancy of FFM potassium content and density

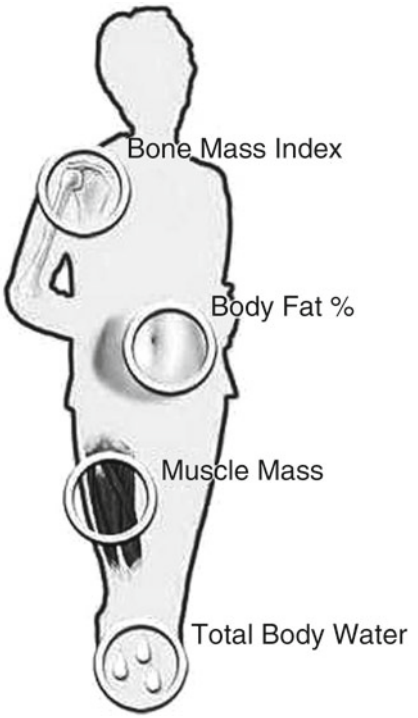

Fig. 10.2 In this cartoon the four main components of human composition are illustrated

(Heymsfield 2008). The two compartment model assumptions were recognized as of limited accuracy under certain conditions, for example, with disturbances in hydration.

A great step forward in in-vivo body composition analyses is connected to the intense development of medical imaging technology, first X-ray CT (Sjostrom et al. 1986) and later nuclear MRI (Foster et al. 1984) and magnetic resonance spectroscopy (MRS) (Boesch and Kreis 1997). This has given us a possibility of refining and detailing the various body composition models. In parallel to this intensive development of advanced analytical methods, there has been a need to develop more simple equipment such as instruments for ADP (to measure body volume as an alternative to UWW, 3D body volume scanning, BIA, as well as for stationary or portable DXA). In Table 10.2, the principal radionuclide and non-radionuclide methods are presented.

The aim of this chapter is to summarize 50 years of development in the field of body composition studies with special reference to the nucleotide methods and give the readers an understanding of the pros and cons of each measurement method.

10.2 Non-radionuclide Methods: Brief Report

(1) **Hydrodensitometry (HD) or UWW**: In this technique, body weight is determined in air and when the subject is fully submerged in the water. Body volume is calculated using Archimedes' principle and after correcting for residual lung volume, body density is obtained. The percentage of body fat can then be estimated from body density by using a number of equations, e.g. Siri' equations (Lukaski 1987). In obese subjects, deviation in FFM can occur because of changes in

Table 10.2 Principal methods for body composition analysis

A. Non-radionuclide methods
1. Hydrodensitometry or underwater weighing
2. Air-displacement plethysmography
3. Bioelectrical impedance analysis
4. Dual-energy X-rays absorptiometry
5. Anthropometry (BMI, circumferences, skinfold thicknesses)
6. Cadaver analyses

B. Radionuclide methods

Ba. Traditional methods
1. Total body water
2. Total body potassium

Bb. New methods
1. Computed tomography
2. Magnetic resonance imaging
3. Positron emission tomography scan
4. Neutron activation analysis

The most important non-radionuclides and radionuclides methods that are used in everyday clinical practice and for research purpose are indicated

hydration or proportion of bone mineral (Ellis 2000). Besides, obese people find the underwater position particularly uncomfortable.

(2) **ADP**: This recent technique uses the same principle as UWW with the difference being the subject is not immersed in water but in a closed air-filled chamber (Air – Displacement Plethysmography, BOD-POD® system) (Ellis 2000). Good correlations have been found between ADP and other methods, although some authors reported an underestimation of FFM and an overestimation of fat mass by ADP (Demerath et al. 2002; Le Carvennec et al. 2007). Although this technique is promising, it has to be tested more extensively for various populations and children.

(3) **BIA**: This technique measures the resistance or impedance, of the total body or body segments, to a small alternating current. BIA allows the determination of FFM and TBW in lean and obese subjects without significant fluid and electrolyte abnormalities, when using specific equations and established procedures (Jebb and Elia 1993). Its use has to be avoided in subjects at extreme BMI ranges (<16, >34 kg/m^2) or for those with abnormal hydration (Kyle et al. 2004).

(4) **DXA**: DXA has emerged as one of the most praised techniques for measurement of body composition. Its use is based on a three-compartment model that divides the body into body mineral, fat-free lean mass and fat tissue mass. Because these tissues have different densities and are penetrated to a different extent by the X-ray beam, DXA can derive the amounts of each tissue present (Ellis 2000). It is becoming the new 'gold standard' in body composition analysis because it provides a high degree of precision, specifically for adiposity evaluation (Mattsson and Thomas 2006). In obesity research, studies show the possibility of DXA estimating abdominal fat using a region of interest at the levels L2–L4 (Park et al. 2002). Cost and limited accessibility are some of the drawbacks of this reliable method.

(5) **Anthropometry (BMI, circumferences, skinfold thicknesses)**
BMI is primarily used to identify subjects as underweight (BMI < 18.5), within normal range (18.5 < BMI < 25), overweight (25 < BMI < 30) or obese (BMI > 30). For obesity, BMI as a predictor of body fat has a relatively large error at 4–6%, since this index does not consider situations such as edema, muscular hypertrophy etc. (Prentice and Jebb 2001).

Circumferences: They provide a good estimate of body composition in most obese populations and can be useful to quantify changes in an individual over time.

Waist Circumference (WC) provides a unique indicator of intra-abdominal body fat and is strongly associated with obesity-related metabolic risk factors. Men with WC > 102 cm and women with >88 are at increased cardiometabolic risk (Klein et al. 2007).

Waist to hip ratio (WHR) is a poor proxy of abdominal fat distribution because this marker is influenced by the size of the pelvis and soft tissues.

The measurement of **skinfold thicknesses** represents an attempt to make a direct measure of adipose tissue at particular sites (biceps, triceps, subscapular and supra-iliac) using specific calipers (Mueller and Stallones 1981). Estimation of total fat mass is then provided using previously standardized prediction equations (Durnin and Womersley 1974). Practical drawbacks of this technique include inter- and intra-observer reliability and the difficulties in accurately measuring the thicknesses in obese individuals (Jebb and Elia 1993).

(6) **Cadaver analyses**

Direct chemical analyses of the adult whole body were mainly reported in the 50s (Forbes et al. 1953) and have served on the reference base for the development of various models of body composition (Ellis 2000).

10.2.1 Key Points

Simple methods based on BMI, skinfolds and circumference measurements along with BIA technique are useful tools in everyday clinical practice to measure body composition and distribution. More accurate techniques using more sophisticated equipment are ADP and DXA.

10.3 Radionuclide Methods

10.3.1 Traditional (Old) Methods

10.3.1.1 TBW

Investigators have used the isotopes of hydrogen, deuterium and tritium, to quantify body water volumes by isotope dilution in healthy and diseased subjects. Some general assumptions of the isotope-dilution technique are that the isotope has the same distribution volume as water and non-toxic in the amounts used. Because of the ease of liquid scintillation counting, some investigators relied upon tritium dilution to measure TBW. The use of a radioactive tracer such as tritium is contraindicated in research involving children or women of child-bearing age. Increased use of deuterium occurred when newer techniques for the assay of deuterium in aqueous solution became available (gas chromatography, mass spectrometry and fixed-filter infrared absorption) (Lukaski 1987; Jebb and Elia 1993).

The procedure for using tritium or deuterium includes either the ingestion or the intravenous injection of a specified quantity of the tracer, an equilibration period and a sampling period. The calculation of TBW volume is based upon the simplified relationship: $C_1V_1=C_2V_2$, where C_1V_1 is the amount of tracer given, C_2 is final concentration of tracer in a biological fluid, and V_2 is volume of

TBW. It is important that the correction be made for urinary loss of tracer (Lukaski 1987; Jebb and Elia 1993).

The quantity of tracer given depends upon the type of tracer administered, the analytical system used and the objective of the research. In general, the smallest dose that allows good analytical precision and accuracy and is the lowest risk to the subject should be given. For healthy men and women a 10 g dose of deuterium oxide mixed with 300 ml of distilled-deionised water is used routinely (Lukaski 1987). When using gas chromatographic methods, it has to be given as an oral dose of deuterium oxide of 1 g/kg body weight. An oral dose of 2 g D_2O has been used for mass spectroscopy (Lukaski 1987). Among researchers using tritium as a tracer, a dose of 50 μCi is common (Lukaski 1987; Jebb and Elia 1993). When repeated body–water determinations are to be performed over short periods of time or in women or children, the use of deuterium as a tracer is suggested. The length of time required for tracer equilibration depends upon the characteristics of the study sample. In healthy men and women, equilibration of deuterium in saliva, plasma and urine occurs 2 h after ingestion of the tracer and remains at a constant concentration in these fluids for the next 3 h (Lukaski 1987). Although plasma or serum tracer concentrations have been used to calculate TBW, saliva concentrations may be useful in some conditions.

The use of oxygen-18 as a tracer to measure TBW was proposed because it avoids the exchange of label with non-aqueous hydrogen in the body that can overestimate body water by 1–5%. Implementation of this technique is difficult outside of a specialized research laboratory (Lukaski 1987).

Application in Obesity

This dilution technique is considered the reference for comparison with other measurements (Ellis 2000). However, while this approach works reasonably well for subjects with physiologic body composition, the error may be substantial for malnourished and obese fluid-loaded patients (Mattsson and Thomas 2006). In obese people, in particular, who present an increase in the hydratation of FFM and sometimes an edema, it is difficult to accurately estimate the true hydratation of FFM in a given circumstance. In addition, during periods of weight loss, changes in body composition may be erroneously estimated since the loss of water in association with glycogen during early weight loss, will be interpreted as a loss of 1.37 kg lean tissue for each kg of water which is lost (Jebb 1998). In a short weight loss study in obese subjects, TBW technique was found to underestimate body fat loss by 20% (Yang et al. 1977).

Other limitations of this method are high radiation exposure, the fact that the use of isotope-labelled water is time consuming and the need for multiple sampling and limited access to specialized equipment and laboratory capacity. Consequently, nuclide methods measuring TBW have essentially remained research tools (Mattsson and Thomas 2006). The precision of the method is 1–3%, the accuracy 5%, and minimum detectable change for an individual is 5% (Ellis 2000).

10.3.1.2 TBK

Potassium-40 (^{40}K) emits a characteristic gamma ray at 1.46 MeV and exists in the body at a known natural abundance (0.012%). Quantification of TBK requires specially constructed counters that consist of a large shielded room (to reduce background radiation from cosmic and terrestrial sources) containing a gamma ray detection system connected to a suitable recording device (Lukaski 1987; Jebb and Elia 1993). The detectors are of two types: large thallium-activated sodium iodide crystals, one or more of which are positioned near the subject, and large, hollow cylinders or half cylinders, the walls of which contain liquid or plastic scintillation material, into which the subject is placed as

to be completely or partially surrounded by the detector. These are referred to as 4π or 2π geometrical counters. The advantages of the crystal system are mainly very good energy resolution and low background (Lukaski 1987).

Different systems (single crystal placed adjacent to the subject or to pass over the subject, utilization 4π ^{40}K counting) were developed to measure ^{40}K and regarding which type of counting system is used, the variability of counting ^{40}K was >5% (Lukaski 1987). The most significant improvement in the whole-body-counting method is the development of techniques to provide absolute quantification of ^{40}K. A uniformly distributed cesium-137 source and a 54-detector whole-body counter are used to measure ^{40}K absolutely. By counting the gamma rays emitted from the cesium source, which is positioned briefly under the subject who is supine on a cot, attenuation factors are determined. These factors are used to correct for differences in body size and geometry and in gamma ray self-absorption for each subject. This permits accuracy and a precision of in-vivo ^{40}K counting within 3% (Lukaski 1987). Another finding that improves counting accuracy is the reduction of background bismuth-214 contamination. Radiobismuth is a decay product of atmospheric radon. Subjects should shower, wash hair, and wear clean clothing before undergoing whole-body counts (Lukaski 1987).

Application in Obesity

TBK has been used basically as a good estimate of body cell mass (BCM) – the body' metabolically active tissues – since potassium is found almost entirely (97%) within the cells (Pierson and Wang 1988). It has also been used to estimate FFM, assuming that TBK occurs at a constant concentration in the FFM. Unfortunately, the potassium content of FFM is variable and more of this element is found in muscles than in other lean tissues. Besides, it changes with age and can be distorted by diseases and use of diuretics (Jebb 1998).

The application of this method is influenced by body size and geometry. Therefore, in an obese state, there are two important limitations. The potassium concentration of lean tissue varies according to adiposity such that the concentration of potassium is lower in obese subjects than lean. Furthermore, adipose tissue (AT) exerts a shielding effect and fewer counts will be recorded in an obese subject as compared to a lean individual for a similar quantity of potassium. Appropriate correction factors must be employed to account for this attenuation (Jebb and Elia 1993).

During energy restriction and weight loss, depletion of potassium exceeds the loss of nitrogen, thus exacerbating the apparent loss of lean tissue and minimizing fat loss. This suggests that TBK method may not be the appropriate method to predict total body nitrogen in a changing nutritional state (Archibald et al. 1983).

The precision of the method is 1–3%, accuracy 5% and minimum detectable changes for an individual is 4% (Ellis 2000). This method does not expose the subject to any extra radiation and so can be repeated frequently.

10.3.2 New Methods

10.3.2.1 Imaging Methods: CT and MRI

The application of CT and MRI represents important advances in body composition analysis and its relationship with various metabolic diseases (Heymsfield 2008). These methods offer a possibility of qualitative and quantitative measurement of various tissues such as bone, skeletal mass, hepatic tissue

and AT (Mattsson and Thomas 2006). They are now considered also as the methods of choice for validation of other methods such as BIA and DXA (Mattsson and Thomas 2006; Kullberg et al. 2009).

CT

This approach relates the small differences in X-ray attenuation to differences in physical density of tissues to construct a two-dimensional image of the underlying anatomy in the scan area. The CT system consists of a collimated X-ray source and detector-rows (4–320) aligned at opposite poles of a circular gantry. Lying on a movable platform, the subject is advanced through the central aperture of the gantry. The field of vision or the designated area to be scanned, is a plane through the middle of this aperture and parallel to the gantry. As the X-ray beam is rotated around the subject, information about the intensity of the attenuated X-ray beams is recorded and stored. The scanner computer then applies complex algorithms to the stored series of profiles to reconstruct cross-sectional images (Hounsfield 1973; Lukaski 1987; Jebb and Elia 1993).

Each CT scan image or reconstruction is a matrix of pixels or picture elements, each about 1 × 1 mm, arranged in rows and columns. Because the depth of the scan or slice thickness is known, this is referred to as a voxel or volume element. For each individual volume of tissue, the CT scanner measures the X-ray attenuation within that voxel independently of the remaining tissue. The reconstructed picture represents not the image at the surface of a cut, rather an average representing the full thickness of the slice (Hounsfield 1973; Lukaski 1987; Jebb and Elia 1993).

The magnitude of the X-ray beam attenuation is reflected in the degree of pixel shading and is scaled as the CT number in Hounsfield Units. The gray scale shown on a CT scan uses the same linear attenuation coefficients used for conventional radiographic film. For example, lower densities appear black and higher densities are white, air and bone at the low and high ends of absorption, respectively. Thus, high image contrast is observed between bone, adipose, and fat-free tissues. Generally, CT scan is completed within 8–15 s. The number of slices depends upon the purpose of the CT scan (Hounsfield 1973; Lukaski 1987; Jebb and Elia 1993).

Different approaches have been used with the CT scanner to analyze body composition (Heymsfield 1985). The structure of interest can be traced directly on the viewing console with a cursor. The cross-section area of adipose, bone, muscle, or visceral organ can then be determined for each image using sophisticated software programs. Because the slice thickness is known, one can calculate the relative surface area or volume occupied by each organ or tissue in the reconstructed picture. These methods have been used to assess changes in muscle and AT in malnutrition (Heymsfield et al. 1982) and to describe cross-sectional differences in abdominal fat distribution during aging.

When no sharp boundaries between structures are apparent but the tissues differ markedly in radiographic density, the pixels in successive slices are plotted as a histogram separating the pixels into fat-free and ATs. Because the volume of each pixel is known, the volume of adipose and fat-free tissue in each slice can be determined from the number of pixels forming each slide and added for all slices performed.

Another method utilizes tissue matrices in which the individual components are smaller than one pixel. This approach has been helpful in diagnosing organ tumours, fatty liver and tissue iron content (Lukaski 1987; Jebb and Elia 1993).

Tomographic pixels derived from an area of AT represent adipocytes (triglyceride and protein matrix) and not just neutral fat. Thus, to determine fat mass one must first assume that a fixed fraction of AT is triglyceride. An alternative approach is to determine the volume of adipose by adding the appropriate number of adipose voxels and assuming a constant density for AT. Neither of these approaches has been validated against standard body composition methods.

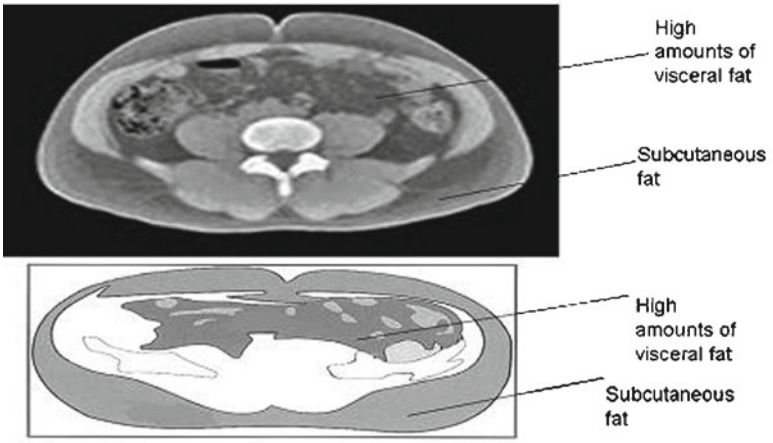

Fig. 10.3 This CT scan image shows the distribution of abdominal fat in an obese individual The visceral fat area is regarded as black colour and the subcutaneous fat area is regarded as grey colour

Application in Obesity

The value of CT scans for body composition studies was initially recognized by Borkan et al. in 1982. The authors suggested, for the first time, that a single abdominal CT scan obtained at the level of the umbilicus provides a good indication of fat content throughout the abdomen and differentiates intra-abdominal from subcutaneous fat (Borkan et al. 1982). Subsequently, a new segmentation approach for measuring regional AT volumes was developed using CT scan (Tokunaga et al. 1983). Thereafter, Sjostrom et al. (1986) compared CT with other radionuclide methods and concluded that the CT-based AT determination is the most reproducible examination available so far.

In more recent years, as more instruments became available, epidemiological studies began to appear that put the accent on adipose tissue topography and linked visceral AT (VAT) – but not subcutaneous AT (SAT) – with obesity metabolic complications and cardiovascular disease (Matsuzawa et al. 1995). In many of these studies, VAT is often reported as the area of a single slice which is usually performed at the L4–L5 level, including omental, mesenteric and retroperitoneal compartments (Fig. 10.3). However, it is important to recognize that single slice studies only provide an area of VAT (cm^2), in contrast to multiple-slice studies which report the volume of VAT (cm^3).

Thanks to recent imaging, a systemic classification of AT was possible based on topographic and metabolic characteristics (Shen et al. 2003). According to this classification, total body AT can be separated into two categories, subcutaneous and internal, the latter into discrete components, visceral and non-visceral. VAT should appropriately include two cavities: the thoracic and abdominopelvic cavity, which can be further divided into intraperitoneal and extraperitoneal region. The coefficient variations (CVs) for repeated SC and VAT measurements by CT are in the range of ~2% (Shen et al. 2003). CT images played an important role in identifying ectopic, metabolically active AT, such as intrahepatic, intramusular or pericardial AT which are associated with insulin resistance disorders and atherosclerosis, more than VAT (Lim et al. 2009; Shimabukuro 2009).

Repeated CT images were able to identify the respective changes of various AT compartments during weight loss achieved by low-calorie diet, pharmacotherapy and bariatric surgery (Chaston and Dixon 2008; Carroll et al. 2009). More importantly, new CT imaging contributed to the prediction and understanding of dysmetabolic conditions such as insulin resistance, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease, etc. (Bredella et al. 2009; Bray et al. 2008; Wagenknecht et al. 2009).

An obstacle to the use of CT, with multiple CT images in particular, is radiation exposure resulting in effective doses of the order of 10 mSV per investigation, precluding its use in young children and pregnant women (Heymsfield 2008). Other practical limitations of CT imaging are the high cost and limited machine availability.

MRI

The introduction of non-X-ray MRI in the 1980s was an important development in the field of body composition studies.

A method with great potential for the safe, non-invasive, direct assessment of human body composition is MRI. Unlike CT, it uses no ionizing radiation, but uses a powerful magnetic field to align the nuclear magnetization of atomic nuclei in the body. To-date routinely used scanners operate at field strengths of 1.5–3 T; however, for scientific purposes scanners with field strengths of 7 T or higher are used. In MRI, radio frequency fields are used to systematically alter the alignment of the magnetization, causing the nuclei to produce a rotating magnetic field detectable by the MR scanner. This signal can be manipulated by additional magnetic fields to build up enough information to construct an image of the body. The most frequently studied nucleus in biology is hydrogen, 1H, and in particular the hydrogen atoms of water molecules in cells and tissues. Hydrogen is the most abundant of atoms (or nuclei for MRI purposes) rather than as a percentage of body weight. The majority of these hydrogen atoms are present as part of water molecules. The hydrogen nucleus is the most amenable to MRI detection. Not only is the natural abundance of 1H high (99.98%), but the sensitivity of MRI to this nucleus, which is simply a proton, is greater than any other atomic nucleus (Lukaski 1987; Jebb and Elia 1993; Mallard 2006). Whereas conventional X-ray radiographic and CT images depend on electron density, MRI depends on the density of hydrogen nuclei and the physical state of the tissue as reflected in the magnetic relaxation times. Anatomical information has been obtained by comparing MRI images and corresponding frozen cross sections of normal animals. Tissue contrast is high between fat and muscle and can be enhanced by changing the magnetic relaxation time variable of the magnetic resonance instrument (Fig. 10.4). Application of MRI to differentiate malignant from benign processes have indicated differences in relaxation times between normal and cancerous tissues in rats and humans. Although exact interpretation of these observations is unclear, the data appear to indicate a correlation with degree of hydration of tissue (Lukaski 1987; Jebb and Elia 1993; Mallard 2006).

These findings have stimulated other investigators to estimate regional and TBW using MRI. Conventional MRI was used to quantify the water distribution of saline-filled and normal rat lungs in isolated and in situ preparations. Studies in isolated lung fragments showed an accuracy of 1%, and images of phantoms had an error of <3%.

In another study hydrogen associated with water was measured as the amplitude of the free-induction decay voltage. Body water calculated by multiplying peak amplitude by the experimentally determined constant for a water standard was similar to that determined gravimetrically in the same baboons. MRI has the capability to generate images in response to intrinsic tissue variables and represent gross chemical characteristics, such as level of hydration and fat content. In addition to hydrogen, MRI can image phosphorous and future prospects include carbon, nitrogen, sodium and chlorine.

Application in Obesity

The first study that reported MRI's ability to distinguish AT from the adjacent skeletal muscle was published in 1984 by Foster et al. In 1988, subcutaneous fat was measured for the first time by MRI

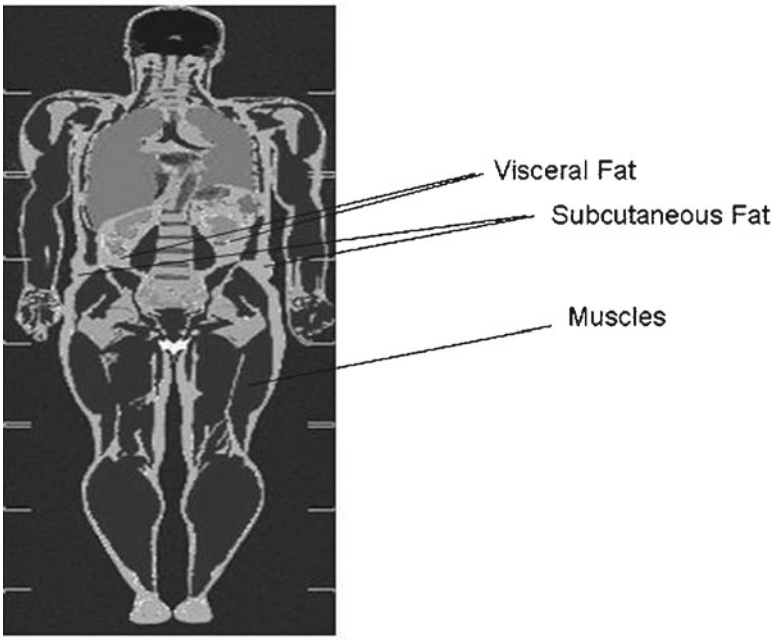

Fig. 10.4 This MRI scan image provides a detailed look at where fat is stored internally in the human body. The image is of an average-sized man who has a normal BMI of 21.7

and compared with other methods (Hayes et al. 1988) and during early 1990s accurate measurements of AT distribution were reported (Fowler et al. 1991; Ross et al. 1993). Since then, several studies have examined body fat compartments and lean tissue in various age and population groups (In utero, newborns, children, lean and obese males/females, etc.) (Ross 2003; Shen et al. 2009). As with CT, the observations in these studies are made with a single cross-sectional image. Several equations have been developed for the calculation of VAT and SAT area based on anthropometric measurements such as WC or skinfolds thickness. Additionally MRI, like CT, can identify and describe young and adult subjects at risk for cardiometabolic disorders such as metabolic syndrome and T2DM (Demerath et al. 2008; Cali and Caprio 2009; Gallagher et al. 2009). A significant advantage of MRI for body composition studies is its potential for providing multiple images without any recognized health risk for the subjects.

During the last two decades important advances have been made with MRI technology, from which research in the obesity field took much profit. These advances include the following: Functional MRI for evaluating the metabolic activity of organ and tissues (Holsen et al. 2006; Farooqi et al. 2007); Proton and phosphorous spectroscopy for quantification of lipid deposition (Johansson et al. 2008); Water-fat imaging for discerning tissue lipid and water content (Kim et al. 2008); Whole-body nuclear MR systems for quantifying total body lipid and water (Napolitano et al. 2008). As with CT, MRI helped in identifying and classifying subcutaneous fat and ectopic fat deposition other than VAT (Shen et al. 2003). The CV for measuring subcutaneous fat is similar in MRI and CT at about 2%, however, CV for VAT measurements is higher in MRI (between 9% and 18%) than CT (~2%) (van der Koory and Seidell 1993). The explanation for this discrepancy is that scan times for CT are shorter than for MRI and CT is thus less vulnerable to image artifacts. However, the one major disadvantage in CT is the radiation dose required per slice for imaging.

PET Scan

PET images biological processes in-vivo three-dimensionally. A specific radiopharmaceutical, labelled with a radioactive isotope is injected (Phelps 2000). PET has a broad scope and is very chameleonic and sensitive. Those facts make it one of the most powerful molecular imaging techniques currently available for clinical use. PET can image key biomedical functions in vivo. It can show them up under basal conditions and also during diverse pharmacological or physiological interventions.

The successful utilisation of PET in clinical use is based on up-regulation of key-enzymes and other proteins which regulate the intermediary cellular metabolism in malignant/inflamed transformed cells. The up-regulation of proteins and enzymes for glucose metabolism, such as glucose transporters and hexokinase is vitally important. These mechanisms are early events during the malignant/inflamed transformation, which proceed to morphological demonstrable changes on cellular or tissue level. This is the reason why PET, using fluorine-18-fluoro-2-deoxy-D-glucose (F-18-FDG) as a marker for glucose metabolism, is of potential value for the early diagnosis of several diseases. Further pros are that the whole body can be conveniently imaged with PET within an acceptable time at low radiation exposure (7–10 mSv whereas a contrast-enhanced CT produces 20–40 mSv) and that there are no pharmacodynamical side-effects (Phelps 2000; Rohren et al. 2004).

The PET scanner does not detect positrons directly, but the mechanism of positron annihilation which is important for the determination of their spatial location. The isotope is transformed by a process called beta decay: a proton turns into a neutron and a positron which is emitted and migrates through the tissue for a few millimetres. In the meanwhile, it loses its kinetic energy and forms a positronium (a positively charged electron). This positronium fuses with an electron in its vicinity. As a result, energy is transmitted and emitted as two gamma photons with 511 keV each (annihilation). This process can be localized and translated into images with photon detectors and photomultiplier tubes. The base of the detection and localization is the fact that the annihilation photons are emitted simultaneously and in opposite directions (Phelps 2000; Rohren et al. 2004).

Application in Obesity and Other Metabolic Diseases

Recently PET scan has been widely used in oncology to localize tumours and metastasis. It was, serendipitously, as a consequence of this use that PET-scan visualized increased tracer uptake in the upper parts of the body; it was then proved that these areas correspond to brown AT (BAT) (Nedergaard et al. 2007) (Fig. 10.5). BAT is known to be a very active tissue metabolically and studies in experimental animals proved its role in increasing energy expenditure in the form of thermogenesis mediated by the expression of the tissue-specific uncoupling protein-1 (UCP_1) (Basu 2008).

BAT has been considered of critical importance in neonates, small animals in cold environments and animals that hibernate, because of its role in cold-induced adaptive thermogenesis. In humans, it was generally believed that this tissue diminishes with age and disappears completely by adulthood (Cannon and Nedergaard 2004). The recent observation from F-18-FDG-PET imaging demonstrated that active BAT is still substantially present in adults – in the range of 10% – and is primarily located in the supraclavicular and neck regions (Nedergaard et al. 2007). The most common location for BAT that was detectable in adults by Positron-emission tomography and computed tomography (PET-CT) was the cervical-supraclavicular depot, in a distinct facial plane in the ventral neck, superficial and lateral to the sternocleidomastoid muscles. In patients with high F-18-FDG-avid fat extended inferiorly between the subscapularis and pectoralis muscles, posterior to the brachial plexus and proceeding through thoracic and abdominal paraspinal sites, with little perinephric activity (Cypess et al. 2009). Animal studies have previously shown that BAT is implicated in the development of obesity (Lowell et al. 1993). Accordingly, recent studies in humans using F-18-FDG-PET scan

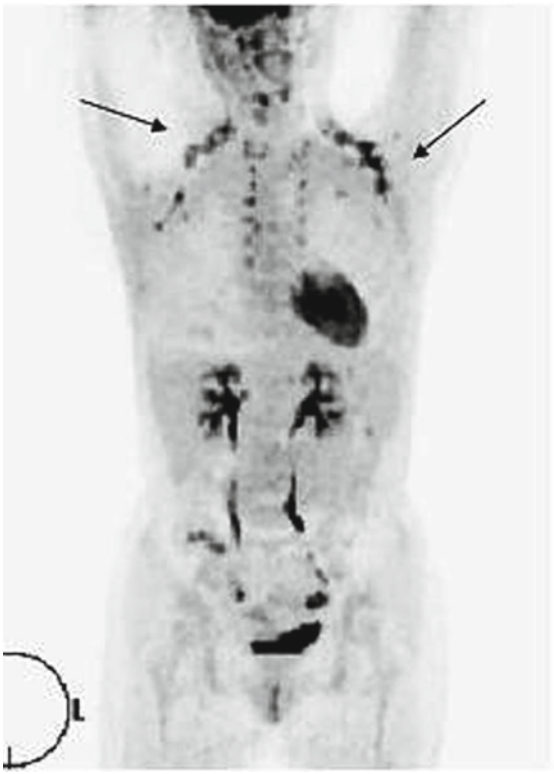

Fig. 10.5 Amount and activity of brown adipose tissue in a 22-year female. As depicted, brown adipose tissue is mainly located in cervical and periclavicular region

combined with CT showed an inverse association between the prevalence of BAT and BMI (Cypess et al. 2009; Saito et al. 2009).

Besides, in an elegant experiment using PET scan, Kajimura et al. (2009) were able to convert both mouse and human skin cells (myoblasts) into brown fat. This synthetic brown fat tissue was found to present the same biochemical characteristics as the endogenous one, and, according to the authors, could provide opportunities for the development of new therapies for obesity and T2DM.

F-18-FDG-PET scan was also used in studies in obese patients with insulin resistance and T2DM and contributed substantially to the understanding of mechanism of insulin resistance in AT and skeletal muscles in these patients (Virtanen et al. 2002, 2005). In abdominal obesity, insulin-stimulated glucose uptake rate is markedly reduced in skeletal muscle and in all fat depots, in target tissues and this reduction is reciprocally (and nonlinearly) related to the amount of intra-abdominal fat; mild, recent diabetes adds little insulin resistance to that caused by abdominal obesity; and despite fat insulin resistance, an expanded fat mass (especially subcutaneous) provides a sink for glucose, resulting in a compensatory attenuation of insulin resistance at the whole-body level in men (Virtanen et al. 2005).

In the future, the increased ability to quantify BAT with PET imaging with F-18-FDG or other radiopharmaceuticals will help to better understand its role in physiology and its potential as a therapeutic target in the treatment of obesity and other metabolic disorders.

NAA

The development of in vivo total-body NNA has proved the only technique currently available for the measurement of the multielementar composition of the human body. Absolute content of calcium, sodium, chloride, phosphorus and nitrogen can be determined safely.

Total-body neutron-activation systems designed for in vivo studies deliver a moderated beam of fast neutrons to the subject. Capture of these neutrons by atoms of the target elements in the body creates unstable isotopes such as calcium-49 and nitrogen-15. The isotopes revert to a stable condition by the emission of one or more gamma rays of characteristic energy. Radiation from the subject is determined using a recording of the radiospectrum of the emissions. The data are obtained from a subject positioned carefully with respect to a detector array in a highly shielded facility. Standard gamma spectrographic analysis is applied. The energy level identifies the element and the level of activity indicates its abundance (Lukaski 1987).

Neutron activation is an analytical technique based on nuclear reactions rather than chemical reactions. The essential variables include neutron flux density, isotopic abundance, cross-section of the target element, half-lives of the product isotopes, and emission energy of the induced activity (Lukaski 1987).

The first application of NNA to the assessment of human body composition was the determination of total body calcium (TBCa). The availability of neutron activation facilities to measure human TBCa is limited to some research centres (cyclotrons to produce neutrons of 3.5 and 8 MeV energy levels). The accuracy and precision of the activation procedure in an anthropometric phantom is 1%. In healthy adults measured over four to 5-year period, the precision of the repeated TBCa determination was 2.5%, which is suitable for studies of longitudinal changes. To quantify clinically meaningful differences in TBCa with aging or metabolic bone disease, specific procedures have been developed to normalize body calcium levels. Most importantly, normalization for anthropometric variables, such as age, gender, height and lean body mass, is necessary to reduce variability in heterogeneous samples. The ability of TBCa to discriminate abnormality may be due to this normalization procedure. The first nuclear methods for direct determination of total body nitrogen (TBN) in humans used the $^{14}N(n, 2n)^{13}N$ reaction and suffered from a lack of specificity because of interference from positron emitters from other body elements. The development of the prompt-gamma technique using the reaction $^{14}N(n, \gamma)^{15}N$, has led to the recognition of the clinical usefulness of body nitrogen measures in body-composition assessment (Vartsky et al. 1979).

Application in Obesity

NAA provides compositional information similar to that of cadaver analyses and, therefore, has become the reference norm most often preferred for evaluation or calibration of the alternate techniques such as CT, MRI, DXA and BIA (Knight et al. 1986; Mattsson and Thomas 2006).

The accuracy of the method is around 5% and values of CV are 4% for carbon as a measure for fat (Jebb and Elia 1993). Newer techniques of NAA (inelastic neutron scattering activation) measuring the carbon/oxygen (C/O) ratio can measure the axial distribution of fat because of the dramatic difference in C/O ration between fat and FFM (Kehayias et al. 1991; Kehayias and Zhuang 1993). The recent development of DXA, CT and MRI methods for determination of body fat distribution has, however, reduced the interest for NAA.

One major concern restraining a more general use of NAA is that of the associated radiation exposure. The doses for each of the in vivo NAA measurements of body carbon, nitrogen and the calcium are ~0.1, 0.3 and 3 mSV, respectively (Ellis 2000). Obviously NAA should be avoided for children and pregnant women. Besides, the equipment is large, uninviting and available in only a few centres worldwide.

A brief evaluation of principal radionuclide methods for body composition analysis in obesity is presented in Tables 10.3 and 10.4.

In conclusion, from the non-radionuclide methods, anthropometric measurements are the most popular in the clinical practice, while DXA is the most widely applicable technique. From the radionuclide methods, CT and MRI represent important advances in body composition analysis and its relationship

Table 10.3 Evaluation of radionuclide methods for body composition analysis in obesity

Method	Principals of method	Advantages	Disadvantages
Total body water	Quantification of body water volumes by isotope dilution	– Estimation of body fluids – Variety of tracers available – Reference method	– Radiation exposure – Blood samples (some methods) – Time consuming – Errors in obese fluid-loaded patients
Total body potassium	Estimation of total body potassium content	– Ideal for estimation of body cell mass – Non-hazardous – Can be repeated frequently (no radiation)	– Influence by body size and geometry – Variation of potassium in tissues – Instrument expensive – Long measurement time
Computed tomography	Attenuation of X-rays when passive through tissues	– High resolution images of various organs – Delineation of adipose tissue topography – New generation CTs; for understanding of dysmetabolic disorders	– Radiation exposure (– Excludes children, pregnant women) – Relative high cost – Limited availability for body composition measurements
MRI	A powerful magnetic field aligns the nuclear magnetization of atomic nuclei in the body	– Direct measure of organs – Assessment of fat distribution and ectopic fat – New generation MRIs for tracking the metabolic activity of tissues – No radiation	– Expensive instruments – Limited availability – Long scan times required – Less accurate for visceral fat than CT
PET scan	It images biological process in vivo three-dimensionally using specific radiopharmaceuticals labelled with a radioactive isotope	– Visualises small but active metabolic tissues (e.g. brown adipose tissue) – Follows substrates uptake in various tissues and helps understanding metabolic disorders	– Instrument very expensive – Limited availability worldwide
Neutron activation analysis	Irradiation of the body with neutrons and measurement of type and intensity of radiation	– In vivo measurement of the multielementar composition of the human body (Ca, Na, Cl, P, N) – Compositional information similar to cadaver analysis – Reference method	– High radiation exposure – Limited availability worldwide – High cost

Principals, advantages and disadvantages of most important radionuclides methods are briefly summarized

Table 10.4 Practical methods and techniques

Method	Patient information/ preparation	Examinations protocol	Results interpretation
Computed tomography	No pregnancy	Scan time: 1 min	Time of scan interpretation: 20 min
MRI	No magnetic material	Scan time: 30 min	Time of scan interpretation: 20 min
PET-scintigraphy	No pregnancy, no breast feeding, fasting condition, glucose levels <135 mg/dl	i.v. administration of PET-tracer, time of distribution: 45 min, scan time: 45 min	Physiological biodistribution: Brain, heart, renal elimination of the tracer time of scan interpretation: 20 min

Patients' precautions, duration of examination and time for results interpretation in the principal imaging techniques are briefly shown

with various metabolic diseases. These methods offer the possibility of qualitative and quantitative measurement of various tissues such as bone, AT, skeletal mass and others. They are now considered as the methods of choice for validation of other methods such as BIA and DXA.

Summary Points

- A number of body components can be quantified using a wide range body compositions methods and models. Mass, volume and distribution of various components (fat and fat-free mass, protein, water and minerals) are the primary measures in the field.
- In obesity, the early and simple methods based on height, body weight, skinfolds and circumference measurements are still in use to predict body composition and distribution. More accurate techniques using simple equipments are BIA, ADP and DXA. They tend to replace older heavy techniques such as body K counting and UWW, which they were considered the 'reference' standard for body fat measurements.
- The introduction and evolution of imaging methods (CT and MRI) opened a new era into the body composition research. These methods offer the possibility of qualitative and quantitative measurements of various tissues such as bone, skeletal mass, hepatic tissue and AT. Thanks to recent imaging, a systemic classification of AT is now possible based on topographic and metabolic characteristics. Besides, these techniques provide a detailed description of tissues changes during weight loss by different diets, pharmacotherapy or bariatric surgery.
- Nuclide imaging by PET scan has recently been widely used to localize tumors in oncology; additionally, using specific radiopharmaceuticals it can visualize active metabolic tissues, (e.g. BAT) and follow substrates uptake (e.g. insulin – stimulated glucose uptake) in various organs, therefore, providing a tool for better understanding the physiology of obesity and related metabolic disorders.
- The ongoing development of new technology such as functional MRI and MRS, together with PET scan will enable studies of the condition of tissues and organs, their composition, nutrient utilization, blood flow and other properties in the field of obesity. However, we should keep in mind that the simple, reliable and cheap methods like anthropometric measures and BIA have to be preferred for obesity and weight loss evaluation in everyday clinical practice.

Key Features of Radionuclides

1. A radionuclide (or radiosotope) is an isotope of artificial or natural origin, which has an unstable nucleus and emits radiation.
2. As radionuclide gathers in an organ or tissue, radioactive signals may be measurable by a detector which is called gamma camera.
3. Radionuclides of familiar elements such as carbon can serve as tracers because they are similar to the non-radioactive nuclides.
4. Radionuclides can be used in two major ways: first for their chemical properties and second as sources of radiation in nuclear medicine.
5. Using their chemical properties, radioactive isotopes are useful for labelling compounds that subsequently are used to investigate various aspects of metabolism of protein, carbohydrates and lipids.
6. In nuclear medicine, radioisotopes are used for diagnosis and treatment. Radioactive tracers emitting gamma rays or positrons can give diagnostic information on an individual's internal anatomy and organs functioning.
7. This principle is used in imaging techniques such as tomography, single photon emission, CT and position emission tomography scanning.

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Chapter 11
Three-Dimensional (3-D) Photonic Scanning: A New Approach to Anthropometry

Jonathan C.K. Wells

Abstract Anthropometric measurements, such as body mass index (BMI) and body girths have long been used to assess nutritional status in all age groups. Although most such measurements are merely one-dimensional (1-D), they are often used to index body shape. Examples include BMI, waist–hip ratio or waist–height ratio, each of which acts as a proxy for whole-body or regional-body shape. Recently, whole-body photonic scanners developed by the clothing industry have appeared, and offer a new approach to body shape assessment. Although a variety of technologies have been developed, all photonic scanners project light onto the surface of the body, and record the surface topography. Initial data capture provides a 'point-cloud', which is then processed using computer algorithms to extract the skin surface topography. Automatic landmark identification then allows an 'e-tape measure' to be applied, extracting multiple girths, distances, diameters and two-dimensional (2-D) cross-sectional areas. Current software allows around 200 such measurements to be extracted, making the technique ideal for large anthropometric surveys. However, the major potential of the technique lies in its ability to go beyond 1-D measurements and extract more complex topographical and shape outcomes. The technology offers numerous benefits over traditional approaches, with the digital data facilitating rapid processing and archiving, the application of diverse analytical software programmes, and repeat scans allowing change in shape to be quantified. 3-D scanning has recently been applied in several large National Sizing Surveys, allowing exploration of the associations of age, gender and nutritional status with body dimensions. Validation studies against manual measurements indicate high consistency in ranking individuals compared with manual measurements, but systematic differences in average values, due to differences in the way that the data is obtained. 3-D photonic scanning is easy, quick and cheap to apply, as well as being non-invasive and well-accepted by the majority of adults. The technology offers a novel approach to anthropometry and is likely to be adopted increasingly in large surveys of size, growth, nutritional status and health.

11.1 Introduction

Anthropometry has been used for centuries to assess growth and nutritional status. Although not often considered from such a perspective, measurements of body shape have arguably been used in this context for over a century. Given the high correlation between body weight and body volume,

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_11,

Quetelet's index (now known as body mass index (BMI), and calculated as weight divided by height squared) can be considered a crude index of relative volume. The higher the BMI value, the larger the shape and weight of the individual. In the 1980s, overweight and obesity were defined as BMI >25 and >30 kg/m^2, respectively (Garrow and Webster 1985), and chronic energy deficiency as BMI <18.5 kg/m^2 (James et al. 1988). BMI has been associated with health outcomes in numerous subsequent studies, with both low and high BMI values linked with poorer health. The main limitation of BMI is that it gives no indication of the composition or regional distribution of weight; hence there has been growing interest in more specific shape indices capable of discerning health and disease risk with greater accuracy.

Throughout the twentieth century, body shape has been assessed by a limited number of anthropometric measurements, most commonly girths of the torso and limbs. Again, these have been used to categorise both under-nutrition and over-nutrition. Mid upper arm circumference is widely used to assess nutritional status in developing countries, with cut-off values of 23 and 22 cm defining adult under-nutrition in males and females, respectively, and lower values defining acute malnutrition (Ferro-Luzzi and James 1996). A similar approach is also used in children. Waist girth, or waist–hip ratio, is widely used to assess central adiposity or truncal obesity. The waist–height ratio, like BMI, gives an indication of relative volume, but with greater capacity to index relative abdominal volume. Waist girths of 100 and 95 cm in adult males and females, respectively have been proposed to define truncal obesity (Zhu et al. 2005), although lower values have been proposed for Asians due to their higher visceral fat content for a given BMI value (Misra et al. 2006). Public health messages have emerged from this work: for example, the recommendation to 'keep your waist to half your height'. In children, ethnic-specific waist girth *z*-scores have likewise been published (Fernandez et al. 2004).

These anthropometric measurements are widely used to assess nutritional status alongside others, such as weight, height and skinfold thicknesses, and have collectively provided the 'backbone' of nutritional status assessment for many decades. Anthropometric measurements are generally simple, cheap, quick, non-invasive and applicable in each of clinical practice, clinical research and large-scale epidemiological studies. These numerous benefits are likely to account for the persistence of their use even though many other outcomes are now measured with substantially greater technological sophistication. Only at the end of the twentieth century did anthropometry begin to benefit from technological advances that would bring it into the new digital age.

For internal body composition characteristics, MRI and CT scanning now provide unprecedented detail on the distribution of adipose tissue and diverse components of lean tissue. The main limitation of these technologies is their high expense and restricted access, such that they can only realistically be applied in small-scale research studies. However, as reviewed previously (Wells et al. 2008a), external measurements of body shape are highly predictive of health and disease, and already play a major role in clinical monitoring and in epidemiological investigations of disease risk. What new photonic technology can now introduce into this arena is the capacity to accumulate a much greater range of anthropometric indices, at a much faster rate of data collection, and with even less physical perturbation of the subject.

These advances have been made possible by the development of three-dimensional (3-D) whole body photonic scanners, a technology originally developed for the clothing industry, but now increasingly explored in biomedical applications. 3-D photonic scanners have been used by the retail industry to improve the fit of garments, both by providing up-to-date information on the range of shape in modern populations, and also by converting 1-D or 2-D measurements into genuine 3-D measurements of shape (Treleaven and Wells 2007). A typical body girth, such as that of the waist, is a 1-D measurement, namely the distance around the torso, and the same distance could, in fact,

derive from numerous different shapes. Thus 2-D measurements can dramatically increase the amount of information available, and given these benefits, it is clear that 3-D measurements offer a further potential improvement.

3-D photonic scanners are now set to transform the measurement of anthropometry and body shape in human epidemiology, clinical research and clinical practice. There is the potential to explore a wide range of novel outcomes, and to test their associations with indices of health and disease. Initial work has been extremely promising, and is uncovering new areas for application. This chapter describes progress to date and indicates future directions.

11.2 3-D Photonic Scanners

Three-dimensional modelling of body shape and tomography emerged independently in a number of branches of medical research. Early work comprised stereo-photogrammetric technology, whereby at least two overlapping photographs of the body are obtained in order to develop contour lines of the body surface (Pierson 1963). Whilst the information was considered valuable, the process was costly due to the mathematical processing, photography and technology required. Subsequent work involved the projection of strips of light onto the body, allowing contour maps of the front and the back of the body to be obtained (Pierson 1963). This approach has subsequently evolved into a rapid-operation and convenient system, by surrounding the body with a number of different cameras.

Over the last 2 decades, whole body photonic scanners, based on either photogrammetric or laser technology, have been developed for clothing industry requirements. Rapid advances in photonic technology, accompanied by similar progress in computerised modelling, have greatly improved the reconstruction of human body surface topography. All photonic techniques involve the projection of light onto the body surface, followed by the use of mathematical algorithms to reconstruct surface topography. Technological approaches can be divided broadly into three categories. First, photogrammetric (light stripe) approaches involve the projection of visible light onto the body, and the use of cameras or a video projector to record the resulting distorted patterns. An example of such instrumentation is the $[TC]^2$ scanner, recently utilised in a number of national sizing surveys (Wells et al. 2007). Second, laser techniques use harmless invisible lasers to project points or lines onto the body, while further cameras offset from the laser source capture this data and use triangulation methods to calculate the location of the points or lines. An example of this instrumentation is the Hamamatsu bodyline scanner, recently used in research on obesity (Wang et al. 2007). Finally, radio wave technologies use linear array radio waves to scan the body through clothing. Although such instrumentation has been developed, such as that produced by Intellifit, it is not yet commercially available and may present ethical issues concerning personal privacy. Nevertheless, several different hardware options are currently available, although some are less suitable for routine use, and further developments are ongoing. Of particular note, whole-body scanners are likely to diverge into two groups: increasingly accurate instrumentation for high-quality clinical data; and increasingly cheap instrumentation for basic widespread epidemiological application.

In practice, currently available scanners tend to take the form of a large photo booth, comprising an array of cameras or light sensors surrounding a central space where the subject stands for a period of a few seconds holding a standardised pose. The subject is requested to wear close-fitting underwear, to ensure that clothing does not obscure the details of the body surface topography. In addition to the scanner itself, a screened area where the subject can dress and undress must be made

available, along with a computer area for operating the technology. Such scanners can be installed without difficulty in clinics and other health-care locations, but are not readily portable due to the need to maintain alignment of the cameras. Mobile scanning units are currently under development, which can potentially be taken to clinics, schools, shopping centres and rural locations, thus greatly improving access to this modern technology.

Over the last decade, large national sizing surveys have been conducted in the UK (Wells et al. 2007), France, United States (Wells et al. 2008a), Mexico, Australia and Thailand, while others continue. These surveys have provided abundant evidence that the vast majority of those aged 16 years or older are willing to undergo a whole body scan, and have no undue concerns about the invasiveness of the process, or data security. Pilot studies on younger age group suggest that general acceptance is again high, although younger children may have difficulties standing still for the required scanning periods, and overweight teenagers may be reluctant to undergo the process due to their heightened sensitivity in relation to their body shape. However, some groups may have concerns about acceptability of the process given that it captures information about body shape, and further work is required to see how this situation can be addressed. Contrary to most participants' assumptions, there is no need for a full-body image to be constructed and visualised during the analysis process, instead anthropometric measurements can be extracted and used in purely digital format.

11.3 Digital Anthropometric Data

One of the key strengths of 3-D photonic technology is its provision of digital information. Such information is readily stored, processed and retrieved, facilitating longitudinal assessments of individuals. Measurements can be exchanged rapidly between locations, allowing data collected in a mobile unit, for example, to be downloaded in the clinic or by a research partner.

Raw scans can be processed with a variety of software, offering the potential to re-analyse existing scans with newly developed algorithms quantifying novel shape outcomes. Each scan also provides a wide range of information, including distances, diameters, girths, surface area, surface topography, and regional and total volumes. New software now allows the change in the shape of an individual to be assessed, by overlaying sequential scans in order to identify body regions that have expanded or contracted. The digital nature of the data also facilitates its integration with other such outputs, potentially including internal MRI data on anatomical tissue distribution, or DXA data on bone characteristics. The possibility of converting simple distances or girths into more sophisticated 2-D or 3-D indices of shape could transform the way in which physical measurements of the body could be used to index health and disease.

Efficient use of this enormous amount of information will require a new generation of software, capable of extracting both detailed information and broader assessments of change over time. The digital nature of photonic data is capable of transforming the use of anthropometry in clinical practice. Inter-observer error has long been one of the limitations of such data, with individuals varying in where measurements are taken, and in what style. 3-D technology can potentially overcome such inter-observer error, by using automatic landmark identification software. Alternatively, the cursor may be moved manually over the scan to extract a particular digital measurement. This manual extraction approach would allow multiple observers to train on a single scan, or the average of two different observers' measurements to be used for each scan, thus improving precision.

Because anthropometric data are a key means of monitoring risk of the metabolic syndrome and of response to treatment, data may be collected at multiple sites using a common photonic approach

and integrated within a database held at the patients' GP practice. With photonic technology set to play an increased role in the clothing industry, in fitness centres and in other areas of retail, there is the potential for body shape data to be collated across different dimensions of an individual's lifestyle, thereby clarifying actual shape changes and linking these with health outcomes. Shape appeals to individuals at many levels (body aesthetics, fashion, fitness), and integrating health issues within this broader niche is likely to prove beneficial to both the individual and the clinician. Such progress will take time, but is clearly possible given the nature of the technology. The software and infrastructure requirements of such an approach are similar to those of other areas recently revolutionised by digital technology, such as online banking.

11.4 Computer Modelling of Body Dimensions

In raw format, photonic technology provides body surface shape data as a point cloud, a series of unconnected data points distributed in 3-D space. In order to convert such information into measurements and dimensions, computer algorithms must be applied. These reconnect the points and reconstruct surface topography. A variety of different mathematical approaches have been used for this purpose, including triangulation methods, spline curve fitting and canonical representation models. Further advances in this area are expected, increasing the sophistication of shape outcomes that can be generated.

Initially, the data are cleaned through the rejection of inconsistent data points that arise from random reflections in the scanning booth. Some software systems incorporate automatic landmark identification, whereby the algorithms automatically extract key anatomical locations. For example, the girth of the waist may be located by first identifying the small of the back, and then calculating the smallest circumference within a certain number of centimetres above or below this point. These automatic landmarks are then used to guide an 'e-tape measure' across the body surface, providing a large number of girths, depths and diametres, as well as the height above the ground at which each measurement was taken. Figure 11.1 illustrates the stages from raw cloud point data to 'e-tape' measure output.

To date, validation studies have shown fair to high accuracy, depending on the scanner model and outcomes assessed. Wang et al. (2006) showed good accuracy for regional volumes and girths measured using a Hamamatsu scanner. Manual and 3-D measurements showed significantly different average values for the TC^2 model, which could be attributed both to differences in the measurement procedure and in the location measured; however, both techniques ranked individuals similarly (Wells et al. 2007). Further work must be directed to validation, but the key strength of 3-D photonic scanning lies in its ability to measure 2-D and 3-D outcomes, and other 3-D techniques, such as MRI and CT, rather than manual girth measurements, will be required to assess accuracy. Precision is a separate issue also meriting attention. Imprecision derives in part from computer algorithms, but also in part from inconsistency in the posture adopted by the subject.

Because the technology was developed by the clothing industry, the initial outcomes were targeted at their needs, and a range of 1-D measurements were provided across the entire body surface to improve clothing fit. New medical software is now being developed to index novel shape parameters likely to be more strongly predictive of health and disease risk. For example, along with extraction of girths at the abdomen, waist and thigh, calculation of the lateral and dorsal diametres and the cross-sectional surface areas is now possible (Wells et al. 2010).

In addition to these novel shape outcomes, a further important component of the technology comprises its capacity to visualise features of the body. Although the technology does not produce

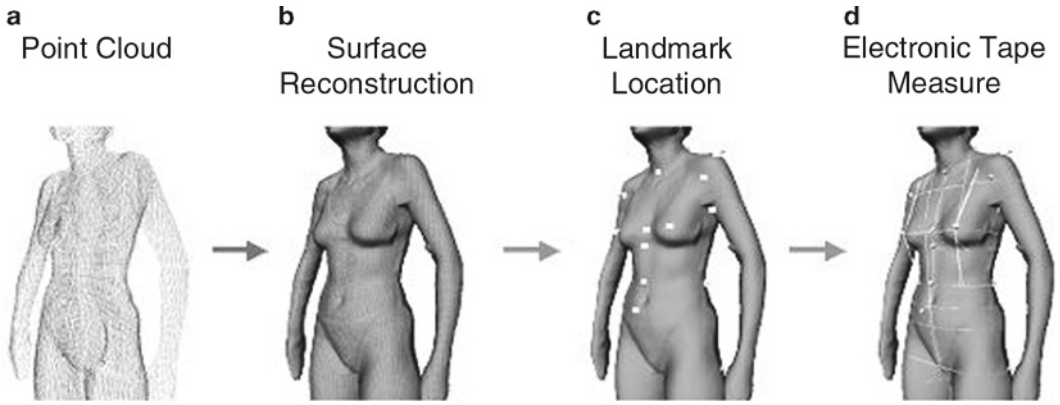

Fig. 11.1 Stages of data processing from capturing raw photonic data to generating final shape output. (**a**) The initial point cloud; (**b**) the application of a smoothed skin surface; (**c**) the automatic location of landmarks and (**d**) the application of a digital 'e-tape' measure. Reproduced with permission (Wells et al. 2007)

outputs of the same image density as conventional photography, the 3-D nature of the images offers novel information. Using 3-D photonic imaging, surfaced topography is explicitly captured rather than inferred, and can then be expressed in diverse formats. Examples include a 2-D silhouette, smoothed or mesh 3-D surfaces, or transverse sections through the body at any height (Wells et al. 2008a). The body topography may be viewed from any plane or angle, allowing a vast number of shape properties and dimensions to be evaluated. Of particular potential value is the capacity of photonic scanning to display within-person change over time. To achieve this, images are superimposed, and colouration used to discern those areas that have undergone change.

Whilst the outcomes described above refer to the anthropometry of the individual, large data sets also enable population-based outcomes to be developed, using more complex statistical approaches. Each individual's reconstructed surface topography can be converted to a common format, using processes such as canonical sampling, template optimisation or voxel representation. They can then be aligned using a generalised procrustes alignment procedure to reduce any orientation error, and hence ensure that only variation in 3-D shapes is captured in subsequent modelling processes. Independent component analysis has been applied to data from the UK sizing survey, in order to identify distinct and independent notes of variation in body shape. Figure 11.2 illustrates four dimensions of variability in female shape, with each image superimposing, for front and side views, the variation in shape of individuals at ±2 SD of the population range for each dimension. Here, the first dimension reflects differences in overall size, the second reflects differences specifically in height and girth of the entire chest and abdomen, the third reflects differences in upper torso posture, and the fourth differences in lower torso posture. This statistical approach is likely to play a key role in enabling access to novel shape outcomes, first by identifying the different independent modes of shape variability, and second by allowing all individuals to be ranked in terms of the population distribution.

11.5 National Sizing Surveys: Main Findings

Initial analysis of sizing survey data was restricted to conventional anthropometric indices, such as a range of body girths. The main findings published to date, therefore, reflect the availability of shape data in large multi-ethnic national samples. Ongoing work is applying novel shape software to these

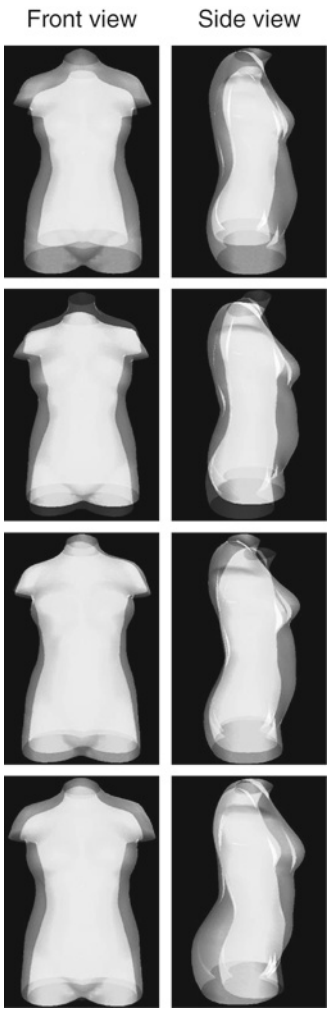

Fig. 11.2 Four dimensions of variability in female shape generated using independent component analysis of data from Size UK. Each image superimposes, for front and side views, the variation in shape of individuals at ±2 SD of the population range for each dimension. Reproduced with permission (Wells et al. 2008a, copyright Tony Ruto)

samples, and is elucidating further information about body shape. Nevertheless, analyses of size UK and size USA have already revealed important biomedical findings.

Analysis of the size UK demonstrated that greater height was positively associated with all body girths except waist girth in males, and thigh, arm and waist girths in females (Wells et al. 2007). This analysis indicates that, whether for physiological or allometric reasons, shape is not constant across the range of height, but rather alters with taller individuals having relatively lower waist girth. Possible explanations include genetic factors affecting both growth and body composition, or a possible link between stunting in early life and subsequent fat distribution. Further analysis demonstrated both significant sex-differences in shape, and varying effects of age on those sex differences (Wells et al. 2007, 2008c). Whereas waist–chest and waist–hip ratios are relatively constant with age in males, they are initially lower in females, but by old-age have converged on the male values. Female body shape also demonstrates a significant redistribution of body weight, presumably fat, between the lower and upper body with age. More detailed analyses indicate that this redistribution occurs independently of any age-changes in BMI.

Analysis of Size USA focused on inter-population and inter-ethnic differences. These analyses demonstrated significant ethnic variability in shape, with Hispanic Americans tending to have relatively greater central adiposity, but African Americans relatively less central adiposity, compared

to white European Americans (Wells et al. 2008b). Although no data on health profile was available in either of these sizing surveys, such ethnic differences in shape are highly consistent with ethnic variability in the metabolic syndrome reported in other studies (Park et al. 2003), although it should be noted that the metabolic syndrome has inconsistent associations with cardiovascular risk across ethnic groups (Mensah et al. 2005).

11.6 Body Shape and Health

3-D photonic scanning is still a relatively new technology, but there is already a substantial and strengthening evidence base linking body shape with a range of health outcomes. This evidence, largely based on conventional manual shape measurements, gives confidence that photonic technology can revolutionise an area of research and practice already much valued in medicine.

The majority of work has focused on the metabolic syndrome, a condition strongly associated with nutritional status and adiposity. Despite continued reliance on BMI for the clinical categorisation of overweight and obesity, studies increasingly demonstrate that body shape parameters are more sensitive indices of clinical risk. Analysing data from over 27,000 adults distributed across 52 countries, Yusuf et al. (2005) found that the risk of myocardial infarction in those of low BMI with high waist girth exceeded those of high BMI with low waist girth. In a meta-analysis, waist-to-height ratio was found to be a better discriminator than BMI for hypertension, diabetes and dyslipidaemia in both men and women (Lee et al. 2008). Figure 11.3 illustrates the odds ratios of diabetes per 0.5 SD increase in either BMI, waist girth or waist–hip ratio (Huxley et al. 2010). These data strongly indicate that the health risks of obesity are disproportionately due to abdominal fat (visceral and deep subcutaneous fat) rather than peripheral subcutaneous fat located in the limbs.

Neither waist nor hip girth is considered particularly invasive by most people, and the majority of adults will be familiar with them in other context, such as when purchasing clothing. Their increasing use in clinical practice offers an advantage over BMI or weight, where changes may be due to lean mass, as well as fat.

Nevertheless, the current utilisation of data on waist and hip girth remains an extremely simplistic approach. Recently, a number of studies have reported the development of more sophisticated body shape outcomes, and have investigated their associations with the risk of diverse diseases and health outcomes. Of particular importance, contrasting with the association of increased abdominal fat with disease risk, peripheral gluteo-femoral fat appears protective against disease. For example, greater hip girth appears beneficial for the risk of diabetes, hypertension, dyslipidaemia and markers of inflammation (Snijder et al. 2003), with this finding replicated across diverse ethnic groups (Snijder et al. 2004). Likewise, thigh girth has tended to be associated with a protective effect for both cardiovascular disease and type 2 diabetes (Snijder et al. 2003). Whilst much of this work has been conducted in adults, the same findings are increasingly emerging in paediatric research. These findings merit further exploration, as childhood interventions may be particularly valuable in reducing prevalence of the metabolic syndrome, and 3-D photonic scanning is suitable for the majority of the paediatric age range.

Collectively, these studies indicate an untapped potential of body shape outcomes to evaluate health status. Most existing work has remained based on 1-D measurements, for example, the distance around the waist, or the distance from the front to the back of the abdomen. Cross-sectional areas of the abdomen or limbs would represent 2-D outcomes, and these could then be summed to provide volumes, or to express more complex body features, such as topographical contours. Thus, despite substantial interest in the association between body shape and health, the 3-D topographical landscape of the human body has yet to be exploited adequately as a source of information. Recent work has considered how girths from different body locations differentially index peripheral vs. internal body fat, or skeletal

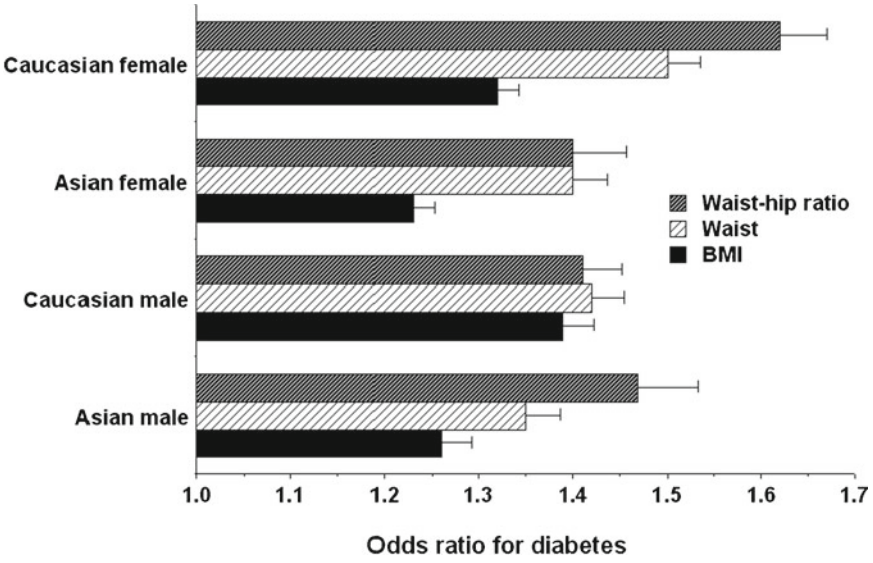

Fig. 11.3 The odds ratios of diabetes per 0.5 SD increase in either BMI, waist girth or waist–hip ratio in Asian or Caucasian males and females. Adapted and redrawn from Huxley et al. (2010)

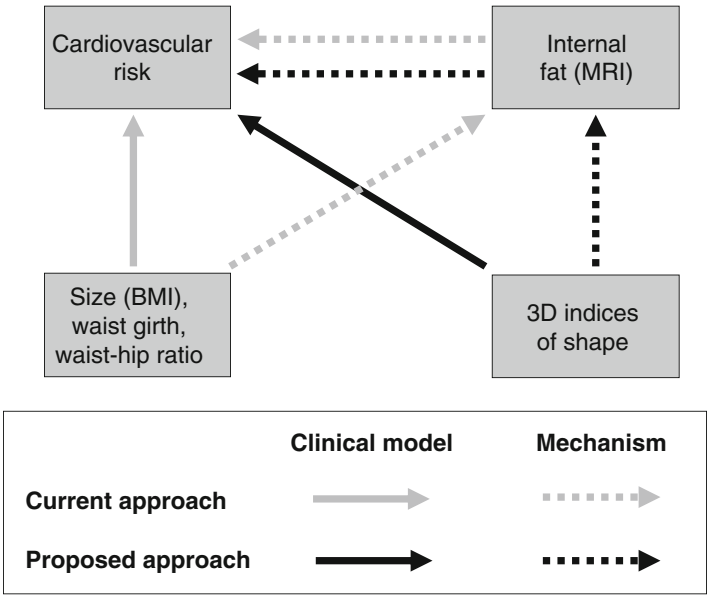

Fig. 11.4 The rationale for 3-D photonic shape outcomes replacing the existing conventional, but crude shape outcomes as indices of cardiovascular risk. 3-D shape can potentially index more subtle components of fat and lean distribution than conventional anthropometry, and hence predict risk with greater sensitivity

muscle mass. Calf and arm girths proved the best indicators of muscle mass, waist girth of visceral fat, and waist and hip girths of internal visceral fat (Heymsfield et al. 2008). The application of 3-D photonic technology to this generic approach is likely substantially to improve such predictions.

Figure 11.4 illustrates the rationale for 3-D photonic shape outcomes replacing the existing conventional, but crude indices of shape as predictors of health. Such an approach would be justified

Table 11.1 Key points

1. Digital anthropometric data can now be obtained using whole-body 3-D photonic scanners. This hardware generates 3-D 'point clouds', which can then be subjected to sophisticated computer processing.
2. Current software uses automatic landmark identification to fit an 'e-tape measure' over the body skin surface, allowing the extraction of around 200 body measurements, such as girths, diameters and distances.
3. Validation studies show systematic differences between such 3-D measurements and manual measurements, due to differences both in the style of measurement (projecting light onto, vs. touching, the skin) and in the exact location measured. Consequently, while the methods show excellent consistency in ranking within a population, cannot be used interchangeably to provide absolute data on any given trait.
4. Digital anthropometric data offer numerous advantages over conventional measurements. The data are quick and easy to obtain, with high acceptance levels encountered in recent National Sizing Surveys.
5. Each 10 s scan provides substantial potential for computer analysis, and current work is addressing not only conventional outcomes (girths, diameters), but also novel 2-D and 3-D indices, such as cross-sectional areas or regional volumes and surface topography.
6. Photonic digital information is readily archived and retrieved, and allows comparison of repeat scans to identify change in shape.
7. Photonic scanning is likely to shift attention away from 1-D anthropometric measurements to more complex 3-D anthropometric shape outcomes.
8. Research is underway to identify more sensitive shape indices of disease risk, focusing, in particular, on the metabolic syndrome, obesity and type 2 diabetes.
9. The technique is particularly valuable because the same data is relevant to, and increasingly used by, the lifestyle and retail industries addressing fitness and clothing requirements.
10. 3-D photonic scanning can change not only the type of anthropometric data collected, but also the way in which it is used in health care monitoring.

primarily by physiological studies demonstrating better associations between 3-D photonic outcomes and internal adiposity, compared to those between BMI or waist girth and adiposity. However, as discussed above, shape may index more than adiposity, and further work should address this issue too. Of critical importance is that studies already suggest that anthropometric outcomes may index risk as strongly as MRI or DXA measurements of internal fat distribution (Sierra-Johnson et al. 2004; Scherzer et al. 2008), suggesting no significant loss of sensitivity from the use of a much cheaper and more convenient technology. The potential for 3-D photonic scanning to transform the use of anthropometry in health care is summarised in Table 11.1.

11.7 3-D Assessment of Obesity

One area of particular interest concerns novel categorisations of obesity. Research has increasingly demonstrated the limitations of BMI as the primary index of obesity, as discussed above. This is particularly the case with children (Wells 2000), where growth further confounds simple interpretation of BMI. Another key problem area concerns ethnicity, with variability in physique again confounding the interpretation of BMI. For example, Asian children tend to have greater body fat content, including visceral fat, for a given BMI value compared to white Europeans, whereas Afro-Caribbean of African children have reduced body fat (Haroun et al. 2010). However, ethnicity is itself a difficult outcome to asses, in part, because categorisations such as 'Asian' or 'black' fail to address the substantial variability within such groupings, and in part, because an increasing proportion of children derive from mixed-ethnic unions. It is possible that more detailed categorisation of physique, based on body landmarks, such as knee girth or ankle girth, will improve the accuracy, whereby excess adiposity (e.g. waist girth) is indexed, thus obviating the need for qualitative information on family ancestry.

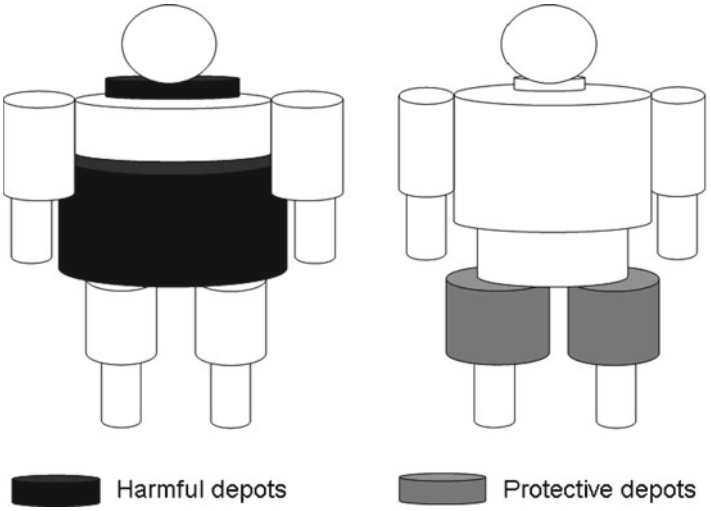

Fig. 11.5 Schematic diagram illustrating contrasting body shape profiles according to the relative size of segmental body volumes. The left-hand figure has enhanced neck and lower abdominal volumes, both associated with increased cardiovascular risk, and reduced gluteo-femoral volumes, associated with protective effects. The right-hand figure shows the inverse shape profile with low-cardiovascular risk

Compared to BMI, measurements of body shape offer more specific assessments of central adiposity, demonstrated by increasing use of waist girth, or waist–height ratio. Photonic instrumentation allows substantially greater information about abdominal shape to be captured. For example, segmental body volumes may be developed; alternatively, cross-sectional areas or diameters may be determined. The distribution of weight between these segmental volumes may then be assessed.

Figure 11.5 illustrates two profiles of body shape, one emphasising enlarged lower abdominal and neck volumes (both indices of cardiovascular risk, as discussed above), and the other emphasising moderate neck and abdominal volumes, but enhanced gluteo-femoral volumes, which have been associated with protective effects. 3-D technology can provide quantitative indices of these contrasting segmental volumes, providing a more sensitive index of obesity profile than BMI. For example, using 3-D scanning, Wang et al. (2007) have shown a disproportionate increase in trunk volume relative to limb volume in obese adults, especially in men. This replicates similar findings in children using more conventional technology (Wells et al. 2006). Indeed, the 3-D approach is likely to particularly beneficial in children, as adjustment may readily be made for variability in age or height. Likewise, ethnic variability in physique may also be addressed by clarifying variable normative ranges of different regional body volumes.

11.8 Continued Development of the Technology

The main focus of development at the current time is improved software for categorisation of body shape outcomes. Automatic landmark location in combination with new topographical features can dramatically improve the capture of information relevant to health from photonic shape data. Also, there is a current paucity of datasets combining 3-D outcomes with indices of cardiovascular risk. Lin et al. (2002) studied novel shape indices in 1,204 adults from Linkou, Taiwan, and found stronger associations with metabolic risk that those for either BMI or waist–hip ratio. Ongoing work by

the author's own group is exploring the association between body shape, internal fat distribution and metabolic risk in adolescents of different ethnic groups. Such work will help demonstrate the potential of photonic technology to play a new role in epidemiological research and clinical practice.

11.9 Applications to Other Areas of Health and Disease

3-D photonic scanning is increasingly used in diverse areas of medical research and practice, as reviewed previously. Lung function is a particularly intriguing area, as 3-D chest measurements may relate to it better than 1-D measurements, and real-time data capture could be used to assess breathing characteristics. Other areas of particular interest include cranio-facial surgery, the construction of high-quality prosthetics, and screening for conditions, such as scoliosis and obesity. The technology offers the capacity for these diverse applications to be integrated, such that on the one hand, nutritional status is addressed when body information on body topography is required, and on the other hand, information on body topography is used to interpret nutritional status. The digital nature of the information is key to this integration, and indicates that anthropometric information can be used much more widely than is currently the case.

Summary Points

- There is now compelling evidence that body shape is associated with a variety of health and disease outcomes, most notably the metabolic syndrome.
- Existing anthropometric shape indices, constructed from manual measurements, are relatively cumbersome to obtain and convey only crude information about shape. 3-D photonic scanning represents a more sophisticated approach to shape assessment.
- 3-D photonic scanning offers many practical advantages over manual anthropometric measurements. The digital data can be readily captured and archived, processed by a variety of different software programmes, and used to assess shape change over time by overlaying repeat scans.
- Large sizing surveys have demonstrated significant variability in 3-D body shape in relation to age, gender and ethnicity. Much of this variability is not revealed by BMI, the conventional index of obesity and nutritional status.
- 3-D body scanning represents a new technique for anthropometric surveys and obesity screening, ideal for large sample sizes and most age groups >4 years. It will shift emphasis from individual girths and dimensions to more composite shape outcomes.

Acknowledgements The author is grateful to his long-standing collaborator Professor Philip Treleaven of UCL Department of Computer Science, with whom this research has been carried out.

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Chapter 12
3D Craniofacial Anthropometry, Simplified and Accelerated by Semi-Automatic Calliper

Constantin A. Landes, Michael Trolle, and Robert Sader

Abstract Anthropometric standard callipers are used in craniofacial conformation assessment of patients with malformations, such as cleft lip and palate, hypoplastic or excessive jaw development, or for aesthetic reasons.

Roentgenocephalogram analysis is the mainstay in diagnosing craniofacial osseous and soft-tissue conformation and development. Also called cephalometry, it is based on lateral and posterior–anterior standardized roentgenographs and several insecure landmarks that show considerable intrarater and interrater variation. Moreover, radiation exposure, constant object positioning and the use of costly roentgen equipment is inevitable.

Anthropometry, as mostly presented in the literature, is time consuming and cannot reproduce 3D craniofacial conformation. Insecure landmark definitions and soft tissue resilience foster systemic measurement errors. Therefore, a few, easily accessible landmarks, closely related to the underlying bone were selected, measured and reconstructed in their 3D conformation as a wire frame. A soft tissue mask, concentrating on the mid-sagittal profile was added. Facial growth was monitored, growth functions generated and postoperative outcomes evaluated against the preoperative situation.

To simplify general anthropometric data acquisition by calliper, a *semiautomatic* calliper was developed. With its data-input switch connected by optical data cable to a standard personal computer (PC), this calliper permitted completion of standard data sheets, interrater and intrarater validated in test collectives and patients.

A major volunteer collective with repeat measurements served for standards and for reliability assessment. Normal growth functions, differentiated by sex, were assessed with 95-percentiles and 5% relative error. Full manual viscerocranial Am was thrice as time-consuming as the semi-automatic calliper-mediated direct data input to the computer. Gauging of the distance of the calliper ends by ruler, taking down the numbers manually, and lastly computer data input were rendered superfluous, and standard relative error decreased.

The developed craniofacial Am proved reliable and valid for measurement of craniofacial growth, diagnosis and treatment control. Relative measurement errors are smaller than the systematic

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_12,

magnification and distortion in lateral cephalograms. The Am allowed reliable, objective, independent calculation of cranial bone relations and soft tissue projection, sensitive to facial asymmetry. Easy application, versatility and economy were obvious in the assessment of facial proportions, soft tissue ratios, operation planning and follow-up. Semiautomatic anthropometric callipered data acquisition was shown to be faster than the manual technique and equally reliable: measurement errors were effectively diminished and oversight errors avoided. The craniofacial anthropometric routine has been in use over 10 years and proven valuable in growth comparison of different regimens of cleft lip and palate treatment as well as with jaw development in microsomia and jaw deformity treatment, such as dysgnathia.

While treating specific craniofacial syndromes, many specialists have needed to assess postnatal growth patterns *as a background consideration*. Normal development and knowledge of soft-tissues-to-bone relationships and their interaction and the interaction between functional–aesthetic regions have been given high importance in prospective treatment rationales and outcome assessments. *Using anthropometric standard callipers, craniofacial features, e.g. of patients with malformations such as cleft lip and palate, dysgnathia (hypoplastic or excessive jaw formation), craniosynostosis are assessed today, as are proportions in the trunk and extremities, with dedicated measurement routines*.

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
Am	Anthropometry
Ar	Articulare
Crtl	Control
CT	Computer tomography
Gn	Gnathion
Li	Labiale inferius
Ls	Labiale superius
Mn	Mandibulare
MRI	Magnetic resonance imaging
Mx	Maxillare
N	Nasion
N’	Soft tissue nasion
P	Postgingivale
PC	Personal computer
Pg	Pogonion
Pn	Pronasale or nasal tip
Rcm	Roentgenocephalometry
Sm	Supramentale or supramental fold
Sn	Subnasale or columellar base
T	Tragus or tragion
Ti	Trichion

12.1 Craniofacial Anthropometry Versus Roentgenocephalometry

In the historical context, after the pioneering work of Aleš Hrdlička (1869–1943) for the head and face region, Hellmann (1932) introduced Am in the craniofacial region shortly after roentgenocephalometry (Broadbent 1931). This has since been developed popularized and summarized by Farkas and Munro (1987), Farkas (1994), and Kolar and Salter (1997) among many others. These authors only showcase over a 100 different anthropometric distances of interest in the head and face region alone.

Metric calliper assessment of craniofacial proportion can valuably be performed by Am (Farkas and Munro 1987; Farkas 1994; Kolar and Salter 1997; Arnaud et al. 2001; Evereklioglu et al. 2002; Farkas et al. 2002; Teichgraeber et al. 2003; Mortenson and Steinbok 2006; Bozkir et al. 2006). This serves for growth-monitoring in order to compare different treatment modalities as in craniofacial malformations e.g. cleft lip and palate treatment (Bitter 1992, 2001), jaw microsomy and dysgnathia management (Landes et al. 2002a, b). Similar anthropometric calliper measurements are also used in the trunk and extremities, e.g. for determination of total body fat or muscle length measurement (Harpenden's calliper).

Simple calliper Am, in spite of its diagnostic value, is not a routine procedure in everyday practice as it requires comparison of individual measurements in large tables and yields no three-dimensionality (Farkas and Munro 1987; Farkas 1994; Kolar and Salter 1997).

Regarding the popular *roentgenocephalometry* on lateral and posterior–anterior projections, Rakosi (1982) cites over 100 methods to analyse craniofacial growth by roentgenocephalometry (Rcm). Correct positioning of anatomical landmarks during roentgenographic examination is mandatory, while projections of anatomical structures are mainly used to measure distances or angles. Natural or pathological asymmetries are not considered when both sides are overprojected, as, e.g., in patients suffering from hemifacial microsomy (Farkas and Munro 1987). Furthermore, both facial sides are projected with different magnification. Focus-object and object–film distance and the divergence of the x-rays create a systematic magnification between 4% and 7%. The positioning of the landmarks by one observer, as well as by different observers, in repeated analyses is variable. It is also difficult to establish a correlative norm because there is insufficient correlation between the biological structures of the human cranium and findings in cephalograms. Therefore, many authors use intraindividual correlations instead of "norm values". Specific individual measures are correlated to judge the skull in two dimensions. Lastly, radiation exposure limits the repeatability of roentgenocephalograms (Landes et al. 2002a). Based on the *Broadbent* (1931; Landes et al. 2002b) standards of cephalometric radiography, cephalograms most often serve for operation planning and control in orthognathic surgery.

Apart from the disadvantages of cephalometry, calliper Am even with recent methods (Evereklioglu et al. 2002; Czerwinski et al. 2005; Farkas and Forrest 2006) cannot reproduce cranial three-dimensionality as photographic optical or roentgenographic scanning (computed tomography) methods do. Only roentgenographic methods can assess soft tissues and bone substructure together within one examination without the registration problem in image fusion. Optical data acquisition is confined to the skin surfaces.

Another disadvantage within any calliper Am technique is that the investigator, clinician and their co-workers are required to perform multiple measurements with an anthropometric or blunt drawing calliper. Their span has to be transferred to a ruler, if not integrated in the calliper, and recorded manually either on paper or computer. These manoeuvres are time-consuming and therefore unpopular.

Electronic callipers have been used; however, data transfer continues to be manual, observers annotating the indicated measures from the digital display (Bozkir et al. 2006). Digital virtual callipers

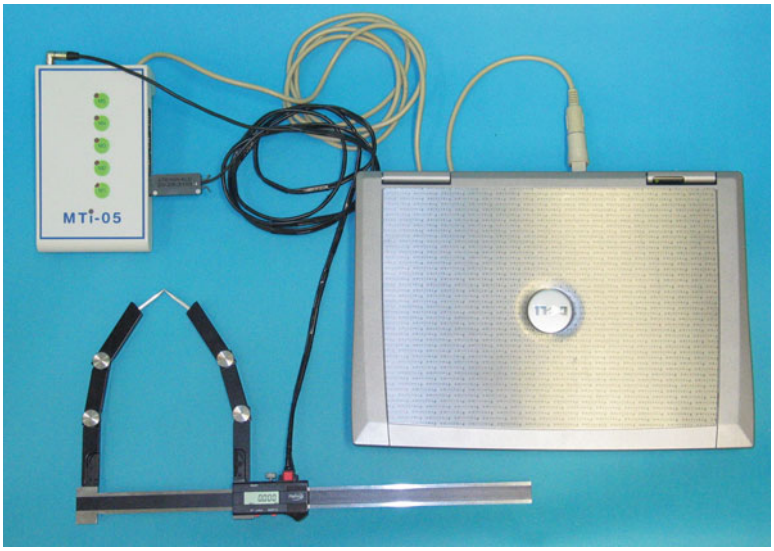

Fig. 12.1 The slide-gauge calliper with optical output, cable, interface to the laptop and footswitch replaced here by a manual control switch. The scale with hand-operated input (*red push button*) can be calibrated to zero in any calliper-arm position. Opening and closing the lock bolts can bend calliper-arms

cannot be used directly on patients, but only in virtual reproductions. These are cone beam computed tomography, or classic computed tomography that require specialized equipment and include radiation exposure and are therefore of limited in their repeatability (Baumgaertel et al. 2009).

12.1.1 Semiautomatic Callipering

To overcome the disadvantage of lack of three-dimensionality and non-haptic conformation assessment in tables, as well as the tedious callipering, a 3D craniofacial Am with a calculation algorithm and an easy-to-use semiautomatic calliper have been developed.

The semiautomatic calliper provides direct computed data input (Fig. 12.1, Landes et al. 2007; Trolle 2008). Moreover, it is designed to be applicable with any anthropometric measurement routine featuring an input table in any PC-keyboard to enter measurement values by footswitch or handswitch in the cursor position in e.g. Excel®- or MS-Access® (Microsoft Company, Mountain view, CA, USA).

Comparative full manual examination was performed with a blunt anthropometric calliper (AA 842, Aesculap, Tuttlingen, Germany) and compared with the semiautomatic anthropometric calliper measurement, both done with identical routines (Landes et al. 2007). The semiautomatic calliper was created on the basis of a technical standard electronic slide calliper (Helios Messtechnik GmbH, Schwäbisch Hall, Germany). Double measurements were performed: fully manual and semiautomatic by the same investigator and repeated at two different interviews. This routine was double assessed by two different investigators to quantify the intrarater and interrater measurement error. The calliper has a 30 cm range (11.81 in.) and a 0.01 ± 0.03 mm measurement resolution, according to the manufacturer. Measurement can be taken in millimetres or inches.

Inwardly curved brass calliper branches with tapered tips were initially attached later replaced by double-hinged arms of tempered steel. These permit free changes of measurement angle and reach less accessible anthropometric landmarks such as the tuber maxillae.

An optical data cable (OPTO RS 232/10 poles, Steinwald Datentechnik GmbH, Marktredwitz, Germany) was connected to the interface. Ten poles were adapted as follows: Pin 1 earthing, Pin 2 data transmission, Pin 9 + 10 with 5 V loading each, to keep the interface charged (Fig. 12.1).

The interface (IMP Ingenieurgesellschaft mbH, Osnabruck, Germany) at the keyboard cable (PS 2-norm) connection to the motherboard has 5 input channels and a hand- or foot-operated switch. The input data are entered at the cursor position; a synchronous acoustic feedback signal is generated. Furthermore, two serial interfaces are included (SIO, "serial in out" 1/2) and the interface's plugging chart obtained from the authors.

A turn-switch modifies the cursor position after data input to either Enter or Space, Tab, to Ctrl function. Windows 2000® (5.0), or Vista® (Microsoft Corporation, Mountain view, CA, USA) equipped standard PCs are used, with Intel Pentium 3® to dual core® processors (Intel Corporation, Santa Clara, CA, USA).

12.1.2 3D Craniofacial Anthropometry

For high availability, portability and low cost, a 3D craniofacial Am was developed of earlier reports and clinically applied (Landes et al. 2002a, b). From the visual configuration of the resulting wire frame, it could be shown that several simple measurements can reconstruct a 3D osseous and soft-tissue "wire-frame". A caveat though: today *3D surface imaging* systems offer a quick and practical method of quantifying craniofacial variation and appear to be highly reliable; however, some sources of measurement error have not yet been thoroughly evaluated. Besides, 3D surface imaging depends on costly equipment that is not always available, at least not globally, and if used for assembling osseous and soft tissue conformation analysis, radiation exposure is inevitable (Heike et al. 2009).

Extraoral, easily accessible anatomical landmarks were selected see Tables 12.1 and 12.2 and marked on the skin, which maintain a close and reproducible relationship to underlying bone:

- Tragus (T also "Tragion" left and right) and
- Nasion (N) form a triangle representing the cranial base
- Maxillare (Mx) also "gingivale superius" at the insertion of the upper median labial frenulum into the maxillary alveolar ridge
- Mandibulare (Mn) also named "gingivale inferius" at the insertion of the inferior median labial frenulum into the mandibular alveolar ridge
- Postgingivale (P) or "tuber" was located at the dorsal endpoint of the maxillary alveolar crest at the tuber maxillae

Generally in calliper Am, soft tissue resiliencies beneath accessible landmarks on the skin are permanent sources of error, and several landmark definitions are insecure. Therefore, osseous landmarks with reduced soft tissue resilience were chosen, as the skin or gingiva is normally thin there. For setting a correlative norm, a collective, of 540 asymptomatic, sex and age differentiated, volunteers are evaluated by Landes et al. (2002a).

The interlandmark distances are measured:

- Tl-Tr (Tragus "left", Tragus "right")
- Tl-N
- Tr-N

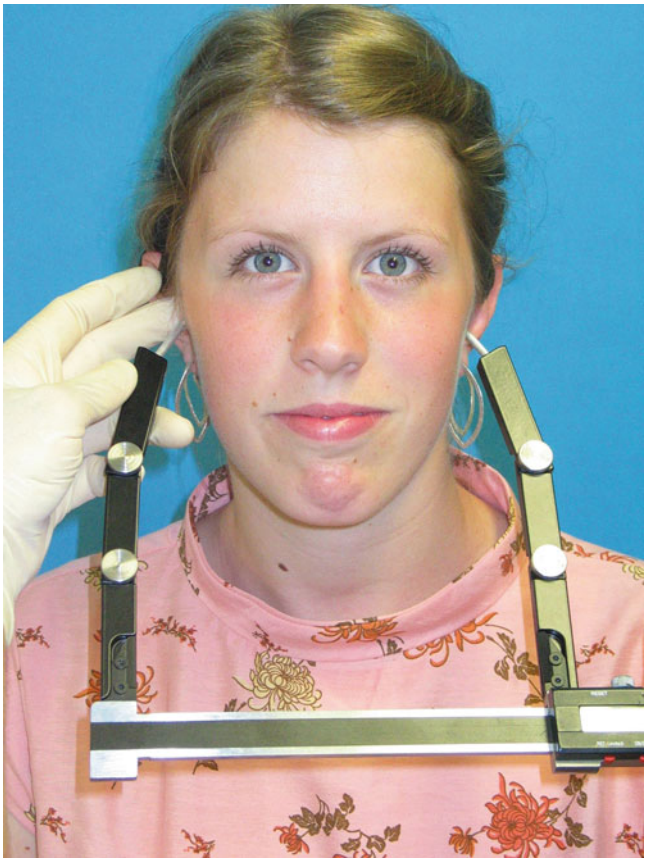

Fig. 12.2 A volunteer patient with the demonstrated tragus left-tragus right distance measurement. The measurement position is a relaxed, upright, sitting posture with moderate pressure on the osseous landmarks

- Tl-Mx
- Tr-Mx
- Tl-Mn
- Tr-Mn
- Tl-Pl
- Tr-Pr
- Pl-Mx
- Pr-Mx
- Pl-Pr
- N-Mx
- Mx-Mn

The measurements are shown with the new semiautomatic calliper prototype in Figs. 12.2–12.5 before wireframes (Fig. 12.6a, b) and growth diagrams are created (Fig. 12.6c). Altogether *14 measurements for osseous conformation of the maxilla and mandible to the cranial base are now established*. Kephalometrie 1.1 is a C^{++} based calculator for a wire-frame in three dimensions, based upon the 14 given triangularly arranged measurements of osseous and soft-tissue landmark distances (free distribution by the author for investigatory use, Bitter 2001; Landes et al. 2002a, b).

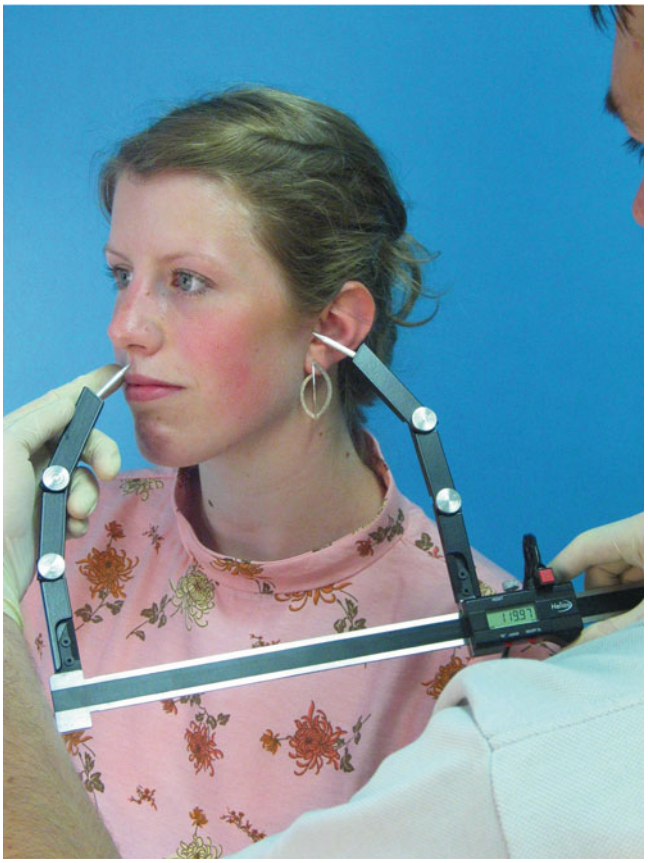

Fig. 12.3 A volunteer patient with the demonstrated tragus left-subnasale distance measurement. Measurement of the distance tragus left to columellar base (subnasale, soft tissue landmark) displayed on the scale in total millimetres and two decimal places

The "Kephalometrie" algorithm reconstructs the triangles to a wire frame in virtual space. For comparison, sagittal projection (assessment of osseous profile conformation, Fig. 12.6a) and axial projection (assessment of lateral asymmetries and lateral rotation of the maxillary triangle, Fig. 12.6b) were mainly used, though *any projection angle can be chosen at will*.

Table 12.1 Key features of 3D-craniofacial anthropometry (Am), simplified and accelerated by semi-automatic calliper

1. Threedimensional craniofacial Am is a considerably simple technique that yields high availability and portability at very low cost.
2. Semiautomatic computer-connected callipers can more than double the registration speed.
3. Measurement in concealed landmarks, not accessible to surface scanning is enabled with anthropometric callipers due to the double hinged calliper arms.
4. A calculator reset is permitted in any measurement position.
5. Measurement of osseous as well as soft tissue landmarks can be done simultaneously.
6. A dislocation of measurement tips and therefore falsification of distances upon calliper removal from the actual landmarks is avoided due to immediate data input at activation of the input button.
7. Three dimensional reconstruction of multiple (triangulated) 2D measurements is possible.

This table lists the key facts of 3D-craniofacial Am and its simplification and acceleration by semiautomatic calliper

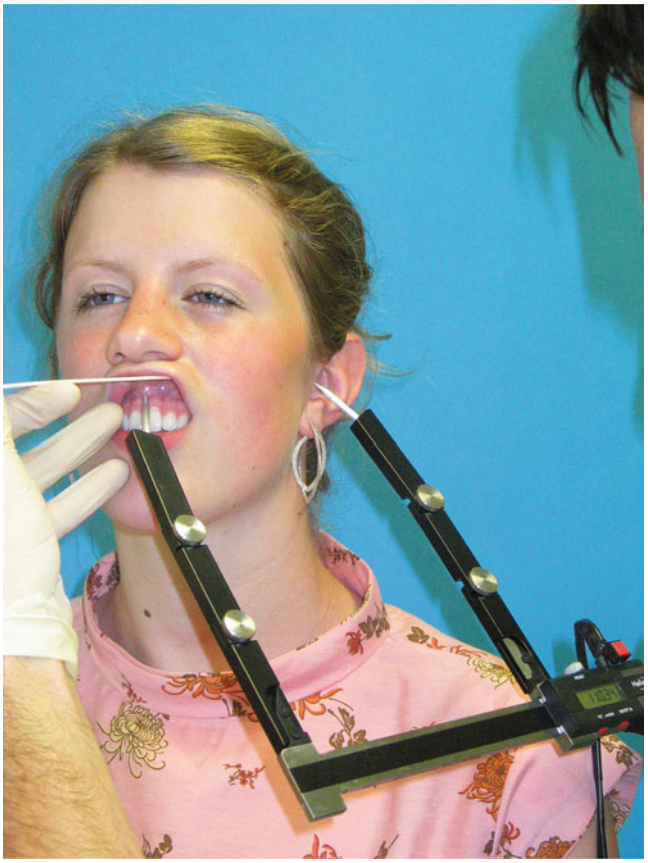

Fig. 12.4 A volunteer patient with the demonstrated tragus left-maxillare distance measurement. Measurement of the distance tragus left to maxillare or supradentale. Therefore the lip is held away by a medical spatula

Table 12.2 Key facts on soft tissue and osseous landmarks

1. Landmarks represent crucial anatomic structures valuable for anthropometric measurements.
2. Landmarks have to be readily accessible for measurement, e.g. the nasal tip
3. Landmarks should be easy to reproduce in order to diminish interrater and intrarater measurement variation.
4. Landmarks have slightly different names in-between different authors and measurement techniques.
5. Landmarks should be picked in sensible numbers: not too many, not too few, in order to clearly represent the region and structures of interest.
6. Landmarks in close relationship to underlying bone are called osseous landmarks; in a radiography they can be virtually located in lieu of osseous structure projection.
7. Landmarks close to essential soft tissue structures are soft tissue landmarks. They often have a variable inconstant relationship to underlying bone.

Some key facts on anthropometric landmarks are listed.

12.1.3 Anthropometry of the Soft Tissue Profile

In the second step, a soft tissue profile projection was included, because on the one hand, photographs and Rcm, acetate tracings or digitized analyses reduce a complex 3D conformation to a practical and manageable procedure. On the other hand, roentgenocephalometry, interprets only a vector displacement due to the shifting of anatomic and constructed landmarks in two dimensions: lateral asymmetry is not considered, both sides become overprojected due to x-ray divergence projection distances being subject to a distortion of 4–7% (Landes et al. 2002b). Photographs display a three dimensional

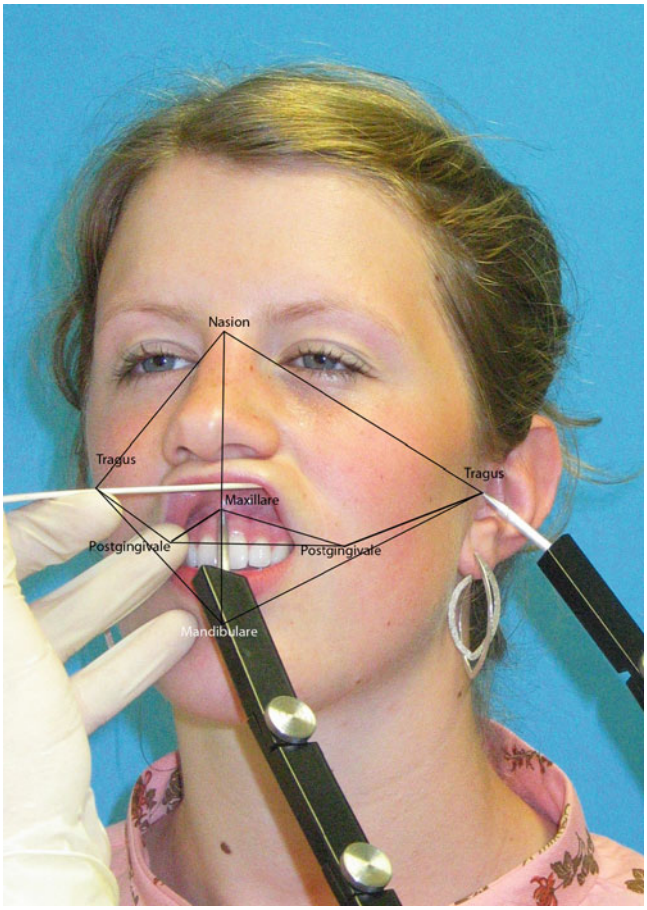

Fig. 12.5 A volunteer patient with the demonstrated tragus left-maxillare distance measurement as in Fig. 12.4. Additionally all osseous distance measurements are drawn. Identical measurement with the osseous distances outlined (tragus right is projected, as this landmark is not visible on the photo). When measurements are put together, they generate the 3D osseous wireframe of craniofacial conformation. That is: skull base, maxilla and mandible, represented by tragus, N, supradentale, infradentale and postgingivale landmarks

situation reduced to two dimensions with a distortion due to perspective and angulation of projection. Although standards of photo-documentation have been established, 3D measurements can only be performed indirectly. Frontal, 45° view i.e. half profile and lateral photographs cannot yield a reproduction of the 3D patient. Postoperative predictions do not integrate different soft tissue tension and tonicity following osteotomy. Thus, soft tissue prediction is insecure (Landes et al. 2002b).

Heike et al. (2009) recently assessed the reliability of stereophotogrammetry for measuring craniofacial characteristics in 40 individuals, including 20 volunteers without craniofacial conditions and 20 with 22q11.2 deletion syndrome. Thirty anthropometric measurements were obtained on participants and on 3D images. Their results showed intrarater and interrater reliability for most interlandmark distances on 3D images, had intraclass correlation coefficients greater than 95%, mean absolute differences of less than 1 mm, relative error measurement less than 5% and technical error of measurement less than 1 mm. The Pearson correlation coefficients of greater than 0.9 for most distances suggested high intermethod reliability between direct and image-based measurements. 3D image-based measurements were systematically larger for the head length and width, forehead and skull base widths and upper and lower facial widths.

In contrast to photogrammometric measurements that merely cover soft tissue landmarks, the developed 3D cephalometry routine covers both, soft tissues and osseous landmarks, that is, landmarks with a close relationship to underlying bone and thin soft tissue cover. Essentially, this soft tissue cover can be thinned by moderate pressure during the measurement.

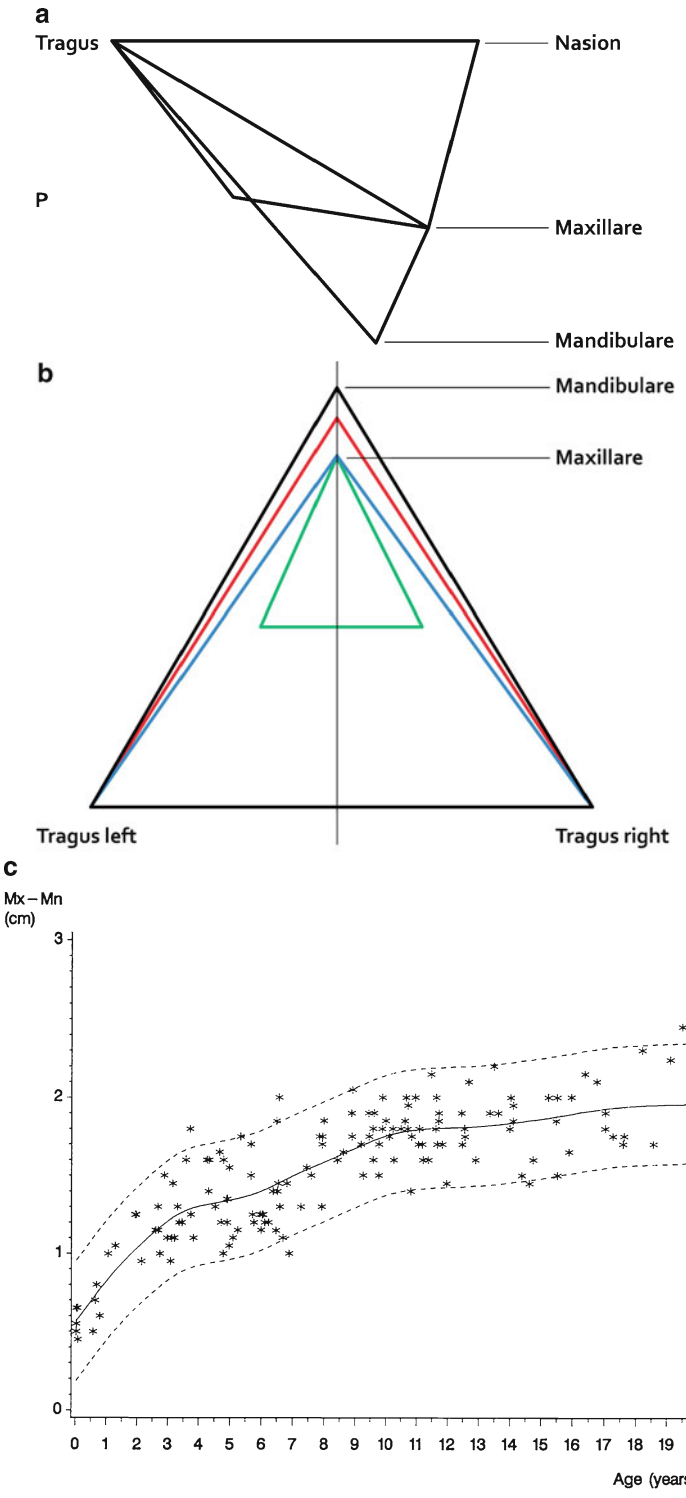

Fig. 12.6 (**a**) The volunteer patient's wireframe resulting from the computation of the osseous distances. The wire frame is shown in sagittal projection of a harmonic osseous conformation of maxilla and mandible relative to the cranial base represented by the distance nasion-tragus. (**b**) The volunteer's wire frame in axial projection. The wire frame shown with axial projection deducts a slightly asymmetric positioned maxilla slightly inclined to the right. (**c**) The volunteer population's growth function of the distance Maxillare–Mandibulare. The growth function was generated by the test collective for the distance Maxillare–Mandibulare in girls (Landes et al. 2002a)

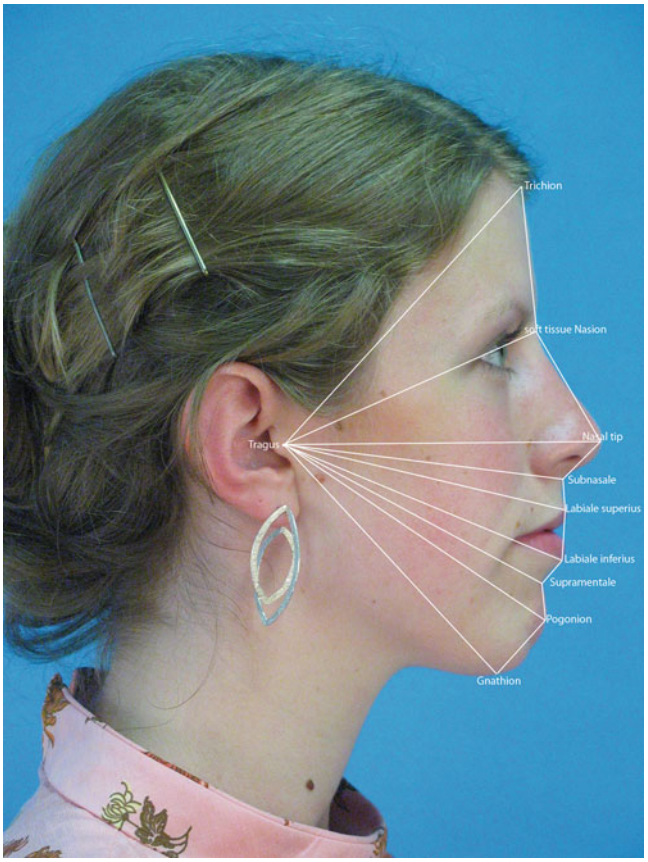

Fig. 12.7 The volunteer in profile with drawn soft tissue measurements. The soft tissue measurements were put together for creation of the wire frame. All landmarks were located according to standard definitions

All soft tissue landmarks that are included are easily accessible, relevant and not too many to keep the measurements comprehensible. Soft tissue ratios have been established without the use of any sophisticated technical means (Landes et al. 2002b). Osseous changes were assessed independently from the soft tissue alterations. Further, inter- and intraindividual measurement reliability was quantified. Lastly, the examination procedure should only require a minor amount of time. A major collective of 100 patients was assessed with repeated examinations preoperatively and postoperatively.

Regular assessment included the above-named landmarks and the following:

- Trichion (Ti) as the crossing of the median sagittal profile-line and the anterior hairline was defined as most superior soft tissue landmark
- Soft tissue nasion (N′)
- Nasal tip (or pronasale Pn)
- Columellar base (or subnasale Sn)
- Labiale superius (Ls)
- Labiale inferius (Li)
- Supramental fold (or supramentale Sm)
- Pogonion (Pg)
- Gnathion (Gn)

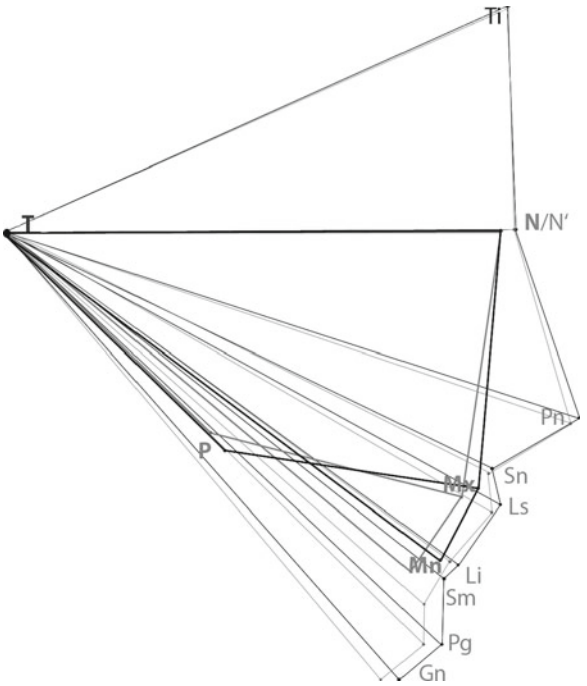

Fig. 12.8 An exemplar patient's preoperative and postoperative wire frame superpositioned in sagittal view. Shows a preoperative and postoperative superposition in lateral view of the measured distances, reconstructed as preoperative and postoperative wire frames. The bold lines represent the osseous landmarks' wireframe, the landmarks are given with their abbreviations, see text. The patient shown here had a mandibular advancement and maxillary impaction

These were selected according to their commonly used definitions (Farkas and Munro 1986). Distances between T and the landmarks above and between neighbouring landmarks were measured (Fig. 12.7). Thus, a slightly more complex soft-tissue wire frame resulted, indicating the facial protrusions from the virtual intertragus line.

Lateral cephalograms taken the same day were parallelly scrutinized for similar landmarks: Porion for T, N, N′, supradentale, infradentale, tuber point, nasal tip, Sn, Ls, Li, Sm, soft tissue Pg and soft tissue Gn (Landes et al. 2002b).

Figure 12.8 shows an exemplar picture of a super-positioned preoperative and postoperative craniofacial conformation when the upper and the lower jaw position were changed within a bimaxillary osteotomy. Within this exemplar operation, the major directions of jaw movement were defined as mandibular and maxillary advancement or setback, maxillary impaction or elongation. Each direction of jaw repositioning was calculated separately in every patient for postoperative soft tissue changes relative to the changes in osseous landmark projection. For assessment of soft tissue ratios in relation to surgical bone repositioning, preoperative distances were subtracted from postoperative distances (Landes et al. 2002b): dTMn – dTLi: Changes in Li projection were compared to changes in the projection of Mn. Comparing data from roentgenocephalometry and Am assessed the validity of Am for planning surgical treatment: e.g. articulare-nasion (Ar-N) as a measure of cranial base length was compared to tragus-nasion (T-N) in Am. The global soft tissue ratios as well as the ratios according to the separate jaw movements were comparable to values obtained from lateral cephalometry or CT reports in the literature (Landes et al. 2002b). However, variation was generally high, and ratios calculated separately according to the direction of jaw movement decreased the standard deviation. Soft tissue responses were bigger following mandibular advancement than after setback. Anthropometry required the same amount of time as did roentgenocephalometry.

12.2 Methodological Considerations

Thinking back to our childhood, most of us spent hours discussing with our mothers whether somebody was actually "tall" or "small", "slender" or "obese". This means Am is really popular and we start using it very early in life though ordinal (Paul is taller than Christine) and later through metric evaluation (last year I measured 135 cm now I am 165 cm tall). Therefore, Am provides the most popular direct way to analyze the 3D conformation of human beings.

This goes also for faces: big nose, crooked nose etc. From the instinctive qualitative evaluation to a more exact compilation, Am becomes more elaborate and is therefore less widespread whether the manual classical callipering method or recent surface recognition scanning methods. Acceptance of more complex anthropometric callipering measurement sequences suffers from the relative measurement effort and, moreover, scanners are limited in distribution due to their high acquisition costs. Calliper Am is currently the only alternative to computed tomography, when *at the same time*, bone and soft tissue landmarks become integrated.

Measurement of direct distances in millimetres is preferred today as most anthropometric distances have to be compared with large lists of norm values or normograms and do not permit a immediate visual assessment of proportions (Landes et al. 2002b).

12.2.1 Acceleration of Calliper Data Acquisition

The semiautomatic calliper is a major acceleration in the calliper data acquisition process. "Kephalometrie" enables calculation of an individual measurement profile at a few mouse clicks, and it is hoped to dramatically accelerate its popularity as norm values and measurement sequences are already established (Landes et al. 2007). Moreover intrarater and interrater absolute and standard error are minimized.

The semiautomatic anthropometric calliper is fairly easy to assemble and every tab-stop in any datasheet can be consecutively filled-out with anthropometric measurements one-by-one, according to the preference of the investigator.

12.2.2 Sources of Error in the Callipering Method in the Craniofacial Area

The absoute and relative error of the callipering method in the craniofacial area was recently given as 0.7–1.5 mm (about 0.7–1.6%) intraobserver error (retesting variability) for correct assessment of the orbitozygomatic complex. The interobserver variability ranged from 2.9 to 9.1 mm (3–9.6%) (Czerwinski et al. 2005).

Another study of sagittal orbital Am discerned 0.2 mm exactness of the orbital anthropometer, which, however, differed significantly from the semiautomatic anthropometric calliper used in this review. Furthermore, 1% intraobserver error and mostly nonsignificant interobserver differences were reported (Kohout et al. 1998). The semi-automatic calliper values were comparable, and the semiautomatic assessment reduced errors successfully (Landes et al. 2007). A further advantage of the semiautomatic measurement is a >60% time saving and less effort on the patient's as well as on the investigator's side. The authors hope that, the introduced technique will simplify regular Am in clinical practice.

12.2.3 Kephalometrie Algorithm

The "Kephalometrie" program can output individual measures in a norm diagram as well as visualize the craniofacial osseous and soft-tissue conformation in a wire-frame. Commercial operation planning software disposes of integrated ratios for an approximate soft tissue prediction. Yet it can create a faulty postoperative image when a minor initial prediction error in the deformation database for the soft tissue reaction to bone repositioning is aggravated in proportion to the distance of the planned jaw movement. Operative bone positioning primarily influences the neighbouring soft tissues. Thus, a separation of the osseous movements in patients with, e.g., simultaneous reposition of the maxilla and mandible or "bimaxillary" surgery according to the direction of jaw movements is rational.

Within the author's earlier measurements, the average soft tissue responses in mandibular advancements were 114% in Am and 130% in Rcm (Landes et al. 2002b).

Labrale inferius moved 106% in Am and 88% in Rcm. Sm moved 103% in Am, 142% in Rcm and Pg 120% (Am) and 188% (Rcm).

In the literature, a 97–100% ratio for Pg and Sm is given, whilst labiale inferius only moves 62% in advancements (Landes et al. 2002b).

Prospectively, the paramedian "social" profile will become integrated with the landmarks: endocanthion, exocanthion, alare, cheilion and Gn. Such refinements will provide estimation, for example, of the accuracy in fragment positioning of different surgical fracture repositioning techniques (Czerwinski et al. 2005). Recognition of patterns of specific conformational proportions, pathognomonic for certain syndromes may even be developed (Farkas and Forrest 2006; Guyot et al. 2003).

Using the ophistocranion as the dorsal landmark (z-axis definition) was considered less exact and reproducible than the *T*.

Several two-dimensional (2D) surgical treatment planning computer programs are in existence, which combine skeletal and soft tissue analysis. However, flaws exist in representing a 3D structure in 2D form: facial depth and shape are not accounted for. In addition, the patient may have some difficulty in fully understanding the postoperative prediction plan because the changes and postoperative prediction are usually displayed as a lateral view only.

Patients are not able to see their own profiles and are more concerned with frontal view problems they can see easily on an everyday basis in the mirror. To address these problems, a 3D modality is required. Although 3D imaging has been regularly used in computer animations, video surveillance, and anthropology, its use in medicine is in its infancy. Recent advances in technologies have generated a variety of 3D techniques to capture facial topography and overcome the deficiencies of conventional photographic and radiographic methods. Cephalometry, morphoanalysis, Moiré topography, 3D CT, 3D ultrasonography, laser scanning, and digital stereophotogrammetry have been included. For many of these recent techniques, normal data are limited. Yet 3D evaluations and the characterization of surface anatomy are fundamental in objectively analyzing facial anatomy. By using the various techniques available, accurate surface measurements can be made, volumetric changes assessed, and the facial shape, texture, and skin tone captured and evaluated in 3D (Honrado and Larrabee 2004).

12.2.4 New Technological Advances

As inherent in any new technological advance, the accuracy of these newly developed 3D imaging systems in recording facial morphology must first be assessed. Several recent studies have focused on determining the reproducibility of identifying landmarks using various 3D modalities. Accuracy values range from 0.2 to 1 mm, meaning that these imaging techniques are very reliable in recording facial morphology and could be used to acquire normal data in three dimensions and to measure and

calculate changes after surgery. As emerging technology yields comparable measurement results, no reliable standard of measurement technique currently exists (Guyot et al. 2003).

Three-dimensional CT and MRI still have problems with measurement of segmental bone movement (McCance et al. 1997). 3D Photogrammetry or holography cannot yet combine osseous and soft tissue capturing (Bongartz et al. 2000). Commercialized operation outcome predictions are based on weak data collections from cadaver studies that are not readily transferable to live patients for tissue tonicity and turgor.

The cost of these 3D imaging systems is the biggest hindrance for a regular surgical clinical department at present. Costs range from $25,000 to $150,000 for the products alone, not including software. In comparison, the presented semiautomatic calliper costs $1,500. Future reduction in price is certain with the common trend of developing smaller dimensions in electronic components as well as infrared or other cordless data transmission techniques. Pressure gauges at the measurement tips may permit reproducible contact pressure for soft tissue and "osseous" landmarks. This will reduce the overlap of, for example, soft tissue nasion and N, as in Fig. 12.8, as well as the systematic error in assessing soft tissue resilience.

12.3 Applications to Other Areas of Health and Disease

A 3D simple wire frame was derived out of triangularly arranged anthropometric measurements for assessment of craniofacial conformation. **Triangular designed measurements can generally be assembled to wire frames and can also be designed for other body regions.**

Wireframes provide a simplified, sizeable, visual 3D impression of the structures under observation.

Semiautomatic measurement significantly speeds up and simplifies measurement in the presented work of maxillofacial conformation including osseous and soft-tissue landmarks.

Systematic error from soft tissue resilience over bone landmarks was reduced by carefully selecting landmarks with thin soft tissue covers, e.g. Mx and Mn.

The semiautomatic calliper used here can be used in any anthropometric measurement beneath the maximum span of 30 cm. However a longer slide gauge in the construction will enable longer distances to be measured with minimal effort. The cursor position controlled by the hand-operated input switch fills out any data sheet independent of the software used.

Rapid callipering speed accelerates the acquisition of the most important soft tissue as well as osseous landmarks of the median profile, cranial base, maxilla and mandible. Prospective inclusion of paramedian landmarks will become possible in the future to allow an analysis also of the "social" 45° of half-profile. **The semi-automatic device can be used with any Am measurement routine, when patient measurements have to be included into a datasheet. Long-term quantified evaluation of developmental, presurgical and postsurgical conformation will assess the individual amount of deviation including the relation of bone landmarks chosen with the above-named confinements of thin soft tissue cover.**

The relative proportion of soft tissue secondary to bone movement was focused on here.

Recognition of patterns of specific conformational proportions, pathognomonic for certain syndromes or diseases may thus be developed.

Summary Points

- The presented semiautomatic calliper can be used with any 2D distance measurement.
- The maximum measurement distance is 30 cm but with a bigger calliper this distance can be increased.

- The footswitch proved to be less available during measurement than the handswitch for data input; the pushbutton was therefore preferred.
- For the measurement routine used here, firm pressure must be exerted upon osseous landmarks to reduce soft tissue resilience and systematic measurement error; for soft tissue landmarks use light pressure.
- Triangularly oriented unidirectional measurements can be assembled to 3D wireframes.
- Craniofacial development can be judged as well as the mandibulomaxillary conformation relative to the cranial base.
- Operative or growth-related changes of jaw position can be monitored.

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Chapter 13
Issues in Measurement of Pubertal Development

Frank M. Biro and Lorah D. Dorn

Abstract Teenagers mature along several areas, including social, cognitive, and biologic realms. The biologic changes called "puberty" can be defined by stage, timing, and tempo. The pubertal stage traditionally has been called "Tanner stages", and more recently as "Sexual Maturity Rating" (SMR). These stages describe changes in breast tissue, pubic hair, and external genitals. There are several approaches to pubertal staging in research projects, including questionnaires and rating by self, parent or trained professional. Rating by a trained professional is considered the most accurate approach, but the research setting may limit the choice available. This chapter discusses historical perspectives in maturation assessment, provides current approaches with practical guidelines, and presents recent data about the timing of pubertal onset and the potential impact of early or late maturation timing.

Abbreviations

BMI	Body mass index
PBIP	Picture-based interview about puberty
PDS	Pubertal development scale
SMR	Sexual maturity rating

13.1 Overview and Historical Perspectives

Teenagers can be described using several different perspectives, such as chronologic age (that is, "teen years"), cognitive development (whether concrete, as contrasted to formal operational), as well as biologic maturation (puberty). There is a rich history relative to the measurement of maturation in the adolescent. For example, the concept of physiologic age, rather than chronologic age, is attributed to Crampton from a paper in the early twentieth century, where he suggested that chronologic age might not best represent the physiologic and morphologic changes experienced by teenagers (Crampton 1908). This was further described and expanded by Boas, who delineated chronologic, physiologic, morphologic, and social processes in adolescents (Boas 1941). Tanner, in his classic treatise

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_13,

Growth at Adolescence, discussed four systems that were utilized to assess developmental age: skeletal age, dental age, morphologic age, and secondary sex character age (Tanner 1962). Similarly, Brooks-Gunn and Warren discussed "maturational events", which included the measurement of secondary sexual characteristics (breast, body and pubic hair, penile and testicular development, and menarcheal status), as well as anthropometric characteristics (bone age, height, weight, and body composition) (Brooks-Gunn and Warren 1985). Tanner noted that skeletal age had been the indicator of developmental age most commonly used, until the introduction and popularization of pubertal maturation systems. Of note, skeletal age is still used in clinical practice to assess physiologic maturation of those with advanced or delayed pubertal maturation or short stature, based on a radiograph of the left wrist and hand, using the same standards published by Greulich and Pyle over 50 years ago (Greulich and Pyle 1950). Given the several studies that note earlier maturation of girls, the research and clinical world may wish to consider whether to update these time-accepted standards of bone age.

A brief discussion of morphologic age is warranted before turning the remainder of the chapter to the assessment of pubertal maturation. Morphologic age is based on size, height, and body proportions. Although height age (the age based on the 50th percentile for that height) is still used by clinicians, the utility of that measure is limited because of the confounding of physical maturation and anticipated height based on gender and mid-parental height. Height may be predicted by examining bone age (physiologic age); height and chronologic age (Bayley and Pinneau 1952); bone age, height, chronologic age, and midparental height (Roche et al. 1975); or simply by determining midparental height and modifying by gender (adding 6.5 cm for boys, and subtracting 6.5 cm for girls) (based on Tanner 1970). Predictive height continues as a useful clinical tool to allow the clinician to understand better the disparity between observed and theoretical height. Other concepts imbedded in morphologic age include body proportions; that is, relative proportions of various body parts. Medawar described a quantitative approach to the developmental changes in volume of head to trunk, and trunk to limb length (Medawar 1944), and Simmons described quantitatively the changes in distal and proximal limb segments during childhood and adolescence (Simmons 1944). Although these constructs provide an understanding of changes during growth, there is a limited specificity for a precise definition of developmental age.

13.2 Pubertal Assessment

Currently, the standard used most frequently to assess physiologic age in adolescents is sexual maturity rating, often described as "Tanner stages." These stages examine pubic hair and breast maturation in girls, and pubic hair and gonadal maturation in boys. It is somewhat unclear who originally described and characterized these changes. A review of the history of breast maturation assessment notes that Stratz early in the twentieth century described four stages of breast development (Stratz 1909); Reynolds and Wines described five stages of breast development as utilized currently, but also incorporated two other measurements, breast shape and breast size (Reynolds and Wines 1948). Tanner utilized the breast staging system of Reynolds and Wines, but not shape or size (Tanner 1962), and he is credited with the breast staging system commonly used, as described below. Several years later van Wieringen published a series of photographs utilizing this five stage system (van Wieringen et al. 1985). Other authors have proposed different mammary maturation systems, based on the areola and papilla (Garn 1952), or the size of the papilla (Rohn 1987; Aygün et al. 1998). These authors have offered that evaluation of breast maturation may be influenced by several factors, especially obesity. It appears that there may be some over-estimation of breast maturation in obese peri-pubertal girls, although breast and areolar maturation assessments are highly correlated with each other (Biro et al. 1992). Pubic hair maturation assessment is attributed to several groups, including Preisel and Wagner, Pryor, Dupertuis et al., Reynolds and Wines, and Marshall and Tanner

(Preisel and Wagner 1931; Pryor 1936; Dupertuis et al. 1945; Reynolds and Wines1948; Marshall and Tanner 1969, 1970). The traditional system incorporates five stages, as described below, although many have incorporated a final sixth stage, as the hair continues to advance to the umbilicus, along the linea alba. In boys, "gonadal" staging has been utilized, as well as assessment of testicular volume. Gonadal staging in boys had been utilized by Marshall and Tanner, Reynolds and Wines, and Stolz (Reynolds and Wines 1948; Stolz and Stolz 1951; Marshall and Tanner 1970). Several groups, however, noted that gonadal staging was an unreliable sign for the onset of pubertal development in boys (Taranger et al. 1976; Largo and Prader 1983; Biro et al. 1995), and recommended evaluation of testicular volume. In these three studies, boys with no pubic hair but with testicular volume of ≥3 ml were found to be in early puberty; additionally, testicular volumes of ≥3 ml were associated with pubertal values of testosterone (Biro et al. 1995; Sorensen et al. 2010).

Several studies have examined the reliability of various maturation techniques: trained professional, self or parent assessment, and utilizing various scales. Although maturation assessment by a trained professional is considered the standard for pubertal assessment (Dorn et al. 2006), there is no perfect agreement between examiners. The Kappa statistic compares observed agreement between examiners to agreement expected by chance alone. Values of Kappa range from 0.50 (based on 25 comparisons) (Hergenroeder et al. 1999) to 0.86 (56 comparisons) (Herman-Giddens et al. 1997), with 0.67 (127 comparison) (Biro et al. 2010) and 0.78 (20 comparisons) (Britton et al. 2004), observed in two other studies. Coleman reviewed the literature and compared different approaches to assessment of pubertal maturation, including several different self/parent report techniques, and noted that professional assessment was the most accurate, the Pubertal Development Scale (PDS) (Petersen et al. 1988) the least accurate, and assessment by the participant or parent the intermediate (Coleman and Coleman 2002). Several papers have examined self/parent-assessment, as well as reviews of the published work in this area. Several studies have suggested that self/parent assessments may serve as a reasonable substitute for the assessment by a trained professional, but many studies suggest that self/parent assessment does not serve as a reliable approach to the determination of maturation status. There is a discrepancy when contrasting agreement by the Kappa statistic or merely association by correlation coefficients. Dorn summarized 14 studies that examined agreement between trained examiner contrasted to the self or parent report; kappa coefficients varied from 0.34 to 0.91 (Dorn et al. 2006). She noted there may be nonrandom errors in the measurement; for example, boys tend to overestimate their maturation. Additionally, those adolescents who matured earlier or later than their peers tend to rate themselves on-time rather than off-time, suggesting a normalization of their pubertal timing. A subsequent study compared self-assessment to assessment by a pediatric endocrinologist; Kappa coefficients were.49–.68, and the authors drew the conclusion that self-assessment was unreliable (Desmangles et al. 2006). Similarly, Shirtcliff compared several different pubertal assessments, including direct examination; the PDS, a picture-based interview about puberty (PBIP); and multiple salivary samples for hormone analysis (Shirtcliff et al. 2009). In this study, the two self-report scales (PDS and PBIP) were moderately correlated with each other, but both had modest agreement with physical examination (Kappa =.36 for both). Feasibility is often cited as a reason to utilize self/parental assessment, but several studies have incorporated professionally trained staff in a variety of settings, including schools and youth serving agencies. Lastly, some studies have utilized hormone analyses of different body fluids, including blood/serum, saliva, and urine. Studies have incorporated less sensitive analytic techniques, such as radioimmunoassay that cannot reliably distinguish between pre- and early-pubertal status; this is contrasted to the recently developed assays that have much greater sensitivity, such as high-performance liquid chromatography followed by tandem mass spectroscopy (Kushnir et al. 2009). In short, evaluation by trained professionals leads to the greatest degree of accuracy, but may not be the most convenient approach in all settings. Given differences in accuracy of these approaches, the investigator should consider carefully what level of accuracy is necessary to yield valid conclusions for the study.

13.3 Practical Techniques

13.3.1 Maturation Staging

Sexual maturity ratings are demonstrated for girls in Figs. 13.1–13.4, and for boys in Figs. 13.6 and 13.7. Figure 13.1 has photographs that demonstrate each breast stage, whereas Fig. 13.2 is a template currently being used in several studies with both graphic and verbal descriptions of breast stages.

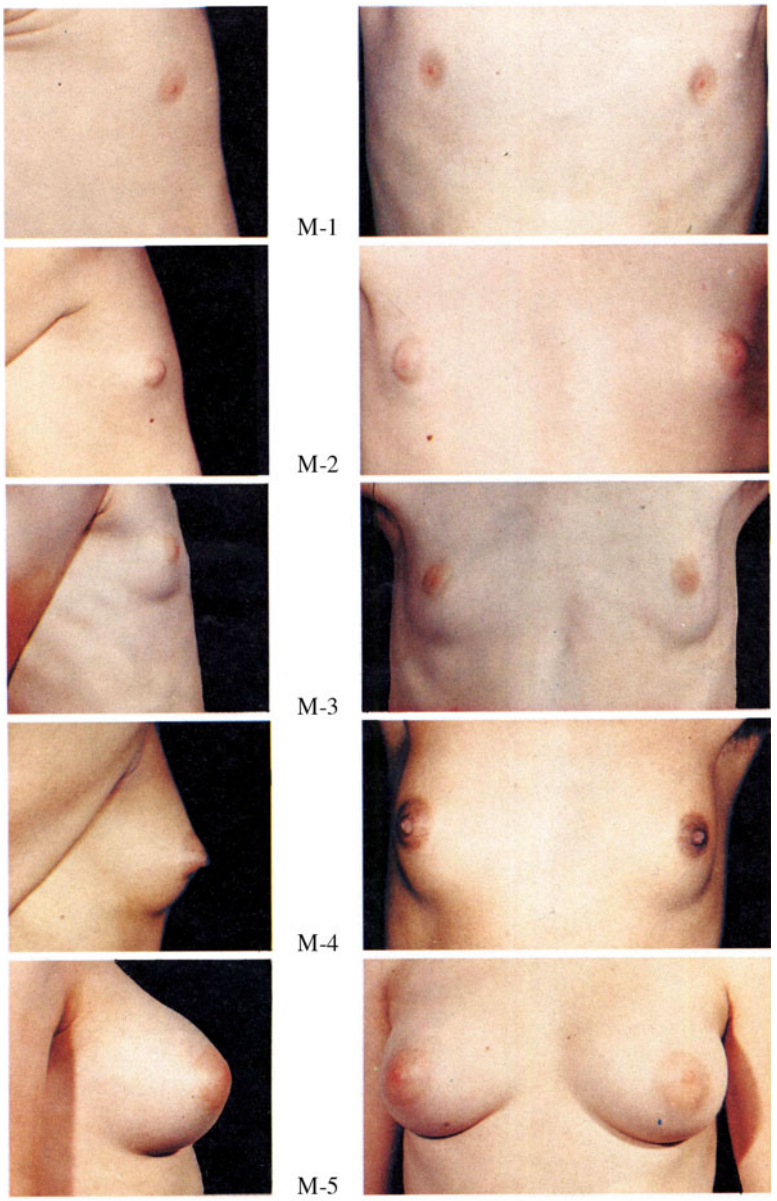

Fig. 13.1 Stages of breast development in girls. Photographs demonstrating stages of breast development; see Fig. 13.2 for the description of each stage

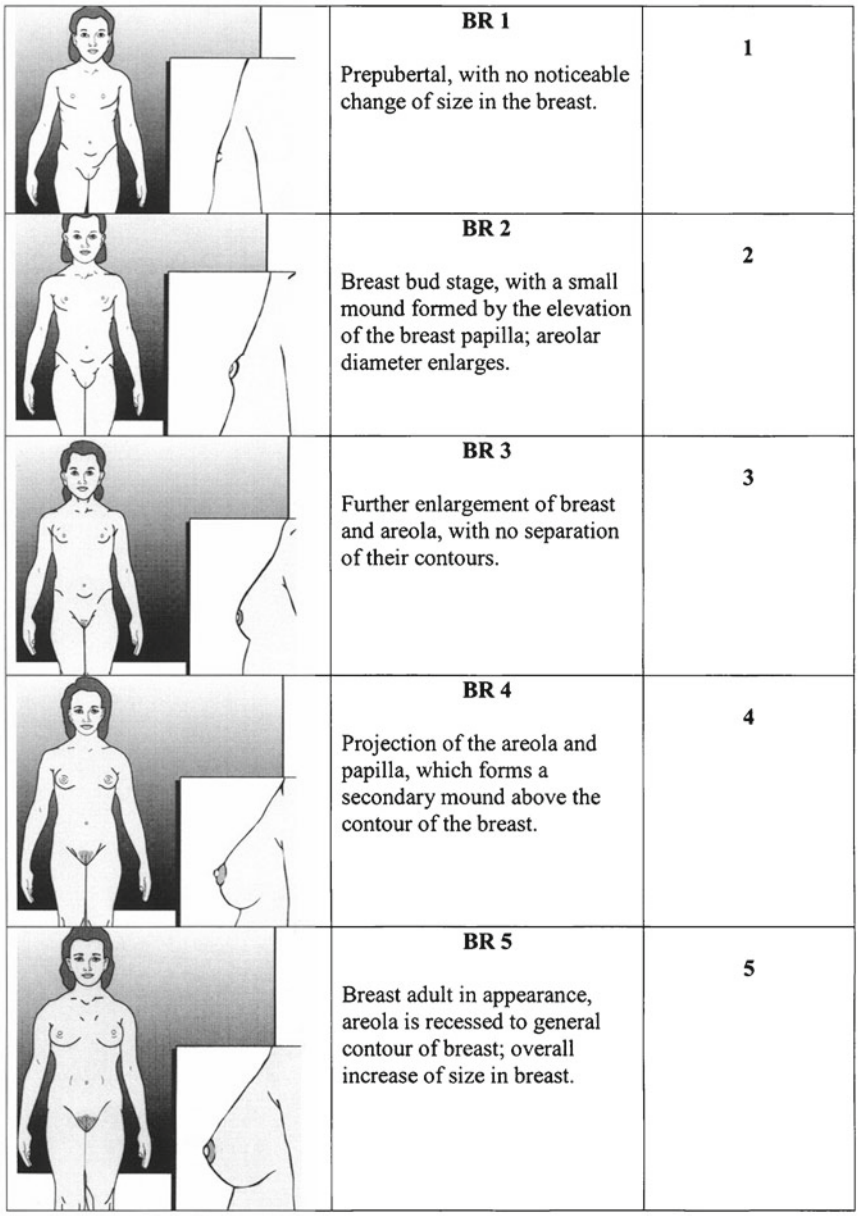

Fig. 13.2 Description of individual breast stages. Template used by ongoing studies exploring pubertal maturation; developed by the first author

Figures 13.3 and 13.4 demonstrate the same principles for public hair staging. Sexual maturity stage 1, regardless of gender or characteristic (that is, breast or pubic hair, or genital stage) represents a prepubertal stage, and sexual maturity stage 5 represents complete maturity of that characteristic. Of note, description of the pubic hair staging system is identical for boys and girls, and some authors have described "stage 6" pubic hair, which refers to hair extending from the pubic area up along the linea alba.

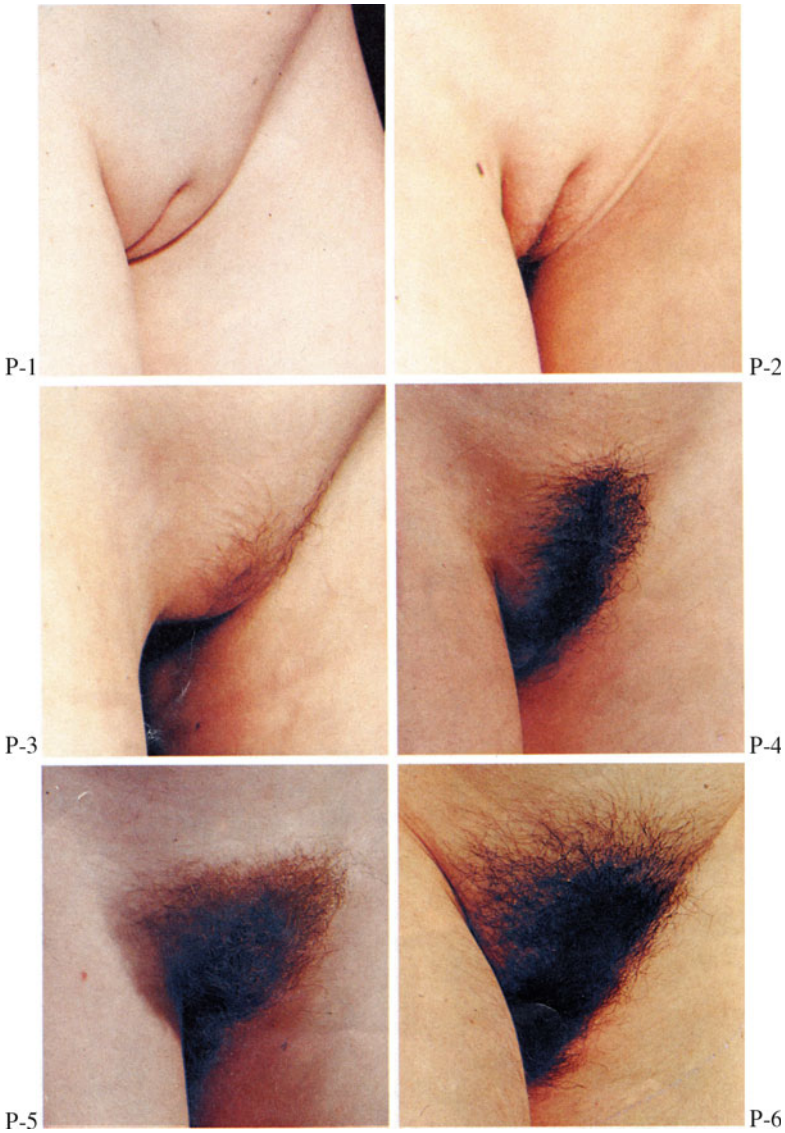

Fig. 13.3 Stages of pubic hair development in girls. Photographs demonstrating stages of pubic hair development; see Fig. 13.4 for the description of each stage

The development of secondary sexual characteristics in girls occurs relatively late in puberty. That is, breast development occurs approximately 1 year after girls begin their pubertal growth spurt (Biro et al. 2006), and studies have demonstrated an increase in ovarian as well as uterine volumes before the development of secondary sexual characteristics (Saladari et al. 1985; Holm et al. 1995). Some authors have proposed that the development of pubic hair, without breast development, may represent a "pathway" into puberty (Biro et al. 2003, 2008; Schubert et al. 2005), rather than solely a manifestation of adrenarche. However, the majority of studies utilize the onset of breast development as the start of puberty in girls. The interrelationships of various pubertal and growth parameters in girls are shown in Fig. 13.5.

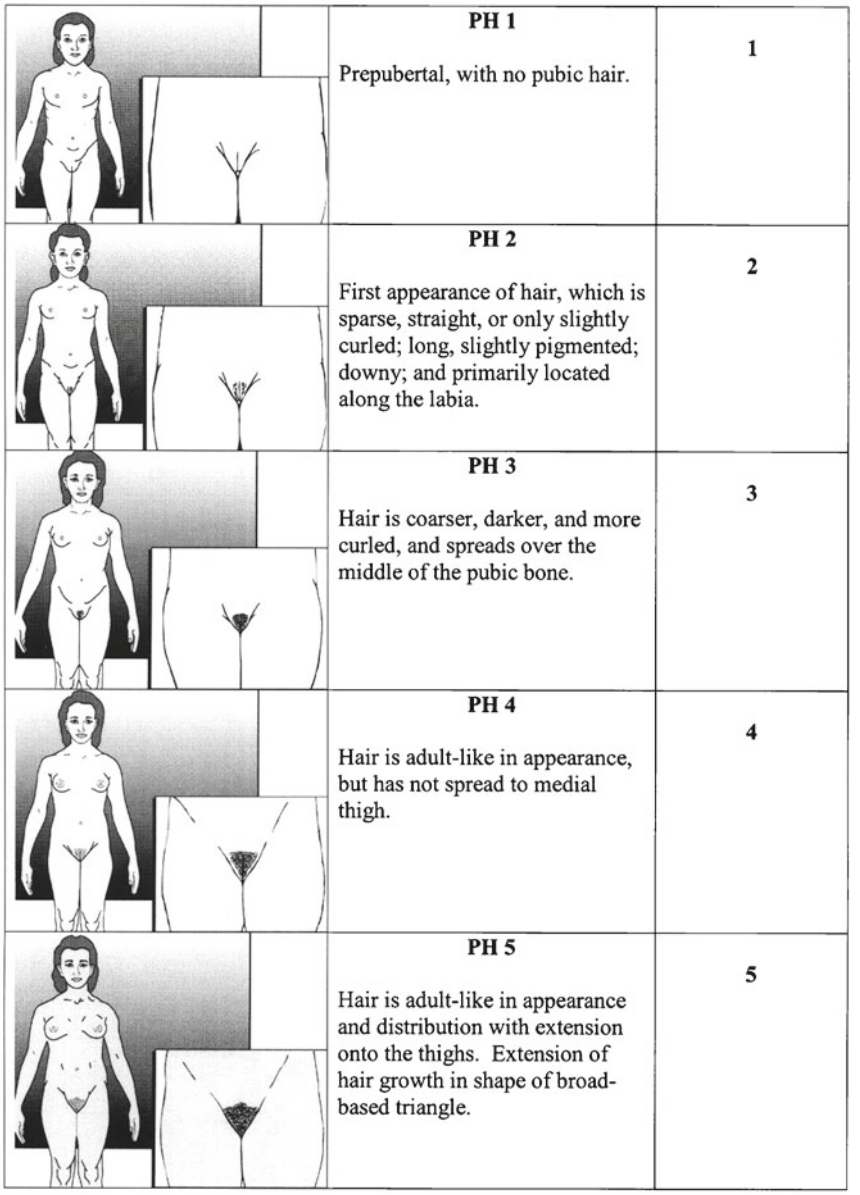

Fig. 13.4 Description of individual pubic hair stages in girls. Template used by ongoing studies exploring pubertal maturation; developed by the first author. Of note, same description applies to the pubic hair in boys

Boys can be measured along several different characteristics, including pubic hair, testicular volume, and genital stage; as noted earlier, the genital stage may be an unreliable system to assess the initiation of puberty in boys (Taranger et al. 1976; Largo and Prader 1983; Biro et al. 1995). Boys typically experience an increase in testicular volume before the development of pubic hair, and puberty in boys typically begins approximately a year later than girls. A system utilizing pubic hair and testicular volume has been proposed by several authors (Zachmann et al. 1974; Largo and Prader 1983; Biro et al. 1995). The Photographs for pubic hair staging in boys are shown in Fig. 13.6.

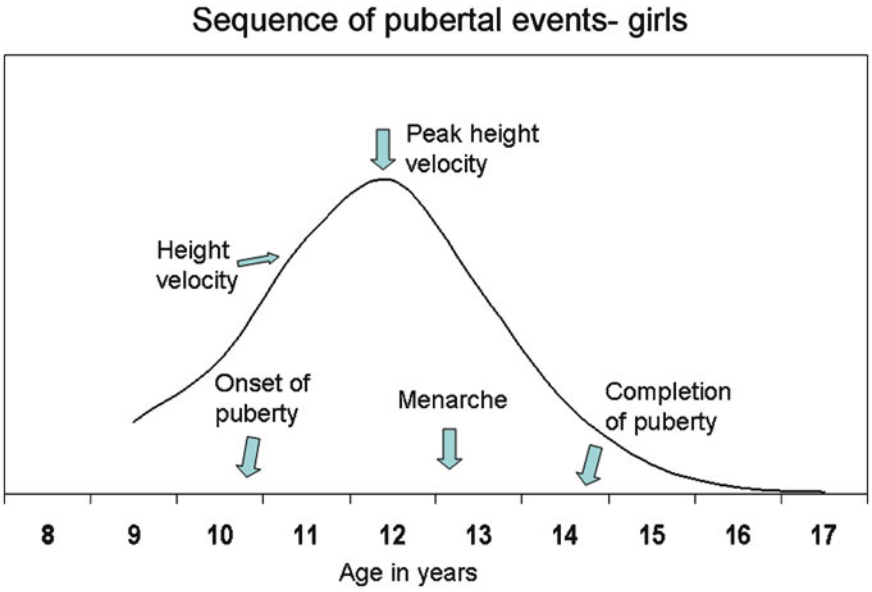

Fig. 13.5 Sequence of pubertal events in girls. Longitudinal data from NHLBI Growth and Health Study (tabular data from Biro 2006)

The relationship between pubic hair stage and testicular volume is shown in Fig. 13.7; the relationship between a modified pubertal stage (pubic hair stage 1 with increased testicular volume) and serum testosterone concentrations has been reported by several authors (Biro et al. 1995; Shirtcliff et al. 2009; Sorensen et al. 2010). The interrelationships of various pubertal and growth parameters in boys are shown in Fig. 13.8.

13.3.2 Contemporary Trends in the Onset of Puberty

A symposium of international experts gathered recently to discuss several topics regarding trends in onset of puberty, as well as potential factors influencing the age of onset of puberty. The majority of the expert panelists agreed that the data were sufficient to suggest a trend toward the earlier breast development onset, and noted that the earlier onset was related to increasing obesity, exposure to endocrine disrupting chemicals (EDCs), and increasing hyperinsulinemia and insulin resistance (Euling et al. 2008). A more recent study examining two cohorts of girls in the Copenhagen puberty study, utilizing the same examiners and technique, noted that girls in more recent cohorts had breast development nearly 1 year earlier, when contrasted to girls born 15 years earlier (Aksglaede et al. 2009). Of note, although the age of menarche in the United States has decreased slightly when compared to data collected 10 years earlier, it appeared that the decline was due to changing racial and ethnic demographics, and, in part, to increasing body mass index (BMI) (Anderson and Must 2005). The expert panel felt that the data regarding earlier maturation of boys were not as strong as the data regarding girls, although several studies did support earlier development of pubic hair (approximately 0.5 years) and genital stage 2 (approximately 1 year) (Euling et al. 2008). More recently, a modest decline in the onset of puberty was noted in boys in the Copenhagen Puberty Study (0.26 years) (Sorensen et al. 2010).

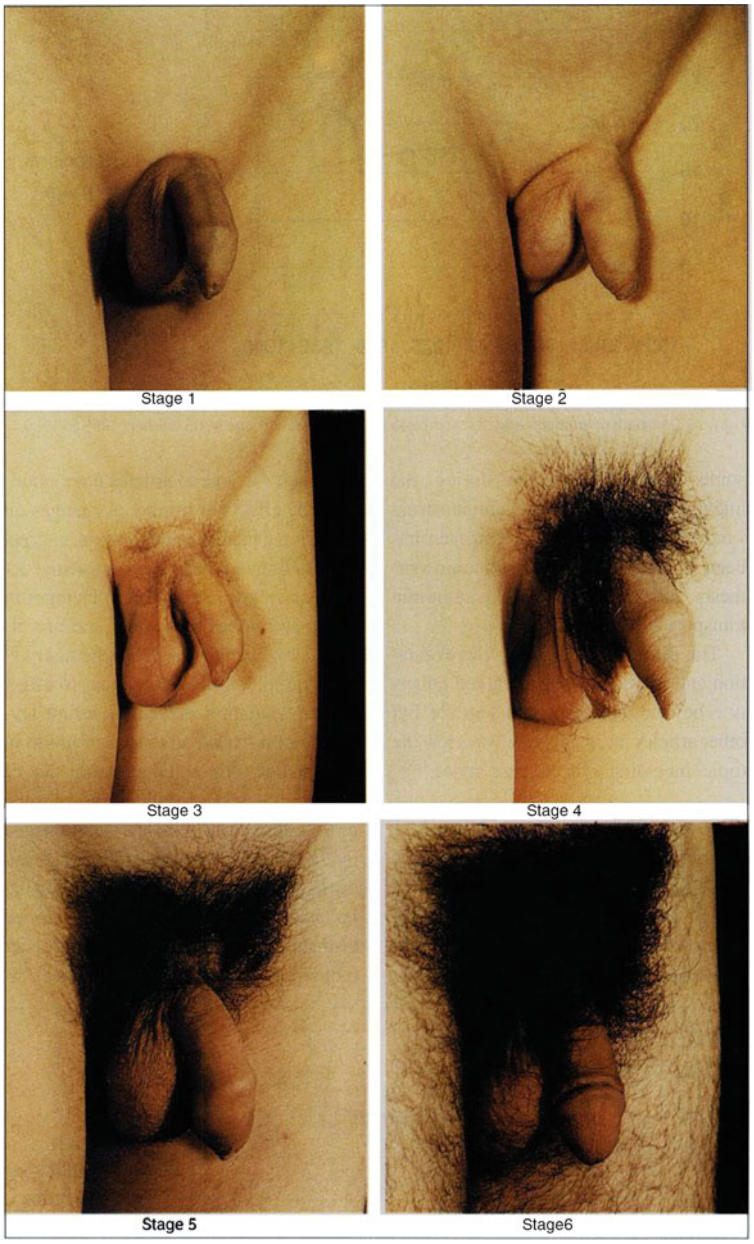

Fig. 13.6 Stages of pubic hair development in boys. Photographs demonstrating stages of pubic hair development; see Fig. 13.4 for the description of each stage

13.3.3 Relative Timing of Puberty

The relative timing of puberty can be defined using several different parameters, as well as through several different statistical approaches. Adolescents can self-report their relative timing of maturation compared to their peers (Graber et al. 1997, 2004; Siegel et al. 1999), and that perception may be as important as any other approach to determine the relative timing of puberty, depending on the

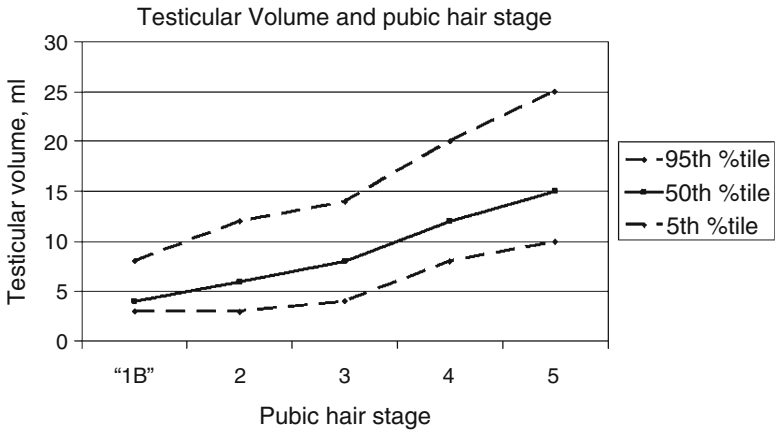

Fig. 13.7 Testicular volume and pubic hair in pubertal boys. Median, 5th, and 95th percentile values for the testicular volume by pubic hair stage; data from Biro (1995)

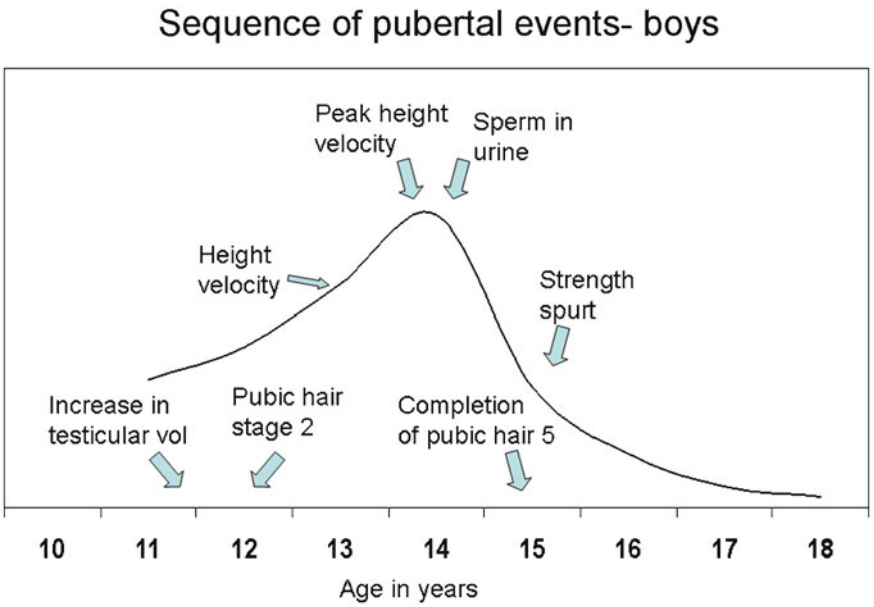

Fig. 13.8 Sequence of pubertal events in boys. Longitudinal data generated from Biro (1995)

question at hand (Dorn et al. 2006). Researchers can utilize different parameters, including scores on self-report instruments such as the PDS (Petersen et al. 1988); through age of menarche (Biro et al. 2001; Ge et al. 2001; Striegel-Moore et al. 2001; Johansson and Ritzén 2005); relative timing of examiner-assessed breast development (Huang et al. 2009); relative height (Wehkalampi et al. 2008); or growth velocity (Ferrández et al. 2009). Of note, there are differences when contrasting timing as established by physical examination to timing as perceived by the adolescent (Dorn et al. 2003). Relative timing of puberty – early, on-time, and late – can have an impact on the adolescent both physiologically as well as socially. Several papers have noted greater weight and BMI among girls who mature early (Biro et al. 2001; Anderson and Must 2005); some studies have noted shorter

height in earlier maturers (Garn et al. 1986; Biro et al. 2001), whereas other studies reported no impact on final adult height regardless of timing (Gasser et al. 2001; Vizmanos et al. 2001). Huang noted when considering timing relative to menarche, early maturers were shorter, but when considering timing relative to breast maturation, early maturers attained the same height as on-time and late maturers (Huang et al. 2009). Alternatively, Bratberg noted that boys and girls who matured early with low central adiposity were shorter, contrasted to those with normal or greater central adiposity, who had similar heights to the other timing groups (Bratberg et al. 2006). A recent review commented that altered puberty timing may result in adverse outcomes, but some of those outcomes may be due to exposure to potential endocrine-disrupting chemicals impacting pubertal timing as well as physiologic or metabolic processes (Golub et al. 2008).

Earlier maturation in girls is associated with lower self-esteem and less favorable perceived body image (Siegel et al. 1999; Striegel-Moore et al. 2001), greater rates of eating problems (Swarr and Richards 1996), and higher rates of depression (Ge et al. 2001) and suicide attempts (Graber et al. 1997; Wichstrom 2000). They are more likely to be influenced by deviant peers (Ge et al. 1996), and have a greater likelihood of substance use (Dick et al. 2000; Lanza and Collins 2002; Graber et al. 2004), and norm-breaking behaviors (Johansson and Ritzén 2005), with earlier onset of sexual intercourse (French and Dishion 2003), although these may be mediated through greater involvement with and influence by deviant peers (French and Dishion 2003). Early maturing girls had poorer adjustment skills and relationships as adults (Graber et al. 1997, 2004), whereas late maturing boys were more likely to have disruptive behavior and substance abuse as adolescents and as adults (Graber et al. 1997, 2004). Of note, later maturing women had greater educational attainment and were more likely to be on-time college graduates (Graber et al. 2004).

Timing of puberty may have an impact on adult morbidity and mortality as well. Age of menarche is noted to be earlier in women with breast cancer. For example, the risk for breast cancer is 1.2–2.2 times greater among those with an earlier age of menarche when contrasted to those with later age of menarche (Garland et al. 1998; Titus-Ernstoff et al. 1998). Women with endometrial cancer also have a younger age at menarche (Brinton et al. 1992; McPherson et al. 1996). Girls who mature earlier have a greater BMI in childhood as well as in adulthood; when examined longitudinally, most of the apparent effect of early menarcheal timing on obesity was due to the influence of childhood obesity on both menarcheal age and adult obesity (Freedman et al. 2003). Earlier maturation (measured by age of menarche) is also associated with hyperinsulinemia, and elevated blood pressure in girls (Frontini et al. 2003).

13.3.4 Closing

This chapter has reviewed trends in the measurement of pubertal development, as well as recent trends in the onset of puberty, relative timing of puberty, and the relevance of off-timing. As noted above, given the mounting data of earlier maturation in girls, and data suggesting earlier maturation in boys, researchers may consider re-examining standards for bone age, redefining on-time, early, and late pubertal maturation.

Summary Points

- Pubertal maturation is characterized by increased growth velocity, development of secondary sexual characteristics, changes in body composition, and the attainment of fertility.
- Pubertal maturation can be assessed in the clinical and research areas through the assessment of sexual maturity ratings, historically called “Tanner stages”. These scales incorporate changes in

secondary sexual characteristics, which include pubic hair, genital changes in boys, and breast development in girls.

- Several studies have suggested that the assessment of pubic hair and testicular volume is a better approach to pubertal staging in boys, rather than assessment of genital changes and size.
- There are several approaches to assess pubertal maturation in a research study, including self- or parent-assessment, completion of checklist forms, and physical assessment by a trained examiner. A trained examiner yields the most accurate approach, although the research question and study setting may determine the best approach.
- Several studies suggest that pubertal maturation is occurring earlier. Experts agree that the scientific evidence supports an earlier onset of breast development of girls, but that the evidence of earlier maturation in boys is not as strong.
- Relative timing of puberty appears to have an impact on several physical, social, psychological outcomes. Girls maturing earlier generally have a greater body mass index (BMI) as teens and as adults, and have a greater risk of insulin resistance and high blood pressure. Additionally, women with breast cancer and endometrial cancer are noted to have a younger age of menarche (first menstrual period). Earlier maturing girls have a lower self-esteem and more norm-breaking behaviors which occur at younger ages. Late maturing boys are more likely to engage in disruptive behaviors and substance abuse.

Key Features

- Teenagers mature along several different lines, including chronologic age, cognitive development (from concrete to abstract thought), and biologic maturation, also known as puberty.
- There are well-defined stages during pubertal maturation that incorporate assessment of physical changes in the genitals and breasts. These are called “Sexual Maturity Ratings”, or sometimes “Tanner stages”.
- Assessment of pubertal maturation represents one of the best choices to determine whether physical changes during the teen years represent physiologic (typical) or abnormal changes.
- There are three components in pubertal maturation – the determination of sexual maturity rating (stage of or sequence in puberty), relative timing (early, on-time, or late), and tempo. Pubertal stage and timing are the two most important concepts, and are related to physical characteristics (such as body size and adiposity), as well as psychosocial outcomes (such as self-esteem and risk behaviors).

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Chapter 14
New Anthropometric History: An Analysis of the Secular Trend in Height

Laurent Heyberger

Abstract In using human-height measurements as a gauge of the biological standard of living of a given population, anthropometry (in this regard not unlike demography) offers an alternative to the standard indexes of economic history. For instance, anthropometry reveals that a paradoxical phenomenon occurred during industrialization in eighteenth-century Europe: a decline in human height – in tandem with downward trends in real wages and in temperatures – was accompanied by a population increase, thereby contradicting, for the first time, the famous Malthusian theory that population growth is eventually checked by widespread famine and disease. The decreasing human height in Europe and North America in the nineteenth century, in spite of improvements in the standard of living as measured in terms of real wages income, is a reminder of the negative consequences of the early industrialization that Marx, among others, decried. In contrast, while the standard indexes record economic stagnation during the first half of the twentieth century, height increased, reflecting improvements in public health, thanks largely to progress in the field of medicine. On another front, anthropometric history, with its reliance on impartial demographic index, permits an accurate appraisal of the economic performances of totalitarian regimes and, more generally, of the well-being of all those populations who have been excluded from the standard indexes of economic and social performance: most notably, Afro-American slaves, eighteenth-century European craftsmen and peasants, and nineteenth-century Western women.

Abbreviations

AGS	Adolescent Growth Spurt
GDP	Gross Domestic Product
GNP	Gross National Product
HDI	Human Development Index
MHR	Minimum Height Requirement

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_14,

Table 14.1 Key facts of industrialization

- Industrialization is a global process, including technological and economic changes, but also urbanization and cultural changes such as the spread of literacy.
- Industrialization began, in the eighteenth century, with improvements in the productivity of the textile industry and in agriculture, and it ended, in the twentieth century, with the tertiarisation of the economy.
- During industrialization, there was a dramatic productivity increase not only in the industrial sector, but also in agriculture, thanks to technological changes.
- During the entire period of industrialization, there was a dramatic increase in the standard of living.

Industrialization is not just a question of improved productivity in the industrial sector but rather a global – economic, social, and cultural – process

14.1 Introduction

Beginning with the early industrialization (Table 14.1), in Europe, about 300 years ago, huge advances in the sciences, industry, and medicine caused both an unprecedented population explosion and a tremendous increase in average human height. This complex interaction between technological improvements and acquired, reversible improvements in human biology is called techno-physio-evolution by Nobel Prize Laureate Robert W. Fogel (Fogel 2004). But why did the stature of Europeans, considered as an index of the biological standard of living, decrease during most of the eighteenth century? Why did North Americans and Australians remain quite tall (compared with Europeans) during industrialization? Why did the United Kingdom, the USA, and Australia, experience significant declines in height whereas Japan, France, and Sweden experienced the opposite? During the nineteenth century, were there significant differences in the height trends for men and women, and for white Americans and American slaves? As for anthropometric changes during the twentieth century, were there significant height differences between the populations of democracies and those living under totalitarian regimes? For 30 years, anthropometric historians have been exploring a variety of original data in order to answer these and other such questions and thereby create a more accurate portrait not only of Europeans but of the populations of all five continents.

14.2 Stature and the Other Economic and Demographic Historical Indexes

14.2.1 Stature and Other Economic Indexes

In the analysis of historical trends in well-being, mean height serves a double function. On the one hand, it obviates a reliance on extrapolations in the absence of standard indexes of the standard of living. For instance, it is nearly impossible to calculate per capita GNP or even real wages (i.e., wage estimates that take into account not only income but also the cost of living) for any eighteenth-century population; nineteenth-century women, because their domestic work is not included in GNP estimates; and for American slaves, since they earned no wages.

On the other hand, when estimates of GNP, per capita income, real wages, or other data are available, height data can complement the standard indexes; this is the case not only for "the early-industrial-growth puzzle" of Europe and the USA (Komlos 1998; Steckel 1998), and for

Table 14.2 Provincial differences in the quality of life according to three measures in the Netherlands, 1820–1913

	Real incomes			Provincial rankings			HDI		
	1820	1850	1913	1820	1850	1913	1820	1850	1913
Urban core	110	109	111	8	8.7	2.7	0.542	0.451	0.722
Noord-Holland	113	110	111	10	7	1	0.568	0.430	0.716
Zuid-Holland	107	109	113	9	9	3	0.522	0.482	0.722
Utrecht	109	107	108	5	10	4	0.537	0.440	0.726
High income agricultural	117	104	85	8.3	5.5	5.7	0.542	0.434	0.648
Groningen	113	94	82	8	4	7	0.526	0.398	0.638
Friesland	125	111	84	6	1.5	2	0.538	0.418	0.639
Zeeland	113	108	88	11	11	8	0.561	0.485	0.666
inland provinces	76	78	73	3.4	4.7	8.2	0.425	0.395	0.607
Gelderland	81	87	97	2	6	6	0.450	0.402	0.689
Overijssel	84	82	77	7	3	5	0.422	0.424	0.613
Noord-Brabant	70	76	69	3	8	11	0.397	0.348	0.606
Limburg	61	67	63	1	5	9	0.394	0.368	0.591
Drenthe	82	79	58	4	1.5	10	0.464	0.432	0.535
The Netherlands	100	100	100	3.4	4.7	8.2	0.489	0.421	0.649

Here the HDI includes per capita GDP, life expectancy at the age of one, infant mortality, the literacy rate and mean height. This HDI describes a decline in the quality of life of city-dwellers in the mid-nineteenth century. This decline is not reflected in per capita real incomes. The negative externalities of modern economic growth and the growing social inequalities that accompany the early stages of industrialization go far to explain this gap

"Real income" means income estimates that take into account the cost of living (index 100 = national average). HDI stands for Human Development Index, GDP for Growth Domestic Product. $N = 135$. The "negative externalities" of modern economic growth are urban pollution, factory labour, diseases, and other threats to biological well-being (Horlings and Smits 1998, with permission of Franz Steiner Verlag)

Table 14.3 Key facts of the HDI

1. The HDI usually comprises three measures of the standard of living: life expectancy, education, and per capita income.
2. It is a non-weighted average of these three measures.
3. It ranges from zero to one (the optimal standard of living).
4. It was created in 1991 by the United Nations.
5. It does not include the political dimensions of well-being (human rights).

Like human height, the HDI provides an alternative to the standard economic indexes

twentieth-century industrialized countries, but also for communist countries, whose official statistics are based on a GDP calculation different from that used by liberal economists, and whose published data are not reliable.

Thus, in the Dutch case presented here (Table 14.2), during the nineteenth century, the HDI (Table 14.3) includes per capita GDP, life expectancy at the age of one, infant mortality, the literacy rate and mean height, but it does not point to the same conclusions as per capita GNP. The indexes are well synchronized for the beginning and the end of the period under consideration. Nevertheless, the HDI describes a decline in the quality of life of city-dwellers in the mid-nineteenth century (compared with their previous position but also with the inland and high-income agricultural provinces), a decline that is not reflected in per capita real incomes. The negative externalities of modern economic growth (urban pollution, factory labour, diseases and other threats to biological well-being) and the growing social inequalities that go with early industrialization go far to explain this gap between the standard economic indexes and anthropometric ones.

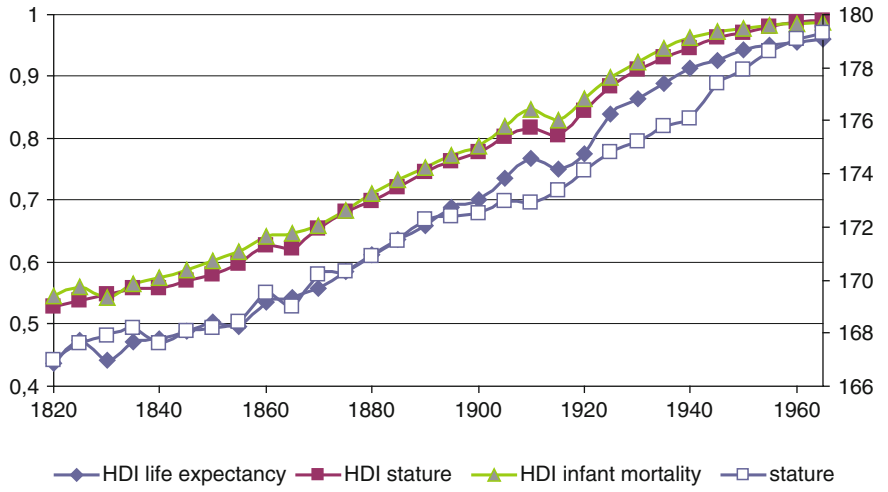

Fig. 14.1 Human development indexes (HDI) and stature in Sweden, 1820–1965. On the historical scale, stature is closely correlated with other demographic indexes such as life expectancy, mortality, and infant mortality. Thus, substituting here life expectancy at age one for stature or for infant mortality when calculating the HDI provides almost identical results throughout the course of industrialization. "HDI" means Human Development Index. "Stature" means mean height (cm), $N = 120$. (Sandberg and Steckel 1997, with permission of the University of Chicago Press)

Thus, the aim of anthropometric history is to identify height trends among populations defined by geography or social groups and to analyze these trends in terms of the standard indexes of economic history.

14.2.2 Stature and Other Demographic Indexes

For numerous reasons, stature is closely correlated with education: educated parents tend to take better care of their children during pregnancy and early childhood; they tend to provide their children with relatively abundant cultural and economic capital; their children are spared the hardships of physical labour and so on. The positive influence of education is noticeable even after control for income. In other words, the link between literacy and stature is of an economic as well as cultural nature.

On the historical scale, stature is closely correlated with other demographic indexes: life expectancy, mortality and infant mortality, which is a major component of the crude death rate and the life expectancy. Thus, the Swedish case presented here (Fig. 14.1) shows that substituting life expectancy at age one for stature or for infant mortality when calculating the HDI provides almost identical results for the entire 1820–1965 period, i.e., throughout industrialization. Stature can complement or even replace other demographic indexes. Anthropometric history was born of a debate over the cause of the decline in the mortality rate during industrialization: a debate between those who claimed that the causes were nutritional and those who claimed that they were epidemiological (Komlos 1998; Steckel 1998). Because of this lack of consensus, and for the sake of clarity, in Sects. 14.4 and 14.5, we present the determinants of height according to crude nutrition (energy input) and net nutrition (input minus the caloric expenditures caused by diseases, physical work, etc.).

14.3 Practical Methods and Techniques

14.3.1 The Data Used by Anthropometric History

Various problems arise when anthropometric historians process their data. Registers of convicts, migrant workers and (mostly eighteenth-century) army volunteers; nineteenth-century passports; nineteenth- and early-twentieth-century school surveys: all of these data sources are problematic because they are confined to one socio-economic group or another. Thus, the class composition of the sample must be compared with the closest census whenever possible. Furthermore, since prisons, military barracks and ships are especially crowded when times are hard, results have to be controlled for the year of measurement and the birth year, the category of the crime committed, etc. The use of statistical regression with several explanatory variables is one of the defining characteristics of anthropometric history.

Contrary to the above-mentioned sources, conscription registers, available in Europe since the end of the eighteenth century, provide information about nearly all of the men in a given birth cohort. Furthermore, there was a widespread problem of incomplete height records, partly on account of absenteeism, in France and Italy throughout the nineteenth century.

14.3.2 The Problem of the Minimum Height Requirement

Military sources pose a particular problem in the case of volunteer armies: the existence of a MHR, below which measurements are rarely recorded. Throughout the eighteenth century, the MHR and the mean height of a given population were nearly identical. The identification of the truncation point of the sample is made through visual inspection of the relevant distribution histograms, which are always expressed in the original unit of measure (Komlos 2004). Most of the statistical methods used when dealing with this problem are based on the assumption that stature follows a normal distribution pattern. However, the distortion of the curve on the left-hand side (over-representation of numbers below mean height due to bad living conditions, mainly during the AGS) makes it preferable to use, when possible, a method that does not pose the hypothesis of the Gaussian distribution and therefore does not lead to an overestimation of the mean height.

14.3.3 Anthropometric History and Auxology

Offering continuous and homogeneous serial data is one aim of historians. Thus observations are standardized, the age of subjects being limited from 23 to 49, as a rule. This policy raises auxological problems, since the AGS of all the subjects did not occur simultaneously and did not have the same amplitude that they would today, but instead varied according to the region, era, and group in question. As a result, the policy has been modified: measurements made during adulthood are now quoted according to the year of birth, since variations in adult height are best explained by living conditions in early childhood.

The maximum socio-economic influence on final height is experienced in the most intensive biological-growth periods: mostly in utero and in early childhood but also during adolescence. Nevertheless, stature is a synthetic index of the standard of living, whereas one knows precisely in which year a GDP or any other index is measured; correspondences between anthropometric and economic data must be made with great care.

Historians in certain fields include in their research an analysis of human skeletons belonging to pre seventeenth-century populations, unaccompanied by any corroborative written data. Thanks to such research the frontiers of anthropometric history now stretch from the Roman Empire by way of medieval Europe to precolonial America. The study of human skeletons remains, for now, a marginal aspect of anthropometric history.

14.4 Explaining Mean Height from the Historical Point of View: The Part Played by Inputs

Mean height can be considered as an index of net nutrition, that is, total nutritional input minus the energy expended on maintaining a basal metabolism, on physical effort and on disease resistance. Although biological and medical studies stress the importance of the synergy in this double process of input and caloric expenditure, historical studies depend on sources that provide explanatory variables only on the aggregate scale, thereby underestimating its importance. For the sake of clarity, we shall examine separately the respective roles of inputs and expenditures.

14.4.1 Stature, Income and Crude Nutrition

The close correlation between per capita income and mean height in the nineteenth and twentieth centuries underlines the positive influence of inputs on stature. Nevertheless, some populations have been taller than their per capita income would lead one to expect: chiefly, those of early-nineteenth-century Ireland and America; this anomaly was thanks to a protein-rich diet and a healthy environment, and therefore was not directly correlated with income.

The positive influence of crude nutrition has been proved in many cases, mostly in the eighteenth and nineteenth centuries. For instance in Italy, the increase of food intake explains 60% of the anthropometric growth between 1854 and 1913, whereas an improvement in environmental conditions generally explains 30% of this growth. In antebellum America, county-level records indicate a positive correlation between surplus food production and stature. This correlation was particularly evident in the peripheral states, which were not yet fully integrated into a nationwide market, and where, therefore, produce was still consumed locally. The positive effects of crude nutrition are confirmed when one adds to the equation the mortality variable, considered as an index of the quality of the epidemiological environment. At this point it becomes evident that crude nutrition and diseases have a synergic effect on stature.

During early industrialization, city-dwellers' nutrition was inferior to that of country dwellers, largely because the cost of transportation increased the cost of food. This discrepancy diminished in the second half of the nineteenth century, with the arrival of railways and, later, refrigerated cars and boats, which also made it possible for city dwellers to add perishable dairy products and more meat to their diet.

14.4.2 Anthropometric Convergence and Divergence

The study of anthropometric convergence and divergence among socially or geographically distinct groups allows one to test the economic theory of Kuznets, according to which social and geographic discrepancies during industrialization formed an inverted-U-shaped curve: at first relatively small;

they steadily increased, eventually levelled off, and then steadily declined. This pattern is found elsewhere as well; early in the industrialization process, an increase in income among the wealthiest part of the population translates into an increase in GNP, but has little or no influence on mean height. Since the quantity and quality of the food consumed by the well-to-do was already satisfactory, its increase did not translate into an increase in average height. On the other hand, even just a small increase in income among the lower classes is reflected in anthropometric measurements, because they used the money to purchase nutritious food, which had previously been beyond their means. Thus, the inequalities in the distribution of wealth which accompanied the rise of modern capitalism would seem to have translated into class-defined inequalities in stature. The British enclosure movement (eighteenth century), like the privatisation of communal lands in Saxony (early nineteenth century) and in Mexico and southern India (late nineteenth century), deprived peasants of essential nutritional resources and thus contributed to the decline or the stagnation in stature among the poorest portion of the British population at that time.

In the Belgian province of Liège, the height difference between the richest and the poorest reached a peak of 8 cm. in the first half of the nineteenth century and later declined, primarily because of a height increase among the poor. The same phenomenon occurred more or less simultaneously in the USA, the UK, and France. The discrepancy was particularly striking among children; the young son of an English lord would have had a 15-cm. height advantage over a street urchin like Oliver Twist. Height data for the early nineteenth century parallel income data; farm and textile labourers are the shortest, white-collar professionals are the tallest, and craftsmen are found somewhere in between. However, the proximity of nutrients still played a positive role, as testified by the fact that farmers and foodstuff traders were taller than their income would suggest.

Contrary to most techniques for measuring the standard of living, those of anthropometric history include the analysis of height trends according to gender, thereby elucidating patterns of energy input and caloric expenditure within the household. It seems that women are more sensitive to economic cycles than men, perhaps because of nutritional and other health-related discrimination, or perhaps because of an innate biological process of adaptation to deprivation. For instance, in Scotland in the 1840s, a decade marked by severe malnutrition, the average height of women steadily declined, whereas that of men, paradoxically, soared. The same phenomenon occurred among emancipated slaves in Maryland. In early-nineteenth-century Bavaria, the average height of women paralleled the unequal distribution of agricultural products among districts more closely than did that of men. However, there are at least two exceptions to this rule: in Australia in the first half of the twentieth century, and in nineteenth-century India, there was no discernible difference between the sexes when it comes to nutrition-related changes in average height. Unfortunately, since military files are the primary source of information available to anthropometric historians, data on women are scarce, and therefore a well-documented analysis of sex-specific height trends remains elusive.

14.5 Explaining Mean Height from the Historical Point of View: The Part Played by Energy Expenditures

14.5.1 Stature and Urbanization

As Rousseau and Dickens observed, the industrialization was especially hard on city dwellers, whose below-average caloric input and above-average caloric expenditure account for their below-average height. As the twentieth century approached, however, improvements in medicine and hygiene on

the one hand and a diminution in the physical hardships of industrial labour (tertiarisation) on the other resulted in a reversal of this trend.

During the early years of the industrialization, the European city was an environment with nothing but negative potential for physical human growth: lack of sewage systems and poor sanitation generally combined with overcrowded living conditions and child labour to create a disease-ridden, malnourished, physically diminished population. The fact that this was a world-wide phenomenon explains why nineteenth-century city-dwellers were shorter than their rural counterparts not only in the UK, but in Italy, Canada, Australia, Austria, Japan and the USA, as well.

There were some exceptions, but they were confined to countries where an archaic social structure persisted, where cities therefore could remain relatively small, and traditional trades were able to survive (this was the case in Spain, Germany, and Russia). The height decline among New Yorkers was, despite a dramatic increase in the city's population, less than that among residents of other American cities thanks to its dominant role in the national and international wheat market, which had obliged the establishment of an efficient system of food distribution as early as the 1850s.

In accordance with a fundamental economic principle, countries that are late to industrialize have an advantage over those countries that were pioneers, because they can learn from the pioneers' problems and remedies. This advantage is reflected in their citizens' superior rate of anthropometric growth. For example, Japan began to industrialize only after other, industrialized nations had instituted public-health policies and researchers had proven that germs caused the spread of infectious diseases; the average height of its population, therefore, did not decline (Fig. 14.5). This was also the case in Sweden, Germany, Austria, Hungary, Poland, the Iberian Peninsula, Italy and Argentina (Steckel 2009).

14.5.2 Stature, Diseases, Child Labour and Medical Care

Japanese prefectural records for the years between the two World Wars reveal direct correlation between improvements in health services and increases in stature. In the case of backward economies, such as that of early-nineteenth-century Sweden, even just a modest increase in public-health spending may have had beneficial effects, reflected in height statistics. In France during the latter half of the nineteenth century, as well as in the first half of the twentieth century in Japan, an increase in the number of midwives in a given region was directly correlated with an increase in average height. This correlation demonstrates the importance of good health care in early childhood and confirms the hypothesis that, during the first year of life, such care has a greater impact on growth than does crude nutrition.

The impact of energy expenditure is more difficult to quantify on a historical scale than is the role of nutritional input. Nevertheless, it seems that malaria and other diseases linked to irrigated agriculture played a role in the stagnation or decline in height that occurred in India and in South-East Spain during the nineteenth-century and in Burma during the rice boom at the end of the century.

In the USA, the fact that the steepest decrease in height occurred in the coal-producing states (mainly in the Midwest) in the 1870s–1890s could be explained by the spread of respiratory diseases. In the UK, the prevalence of tuberculosis, prior to the 1860s in towns and cities may have contributed to a height decline, and the fact that the subsequent eradication of tuberculosis was accompanied by a height increase may not have been merely coincidental. In Australia, the radical decline in stature during the 1890s may have been partly due to the many epidemics, including Melbourne's typhoid fever, that afflicted urban areas.

Finally, child labour may have a negative influence on stature but is very difficult to measure on the historical scale and offers little help to those anthropometric historians trying to solve the early-industrial-growth-puzzle.

14.6 The Early-Industrial-Growth-Puzzle

The social and economic history of the eighteenth- and nineteenth-century features the self-regulating relationship between population and resources, first described by Thomas Robert Malthus in 1798, on the one hand, and the more immediate human cost of the early industrialization on the other. In both matters, anthropometric history provides new evidence. It highlights two main periods during which height declined in Europe: the 1760s to the 1800s (Figs. 14.2 and 14.3) and the 1830s to the 1860s. This second decline extended to the USA, where it persisted into the 1890s.

14.6.1 The First European Decline in Height (Eighteenth Century)

The first period of anthropometric decline shows a considerable decrease in real wages (Table 14.4), and therefore in purchasing power, simultaneous with falling temperatures and a growing population. The decline in grain production, on account of cooler temperatures, not only caused an increase in the price of bread but also had a negative impact on cattle production. Because of increased productivity in the industrial sector (chiefly textiles), the price of manufactured goods increased at a slower rate than that of agricultural products, and, for instance in Great Britain, the price of grain-based products increased at a slower rate than that of meat. Grains, therefore, were substituted for meat, making for a diet poorer in animal protein and richer in carbohydrates. The price for this dietary shift – a secondary consequence of the early industrialization (chiefly the textile industry)– was a decrease in average human height; on the positive side, it permitted the population to increase without falling into the Malthusian trap, that of a massive population decline due to starvation and epidemic disease.

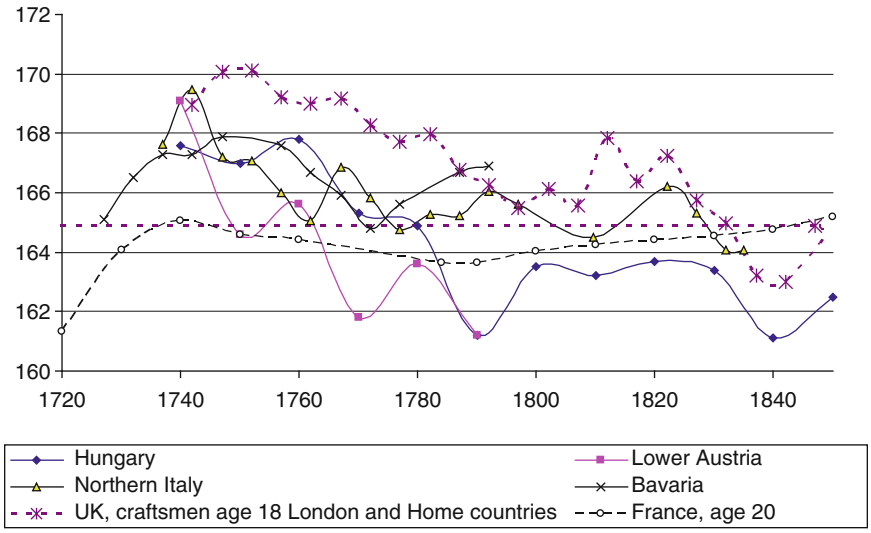

Fig. 14.2 The early-industrial-growth-puzzle in Europe, eighteenth–nineteenth centuries. During industrialization in eighteenth-century Europe, a decline in human height went in tandem with downward trends in real wages and in temperatures. A second decline occurred during the first half of the nineteenth century, in tandem with upward trends in GDP and in real wages, hence the phrase "early-industrial-growth puzzle." Mean heights, cm, $N = 83$. (A'Hearn 2003; Baten 1999; Cinnirella 2008; Komlos 1989 and 2003; Weir 1997)

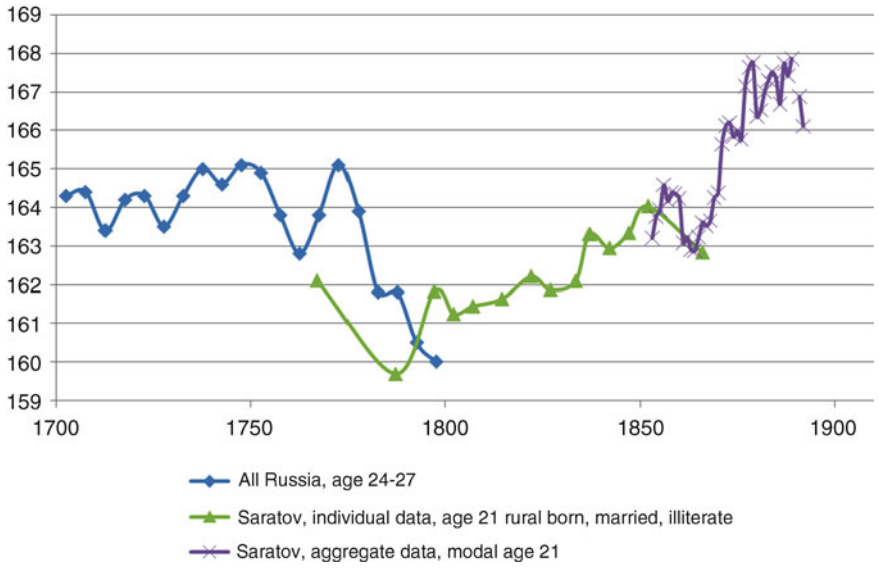

Fig. 14.3 Secular trend of stature in Russia, eighteenth–nineteenth centuries. Not unlike Europe, Saratov, a province of southern Russia, experienced a decline in height in the second half of the eighteenth century. Nevertheless, Saratov experienced no height decrease during the first half of the nineteenth century. Mean heights, cm, $N = 74$. (Mironov 2005; Mironov and A'Hearn 2008)

Table 14.4 Key facts of real income

- Income consists not only of wages, but also of all other sources of income (sales from domestic production, etc.).
- Income is real (as opposed to nominal) when income estimates take into account not only income but also the cost of living, i.e., prices.
- When nominal income increases more than nominal prices, then the purchasing power of the worker increases.
- When nominal income increases less than nominal prices, then the purchasing power of the worker, and hence his real income, decreases.
- The trend in real income depends mainly on which products are chosen for inclusion in the basket of products that is used to calculate whether there has been a change in nominal prices.

Real income is used to estimate the trend in the standard of living by taking into account the trend in prices

14.6.2 The Decline in Height in Europe and America in the Nineteenth Century

During the 3 decades preceding the Civil War, the height of Americans declined and their mortality rate increased, despite sustained economic growth. This paradox is known as the "Antebellum Puzzle" since it had not occurred during the first, European, period of decline, in the late eighteenth century. There was a significant decline in height at this time in the UK, as well, even as the early industrialization got under way: hence the phrase "early-industrial-growth-puzzle." Height declines were also recorded during the first half of the nineteenth century in Italy, Hungary, the Netherlands, Saxony, and some regions of France.

The solution to the Antebellum Puzzle may lie in the notion of net nutrition. Transcontinental migration may help generate wealth, but it also results in a loss of microbial resistance of the human bodies and therefore in the spread of cholera, typhoid, typhus, malaria, and dysentery, which shared

responsibility for both the declining height and the increasing mortality. An American county on a railway or on a waterway was able to profit thereby, but people living here were shorter, thereby confirming the hypothesis that height decreased on account of diseases that exploited the spreading network of transportation routes. In addition, the export to distant markets of meat products, high in protein that had previously been consumed locally had a negative effect on the nutrition, and therefore the height, of people living in peripheral regions.

The fact that only slaves maintained their stature suggests that height loss was primarily due to deficiencies in crude nutrition, for if the height loss were only epidemiological in origin, slaves' height, like everybody else's, would have declined on account of widespread diseases, whereas in fact the only blacks to register a height decrease were freed slaves. Adult slaves were a valuable commodity – their price rose by 64% relative to that of food – so (while slave children were kept undernourished, their diet improving only once they were old enough to work) their owners invested in the maintenance of their physical health.

Mexico and Canada experienced the same decline in height in the second half of the nineteenth century (in fact, Mexico's height decline extended into the twentieth century), although these countries were far less industrialized than the USA. Political turmoil helps to explain the Mexican trend; however the Canadian one is primarily due to urbanization. Australia is another example of a young country in which the development of towns, which as a rule is accompanied by a deterioration in sanitary conditions, led to epidemiological problems that account for the otherwise paradoxical phenomenon of declining height during a period of economic growth (Table 14.5 and Fig. 14.4). The extensive economic systems of three relatively young countries – the USA, Australia, and Canada – meant that at first most of their inhabitants enjoyed a high biological standard of living. Subsequently, at the end of the nineteenth century, urbanization and the development of national markets facilitated the spread of infectious diseases and thus led to decline in height, whereas in Europe height figures turned around after having hit, at mid-century, a record low.

Some Europeans countries were spared a major decline in height during the nineteenth century. France, where industrialization began relatively early and was not concentrated in big cities was the first country to experience the demographic transition, featured a new ability on the part of parents to invest in their children's health. Sweden, where industrialization had even less of an impact than in France, enjoyed an exceptionally high rate of literacy. Along with Denmark, nineteenth-century Sweden experienced no major decline in height.

14.6.3 The Trends in Height in Asia and Other Parts of the World in the Nineteenth Century

The decline in height did not extend beyond Europe and the USA; for instance, Saratov, a province of southern Russia, experienced no height decrease during the first half of the nineteenth century, nor did Argentina. This contradicts the standard, bleak image of postcolonial South America (Table 14.5). The same holds true for India (Table 14.5). Along with other demographic indexes, the stature index permits a reconsideration of the standard notion that the economic divergence between Europe and Asia dates as far back as the end of the eighteenth century. This pessimistic vision of Asia's socio-economic history, based largely on the estimations of economic performance presented by the famous economist Maddisson, has been reconsidered in light of the current acceleration of Chinese economic growth. Records reveal that during the first half of the nineteenth century, average height in southern China stagnated but did not decline (Table 14.5, Figs. 14.2, 14.4, and 14.5). It was only after the first Opium War (1839–1842), by means of which

Table 14.5 Key points of the decline in stature during industrialization in Europe, America, Asia, and Australia, eighteenth–twentieth centuries

Country	Decline in stature	Birth cohorts (approx. dates)	Amount of decline (cm)
Argentina	No	1785–1839 and 1916–1950	
Australia	Yes	1867–1893	3
Lower Austria	Yes	1730–1799	7,9
Belgium (Liège province)	Yes	1800–1869	1.2–3.5 (local estimates)
Burma			
Lower Burma	Yes	1868–1882	2.1
Upper Burma	No	1848–1882	
Canada	Yes	1800–1899	Ill-defined
China	Yes		
southern part		1840–1859	1.5
		1860–1879	1.4
Denmark	No	1830–1962	
France	Yes	1717–1724	2.6
		1741–1760	1.5
Mulhouse (Alsace)		1796–1821	1.2
Limousin (central part)		1790–1799	2.7
Brie (near Paris)		1781–1793	1.9
		1852–1879	1.3
Germany	Yes	1705–1744	4
Saxony		1750–1763	1.2
		1770–1784	1.1
		1780–1839	8.1
Bavaria		1750–1779	2.7
Württemberg		1860–1872	2.5
		1879–1885	2
Hungary	Yes	1740–1799	6.8
Age 21–22		1820–1849	2.6
India	No	1794–1899	
Italy (northern part)	Yes	1740–1779	4.7
		1790–1819	1.6
		1820–1834	2.1
Japan	No	1872–1965	
Mexico	Yes		
(northern part)		1850–1889	2.5
The Netherlands	Yes	1810–1837	3.5
Russia	Yes	1740–1799	5.4
Saratov province		1755–1794	2.4
		1850–1877	1.2
(central part)		1899–1909	2.8
		1913–1918	1.2
		1923–1934	1.8
Spain (South-East)	Yes		
Murcia	urban	1851–1873	1.4
	rural	1846–1873	1.7
Sweden	Yes	1740–1780	Ill-defined
Taiwan	Yes	1863–1883	1.6
UK			
(Men)	Yes	1750–1799	4.6
		1815–1859	5.3

(continued)

Table 14.5 (continued)

Country	Decline in stature	Birth cohorts (approx. dates)	Amount of decline (cm)
(Women)	Yes	1790–1815	2.5
		1835–1855	2.5
US	Yes	1830–1890	4

A'Hearn (2003), Alter et al. (2004), Bassino and Coclanis (2008), Bassino (2009, personal communication); Baten (1999); Boldsen and Søgaard (1998); Cinnirella (2008a, b); Cranfield and Inwood (2007); Drukker and Tassenaar (1997); Heintel et al. (1998); Heyberger (2005); Komlos (1989, 2003); Martínez Carrión and Pérez Castejón (1998); Mironov (2005); Mironov and A'Hearn (2008); Morgan (2009); Olds (2003); Salvatore (1998, 2009); Steckel and Floud (1997); Wheatcroft (1999); Whitwell et al. (1997)

Almost all countries experienced a decline in height during industrialization, $N = 30$ countries or regions. The decline is reported if exceeding 1 cm. On the historical scale, populations can gain – or lose – on average 1–1.5 mm per year. If the answer in col. 2 is "No," dates in col. 3 refer to the extreme dates of the quoted study

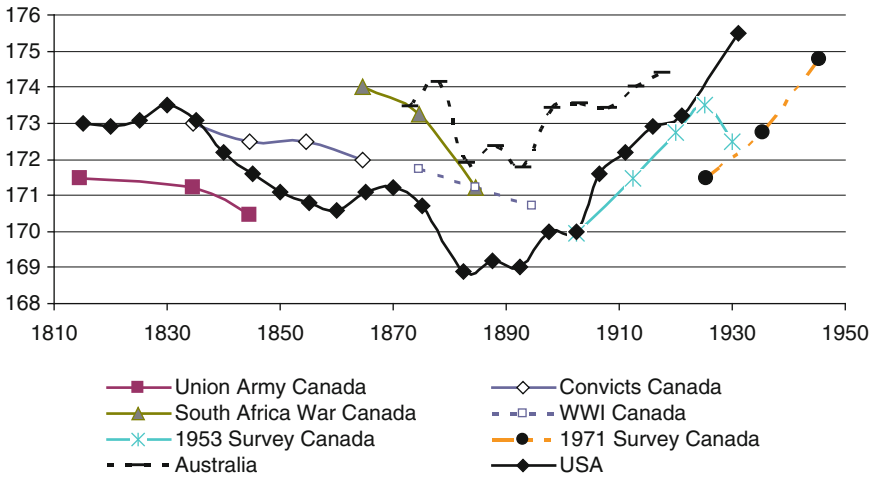

Fig. 14.4 The Antebellum Puzzle in "young countries", nineteenth–twentieth centuries. During the nineteenth century there was a decline in height caused by urbanization and the development of national markets not only in the USA, but also in Canada and Australia. This height decline occurred in spite of improvements in the standard of living, whether it was measured in terms of real wages, of income, or of GDP: hence the phrase "Antebellum Puzzle." Mean heights, cm, $N = 75$. (Cranfield and Inwood 2007; Steckel 1991; Whitwell, de Souza, Nicholas 1997)

the British forced China to open its ports to foreign trade, that stature started to decline. However, this decline was not directly due to the intrusion of foreigners, as Marxist historians would have it, but rather to chronic social unrest in southern China throughout the second half of the century. Northern China was one of the few regions worldwide that experienced a height decline between the late 1890s and the late 1920s. An increase in income in northern India, due to the opening of the market during the third quarter of the century, was reflected in a height increase, which slowed down slightly toward the end of the century and then stagnated until the 1950s, as the population expanded (Brennan et al. 1994, 1997). Then the late period of the British colonization did not provide any improvements in the biological standard of living.

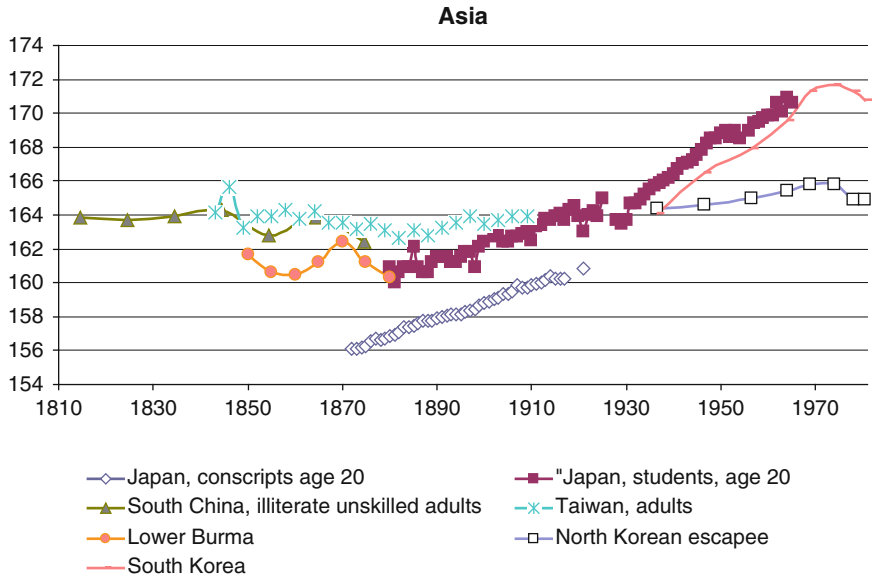

Fig. 14.5 Secular trend of stature in Asia, nineteenth–twentieth centuries. During the nineteenth century Asia, unlike Europe and America, experienced no major decline in height. However, in the second half of the twentieth century there was a secular upward trend in height throughout Asia, with the exception of North Korea. Mean height, cm, $N = 233$. (Bassino and Coclanis 2008; Bassino 2009, personal communication; Morgan 2004,2009 ; Olds 2003; Pak 2004)

14.7 Anthropometric History of the Twentieth Century: Political Issues

The economic history of the twentieth century is primarily about governmental, public policy, not private-business cycles. Anthropometric history can help to expose the truth about Nazism, communism, colonialism, liberalism: ideologies that boasted of their successes on the standard-of-living front. Data used to be derived primarily from registers or studies of adults; now, most data are on children and adolescents and are more abundant than previous data, thanks to the records kept by primary and secondary schools, which are more numerous than ever. The height of a child or an adolescent is in the short term a far more sensitive indicator of biological well-being than is the height of an adult. Thus, height data on children and adolescents provides the most accurate gauge of the success of public-health policies of the countries under study.

The purpose of historical research is not to justify injustice –or justice-. The height of American slaves in the nineteenth century does not make slavery any less immoral. In the same way, the deterioration of anthropometric indexes, which is much more notable during the economic crisis of the first 30 years of the USSR than during the smaller – but equally disastrous – Nazi economic autarchy of the 1930s, cannot be used to assess a so-called superiority of one model over another.

14.7.1 Trends in Height in the Major Western Liberal Democracies

In the Western world, the agricultural depression of the years 1873–1896 caused anthropometric indexes to decline but this was not, surprisingly, the case with the Great Depression for the major Western liberal democracies – the USA, the UK, and France – in spite of the emergence of a new

scourge: mass-unemployment. One explanation is the fact that these three countries had invested in improved public-health policies in the late nineteenth century, providing their citizens with a socio-medical safety net, albeit a minimal one. Such investments are not included in the GDP of the 1930s: hence the lag between standard indexes and anthropometric ones, which measure the standard of living. Argentina provides a similar example: a decline in the cost of food helps explain a height increase during the 1930s, in contrast with the subsequent Peronist years. Again, anthropometric indexes provide a historical perspective that raises questions about the adequacy of standard ones.

14.7.2 Trends in Height in Totalitarian and Authoritarian Regimes

In contrast, children, adolescents or even – more rarely – adults suffered a height decrease during the 1930s in the following countries: the USSR, with its planned economy; Germany, because of the Nazi autarchy; Spain, where the Civil War raged; and Japan, engaged in expansionist military actions. This was also the case for the 1940s and 1970s, as far as the USSR is concerned. Nevertheless, the standard economic indexes paint a rather rosy picture of these countries, not very different from that of the positive political propaganda of the time. Mao's Great Leap Forward (1958–1961) was accompanied by a decline in the height of adolescents that persisted until 1965: scarcely surprising in light of the fact that the resulting famine claimed around 30 million victims.

14.7.3 Anthropometric History and Colonialism

The height of Koreans declined during the 1920s, when the country was under Japanese colonial rule and a considerable amount of its rice was exported to Japan. In contrast, Taiwan actually recorded a height increase during the first years of Japanese rule; this may be because of Japanese efforts to improve sanitary conditions, in an effort to stamp out malaria. Australia offers a simpler scenario: the height of male Aborigines, relegated to the fringes of society, and confined to camps, stagnated at the beginning of the century, whereas the height of whites increased.

14.7.4 The Second Half of the Twentieth Century: Anthropometric History, the Welfare State and the End of Communism

During the twentieth century, the geographical and class patterns in human heights that marked the nineteenth century began to blur. In early-nineteenth-century Great Britain, the working class was on average five inches shorter than the upper class; this gap has narrowed to one inch. After the Second World War, Southern Europe (Greece, Italy, the Iberian Peninsula) caught up with Northern Europe (Austria, Belgium, Denmark, Finland, Ireland, Sweden), despite the fact that the latter continued to experience a height increase. The rise of the welfare state meant a reduction of inequalities and thus a record-breaking adult height in Scandinavia; its demise in the USA helps to explain the current obesity epidemic there.

In Russia, the transition from communism to capitalism had negative consequences, reflected in the anthropometric indexes for babies born shortly after the dissolution of the USSR, in 1991. This

phenomenon, very rare in the twentieth century, confirms the idea of a chaotic Russian transition in contrast with the better-managed Chinese one, a pairing popularized by Nobel Prize Laureate Joseph Stiglitz in *Globalization and Its Discontents* (2002). At the same time in North Korea, one of the few communist countries still in existence, the anthropometric indexes of children began to decline after having held their own for several decades, in sharp contrast with similar indexes for South Korea, despite the fact that the two populations share one genetic heritage (Fig. 14.5).

The life sciences and anthropometric history have much to gain by increasing their cooperative efforts. The life sciences can provide data on a vast array of contemporary socio-economic determinants of height. In turn, anthropometric history can provide historical data that offer new perspectives on current socio-economic policies: not only their causes, but also their possible consequences (Steckel 2009).

Summary Points

- An index of the biological standard of living.
  Contrary to the standard indexes of the standard of living such as per capita Growth Domestic Product, consumption, and wages, the mean-height index helps to account for the negative externalities of modern economic growth. The mean-height index is especially useful when it comes to analyzing eighteenth- and nineteenth-century populations for which indexes are either unreliable or simply nonexistent.
- The existence of the Minimum Height Requirement (MHR) represents the main statistical difficulty that anthropometric history has had to overcome. Reliable methods of analysis are now available to resolve this problem.
- Not only overall income and food-consumption levels, but also their distribution among social and ethnic groups and between the sexes must be taken into account –whenever possible- in any analysis of height trends in a given population over the course of history.
- The high price and scarcity of nutritious food, overcrowded and unsanitary housing, spreading diseases, and inhuman labour conditions go far to explain the decline in average height among city dwellers during the early years of the industrialization.
- During the second half of the eighteenth century, as a result of mounting population pressure and falling temperatures affecting European countries' mainly agrarian economies, the height of Europeans declined. However, the direst consequences of the population principle proposed by Malthus were not realized, thanks to certain beneficial aspects of the early industrialization but at the cost of malnutrition caused by a decline in the nutritional quality of most Europeans' diets.
- Whereas the standard economic indexes emphasize a steady improvement in the first half of the nineteenth century, the stature of Americans and Europeans declined; this is the human cost of the early industrialization, paid by city-dwellers as well as their rural counterparts. At the same time, heights in China and India remained constant.
- Under twentieth-century totalitarian and authoritarian regimes, children and adolescents paid the human cost of the political decisions made by dictators. This was the case in Hitler's Germany, Stalin's USSR, and Mao's China.

Acknowledgments I thank Jean-Pascal Bassino for providing data for Japan (Fig. 14.5), Francesco Cinnirella for providing data for England (Fig. 14.2), Edwin Horlings and Jan-Pieter Smits for their permission to publish Table 14.2, John Komlos for providing data for eighteenth-century France (Fig. 14.2), Gilles Postel-Vinay for providing his unpublished paper, Julie Smith and Laurent Tourrette for the English translation, and the University of Chicago Press and Franz Steiner Verlag for their permission to publish Fig. 14.1 and Table 14.2.

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Part II
Tools and Techniques in Anthropometry: Water, Hydration and Surface Area

Chapter 15
Total Body Water in Health and Disease: A Look at End-Stage Renal Disease

Luigi Vernaglione, Carlo Lomonte, and Carlo Basile

Abstract Methods for determining body composition have improved over the past 20 years, greatly increasing the accuracy and ease of making these measurements. Body composition measurements may be useful in the clinical management of patients suffering from several diseases such as obesity, diabetes, metabolic syndrome and renal failure.

The measurement of body composition may include direct or indirect measurements of total body water (TBW), body fat mass (FM), fat-free body mass (FFM) and bone mass, and sometimes of the distribution of fat between the visceral or subcutaneous compartments. The choice of method depends on which of these compartments is of interest, whether the measurement is for clinical purposes or research, and the degree of precision that is required. For the purposes of anthropometric measurement, for estimating adiposity, fat distribution and body composition, together with densitometry, isotope dilution, impedance measurement and imaging techniques are now available.

For practical reasons, the direct measurement of body composition is essentially limited to research centres. For general uses, indirect methods of predicting body composition, such as the development of regression equations or the bioelectrical impedance analysis (BIA), have been based on anthropometric variables or electrical measurements. In the case of end-stage renal disease, TBW assessment by means of BIA has three main targets: (a) assessment of the body dry-weight; (b) evaluation of the nutritional status (considering TBW together with FM, FFM and body cell mass); (c) calculation of the dialysis adequacy.

Currently available guidelines have underlined the need for sensitive measures of both nutritional and hydration status to prevent malnutrition and oedema in kidney patients; BIA represents an attractive clinical tool to detect early changes in body composition in this clinical setting.

Abbreviations

BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BW	Body weight
CT	Computed tomography

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_15,

DEXA	Dual-energy absorptiometry
DW	Dry weight
ECW	Extracellular water
ESRD	End-stage renal disease
FFM	Fat-free mass
FM	Fat mass
H	Height
ICW	Intracellular water
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
MRI	Magnetic resonance imaging
NCDS	National Cooperative Dialysis Study
TBW	Total body water
TSF	Triceps skin fold
WHR	Waist-to-hip ratio
WHT	Ratio of waist circumference to the height

15.1 Introduction

Methods for determining body composition have improved over the past 20 years, greatly increasing the accuracy and ease of making these measurements. Body composition measurements may be useful in the clinical management of patients suffering from several diseases such as obesity, diabetes, metabolic syndrome and renal failure. This paper will review body composition and the methods available for its measurement. Moreover, the evaluation and the clinical significance of measuring total body water (TBW) in normal subjects and renal patients will be discussed (Table 15.1).

15.2 Models of Body Composition

Body composition can be viewed from five perspectives (Wang et al. 1992):

15.2.1 Atomic Composition

As reported in Table 15.2, in normal subjects weighing 70 kg, oxygen, carbon, hydrogen, nitrogen, calcium, phosphorous, sulphur, potassium, sodium, chlorine and magnesium account for more than 98% of body mass, while less than 2% is contributed by the other 44 elements that are present.

15.2.2 Molecular Composition

More than 100,000 chemical compounds can be identified in the human body, ranging from simple to very complex; water, lipid, and protein are the major components (Fig. 15.1).

Table 15.1 Key features of assessing body composition in health and renal diseases

1. The assessment of body composition covers an important role in establishing nutritional and hydration status both in health and disease
2. Regression equations based on anthropometrical parameters (age, gender, BW, H) have been developed, in healthy people, to predict the body composition
3. Ease of determination, cost and accuracy make BIA a useful tool for assessing body composition. The assessment of body composition by BIA in healthy subjects has allowed the development of estimating equations and the *RXc*-graph method setup
4. Complex changes in body composition occur in patients with kidney diseases of various degrees.
5. Once the patients have started the dialysis the DW, the dialysis adequacy and the nutritional needs can be at least approximately established by means of BIA appropriately performed

This table lists the five main points that will be treated in the chapter

Table 15.2 Atomic composition of the body

	%
Hydrogen	10
Oxygen	61
Carbon	23
Nitrogen	2.6
Calcium	1.4
Phosphorus	<1
Potassium	
Sodium	
Chlorine	
Magnesium	
Other	2

This table lists all the atomic components of the body reported as percentage of the total. Data are considered for a normal subject weighing 70 kg

- Water represents about 60% of the normal male (and 50% of the normal female), of which approximately 26% is extracellular (ECW) and 34% intracellular (ICW).
- Body fat ranges from less than 10% in well-trained athletes to slightly over 50% in obese patients. Two to three percent of lipids in fat are essential structural lipids; the remainder are fat stores.
- Proteins represent 15% of normal body composition.
- Minerals comprise 5% of normal body composition.

Thus, water, lipid, protein, and minerals account for 99.4% of the molecular constituents of the body.

15.2.3 Cellular Composition

The body is composed of cell mass, extracellular fluid, and extracellular solids. Fat cells, osteoclasts, osteoblasts and the cellular elements of blood are components of connective tissue. Muscle cells include skeletal muscle, smooth muscle, and cardiac muscle. Epithelial cells include the cells lining a hollow viscus. The potassium content in the body is the most widely used indicator of body cell mass (BCM) because potassium is the principal intracellular cation (Maynard et al. 2001).

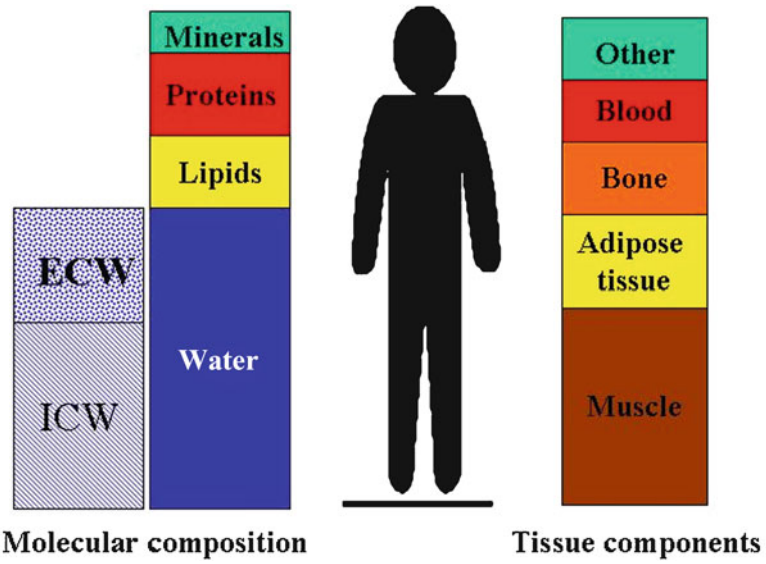

Fig. 15.1 Molecular composition and tissue components of a normal subject weighing 70 kg. More than 100,000 chemical compounds can be identified in the human body, ranging from simple to very complex; water, lipid, and protein are the major components Body weight (BW) represents the sum of the muscle tissue, connective tissue, epithelial tissue, and nervous tissue. Bone, adipose tissue and muscle make up 75% of BW

Extracellular fluid is approximately 94% water distributed into the plasma, in the intravascular space, and the interstitial fluid in the space outside the vascular compartment. Plasma and interstitial fluid account for approximately 5% and 20% respectively, of body weight in normal subjects.

15.2.4 Tissue Components

Body weight (BW) represents the sum of the muscle tissue, connective tissue, epithelial tissue, and nervous tissue. Bone, adipose tissue and muscle make up 75% of BW (Fig. 15.1).

15.2.5 Whole Body

The whole body represents the final perspective on body composition. There are at least ten different components of the whole body that may be measured, including stature, segment lengths, circumferences, skin fold thicknesses, body surface area, body volume, BW, body mass index (BMI) and body density.

15.3 Practical Methods and Techniques of Measuring Body Composition

The measurement of body composition may include direct or indirect measurements of TBW, body fat (FM), fat-free body mass (FFM), and bone mass and sometimes of the distribution of fat between the visceral or subcutaneous compartments. The choice of method depends on which of

Table 15.3 Instrumental methods for assessing body composition

	Cost	Ease of use	Accuracy	Can measure regional fat	External radiation
Hydrodensitometry	Low	Easy	High	Not	
Plethysmography	High	Easy	High	Not	
DEXA	Moderate	Easy	High	Yes	Trace
Isotope dilution	Low	Moderate	High	Not	
BIA	Low	Easy	High	Yes	
K40 counting (^{40}K)	High	Difficult	High	Not	
CT scan	High	Difficult	High	Yes	Moderate
MRI scan	High	Difficult	High	Yes	
Neutron activation	High	Difficult	High	Not	High
Ultrasound	Low	Moderate	Moderate	Yes	

This table lists the costs, the ease of use, the accuracy, the possibility to measure regional fat and the need of radiation of the instrumental methods mostly employed for assessing body composition

these compartments is of interest, whether the measurement is for clinical purposes or research and the degree of precision that is required. Table 15.3 reports the most commonly used methods for determining body composition subdivided according to ease of determination, cost, accuracy, use of radiation and utility for assessing regional body fat.

15.3.1 Anthropometric Measurements

15.3.1.1 Estimates of Adiposity

Height (*H*) and BW are the most commonly measured parameters and can be determined with great accuracy. BW is the easiest measurement of body composition but it does not differentiate between FM and FFM. The overweight is characterized by a rise in BW by 20–40% of the standard values for age and height (*H*); BW higher by 40–100% than standard values configures moderate obesity; severe obesity is defined by a rise of BW above 100% of standard values. Several indices have been proposed to relate *H* and BW; at the present time, the most widely used are BMI, weight-for-height, triceps skin fold thickness (TSF), and waist circumference or waist-to-hip ratio (WHR). BMI is the current standard measure of obesity; waist circumference and WHR are used primarily for research purposes.

The BMI is the most practical way to evaluate the degree of excess BW. It correlates with FM and is relatively unaffected by *H*. It is calculated from the ratio of BW (kg) to the square of the *H* (m^2). BMI varies with age and gender. BMI is a good predictor of adiposity in a healthy population (Maynard et al. 2001). However, BMI is not a direct measure of adiposity, and may slightly overestimate fatness in subjects who are short or have a relatively high muscle mass.

BW-for-*H* measurement is another means to assess adiposity and is the preferred method for clinical assessment of obesity or failure to thrive in children younger than 2 years. Overweight, simple obesity and morbid obesity are sometimes defined as BW-for-*H* measurement greater than 110, 120, and 140 percent of the expected, respectively (Kuczmarski et al. 2000). For children older than 2 years, BMI has replaced BW-for-*H* estimates as the standard measure for adiposity because BW-for-*H* measurements do not correlate well with FM and are affected by *H* to a greater degree.

15.3.1.2 Fat Distribution

The most widely used measure of regional fat distribution is the waist circumference, the WHR or the ratio of waist circumference to the *H* (WHT). Recently the waist circumference has replaced the ratio because it is easier to measure. Waist circumference >102 cm in men or >88 cm in women is indicative of central adiposity. It is measured just above the uppermost lateral border of the right ilium, at the end of a normal expiration. The hip circumference is measured in a horizontal plane at the level of maximum circumference of the hips and buttocks. Men with a WHR of 0.95 or more and women with a WHR of 0.85 or more are considered to be at increased cardiovascular risk. The WHT is another measure of abdominal adiposity that has been associated with cardiovascular risk. Analysis of the data from NHANES III indicates that the WHT may be a better predictor of increased low-density lipoprotein cholesterol, total cholesterol, and fasting triglycerides than BMI in children aged 4–17 years (Kahn et al. 2005).

15.3.1.3 Body Composition

The most widely used anthropometric measurements to assess body composition are the TSF and the mid-upper arm circumference. The TSF reflects body fat and the mid-upper arm cross-sectional area reflects FFM. As the precision and reproducibility of these measures is low, they add little to the clinical evaluation for most patients (Campanozzi et al. 2008).

Measurements of skin fold thickness are used widely because the technique is non-invasive, inexpensive, and easy to perform. However, measurements of skin fold thickness often are less accurate than are measurements of *H* or BW, particularly in obese subjects (Watts et al. 2006). This kind of measurement may be useful in the long-term monitoring of nutritional therapy in subjects who are malnourished, have diseases that are associated with changes in body composition, or are obese (Mascarenhas et al. 1998).

The mid-arm muscle circumference (MAMC) is mostly used in children. It can be calculated from the TSF and mid-arm circumference (MAC) as follows:

$$\text{MAMC} = \text{MAC} - (3.1416 \times \text{TSF})$$

The measured values for TSF and MAC and the calculated MAMC are compared with reference values (Frisancho 1981). Values less than the fifth percentile for age are consistent with acute malnutrition, and values greater than the 90th percentile are consistent with obesity.

15.3.2 Densitometry

The underwater weighing is the oldest method for determining body density; it is mostly performed in children and has been largely replaced by dual energy absorptiometry (DEXA) (see below). Body density is estimated from the BW of the subject in air and water, using appropriate correction factors for temperature, air in the respiratory tract and constants for the densities of FM and FFM (Moore et al. 1968).

15.3.3 Isotope Dilution

Along with densitometry and DEXA scanning (see below), isotopic dilution provides the most accurate assessment of FM. In this technique, the volume of a body compartment is determined by

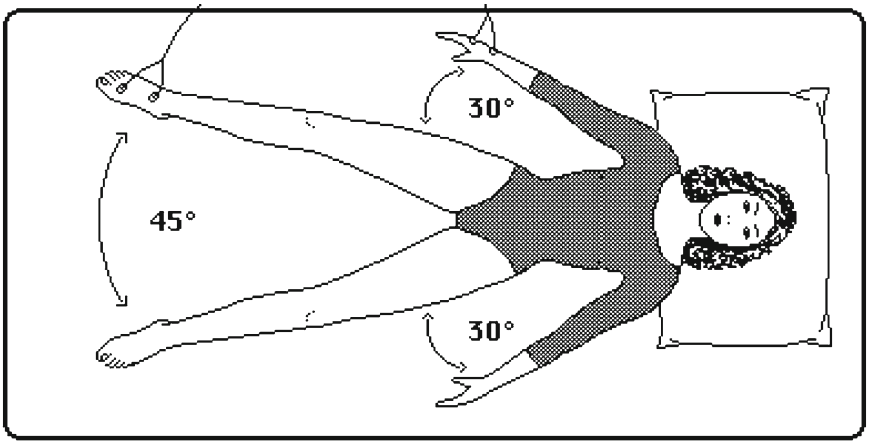

Fig. 15.2 Position of the subject undergoing BIA. The arms should form an angle of 30° with the trunk and the legs should be open with an angle of 45° (see the text for further information)

the ratio of the dose of a tracer, administered orally or intravenously, to its concentration in the body compartment after a sufficient equilibration period has elapsed. TBW, as an example, is estimated by isotope dilution using the stable isotopes of deuterium ($_2H_2O$) or oxygen ($H_{218}O$) (Schoeller et al. 1980). Once the TBW has been determined, the FFM of the body can be calculated, based on the assumption that the hydration of lean tissue is constant across a broad range of ages and for both genders. Isotope dilution is impractical in the clinical setting because of the expense of the stable isotopes and the analytical equipment.

15.3.4 Impedance Measurement

Bioelectrical impedance analysis (BIA) relies on electrical current to measure the FM and FFM of the body (Ellis 1996). The lean tissues of the body, because of their dissolved electrolytes, are the major conductors of electrical current, whereas body fat and bone are relatively poor conductors. The impedance to electrical flow is directly proportionate to the amount of fat and indirectly proportionate to the amount of lean tissue in the body. BIA frequently is used because it is non-invasive, portable and inexpensive. However, small changes in body water result in large differences in the estimate of FFM. In addition, the placement of the electrodes is site-specific and can compound errors of measurement. It should be measured in standardized conditions (quiet environment, ambient temperature of 22–24°C and after being at rest in the supine position for 20 min) by applying electrodes to one arm and one leg on the same side of the body, injecting 800 μA and 50 kHz alternating sinusoidal current with a standard tetra polar technique (Fig. 15.2) (Basile et al. 2008). Impedance is proportional to the length of the conductor and inversely related to the cross-sectional area of the conductor. Accuracy in placement of electrodes is essential because even small variations can cause relatively large errors in the measurement of impedance and corresponding errors in the estimate of TBW considered as the sum of intra- and extracellular body water.

A variety of formulae has been developed to convert the impedance which measures TBW into an estimate of fat. Most formulae for estimating fat from BIA underestimate fat as FM increases (Chumlea et al. 2001). The error in this procedure is similar to that obtained by measurements of skin

fold thickness or *H*/BW indices. However, the relatively low cost of the equipment and the ease with which impedance can be measured have led to its use in a variety of clinical settings (end-stage renal disease, over-/under-nourishment and obesity).

15.3.5 Air-Displacement Plethysmography

Air-displacement plethysmography is a method of determining lean body mass. Using the same whole-body measurement principle as underwater weighing, air-displacement plethysmography measures a subject's mass and volume, from which the whole-body density can be determined. The subject is placed inside the device; computerized pressure sensors then determine the amount of air displaced by the subject's body. FM and FFM can then be calculated (Fields et al. 2005).

15.3.6 Imaging Techniques

15.3.6.1 DEXA

The introduction of photons or low energy X-rays for the measurement of differential energy absorption by tissues has replaced densitometry as the best method for determining body composition. DEXA estimates FFM, FM and bone mineral density by using the differential absorption of X-ray or photon beams of two levels of intensity. DEXA relies on the principle that the intensity of an X-ray or photon beam is altered by the thickness, density, and chemical composition of an object in its path (Lukaski 1993). The precision of DEXA (coefficient of variation) is less than 2%, and it is becoming more readily available in the clinical setting.

15.3.6.2 Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)

MRI or CT can be used to measure visceral adipose tissue in a research setting. The technique usually quantifies adipose tissue in a single-slice cross section at the level of the L4/L5 lumbar disc. The subcutaneous fat (outside the abdominal musculature) may be measured in the same image. These measures of visceral adiposity correlate with insulin resistance, triglycerides, hepatic steatosis and other components of the metabolic syndrome (Taksali et al. 2008).

15.3.7 Neutron Activation Analysis

Body composition techniques, such as electrical impedance, tracer dilution, and DEXA provide information related to tissue density or volume but not chemical content. In contrast, neutron activation analysis allows the direct elemental analysis of the body. Virtually all the major elements of the body can be assayed in vivo: hydrogen, oxygen, carbon, nitrogen, calcium, phosphorus, sodium, chlorine and potassium. The method uses the principle that exposure to a given dose of neutrons generates a known amount of radioactivity within a given mass (Heymsfield et al. 1993). The use of this technique is limited by its expense and radiation exposure.

15.3.8 Total Body Potassium

Total body potassium count, another method that determines elemental composition, measures the content of radioactive potassium ($_{40}K$) in the body while the subject lies between detectors in a well-shielded metal counting chamber (Ellis and Nichols 1993). Radioactive potassium emits a characteristic high-energy gamma ray that in turn serves as a marker for total body potassium, BCM and FFM. Although this method is non-invasive and safe, the limited availability of the instrument renders this method impractical in the clinical setting.

15.4 Applications of Body Composition Measurement in Health and Disease

The measurement of body composition has been assuming greater importance in assessing nutritional and hydration status in both health and disease. Direct measurement, however, is essentially limited to research centres due to practical reasons. For general uses indirect methods of predicting body composition have been based on one or more anthropometric variables. The calculation of whole body composition is essential both in determining and adjusting the TBW values obtained with the different tools that will be discussed below.

For example, Moore et al. (Moore 1963) used multiple-isotope methods in healthy adult subjects of normal *BW* to develop regression equations for calculating body composition. These equations, based on sex, BW and age, predicted TBW with correlation coefficients of 0.61 for males and 0.65 for females. In 1969, Hoeffer et al. (Hoeffer et al. 1969) demonstrated a tight relationship between whole body BIA and TBW and suggested further development of this potentially useful clinical tool. Thus significant relationships between BIA and hydrodensitometry, TBW and total body potassium determination have been reported with the possibility of developing predictive formulae for assessing TBW, FM, FFM and BCM from BIA (Segal et al. 1985).

The accurate measurement of TBW is difficult, requiring isotopic dilution techniques which are not easily applicable to the clinical setting. BIA is a non-invasive method of body composition analysis. Impedance is represented with a complex number (a point) in the real-imaginary plane (*Z* vector) that is a combination of resistance (*R*) (i.e., the opposition to flow of an alternating current through intra- and extracellular ionic solutions, representing the real part of *Z*) and reactance (*Xc*) (i.e., the capacitive component of cell membranes and organelles and tissue interfaces, representing the imaginary part of *Z*) (Ellis 2000; Kushner 1992). Thus, *R* is low for blood, urine and muscle but high for adipose tissue, bone and air, which contain little or no fluid or electrolyte ions (Kushner 1992). For a constant signal frequency (at 50 kHz), the electrical impedance of a conductor is proportional to the specific impedance (Ohm × *m*) multiplied by the length and divided by the cross-sectional area of the conductor (Piccoli 1998; Di Iorio et al. 2004). Since current tends to follow the path of least resistance, measured *R* correlates most strongly with TBW and correlations decrease for other body composition components, depending on the amount of water in these components. In the human body, more than 90% of the measured impedance is composed of *R*. For this reason, most BIA applications use *R*, rather than impedance, to predict body composition (Sun et al. 2003). TBW measured by BIA is highly correlated with TBW measured by the isotopic dilution techniques (Hannan et al. 1994).

Based on these assumptions it is clear that BIA done on healthy subjects has been performed in order to derive an equation for predicting body composition in patients suffering from several diseases. For example, vector BIA (*RXc*-graph method) is a pattern analysis of direct impedance

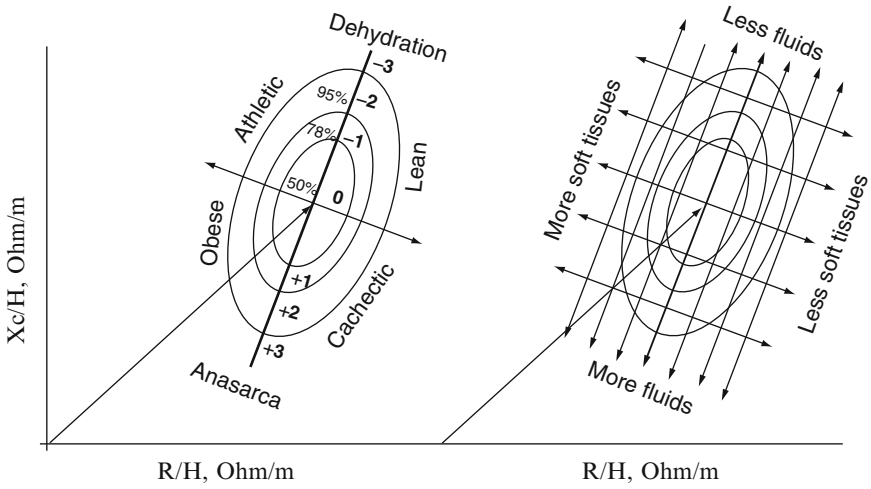

Fig. 15.3 BIA *RXc* graph. The ellipses represent the normal population variability (50%, 75%, and 95% of cases). The association of particular diseases and the graph regions has been verified. The graph allows three kinds of BIA evaluations: (*1*) individual vector; (*2*) follow-up; (*3*) groups of subjects

Table 15.4 Anthropometrical formulas derived for the estimate of TBW in normal subjects

	Males	Females
Watson (Watson et al. 1980)	2.447 – (0.09516 × age) + (0.1074 × *H*) + (0.3362 × BW)	−2.097 + (0.1069 × *H*) + (0.2466 × BW)
Hume (Hume and Weyers 1971)	−14.01 + (0.2968 × BW) + (0.1948 × *H*)	−35.27 + (0.1838 × BW) + (0.3445 × *H*)
Sun (Sun et al. 2003)	1.20 + (0.45 × H^2)/*R* + (0.18 × BW)	3.75 + (0.45 × H^2)/*R* + (0.11 × BW)

This table lists three of the most used anthropometrical formulas for estimating TBW in normal subjects. Age is in years, *H* in centimetres, BW in kilograms and *R* in Ohms

measurements (*R* and *Xc*) plotted as a bivariate vector standardized by the subject's *H* (i.e., expressing *R*/*H* and *Xc*/*H* in ohm/*m*). This method was described as a useful tool for monitoring the hydration status in renal (Sun et al. 2003; Piccoli et al. 1994, 1998) and critical care (Piccoli et al. 2000) patients and in the follow-up of obese subjects during weight loss (Piccoli et al. 1998). In the clinical setting, the advantages of vector BIA reside in the absence of algorithms for conversion of raw impedance data into body composition. Therefore the results are not biased by the choice of the regression equation or the selection of the reference population. However the results of the vector BIA analysis must be stratified according to race or ethnicity, BMI, age and gender (Piccoli et al. 1995). According to the *RXc*-graph methods, each subject can be identified by a point determined by his *Xc*/*H* value on the *Y*-axis (fluid status: dehydration or hyper hydration for higher or lower values of the ratio respectively) and the *R*/*H* value on the *X*-axis (body mass components: overweight or underweight for lower or higher values of the ratio respectively). The reference population (healthy subjects) fall in the 95%, 75%, and 50% confidence interval ellipse in the middle of the graph (Fig. 15.3).An alternate method for body composition assessment is anthropometry. For this purpose many formulae have been derived for the estimate of body composition (Table 15.4). The widely used equations by Watson et al. (Watson et al. 1980) were based on a meta-analysis of

previous studies where TBW was estimated using a variety of dilution techniques and markers of water volume in 458 adult males and 265 adult females. The equations by Hume were derived using tritiated water as a marker (Hume and Weyers 1971). In 2003, Sun et al. (Sun et al. 2003) presented a new way of estimating TBW by means of equations derived by mixing anthropometrical parameters and BIA-derived *R*.

Our group has published a study (Basile et al. 2008) aimed at comparing TBW estimated by means of Watson's and Hume's anthropometrical equations with TBW obtained by BIA equations (Sun's equations), in a very large group of white, disease-free individuals and in a large group of white haemodialysis (HD) patients, pair-matched by age, *H* and *BW*. In our hands anthropometrical equations could be used only within a specific population in order to assess individual differences; they could not be used in order to compare two, not pair-matched populations. Actually, subjects with the same BW or BMI, with or without oedema, had the same TBW estimated by Watson's and Hume's formulae while TBW resulted statistically significantly different only when applying Sun's equations.

The importance of deriving population-specific equations for TBW was already underlined by Chertow et al. in 1997 (Chertow et al. 1997). The authors examined more than 3,000 end-stage renal disease (ESRD) patients with BIA and developed an estimation equation in which age, gender, diabetic status, BW, H were included. The estimated TBW resulted not significantly different from the TBW measured by BIA.

15.5 Focusing on BIA Usefulness in ESRD

The assessment of body composition is assuming an important role in the clinical evaluation of the general population and patients suffering from alterations of the nutritional status and metabolic diseases. Both direct and indirect measurements of the body components are helpful for clinicians in order to make proper therapeutic decisions.

As stated above, water is the most abundant compound in the body and is an essential regulator of its internal environment. TBW must be constantly maintained in normal individuals (Chumlea et al. 2001). However, TBW is largely altered by disease. The choice of method for measuring TBW depends on whether the measurement is for clinical purposes or research and the degree of precision that is required. The calculation of TBW represents a useful tool in the clinical management of patients with chronic liver disease, in under-/over-nourished adults and in subjects with ESRD.

In the ESRD setting the TBW calculation has three main targets: (a) assessment of the body dry-weight (DW); (b) evaluation of the nutritional status (considering TBW together with FM, FFM and BCM); (c) calculation of the dialysis adequacy.

(a) Patients with ESRD are characterized by the impairment of kidneys in handling the body fluids that leads to a status of chronic over-hydration with tendency to develop oedema (Charra et al. 1996). Taking into account this frame, the assessment of TBW by means of BIA in these patients can provide useful information in both clinical practice and research.

From a clinical point of view, the *RXc* graph method is routinely adopted in order to evaluate the position of the patient in respect to the ellipses of the reference population. This comparison allows for the modulation of the DW of the single patient targeting the 95% confidence interval that indicates the normal body composition.

In the field of clinical research the TBW calculation by means of BIA can be used in order to estimate the exact body DW that the single patient has to reach when starting dialysis treatment.

We developed and validated BIA derived prediction equations for DW in haemodialysis patients by using anthropometrical parameters and *R* (Basile et al. 2007):

$$\text{In males} = [(0.008995 \times \text{age}) - (0.01116 \times R) + (0.871078 \times H) - 75.55197] \times \text{post} - \text{dialysis BMI}/23.1$$

$$\text{In females} = [-(0.01389 \times R) + (0.62956 \times H) - 36.31924] \times \text{post} - \text{dialysis BMI}/21.7$$

where age is in years, *H* is in centimeters and *R* in ohms.

(b) Depending in part on the method used and the population studied, from 40% to 70% of patients with ESRD present protein-energy wasting, a complication that appears to be associated with increased mortality (Lowrie and Lew 1990). In 2006 Bellizzi et al. (2006) demonstrated that despite the absence of overt malnutrition or oedema, patients with chronic kidney disease exhibit altered BIA variables (both *RXc* graph and *R* considered alone) from the early phases of renal disease. These alterations are related to the renal dysfunction, are more marked in the presence of diabetes and mainly indicate the presence of over-hydration in the absence of oedema. As a result of the frequency of malnutrition and over-hydration, periodic assessment of nutritional status should be part of the routine care of dialysis patients to permit early recognition and the institution of appropriate therapy. In the clinical assessment of the nutritional status of these subjects, the BIA-derived parameters (FM, FFM, TBW) cover an important role taken together with dietary intake reporting, lab parameters (amino acids, creatinine production, blood urea nitrogen, haemoglobin, serum levels of albumin, prealbumin, transferrin and total cholesterol) and anthropometrical measurements (TSF or MAMC). Also in this field, the RXc graph of the single patient may help clinicians in targeting nutritional treatment.

(c) The National Cooperative Dialysis Study (NCDS) showed that urea clearance is a better measure of dialysis adequacy than time-averaged urea concentrations. As urea rapidly distributes in TBW, its fractional clearance (*Kt*/*V*) is easily determined from pre- and post-dialysis blood samples (Daugirdas et al. 2008). Thus *Kt*/*V* (where *K* = dialyzer clearance; *t* = time of treatment; and *V* = urea volume distribution, equal to TBW calculated by means of Watson's formula) became the standard for assessing dialysis adequacy. This practice seemed to be validated by large observational studies that found associations between *Kt*/*V* and mortality (Daugirdas et al. 2008). As already stated, the *V* of the formula is represented by the TBW estimated by means of the Watson's equations.

Outcome analyses in observational studies showed that smaller patients (low *V*) tended to do poorly relative to their larger counterparts (Daugirdas et al. 2008). The association of outcome with size suggested a relative shortfall in the dose of dialysis provided to smaller as compared with larger patients, despite similar values of *Kt*/*V*. A recent randomized trial, the HEMO Study, found that gender modified the association between dialysis adequacy and mortality (i.e., a beneficial effect of higher *Kt*/*V* in women but not in men) (Daugirdas et al. 2008).

Such results led some authors to find other body size-related parameters as an alternative to *V* in order to avoid these discrepancies (gender and *V* related) in calculating the dialysis adequacy. Body surface area, resting energy expenditure, high metabolic rate and organ mass and liver volume have been proposed (Daugirdas et al. 2008). However, we demonstrated that *Kt*/*R* (where *R* = resistance evaluated by BIA) correlates better than *Kt*/*V* and all the other proposed methods of evaluating dialysis adequacy, with patient outcomes (Basile et al. 2010). Probably, the better performance of *R* in predicting mortality derives from its relationship with TBW. Moreover the use of *R* instead of *V* as denominator avoids all the discrepancies related to gender and size of patients.

Summary Points

- The assessment of body composition covers an important role in establishing nutritional and hydration status in both health and disease. However its direct measurement is essentially limited to research centres due to practical reasons. For general uses, indirect methods of predicting TBW, FM and FFM have been studied.
- Regression equations based on anthropometrical parameters (age, gender, BW, H) have been developed, for healthy people, to predict the body composition. The estimations provided by these anthropometrical equations are less reliable in case of diseased people because anthropometrical parameters could be similar in subjects characterized by different clinical features.
- Ease of determination, cost and accuracy make BIA a useful tool for assessing body composition. By means of BIA physical electrical variables such as *R* and *Xc* can be directly measured and the body composition can be estimated using regression equations or the *RXc*-graph method.
- The assessment of body composition by BIA in healthy subjects has allowed the development of estimating equations and the *RXc*-graph method setup. Thus the BIA has been widely applied to the clinical evaluation of patients suffering from alterations of the nutritional status and metabolic diseases.
- Complex changes in body composition occur in patients with kidney diseases of various degrees. Since the first referral, although non-oedematous, those patients present signs of over-hydration and lower BCM at the *RXc* graph method in the absence of overt signs of malnutrition or pathological estimates made by anthropometrical equations (Di Iorio et al. 2004).
- Once the patients have started the dialysis, DW, dialysis adequacy and nutritional needs can be at least approximately established by means of BIA appropriately performed at any time during the post-dialysis period, provided the hydration status does not change due to food or drink consumption (Di Iorio et al. 2004).

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Chapter 16
Bioelectrical Impedance Vector Analysis for Assessment of Hydration in Physiological States and Clinical Conditions

Henry C. Lukaski and Antonio Piccoli

Abstract Although the importance of assessing hydration is well recognized, traditional laboratory methods and clinical impressions are impractical or lack sensitivity to be useful in physiological and clinical conditions. Alternate approaches using bioelectrical impedance measurements to estimate fluid volumes utilize regression equations and depend on physical models unproven in physiological systems; they result in large errors in the prediction of fluid volumes notably in individuals with altered hydration. Bioelectrical impedance vector analysis (BIVA) overcomes these limitations because it only uses determinations of resistance (*R*) and reactance (*Xc*) normalized for height and yields a vector of specific magnitude (length) and direction (phase angle). This vector, for either an individual or a group, is evaluated on the bivariate *R–Xc* graph, which is a probability distribution derived from a reference population of healthy, matched controls. Comparison of an individual or group vector to the mean vector of the reference population provides reliable and accurate classification and ranking of hydration that is independent of body weight. Applications of BIVA in healthy adults include assessment of over-hydration in pregnancy and weight loss in obesity. BIVA also has broad uses in the evaluation and management of clinical groups including the characterization of patterns of hydration change during hemodialysis (HD) and peritoneal dialysis and use of this information to prescribe dialytic therapy; identification of under-hydration in critically ill patients and guidance for administration of fluid therapy; assessment and monitoring of tissue hydration status in congestive heart failure; and identification of regional edema in patients after vascular surgery. Because of its practicality and reliability, BIVA can be used in observational and longitudinal studies of hydration in patient care and management and in field conditions.

Abbreviations

BIA	Bioelectrical impedance analysis
BIS	Bioelectrical impedance spectroscopy
BIVA	Bioelectrical impedance vector analysis
CAPD	Chronic ambulatory peritoneal dialysis
CVP	Central venous pressure
ECW	Extracellular water

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_16,

E/I	Extracellular water/intracellular water
H	Standing height
HD	Hemodialysis
ICU	Intensive care unit
ICW	Intracellular water
L	Liter
NT	pro-BNP N-terminal pro-B-type natriuretic peptide
PA	Phase angle
PD	Peritoneal dialysis
R	Resistance
TBW	Total body water
UF	Ultra-filtration
Xc	Reactance
Z	Impedance

16.1 Introduction

Assessment of hydration status (under-, adequate, or over-hydration) remains an enigma for clinical investigators despite the recognition of its importance more than 50 years ago (Edelman and Leibman 1959). Knowledge that altered hydration status impacts morbidity and mortality (Manz 2007) and influences physiological function and performance (Armstrong 2007) reinforces the need for practical and reliable methods to assess it. Although an assortment of techniques for the in vivo assessment of altered hydration status (e.g., under-hydration or over-hydration) is available, none has universal acceptance (Kavouras 2002). Standard approaches that use physical or chemical characteristics of urine or blood involve laboratory equipment and can be invasive. Dilution methods also are impractical because of the need for tracers (isotopes and non-isotopes), costly equipment and trained staff; they also are time-consuming and lack reference ranges for interpretation. In contrast, changes in body weight are simple and cost effective, but have limited value because they require baseline measurements at normal hydration and may include changes in body constituents independent of fluid.

Bioelectrical impedance analysis (BIA), which is a safe, practical, and non-invasive method, overcomes many of these limitations. BIA relies on the conduction of an applied, radio-frequency electrical current by the fluid (water) and electrolytes in the body (Lukaski 1996). Many BIA approaches are available to estimate body fluid volumes. Single- and multiple-frequency impedance devices either directly measure or indirectly determine resistance (R), reactance (Xc) or impedance (Z), and are included in multiple-regression equations to predict total body water (TBW) or extracellular water (ECW) and, by calculation, intracellular water (ICW). Bioelectrical impedance spectroscopy (BIS) couples multiple-frequency BIA with the Cole model and mixture theory to predict TBW and ECW (De Lorenzo et al. 1997). Single- and multiple-frequency impedance methods are inadequate to assess hydration status because of large variability in individual predictions of fluid volumes (Sun et al. 2003) attributable to the use of sample-specific prediction models (Jaffrin and Morel 2008) that yield unrealistic estimates of TBW and ECW in patients with altered hydration (Kyle et al. 2004). Similarly, limitations in the application of mixture theory in multicellular, physiological systems of the human body unfavorably limit the validity of BIS to estimate fluid volumes in adults with altered fluid status (Ward et al. 1998; Buchholz et al. 2004; Earthman et al. 2007). Thus, these BIA applications fail to provide precise and accurate estimates of fluid volumes for an individual with altered hydration.

This chapter describes bioelectrical impedance vector analysis (BIVA) and its expanding use in the classification and ranking of hydration status in conditions with perturbations in fluid balance. It discusses the applications of BIVA in physiological conditions in which cases of over-hydration are validated with isotope dilution data, and provides important examples of the use of BIVA to classify hydration in patients, to monitor the changes in hydration in response to therapeutic interventions and to identify opportunities in which BIVA provides unique information to improve patient care and clinical outcomes.

16.2 Bioelectrical Impedance Vector Analysis (BIVA)

An alternative impedance approach is the utilization of the spatial relationships between *R* and *Xc* to assess soft tissue hydration (Piccoli et al. 1994). Use of the hand-to-foot electrode placement and a phase-sensitive instrument (50 kHz) yields a *Z* vector that is a combination of *R* (i.e., opposition to the flow of an alternating current through intra- and extra-cellular ionic solutions) and *Xc* (i.e., capacitative component of tissue interfaces, cell membranes and organelles). The geometric relationship between *R* and *Xc* is expressed as the arc tangent of *Xc*/*R* or the phase angle (PA).

Measurements of *R* and *Xc*, normalized for standing height (*H*) to control for inter-individual differences in conductor length and plotted on a bivariate graph (Fig. 16.1), yield a vector that has length and direction (Piccoli et al. 1994). The length of the *Z* vector is inversely related to TBW (Lukaski et al. 2007), and the combination of the *Z* vector length and its direction, defined as the PA, is an indicator of tissue hydration status (Piccoli 1998; Lukaski et al. 2007).

Assessment of fluid status with BIA becomes a decision of whether to quantify TBW and its distribution or to classify (i.e., normal or abnormal) and rank (i.e., more or less than before intervention) hydration. Estimates of TBW and ECW originate from multiple-regression prediction equations and rely on physiological constants that are invalidated by illness. These models universally use

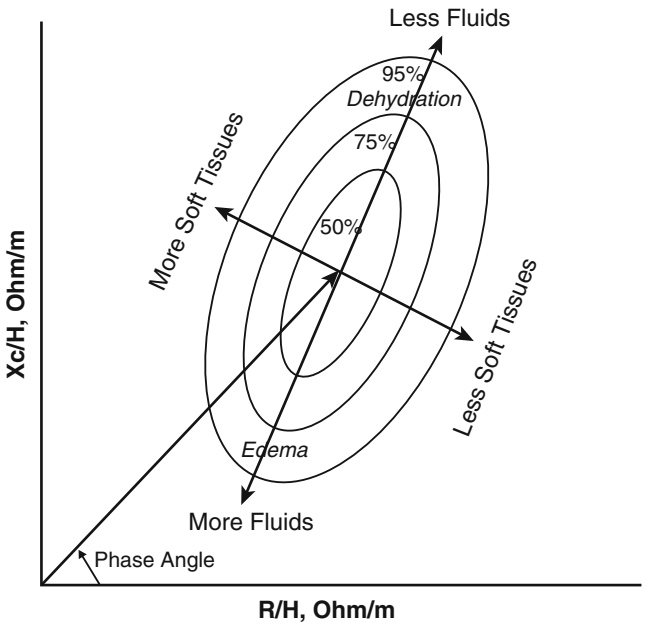

Fig. 16.1 Model of bioelectrical impedance vector analysis to rank hydration and soft tissue mass. A general depiction of the use of an impedance vector used to categorize or classify an individual's or group's level of hydration or soft tissue distribution. *R* resistance, *Xc* reactance, *H* height. (Adapted from Piccoli (2005). With permission)

the impedance index (i.e., H^2/R) and other independent variables, such as extrapolated Z values, body weight, age, gender and H (Kyle et al. 2004). These predictions have multiple sources of error, including BIA measurement error and reproducibility, regression error [SEE of prediction model (>10%; Sun et al. 2003)], technical error in the reference method (i.e., dilution methods), bio-electrical volume model (i.e., anisotropy of tissues and geometry other than a cylinder) and biological variability (i.e., inter-individual body composition differences) that propagate. In contrast, the BIVA method only depends on the reproducibility and accuracy of BIA measurements and intra-individual variability in body composition. Therefore, for an individual, classification and ranking of hydration is more precise and accurate than is quantification of fluid volume because it is independent of regression models that are generated in limited and specific samples and, thus, are not robust in the assessment of hydration outside of the group in which they were developed and illness.

16.3 Reference Intervals

Application of BIVA requires comparison of an impedance vector to reference intervals that have been derived in a large sample of age-, gender- and ethnicity-matched control or healthy subjects (Piccoli et al. 1995, 2002; Bosy-Westphal et al. 2005) on an *R–Xc* graph (Piccoli et al. 1994). The *R–Xc* graph is a probability distribution that classifies a vector according to its distance from the mean vector of the reference population. The distribution of the variability of the reference vector is expressed as percentiles of the tolerance ellipses (Fig. 16.1). Vector position is interpreted relative to the two directions on the *R–Xc* plane. Vector displacements parallel to the major axis of the tolerance ellipses indicate changes in hydration (e.g., more or less fluids). Vectors within the 50th percentile reflect normal hydration, whereas lengthening vectors from the 51st to 75th percentile and >76th percentile in the upper range of the tolerance ellipses indicate mild and severe dehydration, respectively. Conversely, shortening vectors from the 51st to the 75th percentile and >76th percentile in the lower range of the tolerance ellipses designate mild and severe over-hydration, respectively. Vectors positioned to the left of the major axis reflect increased cell mass, whereas vectors to the right of the major axis indicate less cell mass (Fig. 16.1). Analysis of impedance vectors may occur for an individual (e.g., point vector) or a group either for an observational ranking of hydration or longitudinal monitoring of changes in hydration status in response to a physiological condition or an intervention.

Appropriate derivation of the *R–Xc* graph and implementation of BIVA require the proper determination of *R* and *Xc* with a phase-sensitive impedance instrument. Failure to use a phase-sensitive instrument can result in significant errors of up to 10 Ω for *R* and 10–12 Ω for *Xc* (Chumlea et al. 2002). These errors can significantly (8–10%) reposition the mean vector and reference ellipses of the reference population as well as individual and group vectors and, therefore, make reliable and valid assessment of hydration status problematic and dubious.

16.4 BIVA Applications in Healthy Adults

Physiological conditions that result in significant gains or losses of body weight and composition concomitantly impact TBW, its distribution and, thus, hydration. Pregnancy and weight loss are dynamic physiological conditions that profoundly change TBW and have been described by using isotope dilution methods. BIVA affords an opportunity to non-invasively and reliably assess hydration status (Table 16.1).

Table 16.1 Key features of BIVA for classification of hydration in health and disease

- Classification and ranking of tissue hydration depends on measurements of *R* and *Xc* that produce a vector whose position is evaluated relative to tolerance intervals and is interpreted as normal or abnormal hydration based on distance from the mean vector derived from a healthy reference population. Migration of the vector (shortening or lengthening) due to progression of a physiological process, pathology or an intervention indicates changes in hydration (i.e., gain or loss of fluids).
- Classification of hydration status (normal or abnormal) with BIVA avoids the problems of insensitivity (>10%) associated with use of regression equations to predict TBW and ECW; it also does not rely on the use of body weight that limits its validity to assess hydration.
- BIVA accurately detects increases in TBW (vector shortening) measured with deuterium dilution throughout pregnancy and post partum, and specifically identifies individuals with excess TBW gain during the third trimester of pregnancy. BIVA also reliably detects TBW losses (vector lengthening) and identifies individuals with altered fluid distribution (*E*/*I*) before and during weight loss.
- Use of BIVA improves the prescription of ultra-filtration (UF) in dialysis by monitoring the backward–forward displacement of vectors in relation to the wet–dry cycle of hemodialysis (HD). It also enhances decision-making in dialysis by facilitating the interpretation of alterations in blood pressure relative to hydration status and, thus, adjusting UF.
- BIVA at 50 kHz provides important information regarding tissue hydration during dialysis that is not evident with BIS. Examination of *R* values at 50 kHz correlated with other *R* values determined at wide ranging frequencies with BIS reveals high correlations and no unique contributions from BIS for monitoring changes in hydration.
- Among critically ill patients, BIVA is significantly and inversely correlated with CVP. On the *R*–*Xc* graph, impedance vectors of patients with low, normal and high CVP moved downward and outside of the 75% tolerance level with increasing CVP, which indicates excess fluid accumulation.
- Assessment of regional edema following peripheral vascular surgery is enhanced by using BIVA. Measurements of lower limb *R* and *Xc*, corrected for the length, before and after surgery reveal significant downward vector migration only in the affected leg compared to the non-surgical leg. A similar, albeit more modest, pattern is observed when whole-body measurements are made on the surgical compared to the control side.

This table summarizes the fundamental principles and advantages of the bioelectrical impedance vector analysis method, including its applications in the classification of normal and abnormal hydration states in physiologic and pathologic states. *BIVA* bioelectrical impedance vector analysis, *R* resistance, *Xc* reactance, *TBW* total body water, *ECW* extra-cellular water, *E/I* ratio of extra- to intra-cellular water, *HD* hemodialysis, *UF* ultra-filtration, *BIS* bioelectrical impedance spectroscopy, *CVP* central venous pressure

16.5 Hydration Changes During Pregnancy and Postpartum

Hydration status was determined longitudinally with BIVA and deuterium dilution in women before conception, every 90 days during pregnancy and 8–10 week postpartum (Lukaski et al. 2007). Throughout all stages, vector length was inversely related to TBW ($r = -0.79$; $p < 0.0001$), and changes in vector length also were related inversely to changes in TBW ($r = -0.599$; $p < 0.001$). These findings provide the first validation that *Z* vector length is a reliable indicator of fluid volume during dynamic changes in TBW.

With the pre-pregnancy impedance data as the reference, the group vector shortened significantly and displaced downward during the second ($p < 0.007$) and third ($p < 0.0002$) trimesters of pregnancy (Fig. 16.2). These vector displacements were affected by significant decreases in *R*/*H* in the second ($p < 0.02$) and third ($p < 0.0001$) trimesters with a concomitant decrease in *Xc*/*H* ($p < 0.02$) in the third trimester and no changes in PA. The mean postpartum vector was similar to the pre-pregnancy vector.

Examination of the individual vectors of the women during the third trimester of pregnancy shows individuals with over-hydration (Fig. 16.3). The vectors of three women were outside of 75th tolerance ellipse.

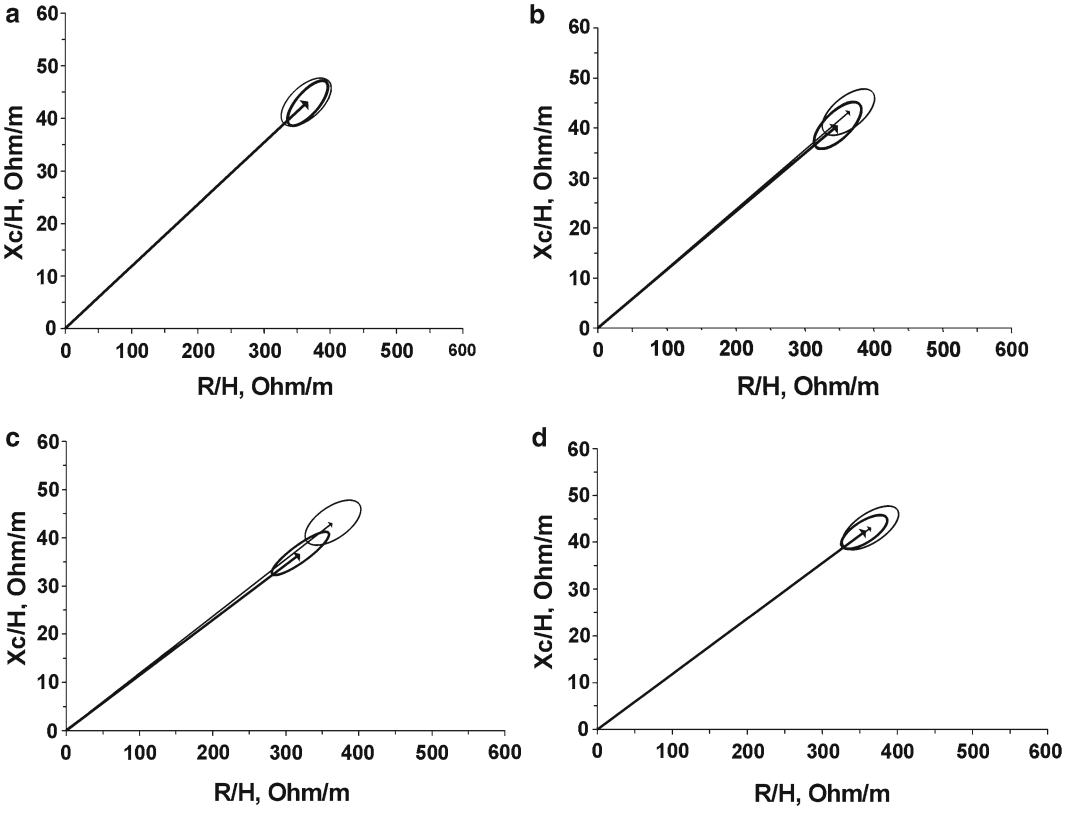

Fig. 16.2 Mean vectors with 95% tolerance intervals of women before, during, and after pregnancy. Panels show mean vectors of 12 women studied longitudinally at trimester 1 (**a**), trimester 2 (**b**), trimester 3 (**c**), and postpartum (**d**) in reference to pre-pregnancy (*light ellipse*). Mean vector length decreases significantly throughout pregnancy and returns to near pre-pregnancy length post-partum. *R* resistance, *Xc* reactance, *H* height. (Reprinted from Lukaski et al. (2007). With permission)

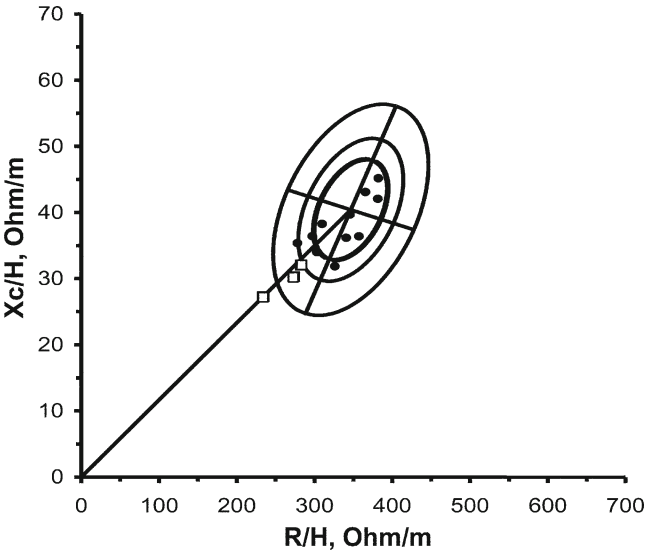

Fig. 16.3 Distribution of individual vectors during third trimester of pregnancy compared to pre-pregnancy reference tolerance ellipses. *Solid squares* indicate individual vectors of three women with over-hydration (see text for details). *R* resistance, *Xc* reactance, *H* height. (Reprinted from Lukaski et al. (2007). With permission)

Review of the TBW data found that the TBW gain of these three women was 10 l compared to only 5 l for the women whose vectors were within the 75th tolerance ellipse. Thus, BIVA correctly identified the women whose hydration was excessive (i.e., over-hydrated) during the third trimester.

16.6 Hydration Changes During Weight Loss

Whereas obesity is characterized by excess adipose tissue mass, alterations in fluid distribution (*E*/*I*) in obesity and after weight reduction have been reported (Waki et al.. 1991; Van Marken Lichtenbelt and Fogelholm 1999). Sixteen obese women participated in a 4-month controlled weight loss program in which BIA, TBW (deuterium dilution) and ECW (bromide dilution) were determined at regular intervals (unpublished observations). Weight loss was 18 kg ($p < 0.0001$) with a 3.5 l loss of TBW ($p < 0.001$). Vector length was significantly and inversely related to TBW throughout weight loss ($r = -0.85$; $p < 0.0001$). Compared to pre-weight loss, the mean group vector lengthened significantly ($p < 0.05$) after weight loss. Before weight loss, the individual vectors of seven women were downward and outside of the 75th percentile and had *E*/*I* ratios of 0.81 compared to 0.70 for the women whose vectors were within the 75th tolerance ellipse (Fig. 16.4). After weight loss, only three vectors exceeded the 75th percentile and the *E*/*I* ratios of these women were greater (0.75 vs. 0.65) compared to the women whose vectors were within the 75th percentile (Fig. 16.4). These preliminary findings support the validity of BIVA to rank hydration status during weight loss.

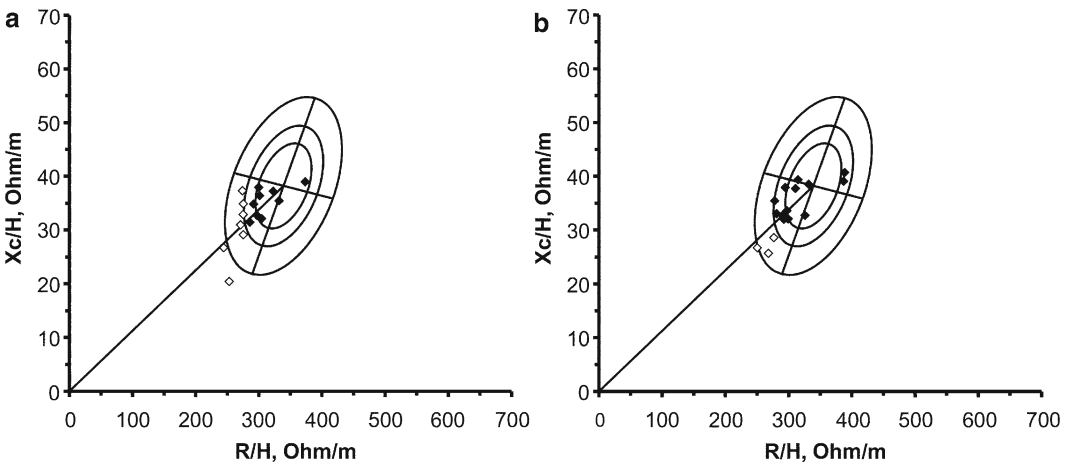

Fig. 16.4 Individual impedance vectors before (**a**) and after (**b**) weight loss in relationship to a reference population of age-matched, non-obese women. *Solid squares* represent individual vectors of seven women with over-hydration compared to nine women with normal or minor over-hydration (*panel A*). Despite an average weight loss of 18 kg, the impedance vectors of three women indicated over-hydration in contrast to the vectors of 13 women reflected normal hydration (*panel B*). *R* resistance, *Xc* reactance, *H* height. Unpublished data from HC Lukaski

16.7 Clinical Applications of BIVA

The principal use of BIVA is the assessment of hydration status in patients with fluid overload and the evaluation of clinical procedures that aim to establish homeostasis without incurring unwanted adverse effects. Renal disease, hemodynamic impairment and vascular surgery are the conditions in which BIVA has been used effectively to classify and rank hydration and to monitor changes in hydration in response to interventions (Table 16.1).

Traditional methods for assessment of hydration are insensitive and ineffective in clinical situations. Anthropometric formulas have limited value because they are functions of body weight and are completely insensitive to fluid overload in patients with apparent edema (Piccoli 2004; Pillon et al. 2004). Determination of TBW with dilution methods is limited because of problems associated with gastric emptying, fluid sequestration and tracer penetration and equilibration in all water pools that contributes to over-estimation of TBW.

16.8 Hydration Status in Dialysis

Dialysis, particularly HD, is an excellent model of fluid removal (1–5 l in 4 h) and overload (1–5 l in 2–3 days). Adequacy of body fluid volume control through UF improves short- and long-term outcomes. The routine evaluation of hydration status based on body weight and blood pressure changes overtime can be misleading because the changes are not uniquely determined by variations in body fluid volume. Edema is not usually detectable until the interstitial fluid volume has exceeded 30% of the above normal (i.e., 4–5 kg of body weight), while severe dehydration can develop before the appearance of clinical signs. Therefore, traditional indicators of over- and under-hydration in patients with renal disease are inadequate and insensitive (Piccoli 2004).

HD often results in bringing the patient either to dehydration or to fluid repletion. Dehydration can be symptomatic (i.e., decompensated with hypotensive episodes in the latter part of the session, malaise, exhaustion, cramps, or dizziness after dialysis) or asymptomatic (i.e., compensated). Fluid overload is mostly symptomatic with pitting edema, worsening of hypertension, edema, or pulmonary congestion during the inter-dialytic interval. The so-called dry weight is the post-dialysis weight at which all or most excess body fluid has been removed. The optimal post-dialysis target weight is determined clinically, in general, as the lowest weight a patient can tolerate without intra-dialytic symptoms or hypotension. However, body fluid volume is continuously changing even in asymptomatic HD patients, in whom euhydration and euvolemia only last for a limited time (i.e., a few hours) in the inter-dialytic period.

Peritoneal dialysis (PD) can also bring the patient either to dehydration, characterized as a decrease in residual urine output and peritoneal UF, or to fluid overload, expressed as pitting edema with worsening of hypertension and impairment of peritoneal UF. Maintenance of euhydration and euvolemia in PD patients is recommended to minimize cardiovascular risk and to maximize UF in the long term.

16.9 BIVA in Hemodialysis

16.9.1 Dynamic Vector Patterns Associated with the HD Cycle

The standard thrice weekly HD cycle of body fluids is characterized by fluid removal with the UF during the dialysis session (3–5 h) and a progressive fluid repletion over the short (48 h) or long (72 h) inter-dialytic period. Figure 16.5 shows vector migration for an individual over a complete HD cycle of

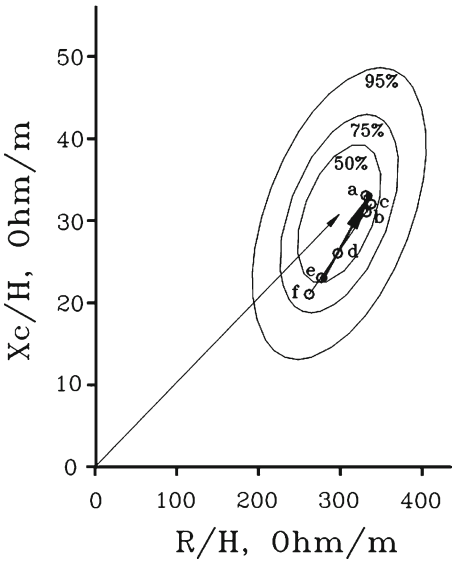

Fig. 16.5 The impedance vector migration associated with the HD cycle over 3 days is depicted on the *R–Xc* graph. Reference values for an individual vector (*thin arrow* to the center of ellipses) are depicted as 50%, 75%, and 95% tolerance ellipses derived for the male, Italian population. Solid circles represent vectors at the start and the end of the dialysis session (fluid removal 2.8 l). *Open circles* represent vectors after 30 (*label a*), 60 (*label b*), 120 min (*label c*), and in the next days, after 24 (*label d*, +1.4 l fluid increase), 48 (*label e*, +1.2 l), and 68 h (label f, +0.8 l for a total of 3.4 l in 68 h). The vector lengthening during the hemodialysis session is represented by the bold arrow in the direction of the major axis. The trajectory followed by vector shortening after dialysis is represented by segments of a linear path still parallel to the major axis of tolerance ellipses. *R* resistance, *Xc* reactance, *H* height, *HD* hemodialysis. (Reprinted from Piccoli and Codognotto 2004. With permission)

three days (Piccoli and Codognotto 2004), during which vector lengthening during UF was parallel to the major axis of tolerance ellipses. Vectors measured within 120 min after the session randomly fluctuated close to the end-dialysis vector. After 24, 48, and 68 h, vectors progressively shortened and returned in the same direction associated with the UF. Interestingly, the vector at 48 h reached the baseline vector position at the start of the HD session, indicating a same fluid repletion, while the vector measured after 68 h shortened further, indicating a greater fluid overload during the long inter-dialytic period. The post-HD random fluctuation for 120 min excludes an "electric rebound" phenomenon and supports the validity of immediate post-HD measurement (i.e., patient's time saving).

The linear trajectory of vectors can be observed during the HD session at any current frequency, which demonstrates the same information at any frequency (Piccoli et al. 2005). The linear trajectory both in the intra- and inter-dialytic period supports validity of monitoring with only pre- and post-dialysis measurements. We previously described in 1116 HD patients how the wet–dry weight cycling was associated with a pattern of cyclical, backward–forward displacement of the impedance vector (Piccoli 1998)

16.9.2 Normal Versus Abnormal Vector Trajectories in HD

The classification of vectors as normal or abnormal with respect to the reference third quartile (75% tolerance ellipse) is based on electrical properties of soft tissues, independent of the body weight of patients. Vectors from 72% of the 1116 asymptomatic HD patients were within the 75% reference

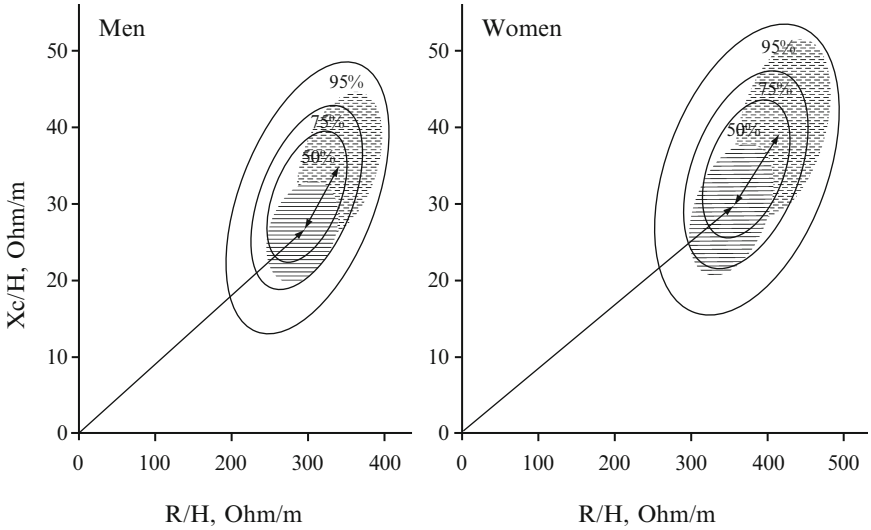

Fig. 16.6 Examples of the effect of hemodialysis on the distribution of the impedance vectors from asymptomatic patients. *Dotted ellipses* represent the distribution of 50% of the impedance vectors from individual HD asymptomatic male and female patients before (horizontal lines in the lower ellipse) and after fluid removal (abbreviated lines in the *upper ellipse*). *Double headed arrows* represent the vector cycling from before to after HD. *Dotted ellipses* are plotted over the reference, gender-specific, 50%, 75%, and 95% tolerance ellipses of the healthy population. *R* resistance, *Xc* reactance, *H* height. (Reprinted from Piccoli 2004. With permission)

tolerance ellipse before the HD session. At the end of the session, vectors of 55% of the asymptomatic HD patients were within the 75% reference tolerance ellipse. Therefore, most vectors cycled within the 75% tolerance ellipse, which indicates that a full restoration of electrical properties of uremic tissues was achieved with HD (Piccoli 1998) (Fig. 16.6).

Figure 16.7 shows vector trajectories (measurements at the start and every hour during HD) spanning within (solid circles) or out (open circles) of the 75% tolerance ellipses during 3–4 h of UF in representative HD patients. Trajectories can be classified into *normal* (within 75%) or *abnormal* (out of 75%) assuming that a normal hydration in HD patients is the normal hydration of the healthy population, as reflected by impedance vector distribution of the reference population (726 males and females, BMI 17–31 kg/m^2; 15–85 years) (Piccoli et al. 1995).

The first and more frequent pattern is a vector displacement parallel to the major axis of the tolerance ellipses. According to the general patterns defined in Fig. 16.1, long vectors migrating across the upper poles indicate dehydration (dry vectors), and short vectors migrating across the lower poles indicate fluid overload (wet vectors). Vector trajectories spanning on the left side vs. trajectories on the right side of ellipses are from patients with more vs. less soft tissue, respectively. For example, the lengthening and steepening of vectors in obese subjects (BMI 31–41 kg/m^2) undergoing a same UF are comparable to those of lean subjects, although spanning in the left side of ellipses (Piccoli et al. 1998).

The second pattern associated with UF is a flat vector migration to the right side, due to an increase in *R*/*H* without a proportional increase in *Xc*/*H* caused by severe loss of soft tissue mass. This pattern is characteristic of patients with severe malnutrition or cachexia, and is never observed in vectors lying on the left of the ellipses. Average pre-HD vectors of 251 hypotensive and malnourished patients were longer and with a smaller phase angle compared to asymptomatic HD patients. The vector displacement induced by a comparable fluid removal was significantly shorter and less

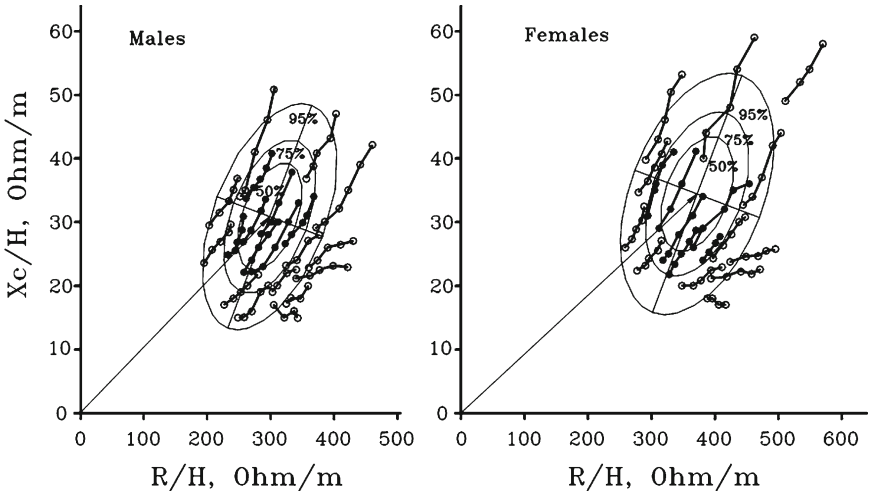

Fig. 16.7 Normal and abnormal trajectories of impedance vectors derived from individual patients during a HD session. *Solid* and *open circles* indicate the vector trajectories that spanned within (normal) or out (abnormal) of the 75% tolerance ellipses, respectively, during 3–4 h of UF in a representative HD patients. Two dynamic patterns of abnormal vector trajectories are characteristic in HD patients during UF. The first and more frequent pattern is a vector displacement parallel to the major axis of the tolerance ellipses, leaving or ending out of the 75% tolerance ellipse. Long vectors overshooting the upper poles indicate dehydration (dry vectors), and short vectors migrating across the lower poles indicate fluid overload (wet vectors). Vector trajectories spanning on the left side vs. trajectories on the right side of ellipses are from patients with more vs. less soft tissue mass, respectively. The second pattern of UF is a flat vector migration to the right, due to an increase in *R*/*H* without a proportional increase in *Xc*/*H* due to loss of cells in soft tissue. This pattern is characteristic of patients with severe malnutrition or cachexia. It is never observed in vectors lying on the left of the ellipses. *HD* hemodialysis, *UF* ultra-filtration, *R* resistance, *Xc* reactance, *H* is height. (Reprinted from Piccoli (2005). With permission)

steep in hypotensive patients, in whom the concentration of both hemoglobin and albumin was also decreased. We speculated that malnutrition was involved through the loss of interstitial gel leading to a reduced volume of interstitial fluid, in both gel and free form, which decreased the effectiveness of the vascular refilling (Piccoli 1998).

16.9.3 Adequate Versus Inadequate Vector Trajectories in HD

As with any diagnostic test, intervention studies are needed to establish whether dialysis prescription that induces normal vs. abnormal trajectories is associated with adequate vs. inadequate UF, ultimately leading to different outcomes. In practice, the first target can be fixed to the normal range whose assessment for adequacy requires clinical validation. The change of vector target will follow in feedback with the clinical course of individual patients. For example, an abnormal, long vector overshooting the upper 95% pole that is associated with an asymptomatic UF and a good control of blood pressure can be considered an adequate (dry) vector. The same abnormal long vector in a patient with hypotensive episodes is an inadequate vector. Yet, an abnormal short vector in a patient with hypotension may be more adequate than a normal vector associated with more hypotension episodes. Thus, the full restoration of the electrical properties of tissues is the first target, but the outcome will ultimately define clinical adequacy of treatment in the individual patient.

In a large multi-center, observational study (3,009 patients in US dialysis centers), shorter pre-HD vectors, indicating more fluid repletion and probably inadequate UF, were associated with a greater multivariate relative risk of death after 1 year of follow-up (Piccoli et al. 2004). In a small observational study, longer post-HD vectors out of the upper pole of the 75% tolerance ellipse were associated with a higher frequency (73%) of symptomatic hypotension and cramps, but 57% of (still) asymptomatic patients were classified as dehydrated due to their long vectors. A follow up of clinical course in the next sessions was not performed. The classification of volume status based on conventional BIA equations was insensitive to the clinical course (Guida et al. 2000).

16.10 BIVA in Peritoneal Dialysis

In chronic ambulatory peritoneal dialysis (CAPD), peritoneal UF is obtained with 2 l of hypertonic glucose solutions (1.36% or more) or icodextrin infused within the abdomen and exchanged with 2 l of fresh solution every 6 h. Increased glucose in the solution stimulates more UF. The process is continuous rather than cyclical as in HD. Adequate UF should keep hydration of CAPD patients close to normal.

Use of BIVA enabled the establishment of the optimal tissue hydration in CAPD patients. Among 200 patients, 149 were without edema and asymptomatic and 51 had pitting edema due to fluid overload. Whole-body impedance measurements were performed before and after 2 l of fluid infusion into the abdomen. There was no difference in both *R* and *Xc* values before and after infusion of the fluid in the abdomen. This finding was expected because the impedance of the trunk is low due to the large cross-section and the contribution of free fluid in cavities is negligible (pure *R* without *Xc* component) compared with fluid in soft tissues. Vector distribution of the CAPD patients was compared with that from 726 healthy subjects, 1116 HD patients and 50 nephrotic patients, all with a same BMI. In asymptomatic CAPD patients, the vector distribution close approximated that of the healthy population (50%, 75%, and 95% tolerance ellipses) and to the distribution of asymptomatic HD patients before the dialysis session (Piccoli 2004) (Fig. 16.8). We also determined the optimal vector distribution of asymptomatic patients undergoing CAPD without edema and with a residual urine output >1,000 ml/24 h and only using 1.36% glucose. There was no significant difference between this group and the asymptomatic group with less urine output and a greater glucose concentration. Vectors from patients with edema were displaced downward on the *R–Xc* graph, were out of the 75% ellipse (88% sensitivity and 87% specificity) and were close to vectors from nephrotic patients not undergoing dialysis. Therefore, the pattern of fluid overload with the vector displacement in the direction of the major axis was also observed in CAPD patients. This pattern can be utilized in dialysis prescription using vector displacement for the feed-back on glucose solutions to keep or achieve a normal hydration without the knowledge of the body weight.

16.11 Key Contributions of BIVA in Dialysis

The methodology of BIVA, applied to whole-body, 50 kHz single frequency impedance measurements can contribute to dialysis prescription with unique information that can not be obtained with currently available techniques or approaches.

The impedance vector of a patient is compared with the tolerance intervals of a reference population, which allows classification of tissue hydration into normal or abnormal, independent of the body weight. Abnormality is ranked as a distance from the mean vector of the reference population.

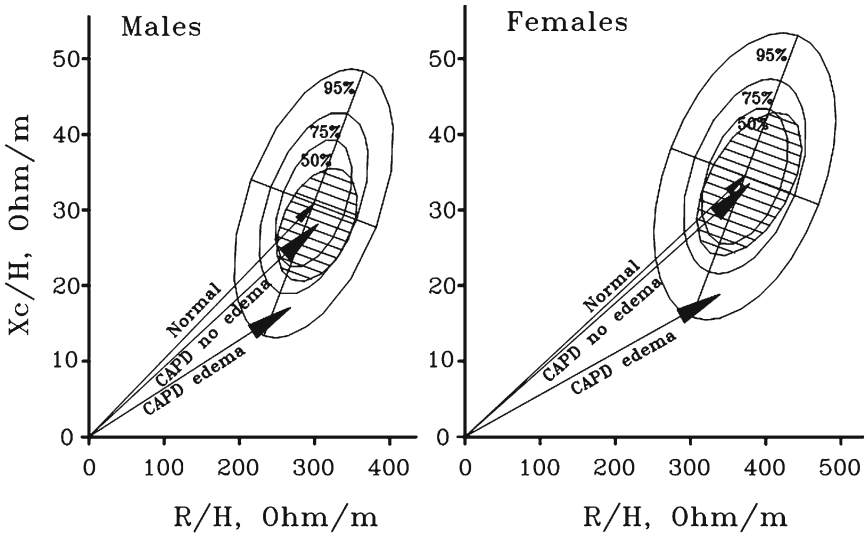

Fig. 16.8 Impedance vector distributions of CAPD patients with and without edema. *Hatched ellipses* represent the distribution of 50% of impedance vectors from individual CAPD patients without edema, plotted on the reference, gender-specific males and females, 50%, 75%, and 95% tolerance ellipses of the healthy population. Two big arrows indicate mean vectors of CAPD groups (edema and no edema). *Large-headed arrows* represent the mean vector of HD patients before (*lower arrowhead*) and after a HD session (*upper arrowhead*). *CAPD* chronic, ambulatory peritoneal dialysis, *R* resistance, *Xc* reactance, *H* height. (Reprinted from Piccoli (2004). With permission)

In particular cases, an abnormal hydration can be considered an adequate hydration if it is associated with less morbidity (see below).

BIVA enables the identification "by exclusion" volume-dependent hypertension and hypotension. Specifically, a long vector indicating dehydration in a patient with hypertension allows exclusion of volume-dependent hypertension. Further UF is not expected to decrease blood pressure. The same vector in a patient with hypotension is compatible with a volume-dependent hypotension, which can be corrected by reducing UF (i.e., feedback with vector shortening). A short vector in a patient with hypertension is compatible with volume-dependent hypertension, which can be corrected increasing UF (i.e., feedback with vector lengthening). The same vector in a patient with hypotension allows exclusion of volume-dependent hypotension. No correction is expected increasing UF.

As shown in Fig. 16.1, different vector patterns indicate the nature or composition of body weight change only based on electrical properties of tissues. This indication is particularly useful in obese patients in whom interpretation of changes in body weight is often impossible to establish with clinical acumen.

The association between impedance and UF is strong although not linear. The wet–dry weight cycling of HD patients is associated with a cyclical, backward–forward displacement of the impedance vector on the *R–Xc* plane (Piccoli 1998). Vector displacement follows a fluid volume change in the order of 500 ml (Figs. 16.5 and 16.7) (Piccoli and Codognotto 2004). Despite this definite association, the linear correlation between vector components and the amount of fluid removed by UF is weak using either single or multiple frequency impedance techniques. UF is the amount of fluid volume that is removed from vessels during a dialysis session or in one day of CAPD. Body impedance reflects the effect of UF on soft tissues through the slow suction of interstitial fluid into vessels in HD (vascular refilling) or into peritoneal cavity in CAPD (Piccoli 2004). Indeed, the change in tissue impedance in dialysis is mainly determined by the change in the interstitial hydration with neither contribution of intravascular volume change nor of peritoneal solution.

As compared to BIS, BIVA provides better information describing hydration during dialysis (Piccoli et al. 2005). Intra- and extra-cellular current flow cause equivalence of information based on functions

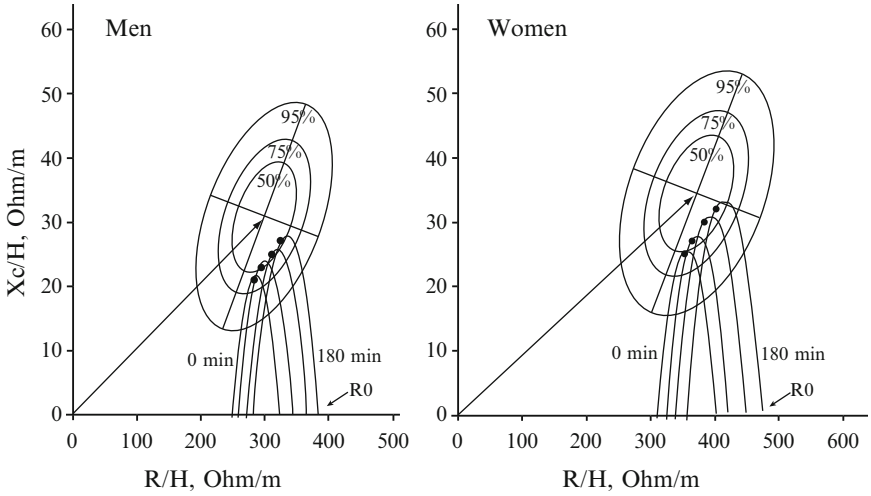

Fig. 16.9 Sex-specific impedance vectors at 50 kHz derived serially during HD approximate the values at the characteristic frequency derived by using the Cole model and multiple-frequency impedance spectroscopy. The 50%, 75%, and 95% tolerance ellipses indicate the sex-specific, reference intervals for an individual random vector (normalized by the stature, *Z*/*H* in Ω/*m*) at 50 kHz, and point vectors represent the mean vectors of dialysis patients, plotted on their hourly Cole's semicircle. Vectors at 50 kHz are close to the top of the semicircles (characteristic frequency and calculated as the mid point between R_o and R_∞). Compared to male patients, Cole's arcs from women were larger and more translated to the right (longer 50 kHz mean vectors at a same time point), but their position in the *R*–*Xc* graph followed a same pattern (comparable hydration status) from 0 to 180 min, with vector displacement parallel to the major axis of the tolerance ellipses. In practice, the centripetal property of 50 kHz vectors with respect to the corresponding Cole's semicircle, allows tracking of fluid removal with a direct comparison of impedance readings with reference intervals of the healthy population. R_o resistance at low or near 0 frequency, R_∞ resistance at very high or near infinity frequency, *R* resistance; *Xc* reactance, *H* height. (Reprinted from Piccoli et al. (2005). With permission)

of *R* and *Xc* measurements made at 50 kHz compared to other frequencies. With whole-body BIS before and during fluid removal (2.5 kg during a session of 0, 60, 120 and 180 min) in HD patients, with increasing current frequency, *R* decreases and *Xc* moves along the Cole's semicircle on the *R*–*Xc* plane. The Cole's semicircles progressively enlarge and move to the right on the *R*–*Xc* plane following fluid removal (i.e., an increase in both *R* and *Xc* values at any given frequency) (Fig. 16.9). *Xc* values at 5 kHz (expected values close to 0 Ω) reach 70% of the maximum *Xc*, indicating an intra-cellular current flows at low frequencies. The correlation coefficient between *R* at 50 kHz and *R* at other frequencies ranges from 0.96 to 0.99. In the clinical setting, the comparison of vector position and migration with target, reference intervals represents an additional advantage of BIVA, which is not allowed with BIS.

16.12 BIVA in Critically Ill Patients

Determinations of fluid volumes or estimates of body composition of patients in the intensive care unit (ICU) are neither practical nor reliable. Limitations in the use of tracer dilution methods and violations of the assumption of constant hydration of soft tissues severely diminish the validity of the dilution method and BIA in critically ill patients. In the critical care setting, however, central venous pressure (CVP) values, obtained from either CVP catheter or more invasive hemodynamic monitoring (i.e., pulmonary artery flotation catheter), are used as a guide for fluid infusion. Low CVP values are observed with true or relative hypovolemia, once a negative intra-thoracic pressure has been excluded. Conversely, high CVP values indicate true or relative hypervolemia and fluid overload.

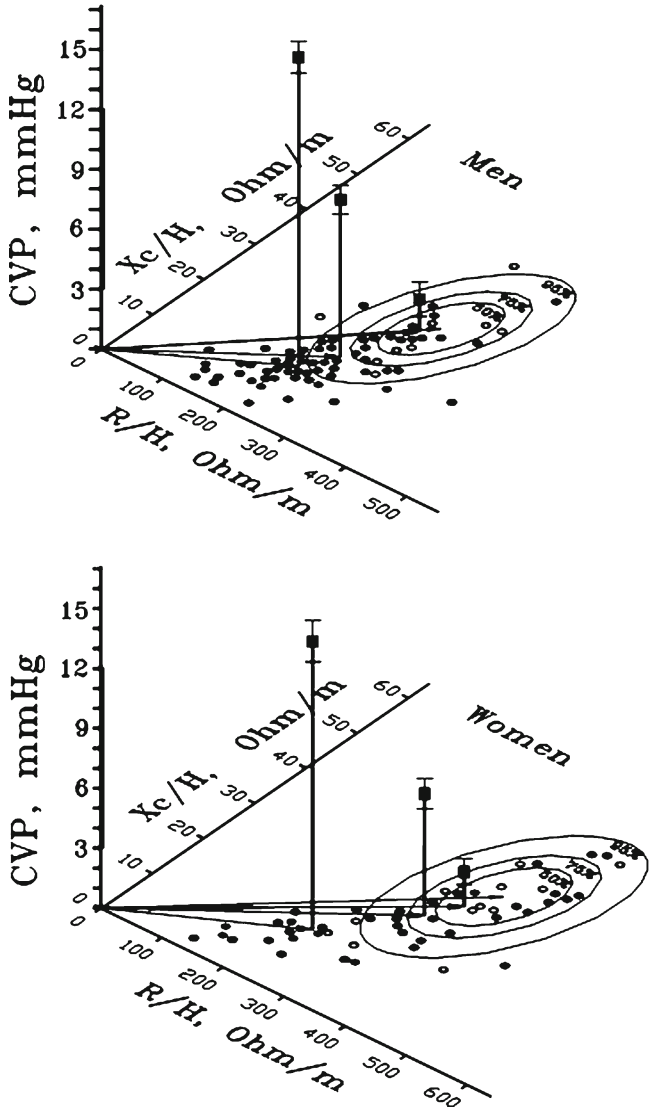

Fig. 16.10 BIVA discriminates mean CVP values in critically ill patients. Three groups of patients are represented with CVP values ranging between 0 and 3 mm Hg (low), between 3 and 12 mm Hg (medium), and above 12 mm Hg (high). Average CVP values are plotted (*solid squares*) vertically with 95% confidence intervals (*bars*) on the corresponding average impedance vector (*solid arrows*) over the reference, gender-specific, 50%, 75%, and 95% tolerance ellipses of the healthy population (average reference vector depicted as *open arrow*). *Open circles*, *donuts*, and *solid circles* represent impedance vectors from individual patients with low, medium, and high central venous pressure values, respectively. *CVP* central venous pressure, *R* resistance, *Xc* reactance, *H* height. (Reprinted from Piccoli et al. (2000). With permission)

BIVA was examined as an indicator of fluid status compared to CVP in ICU patients. Among 121 consecutive patients, CVP values were 8.1 mm Hg on average and ranged from 0 to 20 mm Hg (Piccoli et al. 2000). Both components of the impedance vector were significantly, linearly and inversely correlated with CVP values, namely $r = -0.53$ for R/H and $r = -0.52$ for Xc/H (Fig. 16.10). We classified patients with respect to their CVP values into three groups, namely low (0–3 mm Hg), medium (4–12 mm Hg) and high (13–20 mm Hg).

A progressive increase of the CVP was represented on the *R–Xc* plane with backward and downward displacement of the impedance vector from the target 75% tolerance ellipse to the region of

fluid overload (Fig. 16.10). The agreement between methods in determining the fluid status of the individual patient was greater for higher CVP values and shown as short impedance vectors out of the target ellipse (e.g., BIVA pattern indicating fluid overload), moderate for medium CVP values and poor for lower CVP values, which were associated with most vectors of normal length (62%) and with only 10% long vectors overshooting the upper pole of the 75% reference ellipse (i.e., BIVA pattern indicating tissue dehydration; refer to Fig. 16.1).

In the clinical setting, these results support a new operative definition of the optimal hydration status in ICU patients, considering that tissue hydration is governed by capillary and venous pressure together with systemic and local control factors. Therefore, the combination of a bedside measure of effective tissue hydration (i.e., tissue electrical conductivity) with one of venous system pressure provides a consistent opportunity to score a patient with both CVP values and impedance vectors within norms of the reference population as a patient with optimal hydration status. A patient with a BIVA pattern of tissue dehydration and with low CVP values then can be scored clinically worse than one with normal central venous pressure values. Similarly, a patient with a BIVA pattern of tissue hyper-hydration and with high CVP values can be scored clinically worse than one with normal CVP values.

The combined evaluation of tissue hydration by BIVA and CVP provides a useful clinical evaluation tool in the planning of fluid therapy for ICU patients, particularly in those patients with low CVP. Indeed, a different response or tolerance to fluid infusion is expected in dehydrated compared to well hydrated patients with the same low CVP (in the range of 0–3 mm Hg), where BIVA could identify those with reduced, preserved, or increased tissue fluid content.

16.13 BIVA in Congestive Heart Failure

The clinical validation of BIVA in HD patients allows direct extension of the same BIVA patterns to the congestive heart failure patients. Similar to the HD cycle, heart failure is characterized by a cyclical fluid overload (pulmonary and peripheral congestion) and removal (diuretics, extracorporeal fluid removal with dialysis). Despite current therapy, the high rate of re-admission indicates that the present criteria for discharge, typically based mostly on subjective impressions, correlates poorly with clinical stabilization.

Current practice uses a blood biomarker for interpretation of over-hydration, NT pro-BNP, in the diagnosis of heart failure. Values between the lower threshold point for “ruling out” acute heart failure and the higher, aged-adjusted indicator point for “ruling in” acute heart failure are referred to as “gray zone” values. In the situation of a “gray zone” diagnosis, clinical judgement of congestion is often necessary to ascertain the correct diagnosis. It is possible that the diagnostic and prognostic values of the NT pro-BNP depend on the level of congestion (i.e., “wet” worse than “dry” NT pro-BNP). In 315 patients admitted to the emergency department for acute dyspnea, NT pro-BNP was used as biomarker of heart failure, lung ultrasound was used to detect pulmonary congestion, and BIVA was used to detect latent peripheral congestion (i.e., without apparent edema) (unpublished observations). Patients were classified into two categories: cardiac-related dyspnea ($n = 169$) or non-cardiac-related dyspnea ($n = 146$).

The mean impedance vector was significantly shorter in patients with cardiac-related dyspnea, with a parallel decrease in both R and Xc components. BIVA was able to detect a “latent peripheral congestion” in dyspneic patients with NT pro-BNP in the “gray zone”. Ongoing intervention studies are needed to establish the region of the R–Xc plane where the individual vectors should be brought following an adequate fluid removal; the region where an optimal “dry” patient will decrease the rate of re-admission.

16.14 Segmental BIVA in Vascular Surgery

Direct measurements of segmental *Z* can be evaluated with BIVA. Edema localized in one leg frequently follows a femoral-popliteal bypass. We sought to establish how this localized edema can bias the interpretation of whole-body impedance (Codognotto et al. 2008). Limbs and trunk contribute differently to whole-body *Z* (90% and 10%, respectively). The *R* and *Xc* components of *Z* vector were measured at 50 kHz in 20 adult male patients without edema, before and three days after a femoral-popliteal bypass that induced pitting edema in the leg. Whole-body *Z* was measured from hand to foot of the right and left side. The impedance of each leg was measured from the pair of electrodes on foot and the other pair on the trochanter (Fig. 16.11).

Before surgey, the position of the mean whole-body and leg *Z* vectors from either side of the body was not significantly different (overlapping 95% confidence ellipses). After surgery, mean whole-body and leg *Z* vectors from the side without edema did not change position in the *R–Xc* plane with respect to before surgery position (Fig. 16.12). In contrast, mean whole-body and leg *Z* vectors of the body side with edema significantly shortened according to the BIVA patterns of fluid accumulation (along a down-sloping trajectory), due to a combined decrease in both vector components (*R* and *Xc*).

Because whole-body *Z* vector from the side of the body without edema was not sensitive to the edema localized in the leg of the opposite side, it can be utilized in the assessment of body composition also in patients with edema in one leg. Furthermore, a complete resolution of the fluid accumulation in the leg is expected to bring *Z*-leg to the baseline postition before surgery. Similar evidence cannot be obtained with other BIA methods.

Previously we demonstrated that sensitivity and specificity in detection of fluid overload in renal patients with diffuse edema, obtained with whole-body *Z* at 50 kHz, were comparable to those obtained with segmental *Z* of limbs and trunk.

The fact that in the non-edematous side both whole-body and leg *Z* vectors were insensitive to the fluid accumulation in the edematous leg indicates that the electric current path through soft tissues is largely determined by body geometry, and the contribution of body segments is likely different in any individual subject. This finding indicates that it is impossible to model the contribution of body segments to whole-body impedance.

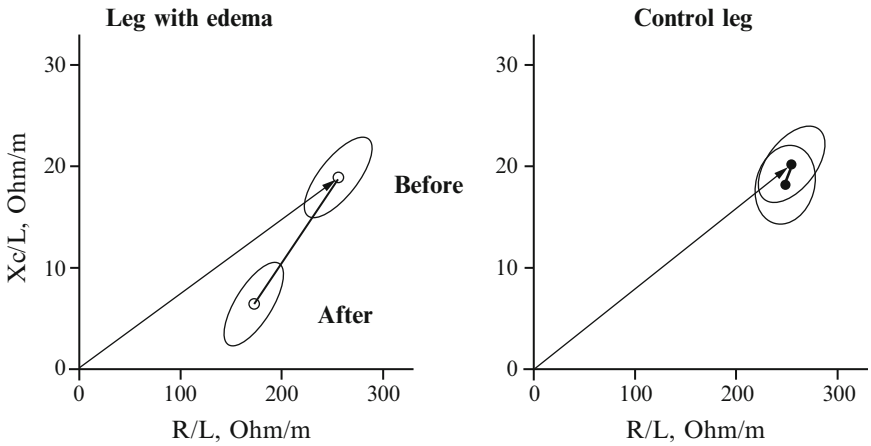

Fig. 16.11 Identification of edema in the leg with segmental BIVA. The mean impedance vector is normalized by the length of the leg (i.e., *Z*/*L*= *R*/*L*, *Xc*/*L*). A significant vector displacement (separate 95% confidence ellipses) was observed after the appearance of edema on the leg that underwent the surgical procedure compared to the non-affected leg. (Reprinted from Codognotto et al. (2008). With permission)

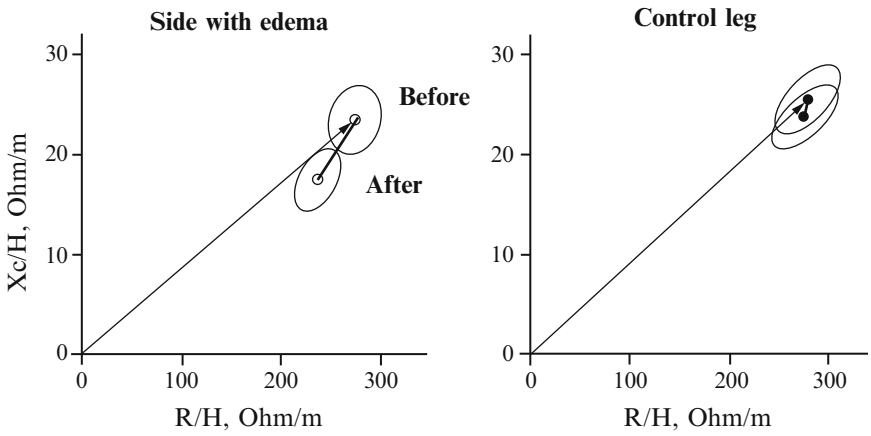

Fig. 16.12 Limb edema identified with the whole-body impedance vector. Whole-body mean impedance vector is normalized by the subject's height ($Z/H = R/H$, Xc/H). A significant vector displacement (separate 95% confidence ellipses) was observed after the appearance of edema on the leg of the body side following surgical procedure. No vector displacement (overlapping 95% confidence ellipses) was observed on the other body side. (Reprinted from Codognotto et al. (2008). With permission)

Summary Points of BIVA and Its Applications in Health and Disease

- BIVA is a safe, practical and non-invasive method. It relies on simple, whole-body measurements of *R* and *Xc* to produce an impedance vector that is compared to tolerance intervals to classify and rank hydration of an individual. Hydration status is characterized by distance from the mean vector of the reference population.
- BIVA offers advantages to conventional methods of assessment of hydration. It does not use regression equations or physiological constants, which are not valid in individuals with altered hydration, or body weight to predict changes in tissue hydration.
- BIVA accurately classifies over-hydration in women during pregnancy and obese individuals before and after weight loss. Thus, BIVA has the capacity to identify individuals at risk for complications associated with over-hydration during pregnancy and in obesity.
- Use of BIVA can contribute uniquely to dialysis prescription because it is able to track changes in tissue hydration status with a minimal detectable change of less than 500 ml. Adequacy of volume of fluid removed during the dialysis session reduces morbidity and improves patient outcomes.
- BIVA discriminates the composition of weight change associated with fluid and soft tissue gain or loss.
- BIVA offers a convenient alternative to the invasive procedures conventionally used in critical care patients to ascertain their need for fluid infusions.
- BIVA offers a potential advance in the assessment and monitoring of cyclical fluid overload in patients with congestive heart failure. Reliance on clinical impressions and many biomarkers fails to provide the sensitivity needed to positively affect readmission rates.
- Direct measurements of the impedance vector of body segments, such as the legs, and analysis with *R–Xc* graph and tolerance intervals provide a novel assessment of regional edema that can not be ascertained with whole-body measurements.

In summary, BIVA is a safe, simple and convenient method for the non-invasive, real-time assessment of hydration status that overcomes many of the limitations of techniques and approaches currently used.

Although its immediate use is in assessment and monitoring of hydration in dialysis, other clinical applications in critical care medicine, congestive heart failure and regional edema would benefit from its incorporation.

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Chapter 17
The Uses and Misuses of Body Surface Area in Medicine

James Heaf

Abstract The practicing physician uses anthropometry in two ways: (1) to adjust variables for body size in order to define "pathological" values and (2) to dose medicine correctly. Two questions need to be answered in this context. Which background population is to be regarded as "normal"? Which is the best method of indexing? Based largely in nineteenth century principles of physiology, medical variables have traditionally been adjusted for body surface area (BSA). There are a number of problems with this approach. BSA is an essentially indefinable concept, its size varying according to the magnification used. Measurements of BSA have been plagued by methodological problems. The current standard BSA of 1.73 m^2 bears little resemblance to the BSA of modern Western populations. Empirical studies of physiological variables, even commonly used ones, such as glomerular filtration rate (GFR) and cardiac output (Q), have shown that BSA is not the best indexing parameter, or is simply wrong. Since anthropometric variables, such as weight, height, sex and ethnicity are easily available, it is suggested that medical correction formulae should be of the form

$$\text{Corrected variable} = \text{Variable} \cdot \left(A + B \cdot \text{Weight}^{C} \cdot \text{Height}^{D}\right) \cdot f_1(\text{Sex}) \cdot f_2(\text{Ethnicity})$$

where *A*, *B*, *C* and *D* are constants, and *f* are defined functions of sex and ethnicity, all of which are determined empirically. Derived constants, such as BSA and body mass index (BMI) should be abandoned, or their use empirically justified. More sophisticated adjustments using fat-free mass (FFM), total body water (TBW) or extracellular water (ECW) may be indicated, but should be justified empirically, as should more complex formulae.

Abbreviations

BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index = Weight in kilogram/(Height in metres)^2
BMR	Basal Metabolic Rate
BSA	Body Surface Area
ECW	Extracellular Water

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_17,

FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
FFM	Fat-free Mass
GFR	Glomerular Filtration Rate
H	Height (cm)
IBW	Ideal Body Weight
LAD	Left Atrium Diameter
LBM	Lean Body Mass
LVM	Left Ventricular Mass
PNA	Protein Nitrogen Appearance
Q	Cardiac Output
SD	Standard Deviation
SV	Stroke volume
TBW	Total Body Water
W	Weight (kg)
%BF	Percentage of Body Fat

17.1 Introduction

The assessment of physiological variables in medicine serves a precise goal, viz. the distinction between health and disease. Traditionally, "healthy" is initially defined as "normal", i.e., within the reference interval. The reference interval is defined as the interval within which 95% of the background population lie, 2.5% being above the interval and 2.5% below. For normally distributed variables, this interval will be almost identical to the mean average ± two standard deviations (SD), but for skewed variables, a more sophisticated analysis is required. "Healthy" is of course not identical with "normal"; subsequent research defines the precise relationship between the two concepts. The application of anthropometry in medicine is necessary for this definition. Since physiological variables often vary according to the size of the patient, small patients will a priori have smaller values for the variable, without this necessarily implying disease. Thus, variables should be corrected ("indexed", "normalised" or "scaled") for body size to achieve a definition of normality that is independent of body size. There is, however, a major problem with this approach: by implication, the background population is regarded as 95% healthy. However, most populations include both obese and cachectic individuals, and, in Western populations, the proportion of obese individuals exceeds 2.5% by an order of magnitude. Both excess and insufficient weight is associated with well-recognized increased morbidity and mortality. Should their physiological variables be included in the definition of "normal"? If not, which cutoff values should be accepted? And if obesity is to be excluded, how is this to be defined? Traditionally, obesity is defined as a BMI > 30 kg/m^2, measured by dividing a patient's weight in kilograms by the square of body height in metres. This definition will, however, include large, muscular individuals, who by any definition would be regarded as healthy.

These problems are particularly pertinent in the choice of indexing method. Most methods will give similar results, for average sized individuals, the main deviation occurring at the extremes of body size.

Table 17.1 Anthopometry-related physiological variables used in medicine

Parameter	Abbreviation	Usual normalisation index
Obesity		$Height^2$
Bone mineral content	BMC	Weight (complex function)
Bone mineral density	BMD	Weight (complex function)
Forced expiratory volume	FEV1	Logarithmic function of weight
Forced vital capacity	FVC	Height
Oxygen consumption		$Weight^{2/3}$
Glomerular filtration rate	GFR	BSA
Protein synthesis	PNA	Weight
Cardiac output	Q	BSA
Left ventricular mass	LVM	BSA

17.2 Indexing Criteria

Indexing methods should fulfill a number of criteria:

1. The indexing parameter should express a fundamental physiological truth, e.g., metabolic rate. Indeed, if the indexing parameter is valid for inter-species comparisons, more faith will be placed on it.
2. The correlation to the investigated variable should be documented in a large background population.
3. The indexing parameter should be linearly correlated to the investigated variable. In principle, more sophisticated equations are acceptable, but complicated adjustments are less likely to be adopted by the medical community, and should preferably be justifiable by reference to criterion (1). A good example of the latter is the reference interval for bone mineral density (BMD). This is conventionally assessed by two indexed variables: the *T*-score, being the number of SDs that the BMD differs from a young healthy individual, adjusted for weight, sex and height; and the *Z*-score, the number of SDs differing from a healthy individual of the same age, weight, sex and height. Both the *T*-score and the *Z*-score require complex formulae. The *T*-score is relevant for assessing absolute fracture risk, while the *Z*-score registers pathological values for bone mass, recognizing physiologically well described reductions in BMD with age and the menopause as being "normal".
4. The correlation line should cross the *Y* axis at an *X* value not significantly different from zero, i.e., one would expect infinitely small individuals to have infinitely small (but positive) physiological measurements. If the indexing parameter fulfills criteria 3 and 4, corrected values of the variable should no longer be correlated to the indexing parameter.
5. After indexing, the variable should result in similar reference intervals for males, females, children and differing races. If not, differences between groups should be explainable as "real", i.e., an expression of a fundamental physiological difference.
6. When comparing indexing parameters, the parameter that reduces the coefficient of variation of the variable the most, is to be preferred.

17.3 Indexing Variables

Various approaches to indexing have been proposed:

1. *Body weight (W)*. The major advantage of this approach is simplicity, and the main disadvantage is that obese and muscular individuals, with radically differing physiologies, will be treated identically.

Table 17.2 Formulae for calculating total body water (TBW) and extracellular water (ECW) in litres from age, weight (W) in kg and height (H) in cm

	Males	Females
TBW		
Watson et al. (1980)	$2.447 - 0.09516 \times \text{Age} + 0.1074 \times H + 0.3362 \times W$	$2.097 + 0.1069 \times H + 0.2466 \times W$
Hume and Weyers (1971)	$-14.01 + 0.1948 \times H + 0.2968 \times W$	$-35.27 + 0.3445 - H + 0.1838 \times W$
ECW		
Peters (2004)	$0.02154 \times W^{0.647} \times H^{0.724}$	$0.02154 \times W^{0.647} \times H^{0.724}$

2. *Body height (H)*. This is rarely used on its own, as it is too inexact a measure of body size. However, it is the logical choice when distance is a factor in the measurement, e.g., in bioimpedance studies where bodily electrical resistance is proportional to the distance between the electrodes.
3. *Body surface area (BSA)*. Rubner (1894) found that basal metabolic rate (BMR) in different mammals correlated better to BSA than body weight with values lying between 900 and 1,200 kcal/m^2/day. The BMR of young healthy adults is constant at 920 kcal/m^2/day. This correlation is plausible, since a large proportion of BMR is devoted to replacing heat losses through the skin. The application of BMR, and, therefore, BSA to other physiological variables relies upon the assumption that these are causally related to BMR.
4. *Total body water (TBW)* or extracellular water (ECW). The justification here is that many body functions, e.g., cardiac function and renal clearance would a priori be expected to correlate linearly with TBW. TBW is, however, difficult to measure directly, and derived equations from weight, height and sex are often used (Table 17.2). The increasing availability of multi-frequency bioimpedance tools allows simple and direct assessment of individual TBW. The measurement of GFR using radioactive tracer excretion rates and integrative mathematical techniques permits the simultaneous determination of ECW, assuming that the tracer is distributed uniformly in the ECW (Visser et al. 2008). TBW is the implicit choice of indexing for virtually all biochemical variables, which are measured per unit blood volume or body fluid.
5. *Fat-free mass (FFM)*, i.e., body mass minus adipose tissue. This is usually measured by dual energy X-ray absorptionometry (DEXA). The concept here is that the metabolic rate of adipose tissue and bone is very low, and that metabolic rate will, therefore, be closely correlated to FFM. Lean body mass (LBM) is a similar concept, usually defined as ECW, cell mass and non-fatty intercellular connective tissue. The concepts are not identical: cell membrane fat is excluded from FFM, but not LTM. TBW is approximately 73% of LBM. Another approach to excluding the effect of obesity is to use the ideal body weight (IBW), i.e., the weight associated with the lowest mortality for the patient's height, derived from actuarial tables, e.g., the Metropolitan Life Insurance Company (1980) (see Table 17.3). Obesity is here defined as the ratio between actual weight and ideal weight. Other concepts of non-obese weight are adjusted body weight and predicted normal weight (the latter two primarily developed for pharmacokinetics).
6. *Assumption-free Modelling*. An alternative approach to indexing is to ignore criteria 1, 3 and 4. Here, the variable is measured in a large background population, and an algorithm derived using multiple regression analysis, allometric scaling and all available indexing parameters, usually height, weight, sex and race. Instead of automatically assuming that the correlation is linear, i.e., the power exponent of the relationship is equal to 1, the optimal allometric exponent is measured empirically. For paediatric populations, the algorithm must be forced to cross the Y axis at an X value of zero, but this is not necessary for adult populations. Criterion 5 will automatically be fulfilled, but the resulting algorithm will make no pretence of expressing any fundamental physiological knowledge. Physiologists are welcome to philosophise as to whether the algorithm parallels BMI, BSA, LBM, BMI, TBW, W or H, or any other theoretical construct, but this is of secondary importance to the practising physician.

Table 17.3 Estimates of non-obese body weight. Weight (W) in kg and height (H) in cm (Green and Duffull 2004)

	Males	Females
Ideal body weight	$50 + 0.89 \times (H - 152.4)$	$45.4 + 0.89 \times (H - 152.4)$
	$52 + 0.75 \times (H - 152.4)$	$49 + 0.67 \times (H - 152.4)$
Fat-free mass	$0.285 \times \text{TBW} + 0.00121 \times \text{H}^2$	$0.287 \times \text{TBW} + 0.000974 \times H^2$
Adjusted body weight	$\text{IBW} \times 0.4 \times (\text{TBW} - \text{IBW})$	$\text{IBW} \times 0.4 \times (\text{TBW} - \text{IBW})$
Predicted normal weight	$1.57 \times W - 0.183 \times \text{BMI} \times W - 10.5$	$1.75 \times W - 0.0242 \times \text{BMI} \times W - 12.6$
Lean body mass	$1.1 \times W - 0.0128 \times \text{BMI} \times W$	$1.07 \times W - 0.0148 \times \text{BMI} \times W$
	$1.10 \times \text{TBW} - 120 \times \text{TBW}/H^2$	$1.07 \times \text{TBW} - 148 \times \text{TBW}/H^2$
Percentage of body fat (%BF) (Gallagher 2000)		
White and Afro-Americans	$48.1 - 809/\text{BMI} + 0.084 \times \text{age}$	$64.5 - 848/\text{BMI} + 0.079 \times \text{age}$
Asians	$51.9 - 740/\text{BMI} + 0.029 \times \text{age}$	$64.8 - 752/\text{BMI} + 0.016 \times \text{age}$

17.4 Problems with Body Surface Area as Indexing Parameter

As stated earlier, the use of BSA is popular, being based on early studies of metabolic rate. There is, however, a number of problems associated with its use (Heaf 2007).

1. The fractal problem. Surface area is a fractal variable (Mandelbrot 1982), i.e., the more it is magnified, the more details become apparent, and the greater the total surface area becomes, virtually ad infinitum. Thus BSA is essentially just as indefinable as the length of the British coastline, and just as immeasurable (Fig. 17.1).
2. The theory for the choice of BSA as index is that it is an expression of a universal physiological law, viz. that body metabolism is proportional to BSA. Thus, metabolism should be proportional to $W^{2/3}$, even when different species are compared. As originally described by Kleiber, this ratio is actually $W^{3/4}$, and the toxicological studies have also supported this ratio. Similarly, the optimal scaling index for oxygen uptake in humans is $W^{0.75}$. The explanation appears to be that muscle mass increases disproportionally with body size. The law that BMR is proportional to BSA breaks down when age is taken into account: the BMR of children falls linearly from 1,300 kcal/m^2/day at birth to 900 at 15, and oxygen consumption from 180 to 150 mL O_2/m^2/min.
3. The most commonly used formula for determining BSA is the Du Bois (1916) formula from 1916. BSA was determined by tightly covering the patients with manila paper moulds (or indeed, in some instances, pouring melted paraffin over the body). The moulds were then removed, opened and placed flat on photographic film. The film was subsequently exposed to light. Finally, the unexposed film was cut out and weighed. The BSA was derived from the weight by dividing by the average density of the photographic area. While the methodology was impeccable, only ten adults and one child were studied. The child was a cachexic girl weighing 6.27 kg at 21 months of age, and the adults included the notorious Mrs. McK, a 1.5 m tall lady weighing 100 kg, who is an outlier in many subsequent equations. Other patients included an 18-year-old with cachexia due to Type 1 diabetes and a 36-year-old man with the physical development of an 8-year-old and two patients with amputations. The derivation of the equation was based on the arguable philosophical premise that, since BSA is two-dimensional, the sum of the exponent power for weight multiplied by three, added to the power for height had to be exactly 2. In addition, the authors described equations for calculating BSA from bodily dimensions.

   Given these methodological problems, it is surprising that the Du Bois formula performs reasonably well in normal adults, but it, however, breaks down in children and the obese. Tucker

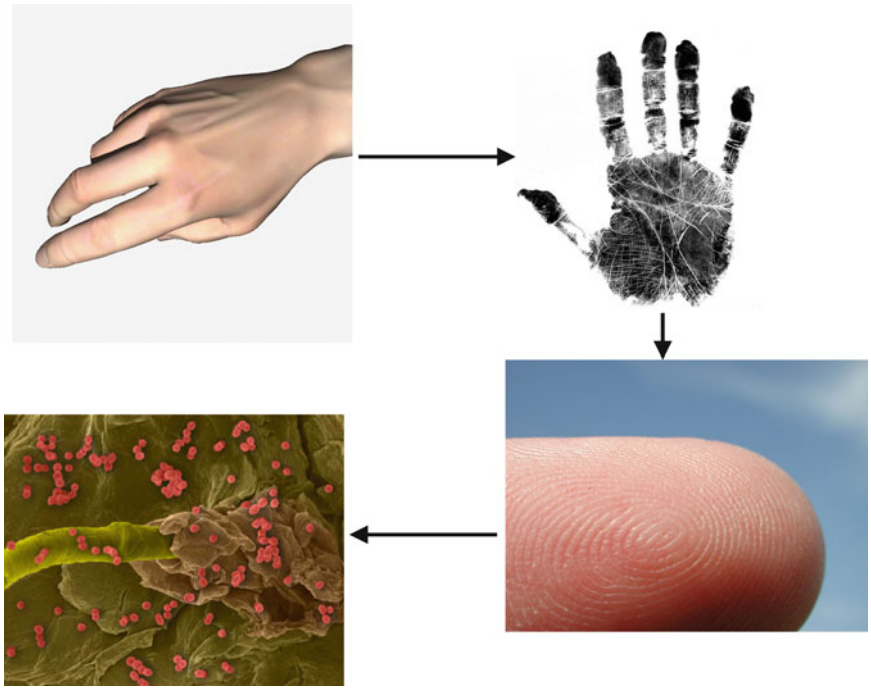

Fig. 17.1 The fractal problem. The body surface area expands with increasing magnification. The BSA can neither be defined nor measured

and Alexander (1960) attempted to assess its relevance for extremely obese patients (>100 kg), but experienced considerable difficulty: "it was difficult for the four obese people to stand up for the time required for the entire taping process"; it was decided to use "the measurement in which the tape followed all the folds of the skin as opposed to a straight-line measurement between two points"; "the exact location of the superior border of the greater trochanter was difficult to determine", etc. (Fig. 17.2). They concluded that the Du Bois formula was reasonably accurate (–11 to +2%), while the derived formulae were unsatisfactory (–8 to +20%). Similarly, Livingstone and Lee (2001) studying obese patients and using the Du Bois derived formulae, found that the Du Bois equation underestimated BSA by as much as 20%. Revised formulae were presented (Table 17.4). The Livingstone formula has been shown to be superior to the Du Bois formula in predicting body volume and body fat percentage. Other approaches are based on the assumption that BSA must in principle scale to $k \times W^{0.67}$, deriving values for k of 0.103–0.123. These formulae perform poorly compared to formulae including height. Most scientists prefer to use the formulae developed by Gehan and George (1970) or Haycock and Schwartz (1978), (for children) both of which are based on a large number of patients (401 and 81 respectively), although the superiority of these formulae to the Du Bois formula remains to be clearly proved (van der Sluys and Guchelaar 2002). Yu et al. (2003) have recently studied 3,951 Chinese individuals using three-dimensional whole body scanning. Their formula could be regarded as the definitive for BSA, but suffers from the disadvantages that the power exponents for height and weight were arbitrarily chosen as 0.5, and the maximum BSA in the study was only 2.09 m^2.

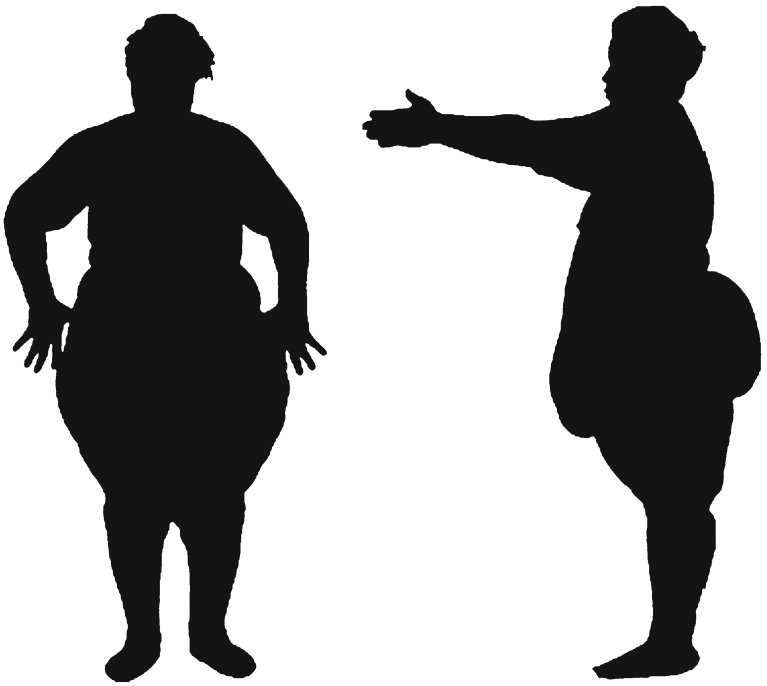

Fig. 17.2 Problems associated with measuring body surface area in the obese. Measuring BSA in the obese is difficult because of skin folds and poorly defined promontories (Tucker and Alexander 1960)

Table 17.4 Formulae for BSA

Equations are of the form

$$\text{BSA}\left(\text{cm}^2\right) = A \cdot \text{Height}\left(\text{cm}\right)^B \cdot \text{Weight}\left(\text{kg}\right)^C$$

Author	No. of patients	A	B	C
Du Bois and Du Bois (1916)	11	71.84	0.725	0.425
Banerjee and Sen	15	74.66	0.725	0.425
Boyd	411	178.27	0.5	0.4838
Gehan and George (1970)	401	235	0.42246	0.51456
Haycock and Schwartz (1978)	81	246.5	0.3964	0.5378
Nwoye (Africans)	21	13.15	1.2139	0.2620
Kurazumi		100.32	0.383	0.693
Lee	65	202.3	0.514	0.441
Fujimoto (Japanese)	201	88.83	0.663	0.444
Livingstone and Lee (2001) (Obese)	45	1,173	0	0.6466
Yu (2003)	3,951	159.2	0.5	0.5
Mostellers adaptation[a]		167	0.5	0.5

[a] $$\text{BSA}\left(\text{m}^2\right) = \frac{\sqrt{H \cdot W}}{3{,}600}$$

17.5 The Origins of the 1.73 m² Norm for Body Surface Area

In these evidence based times, it is perhaps surprising to read how little documentation was required for the derivation of this figure, which first appeared in a study by McIntosh et al. (1928) (Fig. 17.3). On the basis of urea clearance studies of eight children and seven adults, the paper states: "Our experience

> Our experience confirms that of Addis and his colleagues. More constant normal values are obtained if one substitutes *A* (= surface area) in place of *W* in the clearance formulae. We have found it convenient to use as a unit the surface area 1.73 square meters, which is the mean of the areas of men and women of 25, estimated from the adjusted medico-actuarial tables of Baldwin and Wood Published by Fiske and Crawford (5).

Fig. 17.3 The birth of a number. The first mention of 1.73 m^2 as the norm for body surface area was made by Mcintosh et al. in (1928)

confirms that of Addis and his colleagues. More constant normal values are obtained if one substitutes *A* (= surface are) in place of *W* (= weight) in the clearance formulae. We have found it convenient to use as a unit, the surface area 1.73 m^2, which is the mean of the areas of men and women of 25, estimated from the adjusted medico-actuarial tables of Baldwin and Wood published by Fiske and Crawford", The Du Bois formula was used. The tables described young US citizens applying for life insurance. They were not referenced directly, but an adjusted version was published by Fisk et al. in 1927. While these individuals had been examined fully clothed, every effort was made to reach as accurate an estimate as possible: the figures for men were "adjusted from the Medico-Actuarial Tables by subtracting 1 inch from height in shoes, and 5 pounds from weight in clothes", and for women by subtracting 1½ in. and 4 lb, respectively, thereby giving us an insight into American clothing standards in the 1920s. There is a minor error in the calculation: the correct figure derived from the tables is 1.72 m^2.

The figure 1.73 m^2 has served the physiological community well for nearly 80 years, but it is clearly no longer applicable to Western populations, as can be seen from Table 17.5. As early as 1951, Homer W. Smith noted that there was a problem with the value 1.73 m^2. "The figure of 1.73 m^2 is of course arbitrary. The writer has averaged the surface areas reported by 11 groups of investigators… and obtains 1.85 m^2 for 263 men and 1.81 m^2 for 164 women." If we accept the basic premise that the index of normalisation should be the average BSA of US 25-year-old males and females, then a new index of normalisation 1.92 m^2 should be adopted. The approach is, however, problematic. Periodic adjustments, e.g., once every decade, would be required for the foreseeable future. Some physicians might be horrified by the implication that an average BMI of 26.7 kg/m^2 would now be defined as "normal". One possible solution could be to choose a less overtly obese population, such as the European Union. This would improve, but not remove, the normative problem, but might just provide a short respite. Another possible approach follows from the observation that 1.73 m^2 corresponds to a BMI of 22.3, a figure which both then and now, is associated with the lowest mortality. Thus, serendipity has given us an "optimal" value for BSA, which should be preserved for posterity regardless of present and future developments of the reference interval. While accepting that the choice of 1.73 m^2 is arbitrary, the political decision to permanently retain the value will permit comparisons of different populations, separated both by geography and time. Again, to quote Homer Smith: "It is immaterial which figure is used so long as all investigators use the same figure, and since innumerable data are now reported in terms of 1.73 m^2, we may accept this usage as established." A suitable symbol of the decision to create this new fundamental physiological constant could be the deposition of a square platinum-iridium plate of exactly 1.73 m^2 at the Bureau International des Poids et Mesures, Sèvres, Paris.

Fig. 17.4. A new fundamental constant?. A suitable symbol of the decision to create a new fundamental physiological constant, viz. a BSA of 1.73 m^2 could be the deposition of a square platinum-iridium plate of exactly 1.73 m^2 at the Bureau International des Poids et Mesures, Sèvres, Paris

Table 17.5 Evolution of body dimensions 1927–2002

	25-year-olds	USA 1927	USA 2002	EU 2002
Male	Weight (kg)	68.9	83.2	78.6
	Height (cm)	172.7	176.8	177.2
	BSA (m^2)	1.80	2.04	1.98
Female	Weight (kg)	58.5	71.0	64.8
	Height (cm)	162.6	163.1	165.4
	BSA (m^2)	1.62	1.81	1.74
All	BSA (m^2)	1.72	1.92	1.86
	BMI (kg/m^2)	22.3	26.7	24.3

17.6 Applications to Other Areas of Health and Disease

17.6.1 Glomerular Filtration Rate (GFR)

The indexing of GFR is an excellent example of the above discussion. All advanced species require the ability to excrete excess and toxic products that enter the body. Water soluble products diffuse from the TBW to the blood. The blood is filtered in the renal glomerulus, the GFR being the amount of blood water filtered per unit time. Providing there is no tubular absorption or excretion of the product, its clearance is identical to the GFR. Conventional measures of renal function are inaccurate

in this respect. For instance, since creatinine is excreted in the tubules, creatinine clearance will be about 25% higher than GFR. Even slightly reduced GFR (and, in some instances also increased GFR, e.g., early diabetic nephropathy) is associated with increased morbidity and mortality. GFR is correlated to body size; thus, the definition of a normal indexed GFR is of great medical importance. The choice of BSA as the optimal index factor was based on a small study (McIntosh et al. 1928, *vide supra*), and has since been virtually unchallenged. Several studies have now reanalyzed the choice and shown that it does not fulfill the criteria mentioned above. Inter-species comparisons show that GFR scales to $W^{0.72–0.79}$ (Singer 2001), higher than the value expected for BSA ($W^{0.67}$), but similar to the power index for BMR ($W^{0.75}$). The use of BSA for GFR indexation results in low values for children aged 1–5 (Kurtin 1988), a finding which has no obvious physiological explanation. Indeed, the optimal scaling index for babies (<12 months) is $W^{1.30}$, making the BSA assumption wildly inaccurate. On the other hand, while some studies have shown a lower GFR in females, other studies have shown no difference. Thus, BSA correction is probably valid for inter-sexual comparisons, but is inappropriate for children.

The criterion of a linear correlation to BSA passing through the origin is not fulfilled. The correlation between GFR and BSA is low. If GFR is corrected for height, the correlation to BSA is absent. Adjusting for BSA in obese groups results in artificially low values for GFR.

17.6.2 Cardiac Physiology

Cardiac function is assessed by a number of static and dynamic variables: left ventricular mass (LVM), left atrium diameter (LAD), cardiac output (Q) and stroke volume (SV). Traditionally, they have been indexed using BSA. This is a somewhat surprising assumption. Blood flow in adipose tissue is poor and accounts for only 5% of Q, so a priori FFM would be expected to be the optimal index. Inter-species comparisons show that Q scales to $W^{0.78–0.81}$, similar to the measured value for BMR, but higher than the figure for BSA ($W^{0.67}$), while SV scales to $W^{1.05}$. De Simone investigated 970 adults and children, and found BSA appropriate for adults, but not for children. The most accurate indexing factor was, however, $H^{2.7}$. In contrast, Turley et al. (2006) investigating 759 adults found BSA, height, weight and FFM all inapplicable for both Q and SV. Similarly, Neilan et al. (2008), in 15,667 adults, found that simple isometric indices to actually increase the variability of LAD, and found the optimal indexing parameter to be $W^{0.262}$. George et al. (2001) showed that BSA indexing is inappropriate for LVM in 464 junior athletes, the optimal indexing parameter being $W^{0.91}$, while Daniels et al. (1995) found H^{3} to be the appropriate index in 192 children. A study of 254 dialysis patients showed that correcting LVM using the de Simone index of $H^{2.7}$ was superior to BSA in predicting mortality and cardiovascular outcomes. Using BSA instead of LBM to normalize LVM results in an inappropriate difference between men and women. The Framingham Heart Study (Vasan et al. 2000) proposed a simple height and sex based indexing for all echocardiographic variables.

17.6.3 Pulmonary Physiology

Vital capacity is proportional to height, and is 20–25% lower in women than men of the same height. Nevill and Holder (1999) found that forced expiratory volume in 1 s (FEV1) was related to body weight and height in a logarithmic fashion, peaking at 90 kg for men and 84 kg for women, and even declining thereafter for women. Traditionally, peak oxygen uptake has been indexed to weight, but

there is overwhelming evidence that a power function is preferable. Most studies show values between $W^{0.71}$ and $W^{0.80}$, again significantly different for the value if BSA was the correct index. Interspecies studies show that the elastic work of breathing scales to $W^{0.78}$, minute volume to $W^{0.80}$, pulmonary surface area to $W^{0.76}$ and mean expiratory flow rate to $W^{0.77}$ (Singer 2001). All these power values are similar to that for BMR (*vide supra*).

17.6.4 Hepatic Physiology

Surprisingly little research has been performed on size adjustment for dynamic liver function variables. Variables are either not adjusted, or weight or BSA is arbitrarily chosen as the indexing parameter. For instance, the lowest acceptable value for the Indocyanine green clearance is variably reported as 5.2 mL/min/kg or 9%/min. Where investigated (Leevy et al. 1962), variation in hepatic blood flow actually increases when corrected for BSA. An indirect method of assessing the correct indexing factor for liver function is to study the hepatic clearance of drugs. These generally show that LBM indexing gives the best results (Morgan and Bray 1994; Green and Duffull 2004). One notable exception is the clearance of alcohol, which is more closely related to BSA than LBM.

17.6.5 Hematology

A priori, one would expect blood volume to be more closely related to weight than BSA, since both blood volume and weight are three-dimensional variables. However, blood-volume measurements correlate better to BSA than weight. Feldschuh and Enson (1977) confirmed this, but also noted a major negative impact of body fat on the result, with grossly obese patients (defined as a high W/IBW) having less than half the blood volume predicted by BSA. This implies that blood volume is a function of TBW or LBM rather than BSA. The authors recommended scaling for IBW, but LBM indexing would be equally appropriate in this setting.

17.6.6 Drug Therapy

BSA is commonly used for adjusting drug dose to prevent toxicity, particularly for anti-cancer drugs. Previously to 1990, it was presumed that clearance would be a function of BMR and thus BSA. A recent review (Felici et al. 2002) noted, however, that in only 5/23 anti-neoplastic drugs where the relationship had been investigated could one find a significant relationship between BSA and clearance or toxicity. A 5–20-fold variation in pharmacokinetics is common even after adjusting for BSA. The correlation was relevant for highly protein-bound drugs confined to the blood compartment, which is a function of BSA (*vide supra*). The presence of adipose tissue must a priori be expected to influence pharmacokinetics in a number of complex ways: lipophilic drugs will have lower peak concentrations and slower elimination; adipose tissue in the liver will reduce hepatic metabolism. In contrast, the distribution volume of hydrophilic drugs will be unaffected by obesity. Many oncologists have reacted to these findings by capping doses at an arbitrary BSA of e.g., 2 m^2, but there is evidence that this may reduce drug efficacy in the obese. Green and Duffull (2004) found that weight was the best predictor of drug volume of distribution, while clearance was best described by LBM.

Thus, in the absence of pharmacokinetic studies, or sophisticated assessments of hepatic enzyme function, weight is the appropriate index for acute treatments, e.g., anaesthetics, while LBM is the appropriate index for chronic administration.

17.6.7 Obesity

Obesity has traditionally been defined as a BMI > 30 kg^2/m, and the concept of anthropometric correction would seem tautological. However, the physiological concept of obesity is that of a raised body fat percentage (%BF), which is not a linear function of BMI. Body fat percentage is largely independent of height. More advanced models include abdominal girth or waist-hip ratio. Abdominal girth >102 cm (male) and 88 cm (female), and wait-hip ratios >0.9 (male) and 0.85 (female) are associated with increased morbidity. The most sophisticated assessment of abnormal fat accumulation uses DEXA (Gallagher et al. 2000). Here, "unhealthy" was defined as a %BF >25 (male) and >33 (female). Anthropometric formulae for estimating %BF were derived (Table 17.3).

17.7 Conclusion

While the physiologist has a mission to define the underlying principles governing physiological processes, the practising physician pursues more prosaic questions. Is an abnormal value pathological, or just an expression of deviation in body size and obesity? What is the correct dose of medicine? The widespread use of BSA is a consequence of the historical dogma that BMR is proportional to BSA, which is untrue, and that bodily functions are linearly correlated to BMR. This is partly or wholly untrue for a number of variables. The above review shows that, in many cases, FFM, LBM or TBW are better choices, in accordance with basic physiological principles. The medical community needs, therefore, to return to a more empiric approach consisting of two steps:

1. Define the background population. Who is the patient to be compared with? For some purposes, e.g., the prediction of complications, a comparison to a young, healthy population is to be preferred; in others, e.g., the diagnosis of pathological conditions, the comparison should be to a group of the same age and sex. For some questions, "healthy" obese and cachectic individuals should be excluded from the background population, and perhaps supplied with their own anthropometric analysis.
2. The basic model for anthropometric correction is:

$$\text{Scaled variable} = \text{Variable} \cdot \left(A + B \cdot \text{Weight}^{C} \cdot \text{Height}^{D}\right) \cdot f_1(\text{Sex}) \cdot f_2(\text{Ethnicity})$$

where A, B, C and D are constants, and f are defined optional functions of sex and ethnicity. More complex equations can be used where relevant (Nevill et al. 2005). If paediatric populations are included the constant A should be equal to 0, but otherwise no prior assumptions of the constants are made, and their optimal value is measured. Simplified versions of the resulting equation are to be empirically justified, but are hardly required in a computerised age.

Similarly, use of more complex indices, e.g., total body water is to be justified. Different equations for different populations, e.g., children versus adults are acceptable. More complex functions, e.g., logarithmic, are acceptable if empirically more correct. BMI and BSA, being derived functions of weight and height are not included. Previous equations, based on a priori use of BSA, that have been shown not to accord with the facts, e.g., the currently used adjustment for GFR, are to be abolished. It is left to physiologists to determine whether the resulting equations are compatible with existing physiological theories or not.

Summary Points

- Body surface area is indefinable.
- Body surface area is difficult to measure.
- The choice of 1.73 m^2 as the norm for body surface area is inapplicable to modern Western populations.
- Basal metabolic rate is not a linear function of body surface area.
- Body surface area is not the optimal scaling index for most physiological variables.
- Alternatives include total body water, fat-free mass and lean body mass.
- Body surface area does not predict drug toxicity.
- Optimal scaling indices should be empirically determined.
- Complex formulae are not a problem in a computerised age.
- The usual formula for assumption-free modelling is:

$$\text{Scaled variable} = \text{Variable} \cdot \left(A + B \cdot \text{Weight}^{C} \cdot \text{Height}^{D}\right) \cdot f_1(\text{Sex}) \cdot f_2(\text{Ethnicity})$$

  where A, B, C and D are constants, and f are defined optional functions of sex and ethnicity.
- The background population for the reference interval should be defined.

Key Features of Body Surface Area in Medicine

1. Since the nineteenth century, dividing physiological variables by body surface area has been a popular method of adjusting measurements for differences in body size.
2. Body surface area is also used for adjusting medicine dose, larger doses being given to patients with a larger surface area.
3. The reason for this is that BMR, and thus most physiological processes, are assumed to be proportional to body surface area.
4. Body surface area has traditionally been measured by encasing subjects in wax paper, and subsequently measuring the area of the paper. This process is laborious, and numerous equations for calculating body surface area using patient weight and height have been devised.
5. Physiological variables are often adjusted to a "normal" body surface area of 1.73 m^2, the calculated average area of life insurance applicants in the USA during the 1920s.

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Part III
Tools and Techniques in Anthropometry: Muscle

Chapter 18
Anthropometry of Human Muscle Using Segmentation Techniques and 3D Modelling: Applications to Lower Motor Neuron Denervated Muscle in Spinal Cord Injury

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Abstract This chapter describes a novel approach to determining muscle anthropometry using medical imaging and processing techniques to evaluate and quantify: (1) progression of atrophy in permanent muscle lower motor neuron (LMN) denervation in humans and (2) muscle recovery as induced by functional electrical stimulation (FES). Briefly, we used three-dimensional reconstruction of muscle belly and bone images to study the structural changes occurring in these tissues in paralyzed subjects after complete lumbar-ischiatic spinal cord injury (SCI). These subjects were recruited through the European project RISE, an endeavour designed to establish a novel clinical rehabilitation method for patients who have permanent and non-recoverable muscle LMN denervation in the lower extremities. This chapter describes the use of anthropometric techniques to study muscles in several states: healthy, LMN denervated-degenerated not stimulated, and LMN denervated-stimulated. Here, we have used medical images to develop three-dimensional models, including computational models of activation patterns induced by FES. Shape, volume and density changes were measured on each part of the muscles studied. Changes in tissue composition within both normal and atrophic muscle were visualized by associating the Hounsfield unit values of fat and connective tissue with different colours. The minimal volumetric element (voxel) is approximately ten times smaller than the volume analyzed by needle muscle biopsy. The results of this microstructural analysis are presented as the percentage of different tissues (muscle, loose and fibrous connective tissue, fat) in the total volume of the rectus femoris muscle; the results display the first cortical layer of voxels that describe the muscle epimisium directly on the three-dimensional reconstruction of the muscle.

These analyses show restoration of the muscular structure after FES. The three-dimensional approach used in this work also allows measurement of geometric changes in LMN denervated muscle. The computational methods developed allow us to calculate curvature indices along the muscle's central line in order to quantify changes in muscle shape during the treatment. The results show a correlation between degeneration status and changes in shape; the differences in curvature between control and LMN denervated muscle diminish with the growth of the latter. Bone mineral density of the femur is also measured in order to study the structural changes induced by muscle contraction and current flow. Importantly, we show how segmented data can be used to build numerical models of the stimulated LMN denervated muscle. These models are used to study the distribution of the electrical field during stimulation and the activation patterns.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_18,

Abbreviations

3D	Three dimensional
BMD	Bone mineral density
CT	X-ray Computer Tomography
DTI	Diffusion Tensor Imaging
FD	Finite difference
FE	Finite element
FES	Functional electrical stimulation
h-b FES	Home based functional electrical stimulation
HU	Hounsfield units
LMN	Lower motor neuron
MBMD	Mean bone mineral density
MRI	Magnetic resonance imaging
RF	Rectus femoris
SCI	Spinal Cord Injury
UMN	Upper motor neuron

18.1 Introduction

18.1.1 Medical Anthropometry

Computer simulation and modelling of the human body and its behaviour are very useful tools in situations where it is either too risky to perform an invasive procedure or too costly for in vivo experiments or simply impossible for ethical reasons. However, the modelling of these systems may be seriously complex because of the large number of potential variables. Indeed, a system may have such a large number of parameters that they cannot all be identified and considered. Therefore, the modelling approach, especially in biological systems, is designed according to established criteria and objectives and is usually constrained to accurately consider or describe only certain characteristics while approximating or ignoring others. Medical modelling of biological systems is generally applied under certain conditions: (1) to describe mechanical and/or electrical behaviour; (2) to evaluate normal and abnormal morphologies for three-dimensional (3D) visualization of animal anatomy; (3) to simulate biological conditions and surgical treatments; and (4) to study tissue properties or to correlate different tissue characteristics.

An emerging field of anthropometry is the so-called biomodelling, which is the creation of highly accurate physical models of human anatomy directly from medical image data. The process involves capturing human anatomy images, processing these data to isolate individual tissue or organs and then using rapid prototyping techniques (automatic manufacturing of physical items directly from 3D computer data) to provide a physical model.

The main stages of medical modelling process are:

- Medical imaging
  - Select the optimal modality such as CT or MRI
  - Set the appropriate protocol which enables a proper visualization of the region of interest
  - Scan the patient

- Export the data from the scanner in an appropriate format
- Process the data: segmentation of the organs or tissue to be modelled
- Further processing to analyse and model other biological characteristics and properties (such as tissue composition, fibre activation and bone mineral density [BMD]) or rapid prototyping to produce a physical model

18.1.2 Anthropometric Techniques in Clinical Research: Muscle Denervation After Spinal Cord Injury (SCI)

Anthropometry is proving to be an extremely useful tool in medical research and, indeed, has the potential to be very valuable in the evaluation and comparison of anatomic structures in both normal and pathological conditions. One area of specific interest to us is the use of anthropometric techniques in the study of muscle degeneration after denervation. It is known that alterations of functional and structural properties of muscle fibres result from the lack of permanent innervation in SCI patients; however, the specifics vary dependent upon the location of the lesion. The literature offers a good knowledge base concerning the progression of muscle atrophy in response to upper motor neuron (UMN) lesions in human patients; however, much less is known about the time-course of transition from atrophy to degeneration in irreversible lower motor neuron (LMN) muscle denervation. For example, much research shows that muscle mass decreases significantly during the first few months after UMN damage (Lotta et al. 1991) with ultrasound revealing a loss of up to 40% of the mass in the first month post injury (Gorgey 2007; Taylor et al. 1993). After the first few months post injury, the atrophy process slows down, resulting in a stable atrophy (50% of initial muscle mass) with the onset of spastic incomplete paralysis for up to 2 years after SCI (Andersen et al. 1996; Giangregorio et al. 2006). Stable muscle atrophy occurs in long-term paraplegics with complete UMN lesion from 3 to 20 years post SCI (Kern et al. 2007; Biral et al. 2008). Interestingly, most of these studies were related to FES in thoracic level paraplegics and demonstrate that UMN denervated muscles can respond with tetanic muscle contraction when stimulated with commercial electrical stimulators even 20 years after SCI (Kern et al. 2007; Mohr et al. 1997). These features are in sharp contrast, however, to SCI that involve LMN lesions. These injuries generally involve a complete disconnect between the muscle fibres and the nervous system; the accompanying atrophy and degeneration processes are particularly severe when a complete transverse SCI involves all the LMNs of the affected muscles. Complete LMN denervated muscles degenerate quickly and are soon unable to sustain tension during tetanic contractions induced by electrical stimulation (Dulhunty and Gage 1985). Over time, unstimulated muscles become unexcitable with commercial electrical stimulators, so that the long-lasting severe atrophy of the permanently inactive muscles is irreversibly exacerbated by the substitution of myofibres with adipocytes and collagen (Kern et al. 2004; Biral et al. 2008). It is known that in LMN denervated human muscles the degeneration occurs over years; however, the time course is not clear.

18.1.3 Restoration of LMN Denervated Muscle: EU Project RISE

Loss of muscle mass occurs with many pathological conditions and is linked to increased patient disability, morbidity and mortality (Janssen et al. 2002; Fisher 2004) thus, it is important to discover how to deter muscle degeneration. Empirical clinical observations (Kern 1995; Kern et al. 1999) revealed that LMN denervated-degenerated muscle can recover by a specific variation of home-based

daily FES therapy. This is in contradiction to earlier data which suggested that FES was effective only when started immediately after LMN lesion. The observations led to the founding of the European funded project RISE in November 2001. The project aim was to establish the biological basis for a clinical rehabilitation treatment for patients who have permanent muscle LMN denervation in the legs. To this end, it funded research designed to reverse muscle degeneration produced by the permanent lack of innervation in SCI patients using muscle FES. Some of the funding has been used to fund research in rehabilitative centres in Vienna (Austria), Heidelberg (Germany), Hamburg (Germany), Tuebingen (Germany), Reykjavik (Iceland) and Vicenza (Italy). The RISE project has achieved its goal using a multidisciplinary approach to optimize technology to stimulate LMN denervated muscle with custom-designed electrodes and stimulators developed in Vienna, Austria (Mayr et al. 2001). The project encompassed a clinical trial with over 20 voluntary patients and additional animal experiments to research the muscle restoration process by combining physiological, histological, immunohistochemical and biochemical analyses with anthropometric techniques (Kern et al. 2009; Mödlin et al. 2005). Many of the tissue analyses employed to study structural changes occurring in LMN denervated muscle (both after long-term LMN denervation and during electrical stimulation) were performed with biopsies which meant that only a few grams of muscle could be analyzed. Complementary imaging techniques, such as CT scan, were also employed in order to assess and validate histological information. The value of the imaging methods demonstrates that the development and use of non-invasive anthropometric techniques is critical to this area of research.

18.1.4 Objectives

In this chapter, modelling tools and a 3D approach are used to study, display and quantify the structural changes occurring on the quadriceps muscle during long-term denervation and electrical stimulation treatment. In previous studies, the effects on cross-sectional area (CSA) of LMN denervated muscle in SCI patients were monitored by means of CT scans of the thigh, using the top of the trochanter major muscle as the individual reference point. By distally scanning four further cross-sectional (axial) areas at increments of 10 cm, robust morphometric data of the patient's thigh were collected in the course of the EU project RISE. Cross-sectional areas of the left and right thigh muscles, before and after 2 years of h-b FES-training, are reported in Fig. 18.1. The average CSA of *quadriceps muscle* was 27.5 ± 8.2 cm² in the group (n = 25) before FES training (1, red lines), whereas in the FES-trained group (n = 20) it was 36.6 ± 13.8 cm² (2, blue lines). This variation corresponded to the +33% increase in CSA of the h-b FES-trained thigh muscles; this difference was highly significant ($p < 0{\cdot}001$, Mann–Whitney U-test). The CSA values measured by CT scan were very similar in the right (thin lines) and left (bold lines) legs both before and after 2 years of training (red and blue lines, respectively, in Fig. 18.1). This approach provides valuable clinical information, but its limitation is that 5–10 scans over a volume of interest of 40–60 cm are not enough to give comprehensive information on volume, shape and density of the whole muscle.

Here, medical imaging routines, segmentation techniques and special computational tools are developed and used to quantify volumes and tissue characteristics and classify physiological conditions in normal, LMN denervated, LMN denervated-degenerated and LMN denervated muscles treated with FES (in Paragraphs 4 and 5). The results from the segmentation work are used as input to simulate and study activation patterns in muscle to optimize the stimulation techniques (in Paragraph 6). Finally, the induced effects of FES on the quadriceps muscle are measured and displayed on the patella bone (in Paragraph 7).

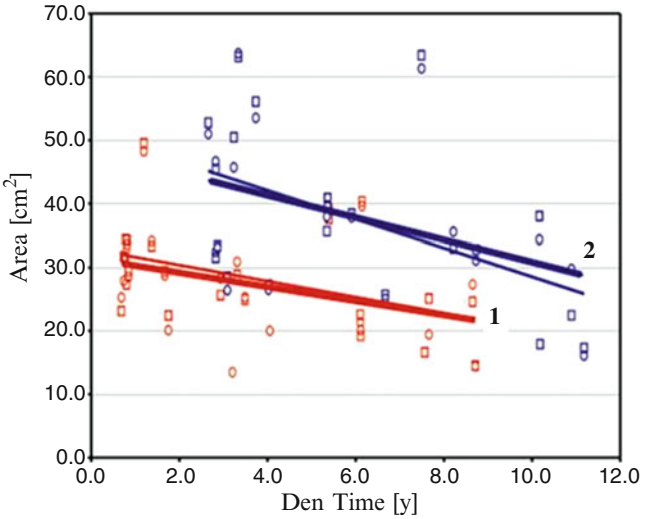

Fig. 18.1 Two years of home-based functional electrical stimulation (h-b FES) of lower motor neuron (LMN) denervated human muscle. Correlation of time spent from spinal cord injury to computer tomography scan area. Muscle cross-section area before (*labeled with 1*) and after functional electrical stimulation (FES) (*labeled with 2*). After FES results are shifted to the right because the values are plotted with respect to the time elapsed from spinal cord injury to computer tomography scans. The medical images are very similar in the right (*displayed with thin lines*) and left legs (*displayed with bold lines*), both before (*labeled with 1*) and after FES (labeled with 2)

18.2 CT Data, 3-D Reconstruction and Segmentation of Muscle and Bone

18.2.1 DataSet Source

X-ray computed tomography (CT) is an imaging method that uses X-rays to produce images of structures 'inside' the body. Patients are scanned slice-per-slice and each slice is scanned several times from different angles.[1] Each imaged volume element (voxel) is traversed, during the scan, by numerous X-ray photons and the intensity of the transmitted radiation is measured by detectors. The measured intensity profile contains information on the densities the beam encountered on its path through the body (i.e. the denser the regions the weaker the signal). With suitable mathematical methods the measured profiles of each slice are transformed into an image of the structures inside – the image is reconstructed, the grey value corresponding to the linear attenuation coefficient.

Three-dimensional data are gathered scanning the patient's lower limbs with spiral CT. The scan starts above the head of the femur and continues down to the knee joint, both legs being covered by one scan. Slice increment is set to 0.625 mm resulting in a total of about 750–900 CT slices, depending on the patient's size.

Every acquired CT slice is subdivided into a matrix of different size, from a minimum of 128 × 128 up to 1024 × 1024 volume elements (voxels). The average linear attenuation coefficient μ of the tissue contained in each voxel is represented by floating numbers in the computer which range from 0.0 up to values equal to 1.0.

Once the image is calculated from the 3D dataset it is converted into a matrix of picture elements (pixels) with each pixel assigned the attenuation value of the corresponding voxel. Linear attenuation

[1]Modern CT scanners might use broader beams and sensor arrays to scan larger regions of the body at once.

Table 18.1 Hounsfield threshold sets for the displaying and the segmentation of main human tissues scanned with Computer Tomography technique

	Threshold sets for computer tomography (HU)	
Anatomical tissues	Min	Max
Bone	226	3,071
Compact bone	662	1,988
Spongial bone	148	661
Muscle	–5	135
Fat Tissue	–205	–10
Skin Tissue	–30	60
Tooth	1,200	3,071

Different intervals of Hounsfield unit (HU) values are associated to main human tissues scanned with Computer Tomography (CT) or spiral CT technique. The intervals are established after experimental experience. The HU value range are set large in order to include, from the same tissue type, HU values from different physiological conditions such as: well trained muscle (displayed with high HU values), atrophic muscle (medium–low HU values), degenerate muscle (low HU values), osteoporosis bone (low HU values) and skin in different dermatological conditions

coefficients are rescaled to an integer range that encompasses 4,096 values, between –1,000 and 3,095. From these intensity readings, the density or attenuation value of the tissue at each point in the slice can be calculated. This scale is called CT number or Hounsfield unit (HU) and it is expressed by the following formula:

$$\text{CT Number} = 1{,}000 \cdot \frac{\mu_{\text{pixel}} - \mu_{\text{water}}}{\mu_{\text{water}}} \tag{18.1}$$

With this scaling, if the linear attenuation coefficient of a given pixel (μ_{pixel}) is equal to that of water, the CT number will be 0. If μ_{pixel} is less than μ_{water} the CT number will be negative which is typical for air spaces, lung tissues and fatty tissues. Values of μ_{pixel} greater than μ_{water} will result in positive CT numbers. Very dense tissue such as bone has large positive numbers.

Table 18.1 is a display of main organic tissues and respective HU intervals.

In the datasets used in this work, each slice consists of 512 × 512 pixels, and each pixel has a grey value in the Hounsfield unit (HU) scale of 4,096 grey-scale values, represented by a 12-bit value. A total dataset from a single scan (for instance of 750 slices) is therefore 512 × 512 × 750 × 12 = 2.36 Giga Bits (ca. 300 MB). This dataset allows a complete high resolution 3D description of the tissue, including the muscles and bones in both upper legs.

18.2.2 Quantitative CT and Calibration

In order to be able to monitor the volume of a patient's muscle in the course of electrical stimulation therapy it is obvious that the volume measurements, which are performed with an interval of several months, have to be comparable and precise, since the smallest change in volume indicates the result of the therapy and answers the question: Is the muscle still degenerating or is it growing in size?

For the volume measurement of the muscle this means that the imaged region must be the same in every scan (i.e. cover the whole thigh in our case) and that the image segmentation scheme applied must not differ either. For the bone density measurements, corresponding areas of the bone have to be identified.

Absolute quantification of muscle density and BMD requires that the CT scans made at different time points be comparable. To achieve this reproducibility, the CT scanner has to be calibrated regularly or even better before each scan. If data are acquired on different CT scanners the standardisation of the scanning protocol and calibration method is essential as well.

In addition to a calibration of the device it is important for the reproducibility to choose the same region of interest. Other factors to take care of are the use of the exact same scanning protocol: slice thickness, X-ray tube voltage and reconstruction algorithm. Selecting the same parameters is essential when the datasets are to be comparable.

Calibration is normally done with a standard phantom. The phantom, typically a circular disk about 5 cm thick and 35 cm diameter, is made up of several different components to estimate spatial and density resolutions. Spatial resolution is tested using decreasing circular rods and density resolutions using rods that gradually decrease in density. These phantoms are also used for testing constancy, that is, to detect possible drift of the scanners' sensors and/or other changes in the scanning instrumentation. If necessary, corrective measures are taken.

In this work we performed phantom measurements for quality assurance of the device once a year. Hydroxylapatite rods are used for single calibration and to determine the BMD equivalent. Additionally, in each scan of the patient's leg, three rods are placed in parallel with the thigh. The rods have a circular cross-section, are different in diameter and one is a pipe containing water. They cover the total length of the scanned region and therefore are present in every CT cross-sectional image. This enables a statistical evaluation and calibration of the density values in all scans.

18.2.3 Image Processing Tools: Segmentation

In the analysis of the objects in images it is essential that we can distinguish between the objects of interest and "the rest." This latter group is also referred to as the *background*. The techniques used to find the objects of interest are usually referred to as segmentation techniques: segmenting the foreground from background. Any segmentation result is a set of pixels that are related to each other in some sense, that is they belong to the same class (e.g. tissue class or an object in an image). This set of pixels is usually called segm*entation mask* or simply *mask*.

In computer vision, segmentation refers to the process of partitioning a digital image into multiple regions (sets of pixels). The goal of segmenting an image is to produce a binary mask image which fulfils the segmentation criteria.

The software environment in which the medical images shown in this chapter were processed and segmented is *MIMICS* (www.materialise.com). The main goal is to reconstruct – from spiral CT data – 3D models of muscle and bones and to isolate RF from other quadriceps muscle in order to study their anthropometrical characteristics in different physiological conditions. The first step in the segmentation process is to establish a threshold, which discriminates the region of interest from the rest by grey value.[2] From the visual point of view, thresholding allows pixels to be highlighted (e.g. in different colours), thereby distinguishing pixels with certain grey values from others. In an M × N CT scan slice, each element in the image matrix *a[m,n]* displays a level of brightness coded by a HU value which varies from

[2]In the case of thresholding, segments (i.e. pixel classes) are defined by ranges of grey values. Spatial information is not used to determine class membership of pixels.

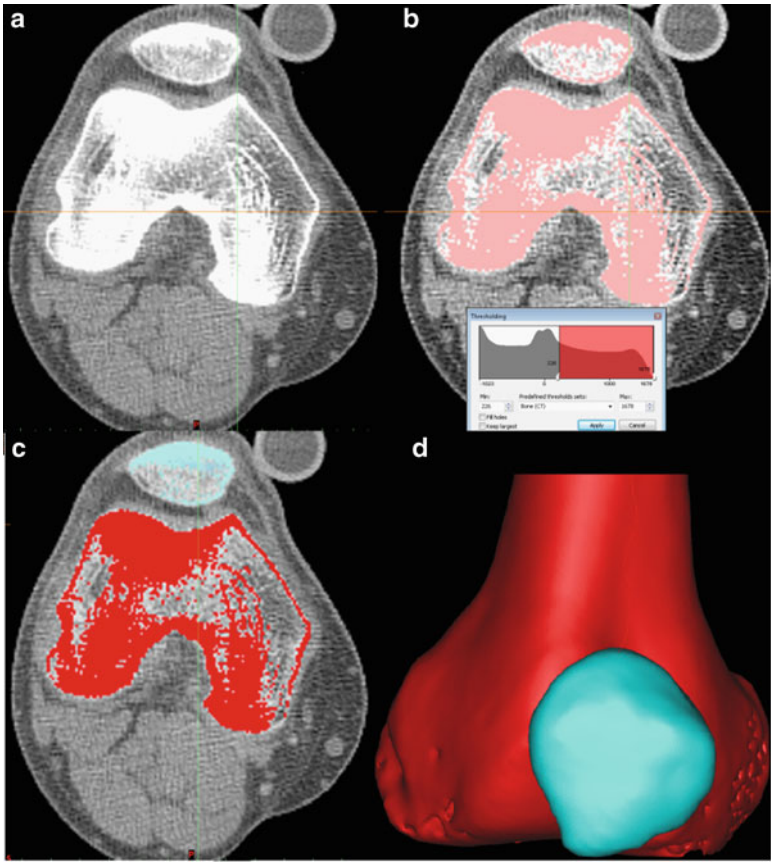

Fig. 18.2 Basic steps to segment medical images: displaying (**a**), thresholding (**b**), region-growing to isolate the region of interest from its surroundings (**c**) and reconstruction and visualization in three dimensions (**d**). Knee cross-section from Computer Tomography scan (**a**). Bones thresholding: 600–2,000 HU (**b**). Selection of the knee cap (patella bone) using region-growing (**c**). Three–dimensional (3D) views from the patella and the femur segment (**d**)

–1024 to 3072. If, for instance, the (HU-) region of interest to be visualized is compact bone in adults (ranging in value between 600 and 2,000 HU), then the threshold test condition will appear as follows:

If $600 \geq a[m,n] \geq 2000$ *then* $a[m,n]$ = *object* = *colour*
Else $a[m,n]$ = *background*

The dataset after thresholding will display only certain information: the pixels having HU values (or more generally grey values when data are not CT scans) within the defined interval are selected and highlighted in color while the others having HU values outside the threshold remain black (Fig. 18.2a, b).

The second segmentation tool which typically follows thresholding is *region growing*. Region growing is an image segmentation approach in which neighbouring pixels of the current region's boundaries are examined and added to the region class if no edges are detected (or more generally some inclusion-criteria is met). This process is iterated for each boundary pixel in the region. An arbitrary *pixel seed* is chosen and compared with neighbouring pixels. The region is grown from the pixel seed by adding neighbouring pixels that are similar, increasing the size of the region. This whole process is continued until all pixels belong to a region.[3] Thus, if in the dataset there are several compact bones not connected

[3]Region growing uses spatial information when determining pixel class membership: pixels that belong to the same region are connected.

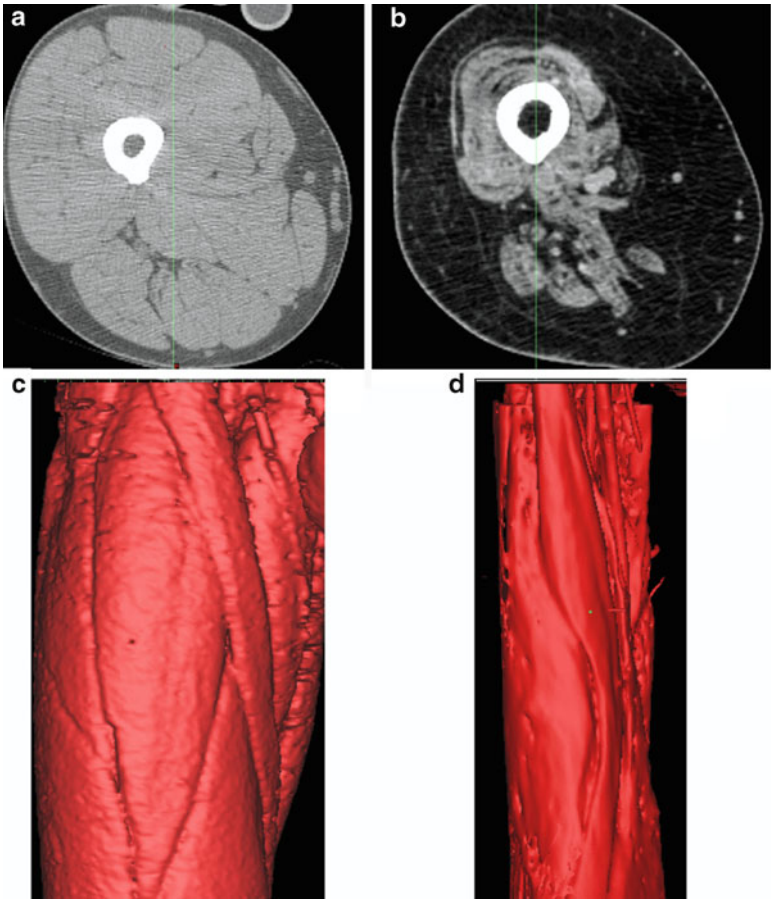

Fig. 18.3 Comparison between muscle morphology in healthy and denervated–degenerated lower extremities. Computerized tomography data from healthy and long-term denervated thigh showing the dramatic muscle volume loss due to degeneration of the muscle tissue: Cross-section healthy thigh (**a**). Cross-section of 4-year-old spinal cord injured thigh (**b**). Three-dimensional model of healthy thigh (**c**). Three-dimensional model 4 years spinal cord injured thigh (**d**)

directly to each other, then using region growing it is possible to display these bones individually though they have the same threshold (600–2,000) (Fig. 18.2c). The region growing condition appears as follows:

If $600 \geq a[m,n] \geq 2000$ *then* $a[m,n] \in$ *pixel seed*
Else $a[m,n] =$ *background*

Typically, the two segmentation techniques described deliver good quality segmentation of the CT images used in this work, sometimes requiring minor manual editing to correct misclassified pixels. After successful segmentation the regions can be converted to and visualized as 3D objects, as seen in Fig. 18.2d.

The main target in this work is to segment and compare quadriceps femoris in normal, long-term LMN denervated, LMN denervated and stimulated muscles. The quadriceps includes four muscles on the anterior side of the thigh: RF, vastus lateralis, vastus medialis and vastus intermedius.

As a consequence of long-term denervation the muscle degenerates dramatically. This can be observed in the cross-sectional areas and the 3D reconstruction of right thighs from normal-innervated after SCI subjects (Fig. 18.3). The muscles become very thin and the single bellies are no longer recognizable in their shape. Only RF remains recognizable among the quadriceps muscles

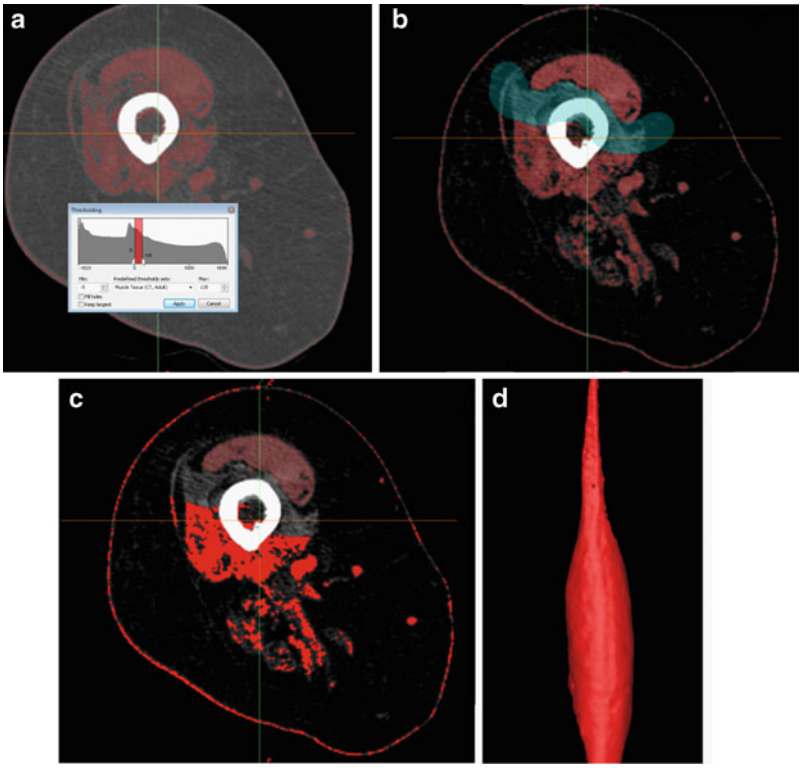

Fig. 18.4 Segmentation of rectus femoris muscle (RF) in lower motor neuron (LMN) denervated muscle. Segmentation of rectus femoris (RF): the muscle threshold is set to –5, 135 HU (**a**); this interval allows a good visualisation of the degenerate muscle belly. Editing contours are used to delete muscle tissues surrounding RF (**b**). Region-growing applied on RF (**c**). Reconstruction and –3D visualization of RF (**d**)

though it is severely degenerated compared to the normal situation. Therefore, 3D modelling and segmentation techniques are used to isolate RF from other bellies and to monitor changes occurring during the degeneration and restoration process.

Besides, accurately measuring changes in RF during electrical stimulation treatment is important to evaluate treatment effectiveness; indeed, surface electrodes are placed on top of the quadriceps and since RF occupies the middle of the thigh it is especially exposed to the current distribution (Mandl et al. 2008). RF is thus the optimal target for monitoring therapeutic effects and morphological changes with a 3D approach (Gargiulo et al. 2007, 2008, 2009).

18.2.4 Segmentation of RF

The threshold interval chosen to segment RF is: [–5, 135] HU. A wide interval is chosen because it must display muscle tissue and allow monitoring of changes, particularly the restoration–degeneration process. Within the selected interval the displayed pixels represent both normal and degenerated muscles, connective tissue and water, but subcutaneous fat is excluded. Thus the surrounding fat in RF is automatically excluded from the segmentation mask (Fig. 18.4a). After thresholding, the next step for the segmentation is to isolate RF from the other muscles. For this purpose special editing tools are used.

The process starts from a cross-section where the muscle boundaries are visible (usually in the middle, along the length of the muscle). A contour is manually drawn around the muscle and projected to the next cross-sections in both directions. If the contour fits the new cross-sectional area well, it is projected ahead unchanged to the next slice, otherwise it is adapted[4] and then projected ahead. The process continues until all cross-sections containing RF cross-sections are edited (Fig. 18.4b). The contour areas are then erased, creating a gap between segmentation target and its surrounding areas. Finally, a new segmentation mask representing RF is created applying a region growing procedure which creates a new mask separating the edited structure that is no longer connected to the surrounding (Fig. 18.4c). The result of the segmentation process and a 3D rendering thereof is shown in Fig. 18.4d.

18.3 Measurement of Volume and Density

Modelling is a unique way to visualize morphological changes occurring due to the degenerative process in LMN denervated muscles and to display electrical stimulation effects on shape and geometry. In addition, the 3D file provides information on muscle density and volume which would otherwise be difficult to access.

Muscle density and volume are immediately available from the segmentation object; these parameters depend on pixel number, size and intensity (generally grey value or HU value in CT scans).

18.3.1 Measurement of Volume

In digital imaging, a pixel or picture element is the smallest piece of information in an image. A voxel instead, is a volume element representing a value on a regular grid in –3D space. The voxel datasets have a limited resolution, as their position is only exact in the centre of each voxel. The value of a voxel may represent various properties; in CT scans it accounts for the opacity of the material to X-rays (the Hounsfield units).

The volume in a 3D file can be generally obtained through the voxel size and number of voxels in the 3D object. In biological tissues this is more complicated and there are additional issues to consider. The image that results from the assumption that a voxel within a dataset is occupied by one single material is an approximation of the reality because of real dimensions involved in biological tissue. As the voxels are not infinitesimal in size, the result is a measured value that is a mean attenuation value for the different materials or tissue types in each voxel. This will be the case especially for the voxels lying at the border of the object or voxels covering objects thinner than the voxel's dimensions. This lack of resolution can be somewhat overcome by assigning mean values to these voxels and then using interpolation algorithms.

In *Mimics* which we use for segmentation and modelling, there are two different algorithms that can be used to compensate partial volume effects. The first is called *contour interpolation* and compensates partial volume effects in 2D (i.e. in each cross-section). The second method is *grey value interpolation* which uses also consider neighbouring voxels in the above and below slices. The latter algorithm is more accurate but tends to deliver noisy 3D models, which makes it less useable for medical images. Incorporating partial volume effect compensation greatly improves 3D model rendering accuracy.

[4]Assuming that shapes change little from one slice to the next the adaptation necessary is small. It is done with active contours that "snap" to boundaries.

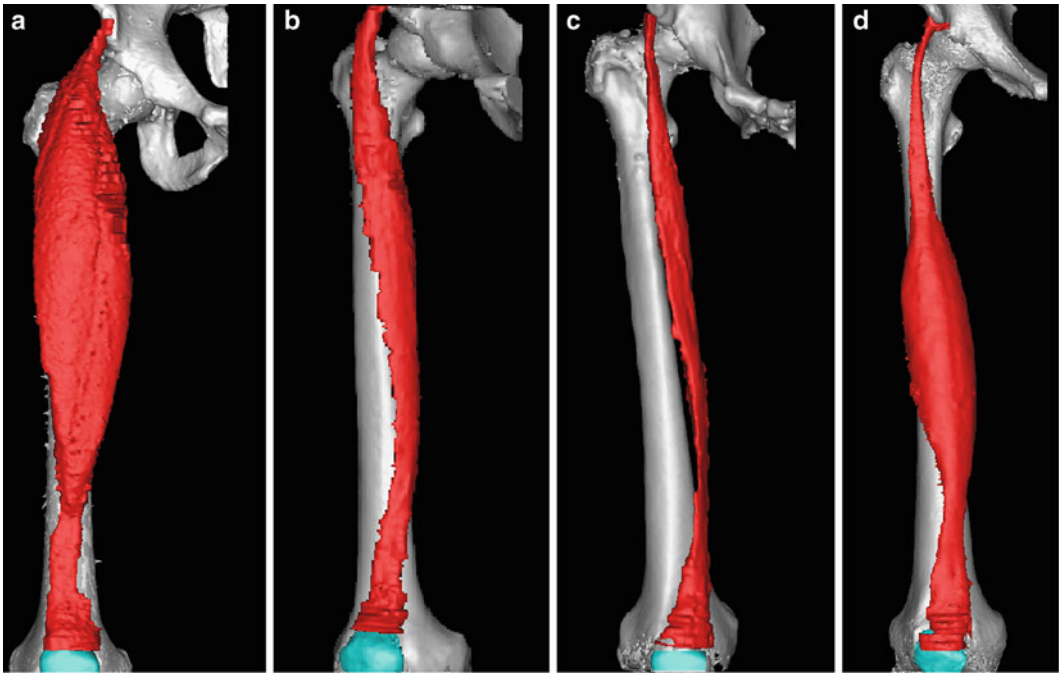

Fig. 18.5 Rectus femoris (RF) in different physiological conditions: reconstruction and –3D visualization. Rectus femoris volume in different physiological conditions: healthy, volume: 354,000 mm^3 (**a**). Ten months after spinal cord injury (SCI), volume: 106,000 mm^3 (**b**). Seven years after SCI, volume: 86,000 mm^3 (**c**). Seven years after SCI with 4 years home-based functional electrical stimulation treatment (h-b FES), volume: 145,000 mm^3 (**d**)

In this work the contour interpolation algorithm was used to visualize the 3D model of RF and the grey value interpolation algorithm to calculate and measure the muscle volume. Figure 18.5 depicts the 3D reconstruction and the volume measurement in: normal, short-term LMN denervated, long-term LMN denervated and LMN denervated-restored RF, while the restoration process is seen in Fig. 18.6.

18.3.1.1 3D Reconstruction and Volume Measurement in: Normal, Short-Term Denervated, Long-Term Denervated and Denervated-Restored RF

Anthropometric techniques have allowed us to follow the degeneration of denervated muscle in terms of muscle volume over a long time course. In Fig. 18.4, we show muscle thresholding of four different RF muscles. The 3D reconstruction of these muscles is shown in Fig. 18.5. The first, in Fig. 18.5a, is a normal RF muscle with a volume of 354,000 mm^3. It is the biggest one of the four with a characteristic distribution of the tissue mass. It has reached considerable diameter already at the height of the trochanter but is slimmer in its lowest one third part. In Fig. 18.5b is a RF muscle 10 months after flaccid paralysis. Its volume is reduced to 106,000 mm^3 in a relatively muscular individual. The upper part of the muscle shows considerable loss of diameter. It can be seen in Fig. 18.5c how the degeneration process continues. The volume of the muscle is reduced to 86,000 mm^3 and it is slim along its entire length. Figure 18.5d shows a denervated-restored RF muscle. After a 4-year period of degeneration, FES was applied for 4 years. In response, the muscle volume increased to 145,000 mm^3 but the tissue distribution in not the same as in a normal RF muscle as can be seen by comparing Fig. 18.5a, d. In Fig. 18.5d the muscle is slim until well

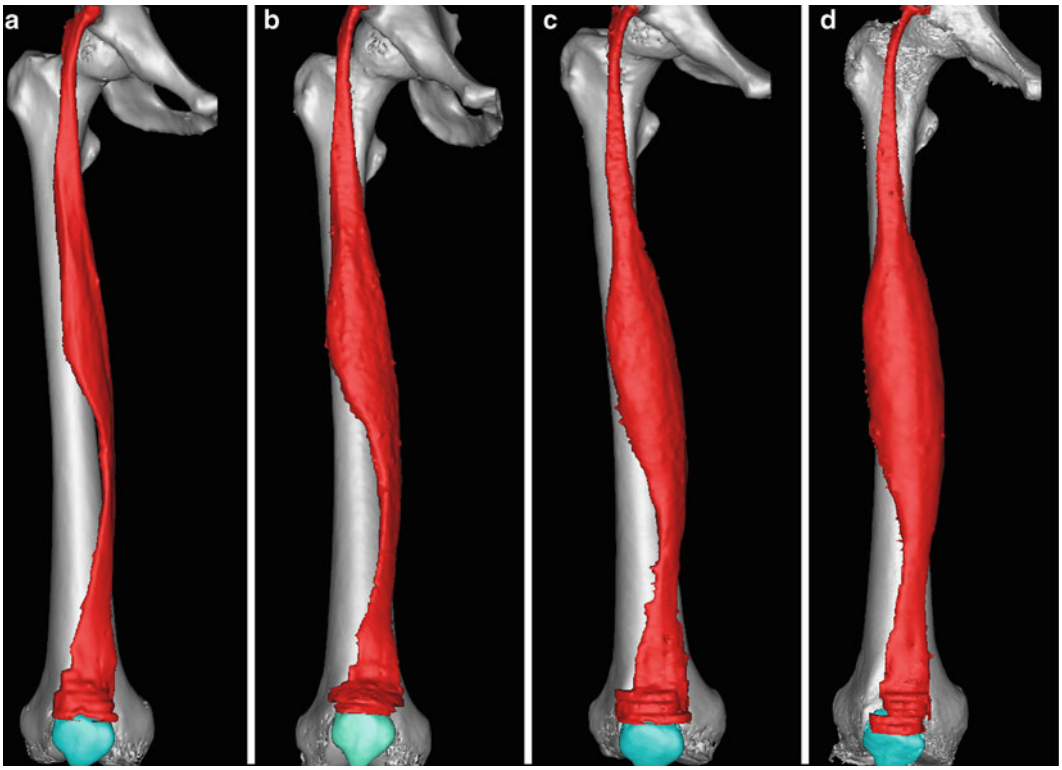

Fig. 18.6 Rectus femoris growth during 4 years of h-b FES treatment: reconstruction and –3D visualization. Changes in muscle volume (RF) during 4 years of h-b FES. The patient started the treatment 4 years after spinal cord injury with RF volume of 93,000 mm^3 (**a**). Muscle volume: 140,000 mm^3 after 1 year h-b FES (**b**). Muscle volume: 165,000 mm^3 after 3 years h-b FES (**c**). Muscle volume: 167,000 mm^3 after 4 years h-b FES (**d**)

below the trochanter and has its biggest diameter in the middle to lower part of the muscle. The explanation of this is probably that the stimulation is not reaching all the muscle fibres in the muscle which is of the pennatus form.

18.3.1.2 Restoration Process: Muscle Volume Measurements Reveal Positive Effect of FES

Volumetric data have allowed us to strongly demonstrate the highly restorative effects of FES. Electrical stimulation treatment is known to increase the volume of spastic muscles (i.e. muscles with an intact LMN). In that case, the neuron connected to the muscle is stimulated, as it has a lower stimulation threshold than the muscle fibres. Each nerve axon is connected to many muscle fibres and by stimulating those axons all connected muscle fibres contract and are "trained". Because this can be done with a stimulating pulse frequency causing tetanic contraction in the muscle fibre, the muscle can be trained effectively.

In a denervated muscle where there is no LMN, the muscle fibres have to be stimulated directly. In a degenerated stage, for example, after 2 years of inactivity, the stimulating threshold of het muscles has risen and the diameter diminished. Activating these muscle fibres requires stimulating currents of two to three orders of magnitude higher than those used for spastic muscles. This means that the duration of the stimulating pulses approach 100 ms limiting the frequency to values below 10 Hz, which is not enough for a tetanic contraction of the muscle fibre.

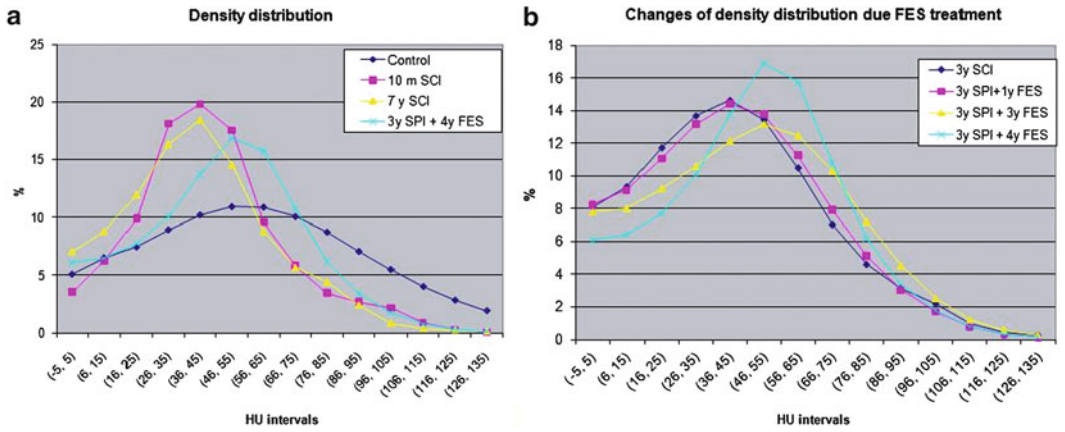

Fig. 18.7 Density distribution from rectus femoris (RF) in different physiological conditions (**a**). Changes of RF density due to h-b FES treatment (**b**). Density distributions from RF in different physiological conditions: control (*circular dots*), 10 months after spinal cord injury (SCI) (*rectangular dots*), 7 years after SCI (*triangular dots*) and 7 years after SCI with 4 years h-b FES treatment (*converging arrow dots*) (a). Density distributions during h-b FES treatment: patient 3 years after SCI at beginning of the h-b FES (*circular dots*), after 1 year h-b FES (*rectangular dots*), after 3 years h-b FES (*triangular dots*) and after 4 years h-b FES (*converging arrow dots*) (**b**)

The initial effect of the electrical stimulation treatment of the muscle fibres is to lower the stimulating threshold, meaning that stimulating pulses can be shortened to values below 40 ms thus enabling frequencies up to 20 Hz. As the stimulation threshold is lowered, training with tetanic contraction of the muscle can begin (Kern et al. 1999). The effect of the tetanic electrical stimulation treatment is a recovery in muscle fibre diameter up to normal values and a rise in muscle force which, however, does not reach normal values (Kern et al. 2005).

Because the action potential is not conducted from one muscle fibre to another, each and every fibre has to be stimulated by the electrical current. This has to be considered when designing the stimulating electrode geometry. If the muscle fibres are lying parallel in the longitudinal direction of the muscle (fusiformis) then they can be more easily stimulated that if they are placed like fibres in a feather (pennatus form).

18.3.2 Measurement of Density

Muscle density is a parameter describing the structural integrity of the tissue. The anthropometric techniques we have applied here, have allowed us to obtain a more accurate measure of muscle density and to better gauge the effects of FES to denervated muscle. To measure muscle density, it was necessary for us to determine the voxel intensity within the muscle volume. In this work, we evaluated the RF muscle density by monitoring the number of voxels in the interval [–5 to 135] HU. To visualize and analyze the distribution, the HU interval is divided into 14 sub-intervals with 10 HU values each and changes are measured between these intervals from datasets taken from the same subject at different points in time.

The number of voxels in each interval is displayed as a percentage of the overall distribution.

Figure 18.7a displays the density distribution in normal, LMN denervated, LMN denervated-degeneration and LMN denervated electrically restored RF. The number of voxels (percentage of

total) is on the ordinate axes and the HU intervals are located on the abscissa. Muscle density distributions from normal, LMN denervated, LMN denervated-degenerated and LMN denervated-restored muscle are displayed in the same panel.

The control distribution shows that in normal muscle most of the values are distributed between 26 and 85 HU with a mean value of 54.5 HU. The situation is completely different in degenerated muscles where, depending on the degree of degeneration, the muscle density is decreased. Density mean values for RF after 10 months and 7 years from SCI are 45 and 40 HU, respectively. A patient who has been injured for 8 years but receives FES for only 4 years shows a mean density value of 47 HU.

The restoration process as change in muscle density is displayed in Fig. 18.7b. The density restoration process induced through the stimulation treatment is qualitatively represented by the shifting of the distribution towards denser values (Fig. 18.7b). The mean density 4 years post SCI is 37 HU. In response to FES treatment, it changes as follows: 36 HU after 1 year, 42 HU after 3 years and 47 HU after 4 years of electrical stimulation treatment.

18.4 Quantitative Analysis of Muscle Tissue by Quantitative Colour 3D Imaging

18.4.1 Muscle Biopsy Versus 3D Modelling

In order to study the changes in tissue composition on a larger muscle section, with the intent of supporting and validating histological analyses from minute tissue biopsies, a new non-invasive method was developed to analyze macroscopic and microscopic structural changes of human skeletal muscle. The advantages of using segmentation technique and 3D modelling are mainly two: (1) the analysis of whole muscle and (2) the potential to isolate single muscle bellies such as RF. We applied the technique to our studies of degenerating muscle as described here.

The degeneration process completely changes muscle physiology and fibre structure. Fig. 18.8a shows the light microscopy aspects of a biopsy harvested from normal human muscle, which is characterized by large, well packed muscle fibres with minimal inter-fibre space. In normal muscle, some loose connective tissue could be observed around the vessels only if the biopsy contained some endomysial tissue. On the other hand, muscle tissue harvested from thigh muscles of paraplegic subjects 4 years after a severe conus cauda lesion is characterized by a patent degeneration of the tissue, which presents as severely atrophied muscle fibres, prevalent areas of loose connective tissue and some adipocytes (Fig. 18.8b). After an additional 3 years of LMN denervation, during which time the subjects performed home-based FES training, the light microscopy specimen of the muscle biopsy shows numerous large muscle fibres despite the still abundant intermyofibre fibrous tissue. The biopsy area covered by muscle fibre transverse sections are indeed more than 95% in the normal muscle, decreased to 14% after 4 years of LMN denervation and recovered to 37% during the 3 years of FES training.

This approach gives important indication of the changes occurring in the muscle tissue but on a very restricted volume. Further, the method is invasive and, therefore, only a limited region can be analyzed and no more than two time points are typically studied in SCI patients.

The size of the volumetric element (a voxel) in the dataset presented in the previous paragraphs is approximately 0.7 mm^3; therefore the CT number assigned to the voxel represents an average of

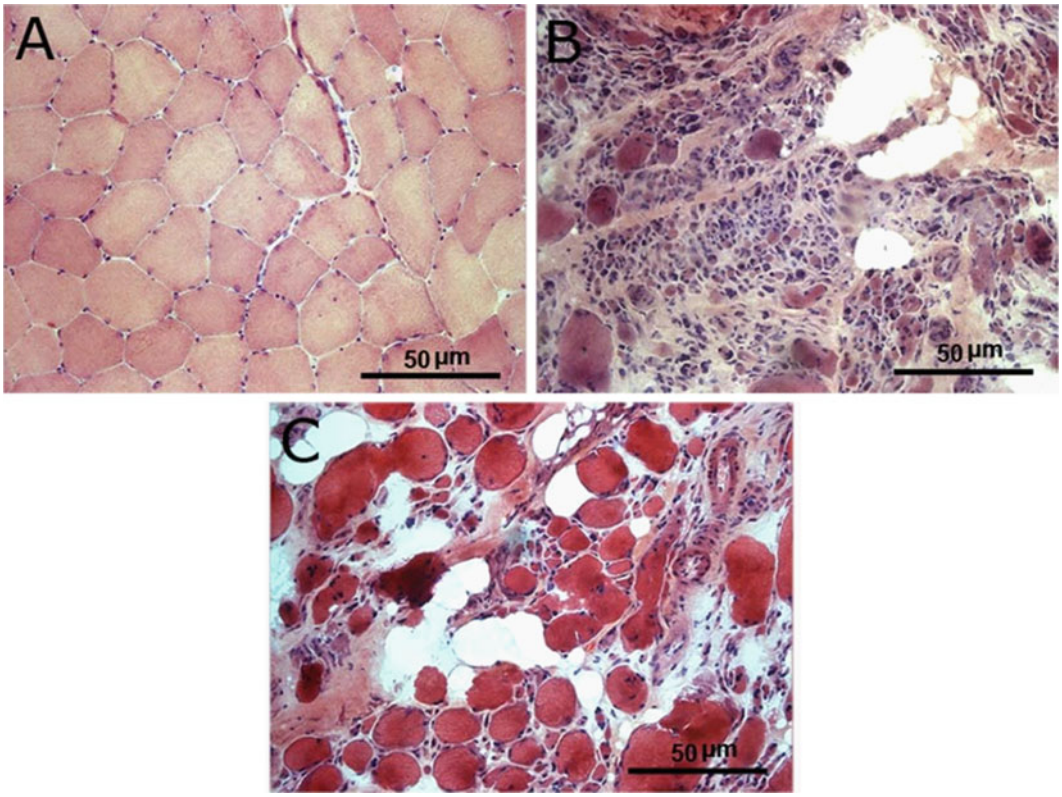

Fig. 18.8 Muscle biopsy from muscle tissue in different physiological conditions. Biopsies harvested from different human muscles: normal-innervated (**a**). Muscle tissue harvested from thigh muscles of a paraplegic subject 4 years after a severe conus cauda lesion (**b**). Biopsies harvested from the same subject after 7 years of LMN denervation, but who underwent home-based FES training during the last 3 years (**c**)

the different biological elements, which may be present within a single elementary volume. For instance, in the case of normal muscle tissue, a voxel would contain the transverse section of 20–50 muscle fibres, which is approximately one tenth of the volume analyzed with the typical needle muscle biopsy (Kern et al. 2004) as displayed in Fig. 18.7 (where a section of around 0.02 mm² presents the cross-sections areas of about 50 fibres).

Muscles are normally displayed with CT number between 40 and 90 HU, though within a normal muscle belly there are also other tissue elements such as connective tissue and fat, which are coded with much lower CT numbers. The different tissue elements express their specific CT number if such tissue completely occupies the voxel volume; otherwise the CT number will be an average of different values. This fact explains the wide range of values present inside a dataset and suggests the definition of various intervals to study muscle structural changes. Therefore, to estimate the tissue composition in the muscle volume, the CT numbers present within the segmented volume are subdivided in four HU intervals and displayed with different colours. Thresholds: [–200; –10], [–9; 20], [21; 40] and [41; 135] representing, respectively, fat (yellow), connective tissue (cyan), low dense/atrophic (pink) and normal muscle tissue (red) (Fig. 18.9). The muscle tissues are generally coded with HU values between 40 and 80 although, in the muscle belly region, a minimum amount of voxels are coded with higher HU values. We account for these values (81–135 HU) as muscle tissue in order to improve segmentation and 3D visualization. Table 18.2 is a display of the percentage values of tissues in RF volume in different clinical conditions.

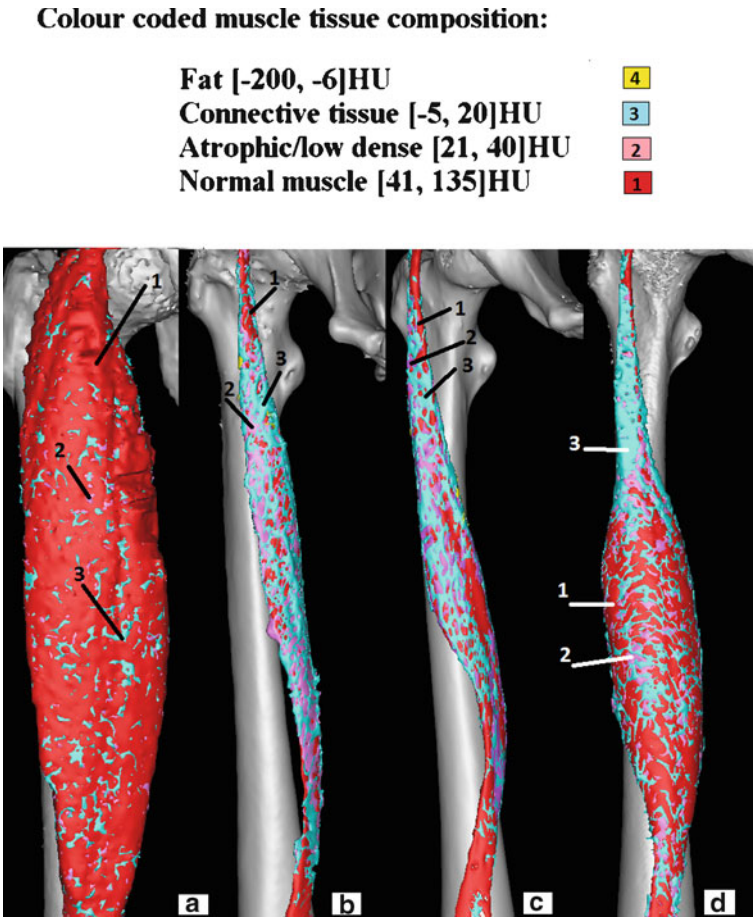

Fig. 18.9 Quantitative muscle tissue composition. Quantitative colour –3D model displaying tissue composition from control-innervated RF according to the muscle tissue composition colour coding legend above: normal muscle fibres (*labeled with 1*) 64%, atrophic muscle fibres 17% (*labeled with 2*), connective tissue 14% (*labeled with 3*) and fat 5% (*labeled with 4 but not visibile on the surface of the 3D-model*) (a). Seven years of muscle LMN denervation without FES: normal muscle fibres 41%, atrophic muscle fibres 31%, connective tissue 20% and fat 8% (b). 4 years of muscle LMN denervation without FES normal muscle 45%, atrophic 24%, connective 23% and fat 8% (c). The same muscle displayed in (c) after 4 years of electrical stimulation treatment: normal muscle fibres 60%, atrophic muscle fibres 20%, connective tissue 16% and fat 4% (D)

Table 18.2 Tissue composition from rectus femoris muscles (RFM) in different physiological conditions

	Percentage of tissue in RF volume			
Subjects	High dense muscle tissue	Atrophic-low dense muscle tissue	Connective tissue	Fat
Healthy Control	64	17	14	5
Patient 1 at 4-years denervation -Before FES	45	24	23	8
Patient 1 at 8-years denervation, with 4 -years FES	60	20	16	5
Patient 2 at 7-years denervation without FES	41	31	20	8

Percentage of tissues in RF volume measured on subjects in different physiological conditions: healthy, 4 years LMN injury (patient 1), 4 years LMN injury and 4 years h-b FES treatment (patient 1) and finally 7 years LMN injury (patient 2)

18.4.2 Quantitative Colour 3D CT Imaging of Normal, Long-Term LMN Denervated and FES Treated Muscle

Quantitative colour 3D analysis is an extremely valuable tool, enabling researchers to evaluate the specific tissue content of muscle structures. This is extremely important because the ratio of muscle to adipose to connective tissues is an invaluable indicator of muscle health. Here, we apply colour 3D CT imaging to the evaluation of FES treatment on normal and denervated muscles.

Figure 18.9a shows the 3D reconstruction of a control-innervated RF and its muscle tissue composition. Although the majority of RF volume has CT numbers above 40 HU, there is still a considerable amount of pixels displaying low density muscle tissues (which are 17% of the total) and different tissues such as fibrous and loose connective tissue and fat (which are 19% of the total). The effects of long-term muscle LMN denervation were evaluated performing Quantitative Colour 3D analysis on two patients in different clinical conditions: (1) 7 years and (2) 4 years after SCI and consequent muscle LMN denervation in the lower limbs (respectively displayed in Fig. 18.9b, c). Both muscles appear to be surrounded with connective tissue and atrophic fibres, suggesting that the fibrous content of the cortical layer of these long-term LMN denervated muscles substantially contributes to the physical properties of the 3D voxels of the muscle external layer (epimisium).

For the second patient, the analysis was performed 4 years after SCI, just before starting the electrical stimulation treatment (Fig. 18.9c). In Fig. 18.9c, d are displayed, respectively, the quantitative colour 3D reconstructions of the same RF with its cortical tissue composition before home-based FES training and 4 years after treatment. It has to be emphasized that clinically speaking, the latter presents a state of additional 4 years of LMN denervation, but 4 years during which the patient was submitted to daily electrical stimulation. The improvement in the muscle volume is clearly visible. The restoration process induced through electrical stimulation treatment is also unquestionable. Indeed as a result of FES treatment, the high density muscle fibres increased from 45% to 60% of the whole volume while connective and adipose tissues were reduced by 30% and 50%, respectively, after the 4 years of treatment. The fact that very large cutaneous electrodes and high energy are needed to stimulate these muscles demonstrates that the recovery is not a result of late reinnervation (which would be very unusual 5 years post LMN SCI).

18.5 Computational Models to Simulate and Study Activation Patterns

The model for FES of degenerated LMN denervated human skeletal muscle consists of four parts:

- Membrane model
- Fibre model
- Electrical model of the external electrical field
- Coupling between external field and fibre

The membrane model is a modified Hodgkin–Huxley model that accounts for changed membrane properties due to denervation (Reichel et al. 1999), e.g. reduced excitability due to an inclined number of ion channels. For the fibre, a compartment model is used that describes the propagation of action potentials along the fibres. In the case of LMN denervated fibres, the muscle tissue is excited directly without the mediation of a nerve. The electrical field created by the electrodes is modelled as a quasi static volume conductor problem and the coupling between the field and the fibre, i.e. the

reaction of the fibre to the externally applied field is described by two activating functions, which are a consequence of the compartment model. The classical, or second order activating function (AF2) allows estimation of the excitation process in the middle of a fibre (Rattay 1990), whereas the terminal or first order activating function is suited for describing activation at the locations of fibre endings (Reichel et al. 2002).

This paragraph illustrates a typical data processing pipeline and the steps involved in the creation of two computational models: a finite element (FE) model and a finite difference (FD) model of the spatial distribution of the electrical potential in human lower extremities during FES. Activation patterns can then be estimated from the potential distribution with the application of the concept of activating functions and fibre models. Membrane model parameters can be varied after the computation of the electrical field: studying activation patterns is therefore decoupled from the electrical field distribution.

The processing pipeline described assumes a properly segmented 3D volume dataset as the starting point; the origin of the data has thus no influence on the model design process: it can be of any 3D capable imaging modality. (See Fig. 18.10 for an illustration of the processing pipeline.) The stimulation electrodes are added to the segmented images as additional segments.

18.5.1 FE Model

The first step in the creation of the FE model is the extraction of the surfaces of the segments with standard image processing methods, i.e. identifying border voxels and subsequent triangularization. The extracted surfaces are represented in the form of triangular surface meshes (Fig. 18.11) and serve as the starting point for subsequent volume meshing. The result is a 3D tetrahedral quality Delaunay mesh (see Fig. 18.12).

The success of the meshing task depends very much on the geometry and topology of the domain in consideration (see below for detailed discussion).

Another approach would be to use all the voxels of the 3D dataset to produce a trivial mesh of the complete region (i.e. mesh every single voxel) and try to simplify the mesh afterwards. Memory consumption of the trivial mesh has to be considered when taking this trail.

There are a number of commercial and open source software packages available for meshing. A prominent and popular package with a free licence for research and non-commercial use is Tetgen (http://tetgen.berlios.de), which was used for all models shown in this paragraph.

After assignment of electrical properties to the segments the FE model is solved. For the distribution of the electrical field in LMN denervated muscle, see Fig. 18.13. The results shown here were produced with COMSOL Multiphysics (COMSOL, Inc. Burlington, MA USA, www.comsol.com)

18.5.2 FD Model

Assigning electrical properties (conductance) to voxels is the first step required for the buildup of the FD model. The actual (large, but sparse) system of linear equations describing the model is then built by considering a discrete formulation of the conductor problem

$$\operatorname{div} \vec{j} = \vec{\nabla} \cdot \left(\vec{\sigma} \vec{E} \right) = \vec{\nabla} \cdot \left(\vec{\sigma} \left(-\vec{\nabla} \phi \right) \right) = 0 \tag{18.2}$$

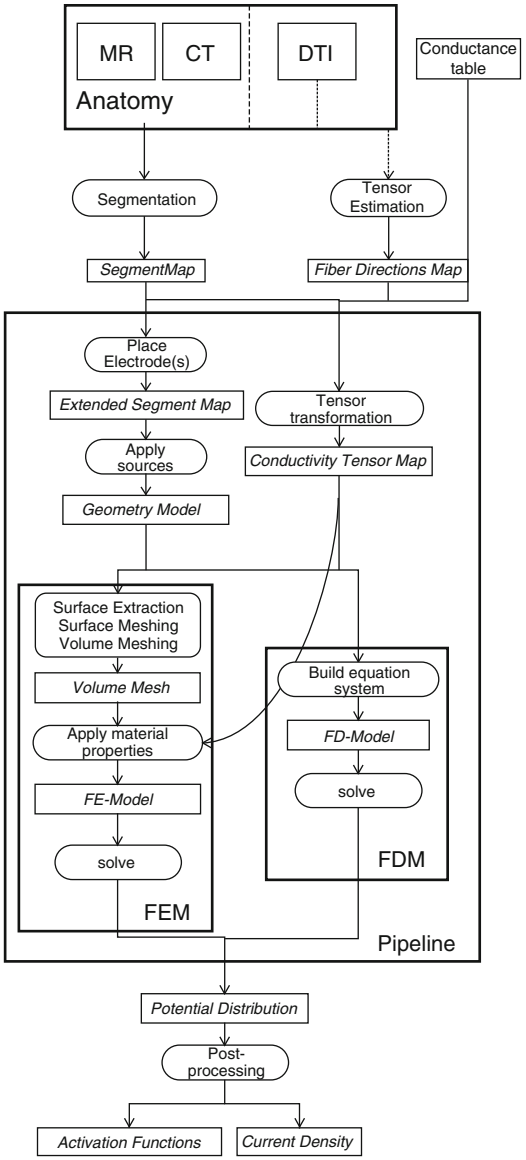

Fig. 18.10 Illustration of a typical Data Processing Pipeline. In the Data Processing Pipeline rectangles represent data, whereas round nodes stand for processing steps. The dotted line shows a possible dataflow that is currently not implemented

for each voxel in the domain. The discrete formulation establishes a relation between a center voxel and its neighbours that leads to the description with a system of linear equations. The result is a number of Voxels x number of Voxels sized matrix that needs to be inverted, which can be done with any suitable solver. All FD models shown in this paragraph were solved with the MATLAB implementation of the minimal residuum method (Barrett et al. 1994; Paige and Saunders 1975).

See Fig. 18.13 for the distribution of the electrical potential.

All calculations and figures shown in this subsection were produced with MATLAB (The MathWorks, Inc, Natick, MA, USA).

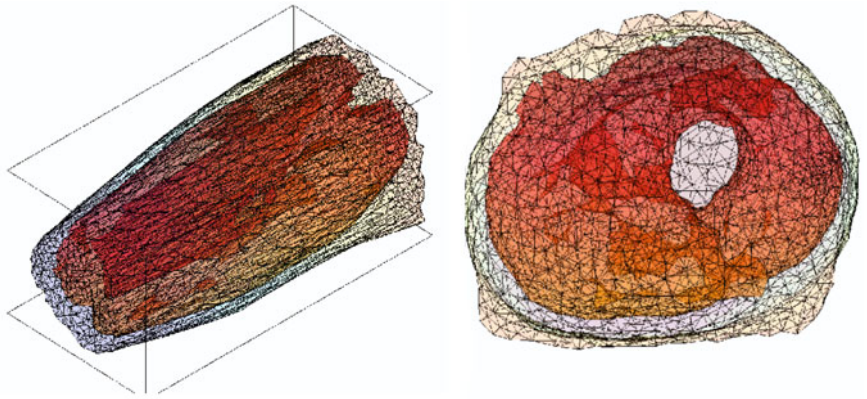

Fig. 18.11 Surface mesh of the fat and the muscle segment in axial (*top*) and general 3D (*bottom*) perspectives. The images illustrate the intersection-free containment hierarchy: the (*inner*) muscle surface is entirely within the surface of the fat segment. The colours used have no significance. For illustration purposes, the dataset was meshed with a lower resolution

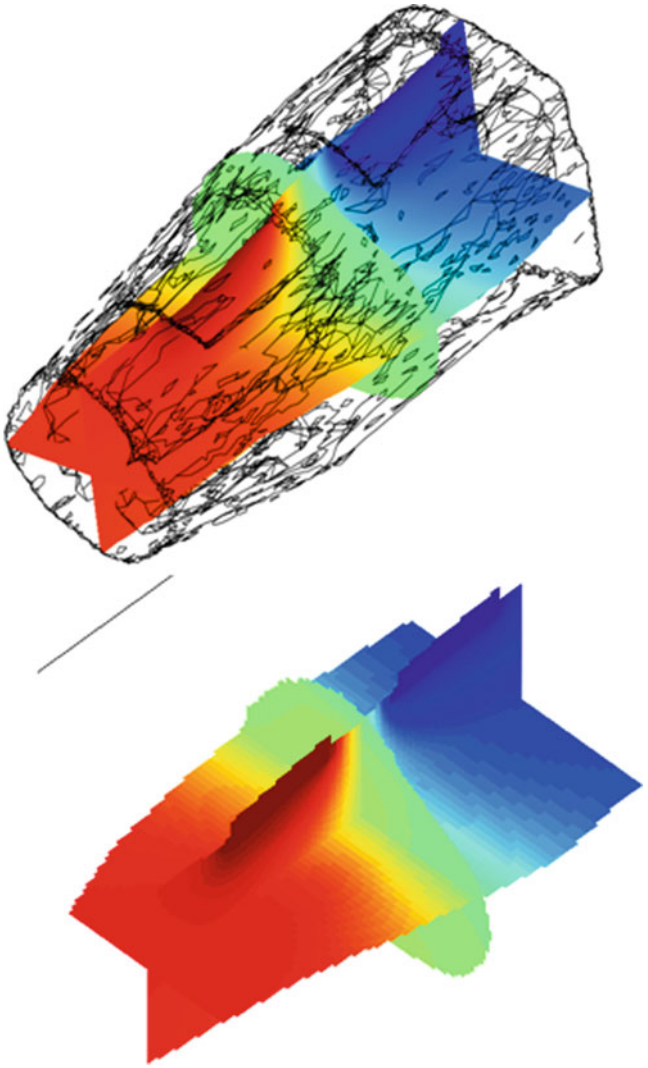

Fig. 18.12 Results of finite element FE (*top*) and a finite difference FD (*bottom*) simulation of the same Geometry Model. The electrodes are modelled as voltage sources (+/–1 V). The first step in the creation of the FE model is the extraction of the surfaces of the segments with standard image processing methods, i.e. identifying border voxels and subsequent triangularization. The extracted surfaces are represented in the form of triangular surface meshes and serve as the starting point for subsequent volume meshing. The figure shows the result which is a 3D tetrahedral quality Delaunay mesh

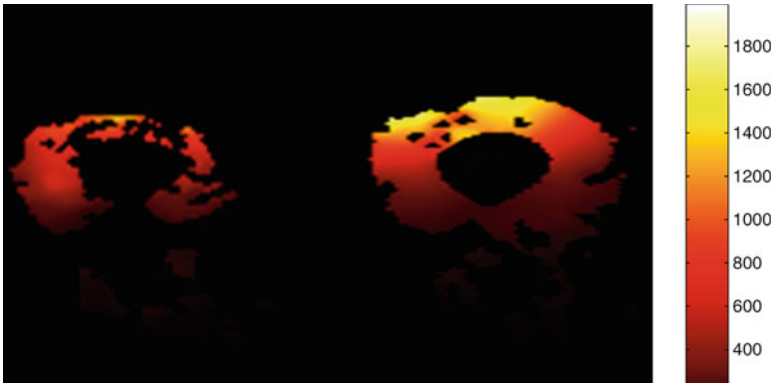

Fig. 18.13 Terminal activation function in a cross-section between the stimulation electrodes of the same patient after 2 years of denervation (*left*) and after another 2 years of FES (*right*). Note how activation extends into the hamstrings, which leads to the experimentally observed co-contractions in well-trained patients as well as the increased spread of activation after FES training

18.5.3 Post Processing

Once the distribution of the electric potential is calculated with either the FE or the FD model, a number of interesting quantities can be calculated with computational software such as MATLAB or octave (www.gnu.org/software/octave). Quantities of interest include the electrical field, current density and the two activating functions. For an illustration see Fig. 18.13. Note how the activation extends into the hamstring muscles, which leads to the experimentally observed co-contractions in well trained patients as well as the increased spread of activation after FES training.

18.5.4 FE Versus FD

The data processing pipeline discussed illustrates the steps typically involved in the creation of two computational models for FES. Similar steps are necessary for other bioelectric problems such as deep brain stimulation. The most difficult or rather sensitive step is the creation of the volume mesh for the FE model. This is because the geometry and topology of biological structures are far from regular and "well behaved" in a geometrical sense. Segments are often broken apart into several regions; especially in LMN denervated patients, there are small and thin structures present as well as more complex topologies, i.e. regions with holes and three-segment borders, e.g. between bone, muscle and fat. All this leads to complications that make the volume meshing process somewhat unstable and challenging. It can, however, be resolved by simplifying the given geometry, e.g. application of erosion or other morphological operations (to the segmented images) to further separate close borders between segments or eliminate small or thin structures entirely. To achieve an intersection-free containment hierarchy of the segments (every closed border of a segment borders only with one other segment) it might be necessary to alter the geometry: dummy slices can be added to extend the domain further (where the influence on the electrical field between the electrodes is assumed to be negligible), thereby ensuring that, e.g., the bone segment is entirely contained within the muscle segment. As a last resort there is also manual mesh optimization and repair, a rather time consuming process.

These troubles should be overcome with the development widespread availability of methods for creating meshes from volumetric data without the intermediate step of surface meshing.

In comparison with the complex and time-consuming meshing process the creation of the FD model seems appealingly straightforward. Complex geometries and topologies pose no problem and do not jeopardize the creation process. However, FD models are less memory sufficient in the sense that high detail (number of elements) is present in areas where it would not be necessary given the geometry and complexity of the problem. In FE models one would start with a coarse mesh and refine the mesh in regions where more detail and accuracy is desirable. In FD models one would have to decrease the grid spacing globally (and thereby increase the number of elements drastically), which produces higher demands on the machinery in terms of memory.

Further, model quality depends heavily on the segmentation it uses as a starting point – this aspect has been discussed elsewhere. However, we might add that a rigorous and robust solution to the automatic segmentation task should lead to significant improvement once it is available. Looking even further upstream in the pipeline, to the source of the medical image data, it seems likely that with higher resolutions, less (or better controllable) artifacts and more advanced imaging technologies the models will improve at the same time. Inclusion of fibre directions with the help of Diffusion Tensor Imaging (DTI) as it is already almost routinely performed in white brain matter will add important aspects and realism to the FES models as well. DTI has already been applied to human skeletal muscle; however, the validity of the information obtained in LMN denervated, degenerated muscle has not yet been verified or validated.

18.6 Effects of Electrical Stimulation on Bone Density

18.6.1 Bone Mineral Loss in Paraplegic

Shortly after the SCI the bones of the paralyzed extremities atrophy and lose minerals. Osteoporosis is one of the major complications in patients with SCI. Immobilization of paraplegic patientsinduces severe bone loss: the bone becomes more and more fragile and there is a dramatic increase in the risk of fracture. SCI causes immediate and permanent gravitational unloading. The result is a disuse structural change with associated metabolic consequences.

Alternative to the medications other treatment like electrical stimulation has been showing beneficial effects on bone strength. Indeed electrical stimulation for bone repair has been used for three decades to treat inadequate healing of the fracture (pseudoarthrosis) and bone non-union (Lind 2001). Mechanical or electrical stimuli of relatively low amplitude and high frequency can influence bone formation and resorption in vitro and in vivo, suggesting that these modalities can be used clinically to inhibit or reverse loss in bone density.

In this section bone density on the patella (knee cap) is measured in different clinical conditions in order to study bone structural changes as secondary effect of the electrical stimulation treatment.

18.6.2 Modelling Patella Bone

The patella bone is chosen as study volume to monitor changes in BMD during FES treatment. The patella bone is a good sample to study changes in density; it is a small bone with triangular shape which articulates with the femur and covers and protects the knee joint from external applied force.

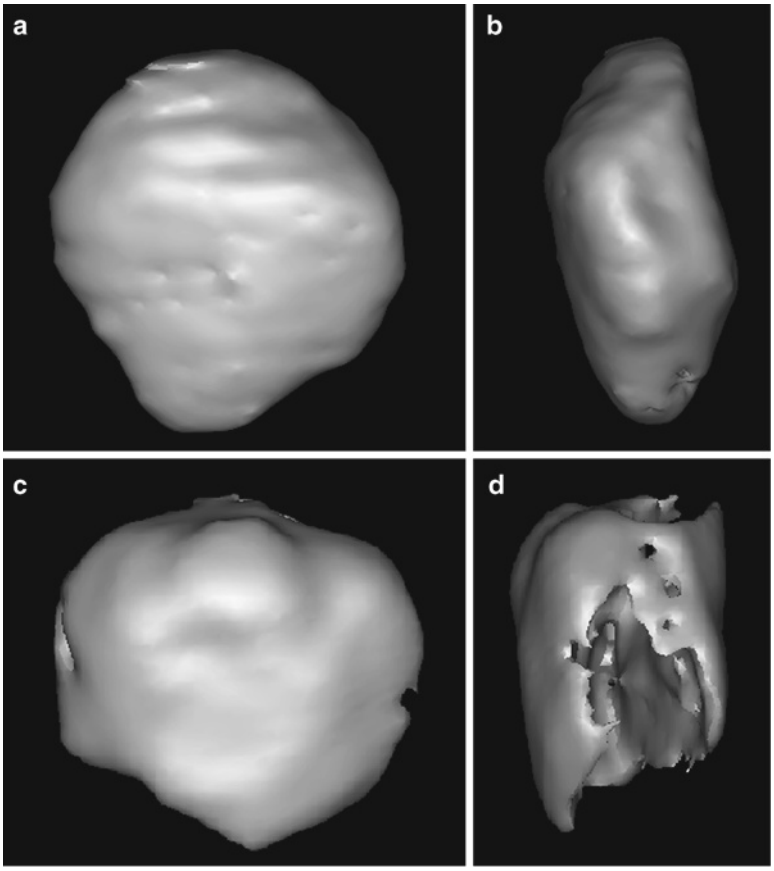

Fig. 18.14 Three-dimensional reconstruction of patella bone: healthy versus 4 years LMN spinal cord injury. Three-dimensional reconstructions of patella bone in normal condition from a healthy subject: front view (**a**) and lateral view (**b**). In spinal cord injured subject, 7 years of LMN paraplegia: front view (**c**) and lateral view (**d**)

Besides, since all four parts of the quadriceps muscle attach to the patella via the quadriceps tendon, the patella bone is a perfect candidate to study structural changes induced by quadriceps contraction. Vastus intermediaus and RF muscle are attached to the base of the patella while vastus lateralis and vastus medialis are attached to the lateral and medial borders of the patella, respectively. The patella bone is attached to the tendon of the quadriceps femoris muscle, which in healthy subjects contracts to extend/straighten the knee.

In paraplegic patients with flaccid paralysis and therefore completely LMN denervated, the patella is unloaded; the only possible load is induced by the contractile activity generated in the muscle with FES treatment. Indeed the patella is outside the electrical field generated by the stimulation and therefore changes in density can be attributed exclusively to the contraction force transferred to the patella from the quadriceps muscle.

The information used to study the patella's bone are extracted from the CT data, in fact the patella is isolated from the surrounding using the segmentation techniques described in paragraph 3.

The dramatic effects of bone loss in SCI are seen in Fig. 18.14: the 3D model reconstruction of patella bones from a control-innervated subject are shown in Fig. 18.14a and 7 years SCI patients in Fig. 18.14b.

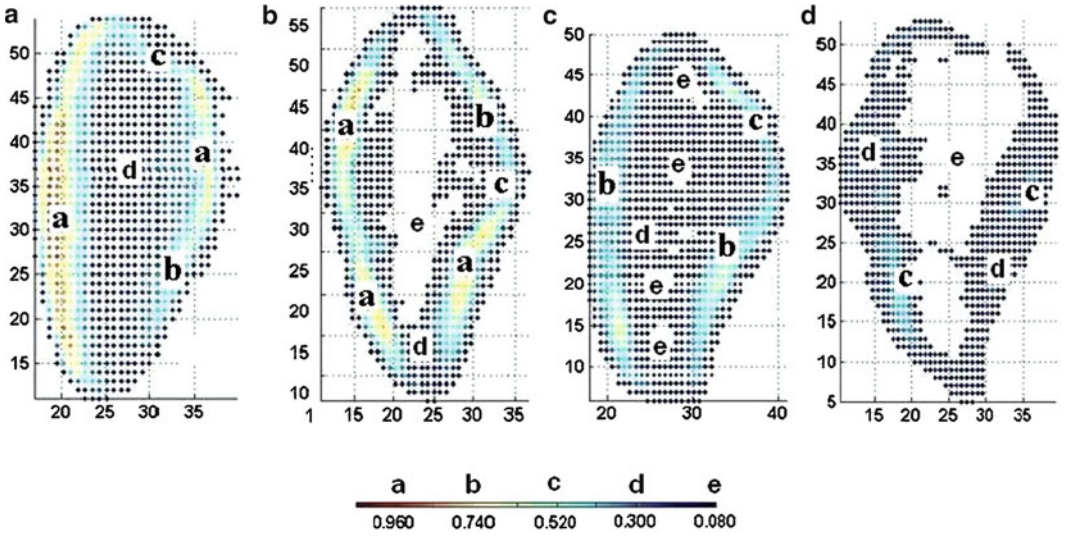

Fig. 18.15 Map the local bone mineral density (BMD) distribution on patellas in different physiological conditions. Axial view and associated mean bone mineral density (MBMD) value from patellas in different clinical conditions: Healthy MBMD = 0.281 g/cm³ (**a**), 6 years denervated with 5 years h-b FES MBMD = 0.193 g/cm³ (**b**), 4 years denervated MBMD = 0.144 g/cm³ (**c**) and 7 years denervated MBMD = 0.106 g/cm³ (**d**).The BMD values are mapped with letters: the pixels with the lowest BMD are marked with e while the pixels with the highest BMD are marked with a.

18.6.3 Bone Mineral Density Measurement on the Patella

Evaluation of the bone density is performed by a conversion of HU values contained in the segmentation masks to the respective BMD values. Bone density is the amount of bone tissue in a certain volume of bone (g/cm^3). Bone mineral density is a test that measures the amount of calcium in a special region of bones. From this information, an estimate of the strength of the bones can be made. BMD helps predicting the risk of a future fracture of the bone, measures the amount of bone mass, and also monitors the effectiveness of treatment. BMD was measured using a special X-ray technique called quantitative computed tomography (QCT) (Jóhannesdóttir 2006; Helgason 2005). The normal, average BMD is around 0.388 g/cm^3 in males and 0.290 g/cm^3 in females. Individuals with a BMD lower than 0.10 g/cm^3 need certain care (Donina 2002).

An algorithm was designed in Matlab (Jóhannesdóttir 2006; Gargiulo 2008) that scaled the data and converted it from HU to BMD. The BMD distributions are displayed in the three segmentation planes: coronal, axial and sagittal. The BMD distributions from patella in different physiological conditions are depicted in Fig. 18.15. The BMD values are colour coded and mapped with letters (Table 18.3): pixels with low BMD in blue (marked with **e**), and pixels with high BMD in red (marked with **a**).

In the control patella a less dense area on the cortical bone facing the knee joint (patella back side) can be noticed, when compared to the front side; this can be seen clearly in the axial and coronal planes. The probable explanation is the fact that the patella function is protecting the knee joint from external force and therefore the front side which is in general more exposed to these solicitations and to unexpected stress (e.g. fall or accident) develops stronger bone structure.

The other panels in Fig. 18.15 show changes in BMD distribution as a consequence of LMN injury and when the muscles are treated with FES. Fig. 18.15b depicted the BMD distribution of a

Table 18.3 Bone mineral density intervals

	Bone mineral density intervals	
Label	Min (g/cm³)	Max (g/cm³)
a	0.800	1.070
b	0.600	0.799
c	0.400	0.599
d	0.200	0.399
e	0	0.199

Letters from **a** to **e** are associated to different BMD intervals in order to localise on the patella's cross sectional areas displayed in Fig. 18.15 where are the regions with high, medium or low bone density

Table 18.4 Patella mean bone mineral density (MBMD) values from subjects in different clinical conditions

Patella's	Mean bone mineral density value (g/cm³)
Control, healthy	0.281
6 years LMN, 5 FES	0.193
4 years LMN, no FES	0.145
7 years LMN, no FES	0.106

The patella's MBMD values are calculated from subjects in different clinical conditions. The table shows that the MBMD value is better in the subject undergoing electrical stimulation treatment for his quadriceps muscle compared to the other two subjects in similar clinical conditions but not undergoing stimulation

patella from 6 years LMN denervated subject treated with FES; though the decrease in bone density is remarkable compared to the healthy subject (Fig. 18.15a) it is clear that the bone density is better here than in Fig. 18.15c, d, respectively, displaying patella's from 4 and 7 years LMN denervated subjects not treated with FES.

To quantify the overall bone mineral content in the patella, the mean bone mineral density value (**MBMD**) is calculated using the following formula:

$$\mathbf{MBMD} = \left(\frac{\sum \mathrm{BMD}}{N} \right) \tag{18.3}$$

where $\sum BMD$ is the sum of BMD values in all voxels in the dataset and N is the number of voxels in the dataset.

The quantitative measures of **MBMD** values for the patellas in Fig. 18.15 are summarised in Table 18.4.

18.7 Applications to Other Areas of Health Care: Medical Modelling for Planning of Maxillofacial Surgery

We demonstrate here that computer modelling techniques and rapid prototyping technologies can be used to enhance biological research, specifically in the area of muscle physiology. These anthropometric techniques are also invaluable to applied medicine. For example, these methods are being employed to develop computer and physical models which are used to plan and support different surgical treatments such as complex fractures, tumours, maxilla traumas and malformations. This present section reviews the use of segmentation techniques and modelling for planning maxilla facial surgery and particularly to support the treatment of retrognathia which is a malformation where the maxilla or the mandible is further posterior than normal. The surgical process in use to correct this malformation is called distraction osteogenesis. It involves gradual, controlled displacement of surgically created fractures which results in simultaneous expansion of soft tissue and bone volume. The procedure of mandibular osteogenic distraction involves sectioning cortical bone at the site of distraction. The distraction device (the distractor) is mounted on either side of the jaw. The distractor either may be attached directly to the bone or may be partially tooth borne. Gradual distraction is then performed at a rate of 1–2 mm/day, which is done incrementally. Distractors, for intraoral use, have been developed to eliminate extra oral scars. It is complicated and frustrating to position and manipulate these devices during surgery.

The use of 3D models makes the operation easier and more accurate; indeed it is possible to adjust the distractor on the physical model (Fig. 18.16) and use the device directly on the patient after a previous sterilization. Further, the mandibular nerve, which must be protected

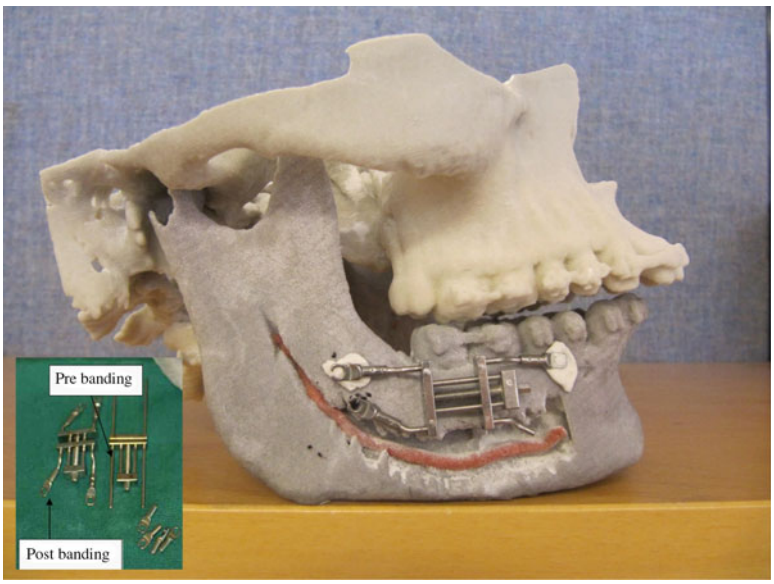

Fig. 18.16 Three-dimensional model used in surgery for the evaluation and planning of maxilla facial treatments. Three-dimensional model of a maxilla and the jaw previous operation; the model displays the mandibular nerve within the bone. The model is used for treatment planning and to bend the distractor device directly on the physical model of the previous surgery

from damage during the treatment, is rendered visible on the model (Fig. 18.16). Using it, the surgeon can check nerve position very accurately during the operation by placing the model in a sterilized bag.

A survey of over 20 surgeries of this type, where 3D models have been used to plan intraoral distraction in mandibular lengthening, shows that the length of time for the surgery was shortened by 25–35% (ca. 1–1.5 h).

18.8 Practical Methods and Technique

18.8.1 Measuring Volume of the Rectus Femoris Muscle

(a) Measuring the volume of the rectus femoris muscle (RFM) we start by taking a spiral computer tomogram (spiral CT) of the whole muscle. The subject is laid on the CT bench –a movable bench that can slide through the circular hole in the CT device – the legs towards the CT device. It is best to have the legs in a parallel position. If the person is paralysed it might be necessary to fix the position of the foot, the ankle joint and the knee with either strap or tape. The legs can be fastened to each other and/or to the bench.

(b) First an overview of the patient is taken with a single projection image to determine the position of the hip and knee joints. Then the spiral CT is taken starting from a tangent between the hip joint continuously down to below the knee joints. This covers the whole RFM including its tendons. By scanning one slice image after another is taken of both legs.

Typically the thickness of a slice is 1.25 mm and the distance between two adjacent slices is 1.25 mm. These parameters can be adjusted independently to some extent. Thinner slices mean higher spatial resolution, higher radiation dose and higher noise. Less distance between two adjacent slices, even less than the thickness of the slices, means not only higher resolution or less noise, but also higher radiation dose. For a 45 cm long scan and 1.25 mm distance between slices, the number of slices is 360. If the distance is reduced to 0.675 mm the number of slices is 667.

The scan data are stored on a CD disk in DICOM format to be read by software for post processing of the images.

(c) Post-processing of the CT scan images can be done with software independent of the CT scanners (e.g. Mimics from Materialise, Leuven, Belgium). CT images in DICOM format can be imported into most post-processing software. Once imported, the task is to isolate the RFM from the other tissue types. This is called segmentation and is done in a specific sequence. First, the upper and lower limits of the tissue density inside the muscle are determined (upper and lower threshold). Second, the computer searches for all voxels with density inside the limits (thresholding). Third, starting with an arbitrary voxel seed, neighbouring voxels of the current region's boundaries are examined and added to the region class if some inclusion-criteria are met. The region is grown from the voxel seed by adding in neighbouring voxels that are similar, increasing the size of the region. This whole process is continued until all pixels belong to some region (region growing). The last step of the segmentation is to separate the RFM from other muscles. This is done in an interactive way since the boundaries cannot

be detected automatically in all cases. A contour is drawn around the muscle and this shape projected to the next cross-section in both directions. This contour is modified to fit the next cross-section if necessary. This is done in all slices.

The contour areas are then erased, creating a gap between segmentation target and its surroundings. Finally, a new segmentation mask representing RF is created applying a region-growing procedure which creates a new mask separating the edited structure that is no longer connected to the surrounding. Now we have segmented the RFM and the volume can be determined, i.e. measured automatically by the software.

Summary Points

- Anthropometry is the study of human body measurements. It can be applied in numerous fields, including engineering, sociology, psychology, physics, biology and medicine. It has a huge potential to improve the quality of human life in many areas, specifically in medicine.
- In this work, anthropometry techniques are applied to research in muscle physiology, with the aim of evaluating long-term changes in denervated human muscle and the therapeutic effects of FES treatment.
- Image processing and segmentation techniques are used to construct (from spiral computer tomography data) –3D models of muscle and bone and to isolate RF from other quadriceps muscles in order to study the anthropometrical characteristics in different physiopathological conditions.
- Segmentation techniques are capable of measuring volumes and density of specific regions of interest.
- Anthropometric techniques demonstrate that the LMN denervation–degeneration process can result in: (1) reduction of muscle volume to 1/5 of a normal muscle; (2) loss of electrical stimulation excitability using commercial devices; and (3) reduction in tissue density.
- Advanced medical imaging tools are used to monitor macrostructural changes occurring in human skeletal muscle undergoing LMN denervation–degeneration. Detailed tissue composition and large muscle surface characteristics are measured and used to support and validate typical histological analyses.
- Image processing and segmentation techniques show that LMN denervated–degenerated muscle can recover in terms of volume and density by home-based daily FES (h-b FES) using large electrodes and high-energy electrical currents.
- Properly segmented medical image data are used to construct patient-specific numerical models in several fields. With a numerical model of FES, the activation patterns of LMN denervated muscle can be simulated, studied, and, most importantly, optimized to establish more efficient training set-ups for the benefit of patients
- Tissue composition analysis by quantitative colour –3D imaging on the whole RF shows increased content of muscle fibres and decrease of connective and fat tissues, the effect of electrical stimulation treatment
- Bone mineral loss measured on knee cap (patella) seems to be decreased in subjects performing home-based electrical stimulation treatment of thigh muscles.

Key Features

Tables 18.5–18.7.

Table 18.5 Key features of image segmentation and medical modelling for LMN denervated muscles

1. Image segmentation and 3D modelling are anthropometric techniques which have broad applications in numerous fields, including physiological research and medicine.
2. Medical modelling is defined as the creation of highly accurate physical and/or computational models of human anatomy and its functions directly from medical scan data.
3. In computer vision, segmentation refers to the process of partitioning a digital image into multiple regions. The goal of segmentation is to extract information about the region of interest from the dataset of a scan.
4. The main stages of the medical modelling process are: (1) to determine the protocol that enables an appropriate visualization of the region of interest; (2) to gather medical images from CT or MRI; (3) to import the data into special image processing software; (4) to segment organs or tissue; and (5) to develop the information to be modelled.
5. Segmentation techniques enable the isolation of anatomic structures (e.g. muscle bellies) and the subsequent study of normal and abnormal morphologies (e.g. the morphology of normal and denervated muscles).
6. Image segmentation and 3D modelling can be used to monitor the effects of medical treatment on anatomic structures and their function (e.g. the effect of FES on muscle size, force and function).
7. Modelling the function and behaviour of biological structures (e.g. LMN denervated muscles) can allow for the improvement of treatment technology and protocols.

This table lists the key facts of image segmentation and medical modelling for LMN denervated muscles, including definitions methods and uses

Table 18.6 Key feature of X-ray and spiral computer tomography

1. Clinical X-ray CT is the measurement of an object's X-ray absorption along straight lines.
2. Clinical CT scanners have an X-ray focal spot that rotates continuously around the patient while a cylindrical detector positioned on the opposing side of the X-ray tube records the absorbed radiation.
3. In spiral CT, data acquisition is performed continuously while the patient moves at constant speed through the gantry.
4. No discontinuities between adjacent images (absence of interscan delay) will result in a spiral CT.
5. Spiral scans provide better image quality than conventional scans. This, however, requires more computational work for optimal image reconstruction.

This table lists the key features of X-ray and spiral computer tomography

Table 18.7 Key facts on DTI and fiber tracking

1. DTI is a Magnetic Resonance Imaging Method based on the MR method of Diffusion Weighted Imaging (DWI).
2. Image contrast in DWI contains information on the diffusion of water[a] in a certain direction specified by the orientation of additional gradients during acquisition.
3. DTI is the acquisition of a series of DWI of several different diffusion directions with the purpose of estimating a diffusion tensor for every voxel. From this tensor, the main diffusion directions of water can be calculated.
4. In highly directional tissue such as brain or muscle tissue the main diffusion direction corresponds to the fibre direction.
5. A method called Fiber Tracking can be employed to estimate fibre paths in tissue from DTIs.
6. Since the diffusion information is a loss of signal (in the DWI images, when compared to non-DWIs) several acquisitions are often necessary for a sufficient signal to noise ratio (SNR). This and the fact that DWIs need to be acquired for several different directions in order to be able to estimate the diffusion tensor with sufficient accuracy makes this a time-consuming method.
7. DTI and Fiber-Tracking methods are applied to estimate fibre tracts in the brain.

This table lists the key facts of Diffusion Tensor Imaging

[a] When the imaged nucleus is ^{1}H, and other ^{1}H-containing compounds are neglected

Acknowledgements The authors wish to express their sincerest gratitude to the following institutions and funds:

RANNÍS the Icelandic Centre for Research, Science Fund of Landspítali University Hospital of Iceland, the Icelandic Students Innovation Fund (NSN), the European Union Commission Shared Cost Project RISE (Contract n. QLG5-CT-2001-02191), the Austrian Ministry of Transport Innovation and Technology "Impulsprogramm", Research Funds from the Ludwig Boltzmann Institute for Electrostimulation and Physical Rehabilitation (Wilhelminenspital, Vienna, Austria), the Italian C.N.R. funds, the Italian MIUR funds and the PRIN 2004–2006 Program.

The authors also wish to express their sincerest gratitude to Dr. Amber Pond of Purdue University, West Lafayette, Indiana for in-depth discussions and critical reading of the manuscript.

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Chapter 19
Upper Limb Muscle Volumes in Adults

Katherine R. Saul, Scott L. Delp, Garry E. Gold, and Wendy M. Murray

Abstract Muscle force-generating properties used in models are derived from measurements of muscle architecture, such as volume, cross-section, and fiber length. While the peak force a muscle can produce is related to its physiological cross-sectional area, several studies of muscle architecture have shown that muscle volume is an excellent predictor of joint moment-generating capacity, and is an important parameter for evaluating strength in the upper limb and for model development. Researchers have classically relied on dissection of cadavers to assess architectural properties of the muscles of the upper limb, including muscle volume, fiber length, sarcomere length, and pennation angle. Medical imaging approaches, including computed tomography, magnetic resonance imaging, and ultrasound have also been used to assess muscle force-generating properties in living subjects. In this review, the strengths and weaknesses of these approaches for assessing muscle volume in the upper limb are discussed. The volumes of muscles in the upper limb as measured by a number of researchers are summarized and compared. A study in which a magnetic resonance imaging approach is used to assess the muscle volumes of all the muscles crossing the shoulder, elbow, and wrist in living subjects is highlighted. It has been shown that the distribution of muscle volume in the upper limb is highly conserved across these subjects with a threefold variation in total muscle volumes (1,427–4,426 cm^3). The studies discussed in this review provide normative data that form the basis for investigating muscle volumes in other populations, and for scaling computer models to more accurately represent the muscle volume of a specific individual.

Abbreviations

CT	Computed tomography
MRI	Magnetic resonance imaging
PCSA	Physiological cross-sectional area
TE	Echo time
TR	Repetition time

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_19,

19.1 Introduction

Humans vary greatly in size and shape, yet biomechanists often use generic musculoskeletal models with average parameters to evaluate muscle function and coordination. While this approach allows researchers to investigate general principles underlying human movement, it is unclear how conclusions derived from studies of generic models apply to individuals of different sizes.

Muscle force-generating properties used in models are derived from measurements of muscle architecture, such as muscle volume, physiological cross-sectional area, and optimal fiber length (Zajac 1989). While the peak force a muscle can produce is related to its physiological cross-sectional area (defined in more detail below), several studies of muscle architecture have shown that muscle volume is also an excellent predictor of joint moment-generating capacity (Fukunaga et al. 2001; Holzbaur et al. 2007a). When compared to an anatomical cross-sectional area, muscle volume is a better predictor of strength in the upper limb (Akagi et al. 2009). Therefore, muscle volume is an important parameter for evaluating the strength of upper limb muscles and for developing models of the upper limb.

Frequently these parameters are determined via cadaveric studies of muscle architecture. However, cadaveric specimens may not accurately reflect the absolute or relative sizes of muscles in young, healthy subjects. Cadaveric studies of muscle architecture often focus on individual muscle groups; this is especially true for the upper limb, where muscle parameters have been measured separately for the shoulder (Langenderfer et al. 2004), elbow (An et al. 1981; Murray et al. 2000), and forearm and wrist (Jacobson et al. 1992; Lieber et al. 1990, 1992). Thus, there are excellent data describing the relative size of muscles acting about a single joint in cadaveric specimens, but the relative sizes of muscle across joints in living subjects has not been evaluated in many studies.

Several fundamental questions must be answered. What are the relative sizes of muscles in the upper extremity? Are the relative sizes of muscles consistent across subjects with different total muscle volume? How is muscle volume distributed among muscles crossing the shoulder, elbow, and wrist? In this review, we describe measurements of upper limb muscle size using dissection and various imaging techniques. In addition, we focus on a study in which these questions were addressed by measuring volumes of 32 muscles of the upper limb in young healthy subjects using magnetic resonance imaging (MRI) (Holzbaur et al. 2007b). This review provides a comprehensive evaluation of muscle volumes in the entire upper extremity.

19.2 Physiological Cross-Sectional Area

The isometric force a muscle can generate depends on the number of fibers in a muscle, the lengths of the fibers, and the orientation of the fibers relative to the tendon (Gans 1982). Physiological cross-sectional area (PCSA) is just one of a number of quantitative measures that are used to characterize the structural design of a muscle, often referred to as muscle architecture (Lieber and Friden 2000; Zajac 1989). PCSA is a measure of the muscle's total volume, normalized so that the maximum isometric force-generating capability of muscles with different numbers, lengths, and orientations of fibers can be directly compared based only on anatomical measurements.

The relationship of PCSA to the maximum isometric force a muscle can produce has been established experimentally. Of particular interest is a study by Spector et al. (1980) that quantified the forces produced by the soleus and the gastrocnemius in adult cats *in situ* and also characterized the architectural design of the contralateral muscles in the same animals. This study demonstrated that if the total volume of a muscle was normalized by optimal fiber length (the fiber length at which

maximum isometric force is produced), and this normalized volume was corrected for the pennation angle of the fibers (the orientation of the fibers relative to the tendon), the resulting "physiological cross-sectional area" was directly proportional to maximum isometric force. Thus, PCSA provides an anatomically based, quantitative measure of the relative force-generating capacity of muscles of different sizes and architectural design. In fact, if PCSA is scaled by the specific tension of individual muscle fibers (the force generated per unit area), which can be considered to be a constant for all muscles (Zajac 1989), maximum isometric force can be accurately predicted.

Important points to keep in mind are embedded in the definition of PCSA. First, calculated PCSA is only proportional to the maximum force a muscle can produce if volume is normalized by *optimal* fiber length (Lieber 1993). This caveat about optimal fiber length is an important point because the force a muscle can produce varies with fiber length and muscles are capable of producing force over a large range of fiber lengths (Gordon et al. 1966). In addition, the traditional definition of PCSA incorporates a correction factor for pennation angle; specifically, the normalized volume is multiplied by the cosine of the pennation angle. This was critical in the study described above because the forces produced by the cat muscles were quantified by attaching their tendons to a force transducer. The force transmitted through the tendon differs from the force developed by the muscle fibers when the fibers are not oriented along the line of pull of the tendon.

Comparing PCSAs among muscles with different architectural designs allows researchers to quantitatively understand differences in force-generating capacity between muscles. However, when comparing the same muscle (i.e., the triceps brachii from a small female to the triceps brachii of a large male) or muscle groups across individuals, it seems that differences in muscle volume dominate the observed variability across subjects. For example, while in one study the relative variance (standard deviation/mean) of triceps volume was 47% (Holzbaur et al. 2007b), optimal fascicle length in triceps long head has been shown to have a relative variance of only 17% (Murray et al. 2000). It is for this reason that muscle volume is an excellent predictor of joint moment-generating capacity (Fukunaga et al. 2001; Holzbaur et al. 2007a), and why muscle volume is of such importance for researchers interested in understanding upper limb function from the context of *in vivo* anatomy.

19.3 Cadaveric Approach

The most common method by which the distribution and architecture of muscle has been assessed has been via dissection of cadaveric specimens. Typically, fresh frozen upper limbs are thawed and the muscles dissected and fixed in formalin, after which the architectural measurements can be made. This approach has the advantage of allowing detailed characterization of the volume, cross section, muscle belly and fiber length, tendon length, pennation angle, and sarcomere length of muscle. It is straightforward to combine these measurements to calculate PCSAs of individual muscles, which can then be scaled by specific tension to calculate the maximum isometric muscle force human muscles can produce. Because muscle forces cannot be directly measured in human subjects noninvasively, these results are of general interest. In addition, maximum isometric force is also an important parameter in biomechanical models (Zajac 1989).

Several studies have characterized the muscles of the upper limb using a cadaveric approach. Architecture of the forearm and hand muscles have been measured by Brand et al. (1981), Lieber et al. (1990, 1992), and Jacobson et al. (1992). The architecture of muscles crossing the elbow (An et al. 1981; Murray et al. 2000) and shoulder (Bassett et al. 1990; Langenderfer et al. 2004; Veeger et al. 1991; Wood et al. 1989) have also been measured. It is notable, however, that none of these studies assessed all of the muscles of the arm in the same specimens. In addition, while dissection of cadaveric specimens permits

characterization of architectural details of muscle, it has some important limitations. The demographics of the specimen population are generally uncontrolled, and therefore may not be typical of the population at large. In particular, as described below, muscle volumes of cadaveric specimens do not represent those of young, healthy adults. In addition, dehydration effects may further underestimate muscle volume by 4–9% (Ward and Lieber 2005). Thus, while cadaveric dissection provides access to all of the parameters necessary to calculate PCSA, and therefore, maximum isometric force, the force magnitudes calculated using this approach are only valid for subjects with comparable muscle volumes to the cadaveric specimens.

19.4 Imaging Approaches

Medical imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound, allow researchers to study muscle volume, fiber arrangement, and cross-sectional areas of muscle in living subjects. All of the modalities have been used to quantify muscle volumes, and have demonstrated accuracies for volumetric measurements between 1% and 5% (Audenaert et al. 2009; Berg et al. 2007; Tingart et al. 2003).

CT is a valuable modality for its speed of acquisition and its capacity to readily distinguish among bone, fat, and muscle. For that reason, it has been used to evaluate the infiltration of fat into muscle, for example in the gluteal muscles (Jolivet et al. 2008). It has been rarely used to characterize the upper limb, though it has been used to analyze the muscle, fat, and bone composition of the forearm in the trained and untrained limbs of male tennis players (Maughan et al. 1986). The difficulty associated with determining borders among individual muscles, as well as the radiation dosage, has limited its use in studies of this type when MRI is available.

MRI has been shown to provide enhanced contrast between anatomical borders of individual muscles while avoiding the radiation exposure of CT (Juul-Kristensen et al. 2000a; Lehtinen et al. 2003). The accuracy of estimating muscle volume from MRI has been established by Tingart et al. (2003); they measured the volume of rotator cuff muscles in cadavers using MRI of the intact shoulder and water displacement of the dissected muscles, and reported differences of less than 4%. While MRI allows one to capture information about a large number of muscles in an acquisition, it is extremely time consuming to manually identify the borders of the muscles to calculate muscle volumes, and reliable tools for automated segmentation of individual muscles have proven difficult to develop despite the enhancement of borders inherent to the imaging technique. In addition, the high clinical costs, long imaging times, and limited access associated with the modality limit its use in large studies. For this reason, cheaper and faster alternatives have been explored.

Ultrasound has also been considered as an alternative to either MRI or CT, as an inexpensive, portable method (Teefey et al. 1999) to accurately image muscle and fat (Juul-Kristensen et al. 2000b; Miyatani et al. 2000, 2004). However, because of the relatively limited field of view of ultrasound, estimates of muscle volume must be made from measurements of muscle thickness, limb length, and knowledge of the approximate shape of the muscle of interest (e.g. cylindrical, Miyatani et al. (2004) or triangular, Audenaert et al. (2009)). This approach has been used to successfully determine the volumes of deltoid (Audenaert et al. 2009), extensor digitorum communis (Brorsson et al. 2008), and elbow flexor and extensor muscles (Fukunaga et al. 2001; Miyatani et al. 2004), as well as fiber length and pennation angle (Fukunaga et al. 2001).

As compared to the cadaveric approach, medical imaging techniques have the benefit of providing a means to quantify important muscle architectural parameters in living human subjects. Thus, these valuable data can be acquired for populations of subjects for whom cadaveric specimens are not

generally available. These populations include young, healthy adults, children, and persons with physical disabilities or musculoskeletal impairments. In contrast, an important limitation to imaging methods is that no imaging technique successfully quantifies all of the parameters necessary to calculate PCSA as traditionally defined (muscle volume normalized by optimal fiber length, corrected for pennation angle). A particularly important limitation is the inability to easily quantify optimal fiber length via imaging techniques. MRI provides a means to accurately quantify muscle belly lengths (e.g. Holzbaur et al. 2007b), and ultrasound is frequently used to quantify muscle fiber lengths (Maganaris et al. 2001). However, how these measured lengths relate to the optimal fiber length of a given muscle in a given subject cannot be quantified using either MRI or ultrasound. Thus, most imaging studies that estimate PCSA from their data normalize the measured muscle volumes by muscle belly lengths or fiber lengths measured from imaging, and scaled to better approximate optimum lengths using ratios of optimal fiber length to fascicle length measured in cadaveric experiments (Holzbaur et al. 2007b; Klein et al. 2001). However, these approximated fiber lengths may not correspond to optimum lengths for the particular subjects. Importantly, exciting advances in imaging techniques include methods that can track fiber architecture using MRI (Sinha et al. 2006), will may ultimately enable measurement of muscle volume, muscle belly length, muscle fiber length, and pennation angle using the same modality. Also, new methods have been developed that allow imaging of muscle at the sarcomere level (Llewellyn et al. 2008), which could ultimately allow fiber lengths measured using ultrasound to be normalized to fiber length.

19.5 Comprehensive Upper Limb Muscle Volume Assessment

One study (Holzbaur et al. 2007b) provides a comprehensive assessment of muscle volume in the upper limb for all muscles crossing the shoulder, elbow, and wrist in the same subjects. This study also presents calculated estimates of PCSAs for these muscles. While the accuracy of PCSA values determined from medical imaging has limitations (as we have described in this review), the authors demonstrated in a follow up study that the muscle volumes were strongly correlated to total isometric strength at the shoulder, elbow, and wrist (Holzbaur et al. 2007a). The strong relationship between muscle volume and joint strength has also been observed in other studies (Akagi et al. 2009; Fukunaga et al. 2001). As such, documentation of muscle volumes, and the variability in volume and distribution across different subjects and populations, is of interest to study.

The dominant arm of ten subjects (5 females, 5 male, 24–37 years, 158–188 cm tall, 50–86 kg) with no history of injury or pathology of the upper limb was studied. The subjects varied from a 20th percentile female to a 97th percentile male (Gordon et al. 1989), based on height (Table 19.1).

Each subject was imaged in a supine position within a 1.5 T MRI scanner (GE Healthcare, Milwaukee, WI). Axial images were acquired from shoulder to wrist using two three-dimensional spoiled gradient echo sequences with 3 mm sections. Images of the muscles crossing the shoulder were obtained with the body coil with TE = 3 ms, TR = 11.6 ms, flip angle (FA) = 30°, matrix = 512 × 192, bandwidth = ±31.25 kHz, and field of view (FOV) = 32 cm, resulting in a 16-min scan time. Elbow and forearm images were acquired using a flexed array long bone coil (Medical Advances, Milwaukee, WI) with TE = 5 ms, TR = 23 ms, FA = 45°, matrix = 320 × 192, bandwidth = ±15.63 kHz, and FOV = 16 cm, resulting in a 22-min scan time.

To calculate muscle volume, the three-dimensional geometries of the 32 upper limb muscles that cross the wrist, elbow, forearm, and shoulder (glenohumeral joint) were reconstructed (Fig. 19.1). Muscle boundaries were identified and manually outlined, or segmented, in the axial images, and a three-dimensional polygonal surface was created for each muscle from the outlines (3D-Doctor,

Table 19.1 Subject characteristics

Subject[a]	Age	Height (cm)	Percentile[b] (height)	Weight (kg)	Percentile[b] (weight)	Humerus length (cm)	Radius length (cm)	Ulna length (cm)	Arm length[c] (cm)	Arm circumference[d] (cm)	Forearm circumference[d] (cm)
F1	24	157.5	20	49.9	5	29.7	21	23.4	50.7	26.7	20.9
F2	36	162.6	50	49.9	5	31.2	23.1	25.8	54.3	25.2	21.7
F3	24	162.6	50	59.0	40	32.1	23.1	24.6	55.2	27.2	23.9
F4	30	165.1	65	52.2	10	31.2	22.2	24.9	53.4	25.9	21.5
M1	28	172.7	35	72.6	30	35.1	24.3	27.6	59.4	33.5	27.5
M2	27	175.3	50	83.9	70	31.5	23.4	26.1	54.9	35.5	28.5
M3	37	175.3	50	93.0	90	34.2	25.2	28.2	59.4	35.1	29.9
F5	26	177.8	99	72.6	90	34.2	24.6	27	58.8	31.5	25.5
M4	27	177.8	65	72.6	30	34.5	25.8	27.9	60.3	34.1	28
M5	27	188.0	97	86.2	75	38.1	27	30.3	65.1	35.2	29.3
Mean female (±SD)	28.0 (5.1)	165.1 (7.6)	56.8 (28.7)	56.7 (9.6)	30.0 (36.6)	31.7 (1.7)	22.8 (1.3)	25.1 (1.3)	54.5 (2.9)	27.3 (2.5)	22.7 (1.9)
Mean male (±SD)	29.2 (4.4)	177.8 (6.0)	59.4 (23.5)	81.6 (8.9)	59.0 (27.5)	34.7 (2.4)	25.1 (1.4)	28.0 (1.5)	59.8 (3.6)	34.7 (0.8)	28.6 (1.0)
Mean total (±SD)	28.6 (4.5)	171.5 (9.3)	58.1 (24.8)	69.2 (15.8)	44.5 (34.1)	33.2 (2.5)	24.0 (1.8)	26.6 (2.0)	57.2 (4.2)	31.0 (4.3)	25.7 (3.4)

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This table presents important anthropometric measurements for the subjects studied in Holzbaur et al. (2007), including height, weight, and length and circumference of the upper limb.

[a] The letter in the subject designation indicates the gender of the subject.

[b] Percentile values based on height and weight are based on Gordon et al. (1989)

[c] Arm length was calculated from the image data as the sum of the length of the radius and humerus.

[d] Forearm and arm circumference was measured from the image data as the largest circumference measured on any axial slice.

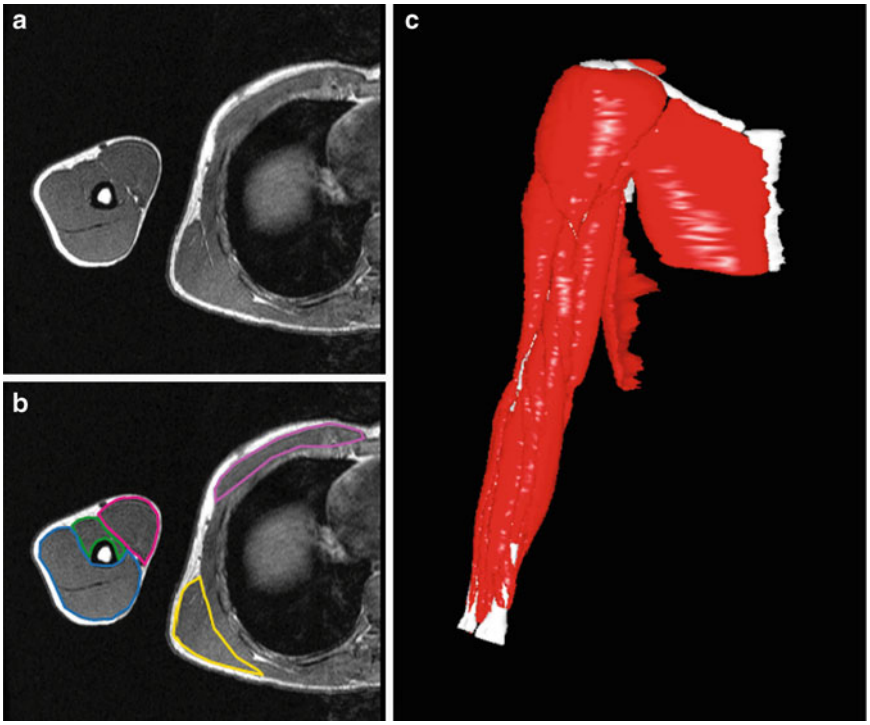

Fig. 19.1 Reconstructed muscle volumes for a representative subject. On each axial image (**a**) muscle structures were identified and the boundaries were manually outlined (**b**). The boundaries were used to create three-dimensional surfaces (**c**), from which volume and length were measured for each muscle. (Reprinted from Holzbaur et al. (2007b). With permission)

Able Software Corp., Lexington, MA). Thirty-two muscles were segmented in 4 subjects; 31 were segmented in 6 subjects. The palmaris longus was not identified in six subjects; this muscle is absent in some individuals (Dalley and Moore 1999).

Muscle volume was determined for each of the 314 muscles from 10 subjects. Total muscle volume of the upper limb was determined for each subject as a sum of all their individual muscle volumes (31 or 32 muscles). The mean volume for each muscle across all ten subjects was calculated, as was the mean total muscle volume.

To determine the distribution of muscle volume among the muscles of a given subject, the volume fraction (Fraction_m), expressed as a percentage of total muscle volume, was calculated for each muscle:

$$\text{Fraction}_m = 100 \times V_m / V_{total}, \tag{19.1}$$

where V_m is the individual muscle volume and V_{total} is the total upper limb muscle volume for a given subject. The mean volume fraction for each muscle across the ten subjects was also calculated. The subject-specific volume fraction across all ten subjects was compared, and the degree to which the mean volume fraction for each muscle represented the volume fraction for an individual subject was examined by comparing the measured muscle volumes to the volumes predicted by multiplying the mean volume fraction by the total muscle volume of a subject.

To determine how muscle is distributed among the shoulder, elbow, and wrist the total volume of muscle crossing each joint for each subject were compared across subjects. Muscles that cross more than one joint were considered with the joint of their primary action (groups indicated in Fig. 19.2).

Physiological cross-sectional area (PCSA), an important parameter in maximal muscle force estimation, was estimated for all muscles based on the measured volumes (V_m), measured muscle length (L_m^{meas}), and muscle length to optimal fiber length ratios $\left(L_m / L_m^o\right)$ available in the literature (An et al. 1981; Jacobson et al. 1992; Langenderfer et al. 2004; Lieber et al. 1990, 1992; Murray et al. 2000) according to the following equation:

$$\text{PCSA} = \left(\frac{V_m}{L_m^{meas}}\right)\left(\frac{L_m}{L_m^o}\right) \tag{19.2}$$

Muscle length was measured from the reconstructed volumes as the length of the centroidal path of each volume from most proximal appearance of the muscle to the most distal (Lieber et al. 1992). Tendon length was not included in this calculation. Some muscles have architectural parameters measured separately for multiple compartments or heads. For these muscles (deltoid, latissimus dorsi, pectoralis major, biceps brachii, triceps brachii, extensor digitorum communis, flexor digitorum profundus, and extensor digitorum superficialis) average ratios of muscle length to optimal fiber length (Langenderfer et al. 2004; Lieber et al. 1992; Murray et al. 2000) were used. Calculations of PCSA for each muscle, PCSA fraction as a percentage of total PCSA of the upper limb, and total PCSA at each joint, and means for these values across the ten subjects were calculated in the same manner as described for the volume calculations above. PCSA fraction was compared to volume fraction for each muscle using a paired *T* test.

Anthropometric measures, including humerus length, radius length, ulna length, total arm length, arm circumference, and forearm circumference, were measured on each subject. Arm length was calculated from the image data as the sum of the length of the radius and humerus. Forearm and arm circumference were measured from the image data as the largest circumference measured on any axial slice. The length of each muscle was compared to the radius length of that subject using linear regression to determine if muscle lengths scale with bone lengths.

19.6 Muscle Distribution in the Upper Limb

As reported by Holzbaur et al. (2007b), the muscles with the largest volume fractions are the deltoid and triceps. The deltoid (DELT) has the largest mean volume fraction of the muscles crossing the shoulder (15.2% ± 1.0%) and coracobrachialis (CORACO) has the smallest (0.9% ± 0.3%) (Fig. 19.2). The triceps (TRI) (combined three heads) has the largest volume fraction of muscles crossing the elbow (14.5% ± 0.7%) and anconeus (ANC) has the smallest (0.4% ± 0.08%). For muscles crossing the wrist, flexor digitorum profundus (FDP) has the largest volume fraction (3.7% ± 0.45%) and extensor indicis propius (EIP) has the smallest (0.2% ± 0.05%).

The distribution of muscle in the upper limb was consistent across the 10 subjects, despite a threefold variation in total muscle volumes (1,427–4,426 cm^3) (Table 19.2). Pectoralis major showed the largest variation, with a standard deviation of 2.0% of total muscle volume, and extensor pollicis longus showed the least with 0.04% standard deviation. The average standard deviation for all muscles was 0.4% of total muscle volume. The individual volume for a given muscle falls close to a line with a slope representing the average volume fraction for that muscle across all 10 subjects (Fig. 19.3). When the volume of an individual muscle was predicted using the mean volume fraction, on average 85% of the variation among subjects was accounted for (average $p = 0.0008$). For all muscles, more than 70% of the variation was accounted for ($p < 0.001$), except for extensor pollicis brevis ($r^2 = 0.52$, $p = 0.015$), supinator ($r^2 = 0.68$, $p = 0.002$), and extensor indicis propius ($r^2 = 0.67$, $p = 0.003$).

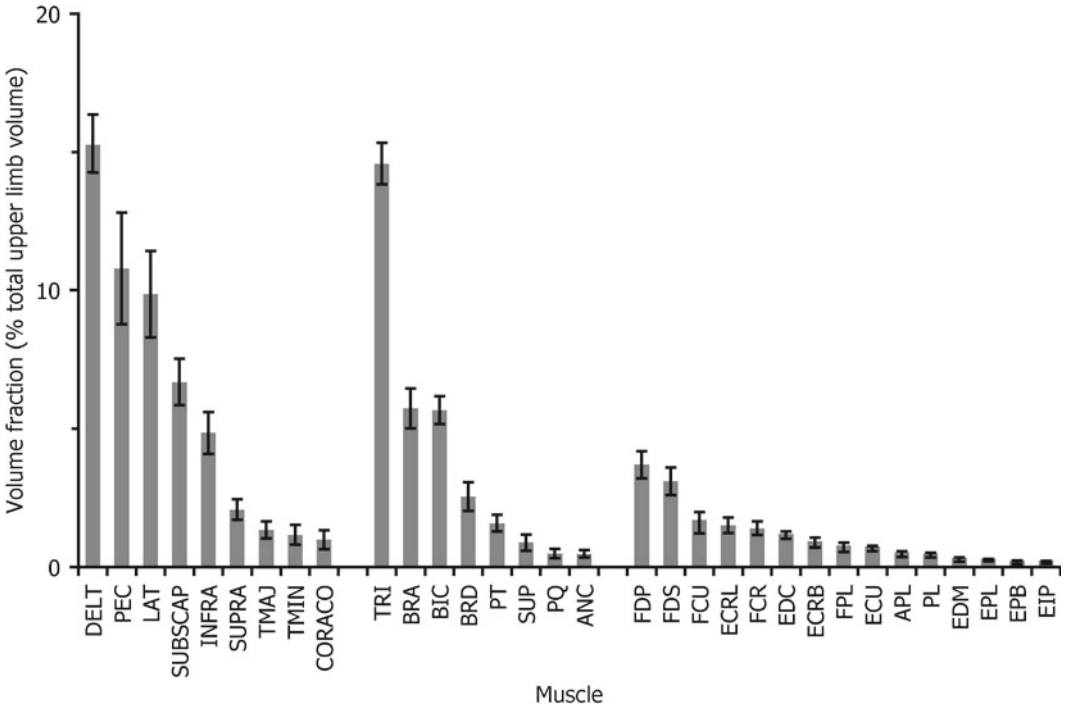

Fig. 19.2 Volume fractions for upper limb muscles. Muscles are grouped by anatomical region (shoulder, elbow and forearm, and wrist) and ordered within each group from largest volume fraction to smallest. The bar for each muscle represents the mean volume fraction with error bars representing one standard deviation for ten subjects. The abbreviations for muscle names are defined in Table 19.2. Reprinted from Holzbaur et al. (2007b). With permission)

The shoulder muscles comprise 52.5% of the total muscle volume, the elbow muscles comprise 31.4%, and the wrist muscles comprise 16.0% (Fig. 19.4). Shoulder adductors made up 28.3% of total muscle volume, while abductors comprised 24.0%. At the elbow, flexors and extensors both made up approximately 15% of total muscle volume (15.3% and 15.0%, respectively). At the wrist, flexors (11.0%) had more than twice the muscle volume of the extensors (5.0%).

On average, the length of the radius accounted for 48% of the variability in muscle length across subjects, although the relationship between bone length and muscle length varied among muscles. For deltoid, teres major, triceps, biceps, extensor carpi ulnaris, flexor carpi ulnaris, extensor pollicis longus, flexor digitorum superficialis, and flexor digitorum profundus, more than 70% of the variability in muscle length was explained by the length of the radius ($r > 0.84$, $p < 0.0008$) (Fig. 19.5). The variability in the lengths of other muscles (pectoralis major, infraspinatus, extensor carpi radialis longus, and abductor pollicis longus) was less explained by radius length, but still had a significant correlation ($r > 0.74$, $p < 0.01$) between these two lengths. Less than 30% of the variability in muscle length was explained by changes in radius length for subscapularis, coracobrachialis, brachioradialis, anconeous, supinator, pronator quadratus, flexor carpi radialis, palmaris longus, flexor pollicis longus, and extensor pollicis brevis ($r < 0.55$, $p > 0.07$).

The PCSA fraction calculated for each muscle was consistent across subjects (Table 19.2). Triceps had the largest PCSA fraction with 18.2% (±0.75%), and extensor pollicis brevis had the smallest

Table 19.2 Muscle characteristics

Muscle	Abbreviation	Average volume (cm^3) (±SD)	Volume fraction (%) (±SD)	PCSA (cm^2) (±SD)	PCSA fraction (%) (±SD)	Length (cm) (±SD)
Latissimus dorsi	LAT	262.3 (147.2)	9.8 (1.5)	13.9 (6.5)	6.2 (1.0)	19.3 (3.3)
Pectoralis major	PEC	290.0 (169.0)	10.7 (2.0)	15.9 (8.3)	6.9 (1.4)	20.2 (2.2)
Deltoid	DELT	380.5 (157.7)	15.2 (1.0)	25.0 (8.7)	11.5 (0.8)	18.1 (1.8)
Supraspinatus	SUPRA	50.0 (20.4)	2.0 (0.3)	4.8 (1.6)	2.2 (0.3)	12.7 (1.2)
Infraspinatus	INFRA	118.6 (46.7)	4.8 (0.7)	11.9 (4.2)	5.5 (0.7)	14.0 (1.0)
Subscapularis	SUBSCAP	164.5 (63.9)	6.6 (0.8)	14.1 (4.4)	6.6 (0.7)	12.6 (1.4)
Teres minor	TMIN	28.0 (13.9)	1.1 (0.3)	3.7 (1.5)	1.7 (0.6)	11.5 (1.7)
Teres major	TMAJ	32.7 (16.3)	1.3 (0.3)	2.5 (0.9)	1.2 (0.3)	10.9 (1.9)
Coracobrachialis	CORACO	25.2 (16.6)	0.9 (0.3)	2.4 (1.3)	1.1 (0.2)	13.8 (2.7)
Triceps	TRI	372.1 (177.3)	14.5 (0.7)	40.0 (15.4)	18.2 (0.8)	27.0 (3.2)
Biceps	BIC	143.7 (68.7)	5.6 (0.5)	8.2 (3.4)	3.7 (0.3)	27.0 (2.6)
Brachialis	BRA	143.7 (63.7)	5.7 (0.7)	14.4 (5.9)	6.5 (0.6)	22.3 (2.1)
Brachioradialis	BRD	65.1 (36.0)	2.5 (0.5)	3.9 (1.8)	1.7 (0.3)	23.5 (2.5)
Anconeus	ANC	10.8 (5.2)	0.4 (0.1)	1.3 (0.6)	0.6 (0.1)	8.3 (1.7)
Supinator	SUP	19.7 (8.4)	0.8 (0.2)	2.3 (0.7)	1.1 (0.3)	8.8 (2.3)
Pronator teres	PT	38.4 (17.2)	1.5 (0.2)	6.5 (2.2)	3.0 (0.5)	16.1 (2.3)
Pronator quadratus	PQ	11.2 (5.8)	0.4 (0.1)	3.7 (1.9)	1.7 (0.5)	4.2 (0.5)
Extensor carpi radialis brevis	ECRB	21.6 (9.1)	0.9 (0.2)	2.5 (0.7)	1.2 (0.2)	17.6 (2.4)
Extensor carpi radialis longus	ECRL	37.5 (19.0)	1.5 (0.2)	2.7 (1.2)	1.2 (0.2)	22.2 (1.8)
Extensor carpi ulnaris	ECU	17.0 (7.4)	0.7 (0.1)	2.3 (0.9)	1.1 (0.2)	21.1 (2.4)
Flexor carpi radialis	FCR	34.8 (17.1)	1.3 (0.2)	3.9 (1.6)	1.8 (0.2)	22.6 (2.9)
Flexor carpi ulnaris	FCU	37.1 (13.6)	1.5 (0.3)	6.6 (2.0)	3.1 (0.6)	24.9 (2.0)
Palmaris longus	PL	10.0 (3.9)	0.4 (0.1)	1.4 (0.5)	0.7 (0.1)	6.0 (7.7)
Extensor digitorum communis	EDC	28.6 (12.7)	1.1 (0.1)	2.5 (0.8)	1.2 (0.2)	19.6 (3.2)
Extensor digiti minimi	EDM	7.0 (3.4)	0.3 (0.1)	0.9 (0.4)	0.4 (0.1)	17.6 (2.6)
Extensor indicis propius	EIP	4.2 (1.6)	0.2 (0.1)	0.8 (0.2)	0.4 (0.1)	9.5 (2.2)
Extensor pollicis longus	EPL	6.6 (3.4)	0.3 (0.0)	1.3 (0.5)	0.6 (0.1)	13.0 (2.9)
Extensor pollicis brevis	EPB	4.4 (2.2)	0.2 (0.1)	0.6 (0.2)	0.3 (0.1)	11.1 (2.6)
Flexor digitorum superficialis	FDS	74.2 (27.4)	3.0 (0.5)	6.0 (1.9)	2.8 (0.3)	24.5 (1.7)
Flexor digitorum profundus	FDP	91.6 (39.3)	3.7 (0.4)	8.4 (3.2)	3.8 (0.4)	23.4 (1.6)
Flexor pollicis longus	FPL	17.1 (6.3)	0.7 (0.2)	3.8 (1.3)	1.8 (0.3)	13.8 (1.7)
Abductor pollicis longus	APL	11.9 (5.7)	0.5 (0.1)	1.7 (0.6)	0.8 (0.1)	15.5 (2.1)
Total muscle volume		2554.0 (1166.7)				

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This table summarizes the mean values for muscle volume, PCSA, volume and PCSA fraction, and muscle length for the 32 muscles of the upper limb.

(0.28% ± 0.07%). At the shoulder, deltoid, pectoralis major, and latissimus dorsi had PCSA fractions that were significantly smaller than the volume fraction for the same muscles ($p < 0.001$). At the elbow, triceps, pronator teres, and pronator quadratus were significantly larger for PCSA fraction than for volume fraction ($p < 0.001$), and biceps and brachioradialis had significantly smaller PCSA fraction than volume fraction ($p < 0.001$). At the wrist, flexor carpi ulnaris, flexor pollicis longus, extensor carpi ulnaris, extensor pollicis longus, and extensor indicis propius had a significantly larger PCSA fraction than volume fraction ($p < 0.001$).

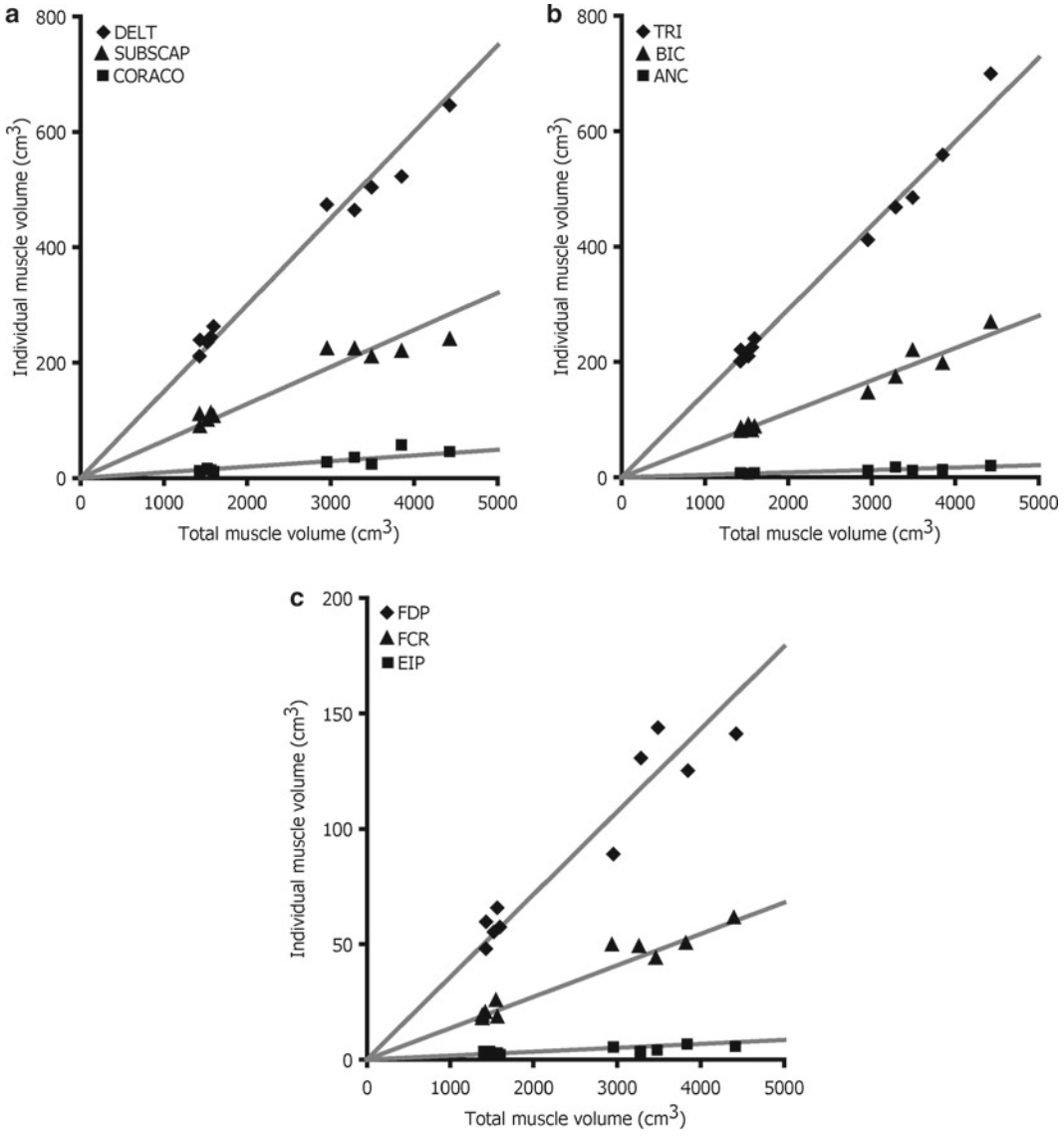

Fig. 19.3 Individual muscle volumes compared to total muscle volume for muscle crossing the shoulder (**a**), elbow (**b**), and wrist (**c**). The muscles with the largest volume fraction (*diamonds*), smallest fraction (*squares*), and an average fraction (*triangles*) for each muscle group are shown. For each muscle, the slope of the corresponding line is the average volume fraction calculated for ten subjects. For all the representative muscles shown, the volumes fall close to the appropriate average line, demonstrating consistent muscle distribution across all subjects. (Reprinted from Holzbaur et al. (2007b). With permission)

Pectoralis major had the largest variation of PCSA fraction across subjects, with a standard deviation of 1.4% of total muscle PCSA, and extensor pollicis longus had the least variation (standard deviation of 0.06%). The average standard deviation was 0.4% of total muscle PCSA.

Measurements of volume fraction have also been made for muscles of the forearm and hand by Brand et al. (1981). Substantial agreement was observed between the volume fractions measured for muscles common to both the Brand et al. and Holzbaur et al. studies ($r^2 = 0.9381$, $p < 0.00001$).

A summary of muscle volumes reported by a number of studies is included in Table 19.3.

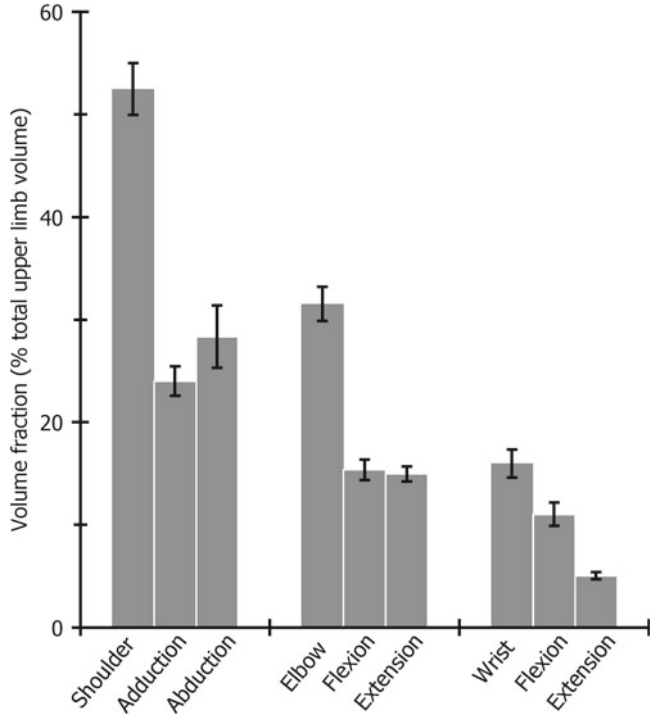

Fig. 19.4 Volume fraction for muscles crossing the shoulder, elbow and forearm, and wrist. Muscles are grouped with the joint of primary action (largest moment arm). The first bar in each group indicates the total volume fraction of all muscles crossing the joint of interest. The second and third bars in each group indicate volume fraction of muscles at a joint capable of creating abduction or adduction of the shoulder, flexion or extension of the elbow, and flexion or extension of the wrist. (Reprinted from Holzbaur et al. (2007b). With permission)

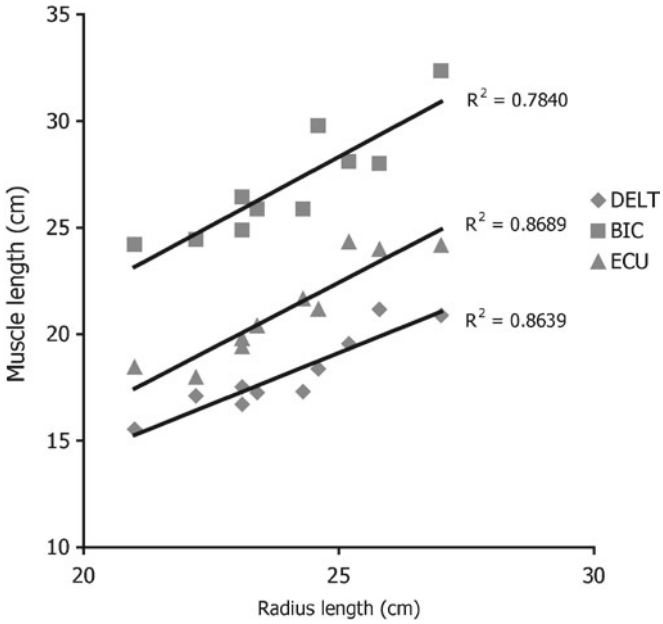

Fig. 19.5 Muscle length compared to radius length. The length of several muscles, including the deltoid (DELT, *diamonds*), biceps (BIC, *squares*), and extensor carpi ulnaris (ECU, *triangles*), correlated well ($r^2 > 0.7$) with radius length. (Reprinted from Holzbaur et al. (2007b). With permission)

Table 19.3 Summary of muscle volumes from multiple studies

		Average volume (cm^3)								
Muscle	Abbreviation	Holzbaur	Garner	Langenderfer	Veeger (1991)	Veeger (1997)	An	Murray	Lieber et al. (1990)	Lieber et al. (1992)
Latissimus dorsi	LAT	262.3	549.7	193.2	226.1					
Pectoralis major	PEC	290.0	676.4	127.5	202.6					
Deltoid	DELT	380.5	792.9	204.4	314.4					
Supraspinatus	SUPRA	50.0	89.2	23.8	36.2					
Infraspinatus	INFRA	118.6	225.4	64.5	109.8					
Subscapularis	SUBSCAP	164.5	318.6	86.3	138.6					
Teres minor	TMIN	28.0	38.7	18.7	28.3					
Teres major	TMAJ	32.7	231.4	49.3	88.3					
Coracobrachialis	CORACO	25.2	80.0	16.1	30.6	42.0				
Triceps	TRI	372.1	620.0	152.3	99.7	379.0	152.6	153.5		
Biceps	BIC	143.7	365.8	56.2	111.2	128.0	64.2	69.4		
Brachialis	BRA	143.7	266.0	72.6		122.0	59.3	53.5		
Brachioradialis	BRD	65.1	83.2	20.2		66.0	21.9	21.2		18.0
Anconeus	ANC	10.8				11.0	6.7			
Supinator	SUP	19.7	34.1			17.0	10.9			
Pronator teres	PT	38.4	80.4			33.0	18.7	15.4		16.9
Pronator quadratus	PQ	11.2				12.0				5.3
Extensor carpi radialis brevis	ECRB	21.6					15.8		14.6	
Extensor carpi radialis longus	ECRL	37.5	166.6[a]				18.3	13.8	12.5	
Extensor carpi ulnaris	ECU	17.0	28.7				14.9		14.4	

(continued)

Table 19.3 (continued)

Muscle	Abbreviation	Average volume (cm^3)								
		Holzbaur	Garner	Langenderfer	Veeger (1991)	Veeger (1997)	An	Murray	Lieber et al. (1990)	Lieber et al. (1992)
Flexor carpi radialis	FCR	34.8	57.0				12.4		11.5	
Flexor carpi ulnaris	FCU	37.1	67.7				15.2		16.3	
Palmaris longus	PL	10.0					5.1			4.2
Extensor digitorum communis	EDC	28.6					23.5			16.9
Extensor digiti minimi	EDM	7.0								4.2
Extensor indicis propius	EIP	4.2								3.2
Extensor pollicis longus	EPL	6.6								5.3
Extensor pollicis brevis	EPB	4.4								
Flexor digitorum superficialis	FDS	74.2					35.9			42.2
Flexor digitorum profundus	FDP	91.6								57.0
Flexor pollicis longus	FPL	17.1								10.6
Abductor pollicis longus	APL	11.9								

This table summarizes the mean muscle volume measurements for several representative studies of upper limb muscle volume (An et al. 1981; Garner and Pandy 2003; Holzbaur et al. 2007b; Langenderfer et al. 2004; Lieber et al. 1990; Lieber et al. 1992; Murray et al. 2000; Veeger et al. 1991, 1997).

[a]The value for ECRL represents the combined ECRL and ECRB (Garner and Pandy, 2003).

19.7 Distribution of Muscle Across Joints

It has been shown that volume fraction and PCSA fraction were consistent across individuals with different total muscle volumes. A number of interesting observations about the way muscle is distributed across joints with respect to their function can be made. Interestingly, the muscle volume crossing the wrist on the flexor side is twice as large as the extensor side (Fig. 19.4). The wrist has the largest imbalance between antagonist muscle groups of any joint in the upper limb. In addition, the two largest muscles crossing the wrist are the flexor digitorum profundus and flexor digitorum superficialis, two muscles that flex the fingers. This highlights the importance of considering the role of the finger muscles when examining the function of the wrist (Gonzalez et al. 1997).

19.8 Physiological Cross-Sectional Area Distribution

By comparing the PCSA fraction and the volume fraction for muscles of the upper limb, one can observe the possible effects of including a muscle length measurement on the distribution of muscle. At the shoulder, the muscles for which the volume fraction and PCSA fraction were statistically different always had a reduced PCSA fraction. This is consistent with the fact that muscles crossing the shoulder have relatively long optimal fiber lengths (average = 12.9 cm) (Langenderfer et al. 2004). At the wrist, the muscles for which the PCSA and volume fractions were different demonstrated increased PCSA fraction. This indicates that these muscles had relatively short optimal fiber lengths (average = 6.5 cm) (Jacobson et al. 1992; Lieber et al. 1990, 1992). There was no distinct trend for muscles crossing the elbow.

It should be noted that in the calculations of PCSA made by Holzbaur et al. (2007b), scaling by the cosine of pennation angle was not performed. In this case, only the force-generating capability of the fibers themselves is considered; scaling by pennation can be incorporated by researchers as a separate step. Further, an estimate of fiber length was used rather than optimal fiber length in the PCSA calculation because measures of sarcomere length were unavailable. As discussed above, to date, medical imaging approaches are not able to capture information about optimal fiber length in living subjects.

19.9 Gender Differences

The Holzbaur et al. (2007b) study included both male and female subjects, and was able to note some differences in the subject groups. Male subjects were observed to have a stronger relationship between height and weight and total muscle volume than did the female subjects. There was very little difference in total muscle volume among the five female subjects, despite the large range in their height and weight. For the male subjects, there was a trend toward increased muscle volume with height ($r^2 = 0.77$, $p = 0.05$) and weight ($r^2 = 0.40$, $p = 0.25$). Further study is necessary to determine if these relationships are observed in a larger group of subjects.

Though there were observed differences between genders with respect to total muscle volume, a difference between genders with respect to the distribution of muscle was not observed. Therefore, these data suggest that once the total muscle volume of a subject is known, individual muscle volume

can be estimated without regard to gender. No strong relationships between total or individual muscle volumes and the other anthropometric measurements were observed.

19.10 Scaling of Muscle Volume

The strong scaling of individual muscles and muscle groups with total muscle volume can be highlighted by normalizing the subject-specific volumes by the corresponding mean volumes for all ten subjects (Fig. 19.6). When the normalized total volume for a subject is compared to the normalized volume of muscle crossing each joint, all points fall near a line of unity slope with r^2 = 0.9818. This indicates that, for each subject, the size of individual muscles relative to the mean muscle volumes is the same as the ratio of total upper limb muscle volume to the mean total upper limb volume. For example, the tallest subject in the Holzbaur et al. study had a total muscle volume that was approximately 1.7 times the mean found in that study. This subject also had a volume of muscle crossing the shoulder that was approximately 1.7 the mean volume of muscle crossing the shoulder. That is, a single number, the scaling ratio, can be used to represent the total and individual muscle volume of a subject. For a given muscle, a ratio greater than 1 indicates that its volume is larger than the mean. By assessing the volume of just a few muscles, the size of any subject can be estimated and the volume of all muscles can be determined using the volume distributions reported in this study.

To facilitate comparison of muscle volumes measured from a number of the studies discussed in this review documenting muscle volumes at the shoulder (Langenderfer et al. 2004), elbow (An et al. 1981; Murray et al. 2000), and wrist (Jacobson et al. 1992; Lieber et al. 1990, 1992), the volumes measured in these studies were normalized by the corresponding mean muscle volume measured in the Holzbaur et al. study (Fig. 19.6). In this way, scaling ratios from all of these studies could be readily compared. The distribution of muscle measured in cadaveric studies of muscles crossing the shoulder, elbow, and wrist was the same as the distribution measured in the Holzbaur et al. study in living subjects, as evidenced by the fact that the average scaling ratios for these studies also fall on the unity line. However, the total muscle volume reported by these previous studies is consistent with the smallest female subjects. One previous study used the volumes of the Visible Human Male (from the National Library of Medicine, National Institutes of Health) to investigate muscle architecture and force-generating capabilities (Garner and Pandy 2001). This individual exhibits less constant scaling ratios among the muscles crossing different joints than did the subjects in the other studies; the volume of muscle crossing the shoulder was relatively larger than that crossing the elbow, and the volume of muscle crossing the wrist was relatively smaller. Only muscles common to the Garner and Pandy and Holzbaur et al studies were considered in this analysis. In addition, the total muscle volume of the Visible Human Male was very large compared to that of the other subjects and specimens in the literature. The difference in muscle distribution in the Visible Human Male may be due to exercise related adaptation. Comparing the mean muscle volumes from cadaveric studies and imaging based studies also reinforces the conclusion that muscle volumes in younger subjects are much larger than those measured in cadavers (Table 19.3).

This review summarizes a wealth of data regarding the range of total muscle volume in normal adults of both genders and the distribution of this volume among the muscles. Given the mean volume fractions reported here, it has been shown that a single parameter is sufficient to scale all of the muscles in the upper limb to represent a typical individual with different total muscle volume. This is powerful information for understanding the relationship among muscles of the upper limb and for supporting the results of modeling and simulation that use mean muscle properties to understand muscle function.

19.11 Applications to Other Areas of Health and Disease

In this review, muscle volumes and PCSAs and how they scale for individuals of different size have been presented. Muscle fiber length, optimal fiber length, and moment arms may also scale with an individual's size. For example, there is evidence that moment arms for muscles crossing the elbow may scale with bone length or other bone dimensions, and that the degree of this scaling varies across muscles (Murray et al. 2002). It is unknown how moment arms may scale for muscles crossing other

Table 19.4 Key features of upper limb muscle volume in young adults

1. Muscle volume and fiber arrangement, also called muscle architecture, are the major determinants of the force-generating capacity of muscle.
2. Imaging and dissection methods are both useful for characterizing muscle volume and architecture.
3. PCSA is an important measurement for predicting individual muscle force-generating capacity, while muscle volume can be used to evaluate differences in overall strength between individuals.
4. Volume fraction is consistent among healthy adults with different total muscle volumes.
5. Total muscle volumes vary substantially among individuals, and between studies of cadavers and living subjects.
6. The wrist has the largest volume imbalance between antagonist muscle groups of any joint in the upper limb.

This table lists the key facts regarding upper limb muscle volume, including how it is assessed, how it is distributed in the upper limb, and how it varies among individuals.

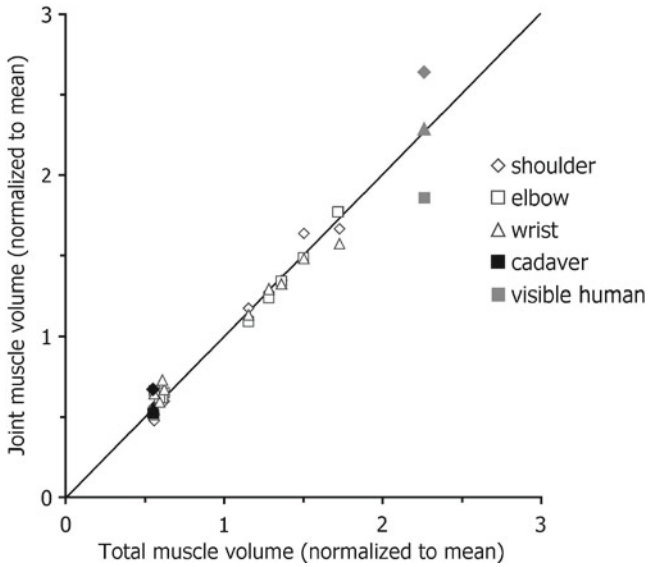

Fig. 19.6 Volume of muscles crossing a joint (normalized by mean muscle volume crossing the joint) compared to total muscle volume (normalized by mean total muscle volume). The subjects in the Holzbaur et al. (2007b) study (*open data points*) demonstrated uniform scaling of individual muscle volume with total muscle volume, as demonstrated by the points falling on the unity line. Data from cadaveric studies (An et al. 1981; Jacobson et al. 1992; Langenderfer et al. 2004; Lieber et al. 1990; Lieber et al. 1992; Murray et al. 2000) (*black data points*), when normalized by the corresponding mean volumes from this study, also fall on this line, indicating muscle volume distribution equivalent to that found in Holzbaur et al. Muscle volumes from cadaver studies are equivalent to the smallest females in Holzbaur et al. Muscle volumes from the Visible Human Dataset (from the National Library of Medicine, National Institutes of Health) (*grey data points*, Garner and Pandy 2001), when normalized by the means from Holzbaur et al. do not fall on the unity line, indicating that the shoulder muscles are relatively larger and the elbow muscles are relatively smaller than those found in other studies. In addition, the volumes from the Visible Human Dataset are almost 2.5 times the mean found in Holzbaur et al. (Reprinted from Holzbaur et al. (2007b). With permission)

joints. Future work to determine scaling rules for moment arm and fiber length is necessary to create subject specific models that account for variations in these parameters.

The studies presented in this review provide a normative data set that allows for investigation of other populations. Many researchers study populations that may have different distributions of muscle, such as children, athletes, or patients following spinal cord injury or stroke. We may now be able to detect differences in muscle proportions from healthy adult subjects, which may help researchers uncover changes in muscle function with training or disease.

Summary points

- Physiological cross-sectional area is an important measurement for predicting individual muscle force-generating capacity, while muscle volume can be used to evaluate differences in overall strength between individuals.
- Imaging and dissection methods are both useful for characterizing muscle volume and architecture.
- Dissection methods allow researchers to obtain measurements of muscle volume, optimal fiber length, and pennation angle in the same specimens, and permit accurate calculations of PCSA.
- Volumes in young healthy subjects are much larger than cadaveric specimens, so forces calculated from PCSAs measured in cadavers may be of limited applicability.
- Muscle volumes measured with medical imaging approaches are strongly correlated with strength in living subjects.
- Volume fraction is consistent among healthy adults with different total muscle volumes.
- Various studies of upper limb muscle show consistent volume fraction measurements; however, magnitudes of muscle volume can vary widely across individuals and studies.
- The wrist has the largest volume imbalance between antagonist muscle groups of any joint in the upper limb, with approximately twice as much as muscle volume on the flexor side.

Acknowledgements We would like to acknowledge the funding support of the Whitaker Foundation, Medtronic Foundation Stanford Graduate Fellowship, the Rehabilitation Research and Development Service of Veterans Affairs (#A3741R), NIH R01 HD046774, and NIH-EB002524. We would also like to thank the subjects for participating in the study described by Holzbaur et al. (2007b), and Silvia Blemker for help with data collection. Portions of the text, figures, and tables were originally published in the Journal of Biomechanics (Journal of Biomechanics 40 (2007) 742–749), and have been reprinted here by permission of the publisher, Elsevier.

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Chapter 20
Bioelectrical Impedance to Predict Muscle Mass in the Elderly

Lars Ellegård and Marja Tengvall

Abstract In ageing, body composition changes gradually and will ultimately reduce function and health. In healthy elderly, deterioration of muscle mass and development of sarcopenia may be masked by weight stability. There is an increasing interest in specific estimation of skeletal muscle mass, as it may better reflect the body protein reserves and nutritional status in disease and aging.

Bioelectrical impedance analysis is an easily performed and non-invasive indirect method to measure body composition based on the different conductive/resistive properties of body tissues. There are several prediction equations to estimate skeletal muscle mass by BIA. In the elderly, some of the assumptions in the impedance technique may be violated, and thus their validity must be assessed by a reference method in the population under study.

Reference values for muscle mass in the elderly have been published based on both single-frequency and impedance spectroscopy data. Impedance methods are suitable for measurement of muscle mass in the elderly because they are convenient and precise. This chapter presents various aspects of bioimpedance techniques to estimate muscle mass or muscle function in the elderly.

Abbreviations

BCM	Body cell mass
BF	Body fat, fatness percentage body fat
BFI	Body fat mass index
BIA	Bioelectrical impedance analysis
BIS	Bioelectrical impedance spectroscopy
BIVA	Bioelectrical impedance vector analysis
BMC	Bone mineral content
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
ECW	Extracellular water
FM	Fat mass
FFM	Fat free mass

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_20,

FFMI	Fat free mass index
ICW	Intracellular water
LSTM	Lean soft tissue mass
MRI	Magnetic resonance imaging
SMM	Skeletal muscle mass
SMMI	Skeletal muscle mass index
TBSMM	Total body skeletal muscle mass

20.1 Introduction

In ageing, body composition changes gradually and will ultimately reduce function and health (Woodrow 2009). In general, the proportion of fat free mass falls in people of older age (Chumlea et al. 2002; Dey et al. 2003; Ding et al. 2007). More specifically, there are reductions in bone mass, body cell mass (BCM) and muscle mass (Gallagher et al. 1997; Kyle et al. 2003). Initially in senescence, fat mass may increase but over the years total body fat tends to decrease. In healthy elderly, deterioration of muscle mass and the development of sarcopenia may be masked by weight stability (Gallagher et al. 1997). Thus, body weight measurements do not accurately detect such changes, and other measures of body composition will be of interest. However, it must be kept in mind that most body composition methods are based on assumptions that, although relevant for healthy adults, might lead to errors when applied to an elderly population (Woodrow. 2009). Many body composition methods are applications of the two-compartment model, where the body is divided into fat mass (FM) and fat free mass (FFM). Fat free mass consists of body cell mass, including muscles and internal organs, as well as bone and extracellular water (ECW). In order to discriminate between these entities, additional techniques or combinations of techniques are necessary, as outlined below. Body cell mass (BCM) has been proposed as a more specific marker for nutrition and wasting, but there is a lack of normal reference range data for the ageing individual (Woodrow. 2009).

There is an increasing interest to specifically estimate skeletal muscle mass (SMM), as it may better reflect the body protein reserves and nutritional status in disease and ageing (Kyle et al. 2003). Muscle wasting or muscle loss, often termed sarcopenia, is a process associated with ageing as well as with several diseases (Kyle et al. 2003). Sarcopenia has been found to be associated with functional impairment (Janssen et al. 2002). The prevalence of sarcopenia is obviously dependent on age classification, but has been reported to apply to 50% of men and 72% of women over 80 years of age in a large US population study (Janssen et al. 2002). This chapter presents various aspects of bioimpedance techniques to estimate muscle mass or muscle function in the elderly, defined as persons above 65 years of age.

20.2 Spectrum of Bioimpedance Techniques

Bioelectrical impedance analysis (BIA) is an easily performed and non-invasive method to measure body composition based on different conductive/resistive properties of body tissues. The theory, practice and clinical application of bioimpedance analysis have recently been extensively reviewed (Kyle et al. 2004a, b). Single frequency-BIA (SF-BIA) is commonly used to estimate total body water and fat free mass (FFM). Multifrequency-BIA (MF-BIA) and bioelectrical impedance spectroscopy (BIS) estimate both intracellular water (ICW) and extracellular water (ECW) and from

them fat free mass (FFM) (Kyle et al. 2004a). Body fat (BF) is generally calculated as the difference between body weight (BW) and FFM. Bioimpedance vector analysis (BIVA) does not primarily predict volumes or quantify muscle mass but instead plots resistance and reactance against reference values to estimate hydration status and body cell mass (Piccoli et al. 1996).

Skeletal muscle mass forms the largest proportion of the fat free mass, and as it is a tissue rich in electrolytes it has low resistance and hence is a dominant conductor. Thus, bioimpedance analysis might be especially suitable for the clinical estimation of muscle mass. However, as impedance methods are only indirect methods, they have to be validated by direct methods (Kyle et al. 2004a). Dual-energy X-ray absorptiometry (DXA) is increasingly accepted as a reference method to evaluate bioimpedance methods (Kyle et al. 2004a). DXA yields information on body fat, lean soft tissue (LST) and bone mineral content (BMC). The extremities consist primarily of three components: skeleton, fat and muscle mass (Heymsfield et al. 1990). The sum of lean soft tissue in the extremities, sometimes referred to as appendicular lean soft tissue (ALST), has also been termed appendicular skeletal muscle mass (ASMM) (Kyle et al. 2003). Appendicular skeletal muscle mass forms the major proportion of total body muscle mass and the ratio ASMM/0.75 has been proposed to represent total body muscle mass (Heymsfield et al. 1990). DXA has successfully been validated both by total body potassium and total body nitrogen (Hansen et al. 1999) and by MRI (Kim et al. 2002, 2004) for the estimation of total body skeletal muscle mass (TBSMM or SMM), both with and without correction for intra-muscular fat.

20.3 Single-Frequency Bioimpedance Analysis (SF-BIA)

There are several prediction equations to estimate skeletal muscle mass by BIA (Table 20.1). A single-frequency BIA equation was suggested by Janssen to predict whole body skeletal muscle mass among healthy Caucasians aged 18–86 years, validated against MRI (Janssen et al. 2000). The large US National Health and Nutrition Examination Survey (NHANES III) study included 4449 subjects older than 60 years of age screened by single-frequency BIA, and later reanalyzed for the determination of muscle mass calculated according to the Janssen equation, without validation (Janssen et al. 2004) (Table 20.2).

The Janssen equation has recently been reported to be accurate also for Asians, although only subjects 20–40 years of age were included in the validation (Chien et al. 2008). When applied to community dwelling elderly Taiwanese volunteers with a mean age close to 75 years, the predicted height-adjusted skeletal muscle mass indexes were actually higher than reported for US citizens (Table 20.2).

Another single-frequency BIA equation used data from healthy volunteers aged 22–94 years to predict appendicular skeletal muscle mass validated by DXA (Kyle et al. 2003). However, a recent authoritative review has not recommended the use of general BIA prediction equations across different ages and ethnic groups without prior testing of their validity (Kyle et al. 2004a). This is underlined by our experience where we found the equations of Janssen and Kyle to overestimate skeletal muscle mass in non-institutionalized subjects aged 75. The overestimations were larger for men than for women for both equations. This could be due to the fact that both muscle mass estimates were developed to include a wide range of ages, perhaps at the cost of less accuracy among the elderly. Hence, we found it necessary to develop an age-specific prediction equation. We developed an equation for the assessment of skeletal muscle mass based on 50 kHz measurements extracted from Xitron 4200 Hydra data using the same independent predictors as Kyle and Janssen.

Table 20.1 Muscle mass equations in impedance analysis

Equation	Entity	Reference	#
(height^2/*R* * 0,401) + (sex(men = 1, women = 0) * 3,825) + (age * –0,071)+5,102	TBSMM	BIA (Janssen et al. 2000)	**1**
–4,211 + (0,267 * height^2/*R*) + (0,095 * weight) + (1,909 * sex (men = 1, women = 0)) + (–0,012 * age) + (0,058 * Xc)	ALST	BIA (Kyle et al. 2003)	**2**
–24,021 + 0,33 * Ht – 0,031 * *R* + 0,083 * Xc – 1,58 * gender + 0,046 * weight	TBSMM	BIS (Tengvall et al. 2009)	**3**
–23,953 + 0,333 * Ht – 0,004 * Ri – 0,010 * Re – 1,727 * gender + 0,042 * weight	TBSMM	BIS (Tengvall et al. 2009)	**4**
–24,05 + 0,365 * Ht – 0,005 * Ri – 0,012 * Re – 1,337 * gender	TBSMM	BIS (Tengvall et al. 2009)	**5**

Predictive equations to estimate total body skeletal muscle mass (TBSMM) or appendicular lean soft tissue mass (ALST) from bioelectrical impedance, both by single-frequency data (BIA) and impedance spectroscopy data (BIS)
Ht height in cm, *R* Resistance at 50 kHz, *Xc* Reactance at 50 kHz, *Ri* Resistance of intracellular fluid, *Re* Resistance of extracellular fluid
Sex (eq 1–2) women = 0, men = 1
Gender (eq 3–5): women = 1, men = 0

Table 20.2 Muscle mass in elderly populations

	Women			Men		
	SMMI	Body height	Age	SMMI	Body height	Age
	Mean (SD)	Mean	Mean	Mean (SD)	Mean	Mean
Janssen eq #1						
Sweden *n* **= 574** (Tengvall et al. 2009)	**7,0 (0,8)**	161	75	**9,7 (1,1)**	175	75
US *n* **= 4449** (Janssen et al. 2004)	**7,0 (1,1)**	159	71	**9,9 (1,2)**	173	70
Taiwan *n* **= 302** (Chien et al. 2008)	**7,3 (1,0)**	153	74	**9,8 (1,1)**	164	77
Tengvall eq #3						
Sweden *n* **= 574**	**6,6 (0,8)**	161	75	**8,6 (0,6)**	175	75
Australia *n* **= 119**	**6,3 (1,0)**	156	75	**7,9 (1,3)**	170	75

Total body skeletal muscle mass index (SMMI) in elderly populations estimated by predictive equations from bioimpedance analysis

This equation has been successfully validated by DXA in an Australian population of 119 elderly subjects referred for body composition analysis, while the Janssen and the Kyle equations were both shown to overestimate muscle mass as compared to DXA (Bosaeus Strauss 2009). All three equations are presented in Table 20.1, and the resulting muscle mass values are presented in Table 20.2. The muscle mass indexes in different populations of elderly are remarkably similar, when estimated by identical equations. However, the high SMMI for the Taiwanese population might be an overestimate as the equation was validated only in a younger population. The difference between the Swedish and the Australian populations in muscle mass estimated by the same equation might be explained by the different recruitment approaches, as the Swedish elderly was a population-representative sample whereas the Australian elderly were all individually referred for body composition examination.

20.4 Multifrequency-Bioimpedance Analysis (MF-BIA)

Multifrequency bioimpedance analysis uses at least two different frequencies for the alternating current in order to assess both intra- and extracellular volumes. No equations based on multifrequency bioimpedance analysis explicitly designed for muscle mass in the elderly have been derived. However, equations have been published for the assessment of body cell mass in apparently healthy,

well nourished but non-obese elderly, validated by total body potassium (Dittmar and Reber. 2001). The authors failed to find any advantage of multiple as compared to single frequency BIA for the prediction of body cell mass.

20.5 Bioimpedance Vector Analysis (BIVA)

In bioimpedance vector analysis (BIVA) plots of height adjusted resistance and reactance are compared with gender-specific bivariate tolerance intervals for the impedance vector to estimate hydration status and body cell mass (Piccoli et al. 1996). Bioimpedance vector analysis is suggested to give a qualitative measure of body tissues, where vector length indicates hydration status and sideways migration in the diagram indicates changes in tissue structure and mass (Norman et al. 2009). Bioimpedance vector analysis does not predict any volumes, and thus does not require any data on body weight, which would be valuable in many clinical settings, especially among the elderly. Recently bioimpedance vector analysis was reported to correlate strongly (r^2=0.71) with hand grip strength and its development over time in late middle age Europeans (mean age 63 years) (Norman et al. 2009).

20.6 Bioelectrical Impedance Spectroscopy (BIS)

We have reported BIS, using Xitron equations, to be valid for estimating average FFM in non-institutionalized elderly Swedes when compared to DXA (Tengvall et al. 2009). However, previously published BIA prediction equations (Janssen et al. 2000; Kyle et al. 2003) for skeletal muscle mass applied on the 50 kHz data both tended to overestimate muscle mass when compared to DXA.

Based on DXA-measurements of skeletal muscle mass we developed two new predictive equations applicable for BIS data; with and without body weight as a predictor (Table 20.1). The trunk has limited impact on whole body impedance because of its large cross-sectional area although it constitutes at least half of total body weight (Kyle et al. 2004a). Thus, changes in fat free mass in the trunk are probably inadequately detected by whole body impedance, although it contributes to body weight. In addition, the relative proportions of trunk and extremities may vary between subjects, and especially so in the elderly due to compression of the axial skeleton. Hence, excluding body weight as a muscle mass predictor may reduce that source of bias. Average differences for total skeletal muscle mass from the BIS-equations compared to DXA were less than ¼ kg without any significant systematic bias (Tengvall et al. 2009).

These muscle mass equations could successfully predict average total body skeletal muscle mass, with 85% of the individual predictions within ±10% of the reference method, as demonstrated in Fig. 20.1. 91% of the variation in muscle mass could be attributed to the BIS-data (Tengvall et al. 2009).

Based on a DXA-validated subsample we constructed reference values and ranges for total body skeletal muscle mass in elderly non-institutionalized Caucasians, as presented in Table 20.3. In institutionalized elderly in residential care facilities, muscle mass appears to be lower as judged by ICW from BIS, although without any validation from reference methods (Carlsson et al. 2009). Reported ICW was only 2/3 of our reference values, with some extremely low values, again raising doubts as to the feasibility of bioimpedance spectroscopy in extreme situations without proper validation.

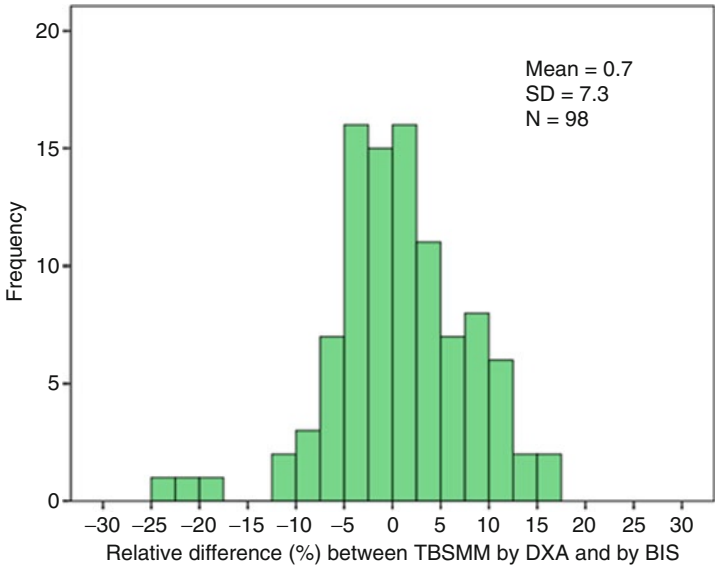

Fig. 20.1 Relative variation in muscle mass prediction. Relative difference (%) between muscle mass predicted by BIS-equation #5 and muscle mass quantified by DXA in 98 free-living elderly subjects. 85% of the individual predictions were within ±10% of the reference method (Adapted from Tengvall et al. 2009)

Table 20.3 Body composition by BIS in the elderly

	Women n = 345			Men n = 229		
	Mean (SD)	Perc. 5	Perc. 95	Mean (SD)	Perc. 5	Perc. 95
TBSMM (kg)	**17,4 (2,9)**	12,4	21,7	**26,3 (3,0)**	20,8	31,0
SMMI (kg/m²)	**6,6 (0,9)**	5,1	7,9	**8,6 (0,7)**	7,5	9,6
Re (Ω)	**679 (73)**	564	803	**574 (73)**	459	701
Ri (Ω)	**1600 (289)**	1160	2147	**1308 (242)**	935	1750
ECW (l)	**14,1 (1,8)**	11,2	16,9	**19,1 (2,6)**	14,6	24,2
ICW (l)	**16,5 (3,0)**	12,0	21,4	**22,8 (4,0)**	16,9	29,9
ECW/ICW	**0,87 (0,10)**	0,69	1,05	**0,84 (0,09)**	0,69	1,01

Reference values for BIS-derived body composition parameters including total body skeletal muscle mass in non-institutionalized elderly Caucasians (Tengvall et al. 2009)

20.7 Application to Other Areas of Health and Disease

Comparison of the equations to predict muscle mass, based on either 50 kHz single frequency BIA or impedance spectroscopy, resulted in small average differences. Thus, in our experience, there seems to be neither any advantage nor any disadvantage to predict muscle mass from single-frequency BIA compared to BIS. Two equations that included BIS measurements with or without body weight gave only slightly different results. Thus, the inclusion of body weight as an independent predictor of total body skeletal muscle mass will only slightly increase the explanatory power. Hence, we suggest the use of muscle mass predictive equations without body weight in future studies.

Bioelectrical impedance analysis offers, in general, good opportunities to study changes in muscle mass over time, thanks to high reproducibility. However, in ageing, violations of the

assumptions used in the method software presumably increase, and thus such violations must be checked by validation of BIA results with reference methods in the specific population under study.

Summary Points

- Impedance methods are convenient to use and show good precision
- Impedance is only indirectly associated with muscle mass; thus, predictive equations are required
- In the elderly some of the assumptions in the impedance technique may be violated
- Impedance methods must be validated in the population under study
- Reference values for muscle mass in the elderly have been published, based on both single-frequency and impedance spectroscopy data

Key Facts of the Elderly

- Elderly people are defined as those 65 years of age or older
- Almost 1 in 5 citizens belong to this group
- The prevalence (proportion) of elderly in the society is steadily increasing, being 18% in Sweden in 2008
- Women tend to live longer than men, thus the proportion of women among the elderly is approximately 55%, and the proportion increases with age
- In the elderly, bone mass, body cell mass, muscle mass and fat mass gradually decrease with age

Key Points on Impedance and Muscle Mass in the Elderly

- Bioimpedance methods are suitable for measurement of muscle mass in the elderly because they are convenient and precise
- The validity must be assessed by a reference method in the population under study

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Part IV
Tools and Techniques in Anthropometry: Adipose Tissue, Other Compartments and Relationships

Chapter 21
Anthropometry of Body Fat: How Anthropometric Measures Predict Mortality and Especially Cardiovascular Mortality

Eddy Mizrahi-Lehrer, Beatriz Cepeda-Valery, and Abel Romero-Corral

Abstract The World Health Organization defines overweight and obesity as an abnormal or excessive fat accumulation that impairs health. However, there are no well established cut-offs to define obesity based on body fat. The NIH, WHO, the American Association of Clinical Endocrinologist, and the American College of Endocrinology define obesity as an excess of total body fat, specifically body fat that is 20–25% of total body weight in men, and 30–35% in women. But there are not enough data supporting these cut-offs as predictors of adverse outcomes. Furthermore, because direct body fat is difficult to measure, more widely available and easier to perform anthropometric measurements are used in clinical practice.

Body mass index is the most commonly used and accepted anthropometric measure to define obesity. It is a well known conditional risk factor for the development of several cardiovascular risk factors, such as diabetes mellitus type 2, metabolic syndrome, systemic hypertension, dyslipidemia, obstructive sleep apnea, etc. However, recently scientists have questioned its usefulness as slightly increased body mass index (overweight and mild obesity range) has been related to improved survival and fewer cardiovascular events when compared to subjects with a normal body mass index, a phenomenon known as the "obesity paradox".

Anthropometric measures of obesity that take into consideration body fat distribution, mainly truncal and/or abdominal obesity, such as waist circumference and specially waist-to-hip ratio appear to better predict cardiovascular risk than BMI alone, but this remains to be proven. Interestingly, despite body fat being the gold standard to define obesity, very little is known regarding its impact as a predictor of all-cause and cardiovascular mortality. The following chapter will analyze the different anthropometric measurements including body fat and lean mass and their impact on mortality with a focus on cardiovascular mortality, the leading cause of death worldwide.

Abbreviations

BMI	Body mass index
CV	Cardiovascular
HC	Hip circumference
NIH	The National Institute of Health

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_21,

WC Waist circumference
WHR Waist to hip ratio
WHO World Health Organization

21.1 Introduction

In the US the prevalence of obesity is estimated to affect 34% of adults over the age of 20, according to an analysis released by the Center for Disease Control and Prevention (CDC 2007). This translates roughly to more than 70 million Americans having a body mass index (BMI) >/= 30 kg/m^2. The World Health Organization (WHO) estimates that obesity rates have tripled over the last two decades in developing countries (WHO 2006). Asian-Pacific countries are not immune to this epidemic either: countries like Japan, with historically low rates of obesity, are now facing a challenge of increased prevalence: a twofold increase in the age group 20–29 years (Gill 2001). Unfortunately, the future doesn't seem very bright, as estimates project 2.3 billion overweight adults and 700 million obese children by 2015 (WHO 2006).

The National Institute of Health (NIH), WHO, American Association of Clinical Endocrinologist, and American College of Endocrinology define obesity as an excess of total body fat, specifically body fat that is 20–25% of total body weight in men, and 30–35% in women (WHO 2006, NIDDK-NIH 2008, AACE/ACE 1998). However, there are poor data to justify these cut-offs, which are somehow arbitrary. Moreover, measurement of body fat is neither a common procedure nor easy to perform on a routine basis. That is why in clinical practice and epidemiologic studies, other measurements are more widely used. These measurements reflect either general obesity, such as weight, BMI, body surface area or more recently central adiposity, such as waist circumference (WC) or waist-to-hip ratio (WHR).

BMI remains the most widely used measurement to quantify obesity. Its simple calculation has allowed clinicians and scientists to compare body habits, body weight changes and the impact of obesity on several diseases, with special emphasis on cardiovascular (CV) diseases (Poirier et al. 2006). However, recent evidence suggests that BMI might not be the best measure of obesity to predict total and CV mortality. Other anthropometric measures of obesity, including those taking into account body fat distribution or even body fat or lean mass, might be necessary for better risk prediction. Despite the increasing prevalence of obesity, the impact of anthropometric measures and their prognostic impact on total and CV mortality remains unclear, and this is the main theme of this chapter (Table 21.1).

Table 21.1 Key facts of sensitivity (%), specificity (%), positive predictive value (%) and negative predictive value (%) (Rao 2004)

1. Sensitivity, specificity, positive predictive value and negative predictive value are collectively known as the test characteristics and are important ways to determine the usefulness of diagnostic test.
2. Sensitivity is the capacity of the test to correctly identify diseased individuals in a population, also known as the "true positive". The greater the sensitivity, the smaller the number of unidentified cases or "false negatives".
3. Specificity is the capacity of the test to correctly identify individuals who are free of disease in a population, also known as the "true negatives". The greater the specificity, the smaller the number of "false positives".
4. Positive Predictive Value is the probability of the disease being present among those with a positive test result.
5. Negative Predictive Value is the probability that the disease was absent among those whose diagnostic test results were negative.

21.2 Body Mass Index, Waist Circumference and Waist-to-Hip Ratio and Its Relationship to Cardiovascular Risk Factors

The negative impact of increased BMI on health has largely been studied, especially for CV disease. In fact, the American Heart Association and the American College of Cardiology guidelines list obesity as a major modifiable risk factor for CV disease (Smith et al. 2001). Whether obesity is an independent risk factor for CV disease or only acts as a conditional risk factor for developing CV risk is still matter of ongoing research (Krauss et al. 1998).

There are overwhelming data suggesting that obesity plays a significant role in the development of several CV risk factors, the better established being links with systemic hypertension (Barret-Connor and Khaw 1985, Lewis et al. 2009), diabetes mellitus type 2 (Sharper et al. 1997), dyslipidemia (Poirier et al. 2006), and obstructive sleep apnea (Somers et al. 2008).

Most of the studies assessing the impact of obesity on CV risk rely on BMI. But recently, anthropometric measures that take into account body fat distribution, such as WC and WHR have also been associated with CV risk. Moreover, in some studies, these measures appear to be more closely related to cardiometabolic dysregulation than BMI and may be the reason why they could be better predictors of total and CV mortality.

For instance, abdominal obesity, as measured by WC, is associated with, increased triglyceride levels and lower HDL-cholesterol concentrations. It seems that WC has a higher degree of correlation with lipid variables than BMI, HC or WHR (Reeder et al. 1997; Després et al. 1998). Interestingly, not only accumulation of fat in the waist but also around the hip may play an important role in the development of CV disease. Heitmann and colleagues (Heitman 2004), have shown that in a random subset of ~3,000 adult Danes, a large hip circumference seems to have independent and positive effects on CV disease, especially in women. This could be explained by studies that have shown that fat located around the hip is associated with better lipid profile (Snijder et al. 2003).

Another example of the usefulness of central obesity measures to assess CV risk is the study conducted by Ito and colleagues. In this study researchers recorded different anthropometric measurements among 2,728 Japanese individuals and studied their relationships with different CV risk factors. They concluded that WHR and fat mass-trunk-legs ratio predicted CV risk factors like hypertension, dyslipidemia and diabetes mellitus more accurately than BMI alone (Ito et al. 2003).

Many other studies worldwide have confirmed the utility of central obesity measures in assessing CV risk but are beyond the scope of this book chapter. Nonetheless, it is clear that health care providers and researchers need to complement their body weight assessment with anthropometric measures that take into account body fat distribution to adequately assess the effects of obesity on CV disease.

21.3 Anthropometric Measures of Obesity as Predictors of Total and Cardiovascular Mortality

Although there is a clear association between obesity and increased mortality, there is an ongoing controversy regarding which measure of obesity is the best to assess and predict CV risk. The following paragraphs will discuss in greater detail the association between anthropometric measures of obesity and their relationship with total and CV mortality.

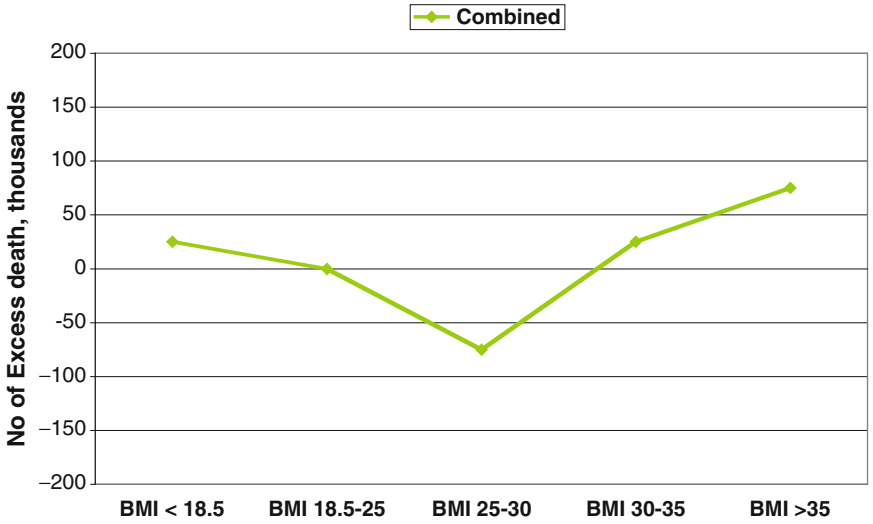

Fig. 21.1 Estimated numbers of excess deaths in 2000 in the United States relative to the Healthy Reference BMI Category of 18.5 to <25 kg/m^2, *BMI* Body Mass Index. All estimates are based on the covariate distribution from National Health and Nutrition Examination Survey (NHANES) 1999–2002, the number of deaths in 2000 from US vital statistics data. Relative risks estimated from combined data from National Health and Nutrition Examination Surveys I, II, and III (Adapted from Flegal et al. 2005)

21.3.1 BMI and Its Association with Total and Cardiovascular Mortality

Till date, most of the studies assessing obesity and mortality have relied on BMI as the defining marker. Emerging data has prompted scientists to question BMI's ability to predict total and CV mortality (Romero-Corral et al. 2008a). This controversy is mainly due to large epidemiologic studies showing that the relationship between BMI and mortality and CV mortality follows a U or J-shaped association with the lowest mortality in the BMI range corresponding to overweight and mildly obese subjects (Allison et al. 2002; Flegal et al. 2005; McGee et al. 2005; Romero-Corral et al. 2006; Adams et al. 2006; Flegal et al. 2007). These unexpected results are now known as the "obesity paradox".

The U or J-shape relationship between BMI and total (Fig. 21.1) and CV mortality has been described in many other studies (Allison et al. 2002; Flegal et al. 2005; McGee et al. 2005; Adams KF et al. 2006; Flegal et al. 2007). Interestingly, even in subjects who theoretically should be at higher risk for total and CV death, such as those with established coronary artery disease, this U-shape (Fig. 21.2a, b) association has been reported (Romero-Corral et al. 2006). Several theories have been proposed to explain these unexpected results relating overweight and mild obesity to improved survival, and they will be discussed below.

Reverse causality is a term referring to data confounded by a previous medical condition not identified. An example would be a patient who had cancer at the time or before the study resulting in weight loss and consequently relating low BMI to increased mortality. This increased mortality in the low BMI group could then be attributed to similar medical conditions associated with chronic wasting diseases rather than having a low BMI per se. On the other end of the curve, in the overweight/obese population, there is the possibility of bias due to a more aggressive implementation of effective secondary prevention therapies, such as healthy diets, exercise programs, etc. as compared to the groups with normal or low BMI, thus resulting in improved survival.

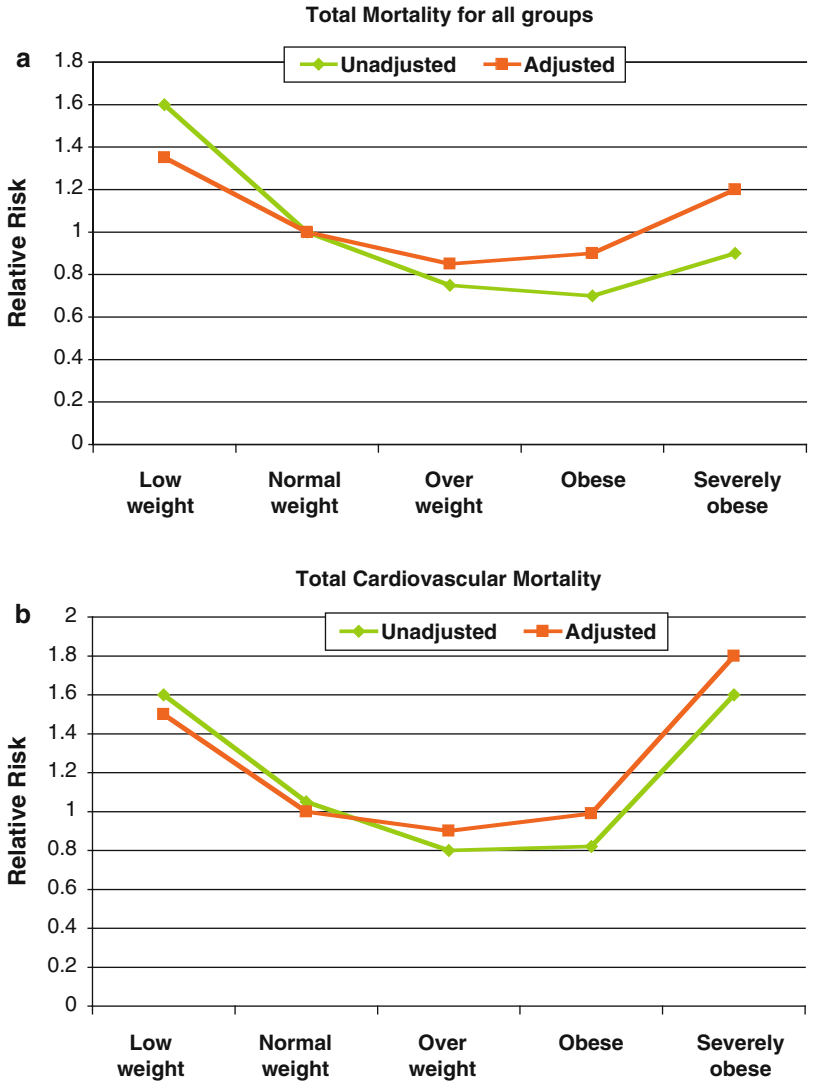

Fig. 21.2 (**a**) Unadjusted and adjusted relative risk for total (**a**) and cardiovascular (**b**) mortality according to body mass index groups in patients with coronary artery disease. (**b**) Unadjusted and adjusted relative risk for total mortality in patients with coronary artery disease by body mass index groups (Adapted from Romero-Corral et al. 2006)

Another potential bias is reclassification. During the follow-up of the study, subjects might shift from one group of BMI to another. For example: an obese man who lost weight due to diet and/or exercise. The opposite might also apply: a normal weight subject who became obese due to poor diet and inactivity. Both scenarios could theoretically result in "shifting" their risk of dying based on their body weight. Regretfully, this "change in body weight" is not accounted for in most of the studies, as only baseline weight/BMI is used to perform analyses.

Over-adjustment of confounders has also been listed as a potential explanation to the obesity paradox. This issue could be exemplified by the following example: if BMI contributes to the development of diabetes, systemic hypertension, dyslipidemia, obstructive sleep apnea, etc., all of which are potential risk factors for CV death, then adjusting for all these confounders could "dilute" or "modify" the effect of BMI on total and CV mortality. An example of this could be the Munster

Heart Study (PROCAM) (Schulte et al. 1999). In this study, the researchers followed 16,288 men and 7,328 women for up to 7 years, and concluded that the increased mortality in the higher BMI group was completely accounted for by other risk factors measured in the study, suggesting that an increased BMI had no relationship with total mortality, but the results could also be potentially due to over-adjustment of the risk models.

Lack of statistical power is extremely common in studies exploring the association between obesity and mortality, as most of the studies have few patients and/or short follow-ups. This may be a conceivable explanation, as very large studies have shown a gradual increase in mortality as BMI increases. An example of this is the prospective studies collaboration. These analyses included ~900,000 patients with 66,552 all-cause deaths and 30,416 vascular deaths with a follow-up of ~13 years (first 5 years were not used in analyses trying to avoid reverse causality). This study did not show a lower all-cause or vascular mortality in the overweight group defined by BMI. In fact, for every 5 points of increment in BMI were associated with a 30% increased risk in all-cause mortality and a 40% increased risk in vascular mortality (Prospective Studies Collaboration 2009).

Another study, conducted by Calle and colleagues, supports the usefulness of BMI in very large samples of over a million people (457,785 men and 588,369 women), with 201,622 deaths that occurred during 14 years of follow-up. This study showed that an elevated BMI, including the overweight range, was associated with higher rate of deaths among both men and women in all age groups (Calle et al. 1999). However, requiring such large numbers for BMI to demonstrate its impact on mortality speaks against its usefulness, and suggests that more reliable anthropometric measures to assess total and CV mortality are needed, especially when trying to individualize risk.

Another possible explanation for the inconsistent results between BMI and outcomes, that has recently gained attention, is that BMI by itself is a poor anthropometric measure to diagnose obesity (Romero-Corral et al. 2008b). When BMI was first introduced in the nineteenth century by Adolphe Quetelet, he described body weight as being proportional to the squared height in adults *with normal body frames*. What seemed to be an accurate equation then may not be valid now as the obesity epidemic rises, as what was considered a normal/standard body frame may no longer apply.

To test the hypothesis that BMI performs poorly as a measure of obesity, mainly due to its inability to differentiate between body fat and lean mass, Romero-Corral and colleagues used data from 13,601 subjects from the Third National Health and Nutrition Examination Survey (NHANES III) in whom body fat was estimated using bioimpedance. The diagnostic performance of BMI was assessed in relationship to the gold standard definition of obesity (excess in body fat), using as cut-offs >/= 25% in men and >/= 35% in women. Table 21.2 shows that BMI >/= 30 kg/m^2 has a high specificity but a poor sensitivity in detecting an excess in body fat and misses more than half of subjects with increased body fat. On the other hand, a BMI >/= 25 kg/m^2 has a good sensitivity but poor specificity, resulting in misclassification of subjects as obese when in fact they may have an increased lean mass.

Interestingly, in subjects with a BMI in the normal to overweight range, where most of the disagreement in results have been generated, BMI has its worst diagnostic performance. Figure 21.3 illustrates that men and women with a BMI of 25 kg/m^2 have a very wide range in the amount of body fat. The variability in body fat is so great that based on body fat subjects could be classified as malnourished or even obese, despite all of them having a "normal BMI". Authors conclude that the poor diagnostic performance of BMI as an anthropometric measure of obesity might be explained by BMI's inability to differentiate between body fat and lean mass, as shown by the similar correlation between BMI and both body fat and lean mass (r = ~0.75 between BMI and body fat and r = ~0.73 between BMI and lean mass).

Based on all of the above, it is clear that although BMI might be useful in large epidemiological studies, it has important limitations, especially at the intermediate range (normal to overweight) and on an individual basis. This becomes highly relevant, if we take into consideration that one third of the US population is overweight and another third has a normal BMI. In fact, the American Heart

Table 21.2 Diagnostic performance of body mass index in detecting excess in body fat* using body mass index cut-off points of >/= 30 kg/m^2 and >/= 25 kg/m^2 by sex (Adapted from Romero-Corral et al. 2008)

Anthropometric measure[a]	Sensitivity (%)	Specificity (%)	PPV[a] (%)	NPV[a] (%)	+LR[a]	-LR[a]
BMI >/=30 kg/m^2						
Male (n = 6,580)	36 (35–37)	95 (94–96)	87 (86–88)	60 (59–61)	6.7	0.67
Female (n = 7,021)	49 (48–50)	99 (98–100)	99 (98–100)	54 (53–55)	43.1	0.52
BMI >/=25 kg/m^2						
Male (n = 6,580)	84 (83–85)	62 (61–63)	69 (68–70)	80 (79–81)	0.2	0.25
Female (n = 7,021)	88 (87–89)	84 (83–85)	90 (89–91)	81 (80–82)	5.4	0.14

*Excess in body fat is considered as >/= 25% of body fat in men and >/= 35% in women
95% CI values are given in parentheses
BMI body mass index, *NPV* negative predictive value, *PPV* positive predictive value, *−LR* negative likelihood ratio, *+LR* positive likelihood ratio, *CI* confidence interval corrected for continuity
[a]Predictive value standardized to a prevalence of obesity based on body fat % of 78.9% in that population

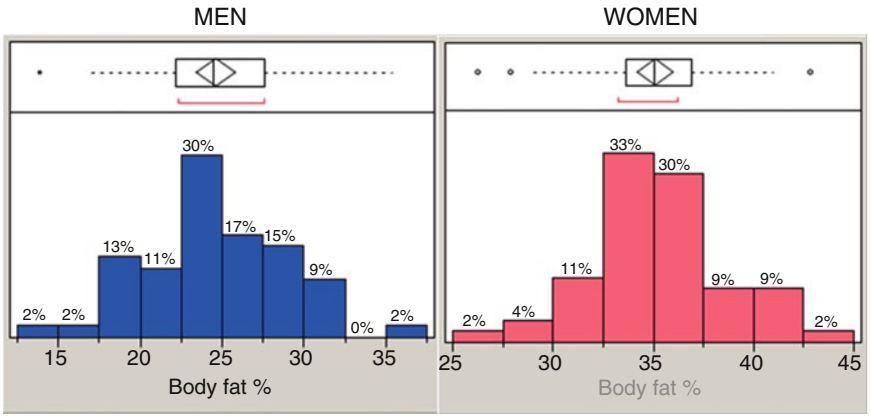

Fig. 21.3 Variability in body fat % among men and women with a BMI of 25 kg/m^2. Variability of body fat for men and women with a BMI of 25 kg/m^2. Percentages above bars show to the percentage of patients with that amount of body fat (Adapted from Romero-Corral et al. 2008)

Association released a Science Advisory statement in June 2009 regarding the conflicting results about mortality in overweight subjects (Lewis et al. 2009). Although they clearly state that there is insufficient evidence to assess if overweight subjects have a lower mortality of not, they are clear that the adverse effects of having an excess in body weight are not limited to mortality. It is well established that overweight subjects are at increased risk for the development of diabetes, dyslipidemia and systemic hypertension, thus blood pressure as well as glucose and lipid profile should be carefully monitored in this group. Moreover, both healthy eating and physical activity are advisable to lower CV risk regardless of bodyweight and should still be encouraged.

21.3.2 Waist Circumference and Waist-to-Hip Ratio and Their Association with Total and Cardiovascular Mortality

Recently, it has been proposed that central measures of obesity might correlate better with the development of adverse CV events and death than BMI. Data of large epidemiologic studies like the one conducted by Pischon and colleagues are now being published more often. This study followed

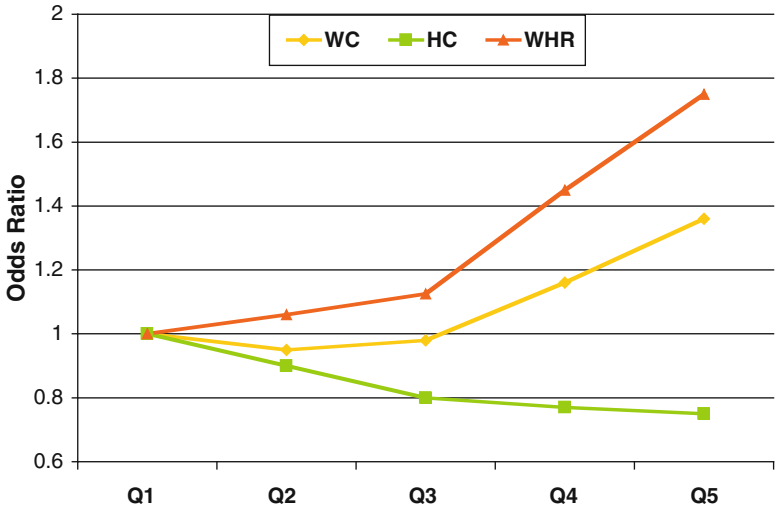

Fig. 21.4 Risk of myocardial infarction associated with increasing waist circumference, hip circumference and waist-to-hip ratio. Association of increasing waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR) with myocardial infarction risk. Odds ratios adjusted for all risk factors identified in INTERHEART (Adapted from Yusuf et al. 2005)

359,387 participants from nine European countries from the European Prospective Investigation into Cancer and Nutrition (EPIC) group for almost 10 years. BMI, WC and WHR were recorded. The study concluded that general (BMI) and abdominal (WC and WHR) adiposity were independently associated with the risk of death (Pischon et al. 2008). As previous studies, the relationship between BMI and risk of death followed a J-shaped curve, whereas once general adiposity was adjusted for, abdominal obesity remained positively associated with the risk of death. Although, this study was not designed to demonstrate which anthropometric measure is a better predictor for mortality, the fact that mortality increased among participants with normal weight but abdominal obesity, demonstrates the need to perform these measurements.

Another study assessing not only the relationship between measures of total and central obesity with acute myocardial infarction, but also how prevalent they are in the population is the INTERHEART study. This is a large case–control study of 27,098 participants with acute myocardial infarction conducted in 52 countries (12,461 cases and 14,637 control) exploring the relationship between BMI, WC, hip circumference, and WHR with myocardial infarction risk. This study confirmed the J-shaped association between BMI with myocardial infarction. Interestingly, WC also showed a J-shape association, but increased hip circumference was associated with lower risk of myocardial infarction. After adjustment for age, sex, region of study and smoking, WHR showed a dose–response relationship with myocardial infarction (Fig. 21.4). More importantly, the population-attributable risks (which speaks of the prevalence of a condition in a population) of myocardial infarction for increased WHR in the top two quintiles was 24.3% as compared with only 7.7% for the top two quintiles of BMI (Yusuf et al. 2005). Authors concluded that WHR ratio increases the population attributable risk resulting from obesity by over three-fold when compared to BMI.

Whether obesity measures that take into account central obesity are better associated with CV risk factors remains controversial, but based on recent data it is clear that they are needed to better estimate the risk for CV events. In a recent meta-analysis, de Koning et al., included 15 prospective studies with >250,000 subjects to assess the effect of WC and WHR on CV risk. For every centimeter increase in WC, the risk for CV events increased by 2%, while it increased by 5% for each 0.01 increment on

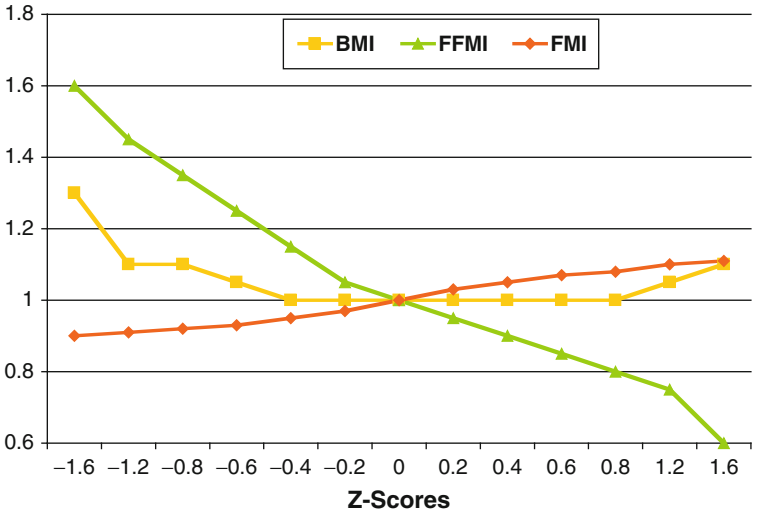

Fig. 21.5 Hazard ratios relative to *Z*-scores of zero for body mass index, body fat and lean mass. BMI shows a J-shaped association with all-cause mortality. Body fat shows (FMI) a positive relationship with all-cause mortality. Lean mass (FFMI) shows a negative relationship with all-cause mortality (Adapted from Allison et al. 2002)

WHR. Notably, besides central obesity measures being useful to predict risk, data suggest that it might also help to identify subjects at risk that could be missed by measuring total obesity alone. Zeller et al. followed for 1 year 2,229 subjects who suffered a myocardial infarction. In this study, even in subjects with a low BMI, increased WC was associated with higher mortality after a year of follow-up, stressing the need to account for measures of central obesity even when having a low or normal BMI (Zeller et al. 2008).

Regretfully, despite WC and WHR proving their value in predicting all-cause and CV mortality, most of the times are not measured in clinical practice. It is imperative to educate not only physicians, but all health personnel, and stress the importance of performing and adequate anthropometry in every patient to help establishing an adequate prognosis for many common medical conditions.

21.3.3 Body Fat and Lean Mass and Their Association with Total and Cardiovascular Mortality

Despite body fat being the gold standard definition of obesity, very little is known regarding its association with total and CV mortality. To our knowledge, there is only one large epidemiologic study conducted by Allison and colleagues addressing this question. This longitudinal prospective cohort study evaluated whether all-cause mortality is dependent on body fat (estimated by skinfold thickness) or lean mass rather than BMI or weight alone. A total of 10,169 male subjects aged 25–75 years old were followed for a mean of 12 years. After adjusting for age, smoking, race and educational level, BMI had a J–shaped association with mortality. Nevertheless, body fat (measured as fat mass index) showed a positive and significant relationship with all-cause mortality (HR = 1.03, $p = 0.02$) whereas lean mass (measured as fat free mass index) showed a significant negative linear relationship with all-cause mortality (HR = 0.93, $p < 0.0001$) (Fig. 21.5) (Allison et al. 2002). Based on these results, we can speculate that that the J-shape relationship between

BMI and mortality may be the result of the inverse and independent effects of body fat and lean mass on mortality.

Allison DB and colleagues study, also supports the notion that at least part of BMI's inability to accurately predict mortality is be due to its inability to differentiate between body fat and lean mass. It also highlights that studies to assess the relationship between mortality and body fat and its distribution measured by other more accurate techniques, such as dual energy X-ray absorptiometry are needed. In addition, the possible effect of visceral fat measured by MRI and or CT on predicting adverse events are also largely unknown, and research is still needed to answer these important questions.

The relationship between obesity as an independent risk factor for CV disease is still not absolutely clear. The quest for an anthropometric measure that accurately predicts total and CV mortality independently of other CV risk factors is far from over and requires extensive research. More data should be analyzed to answer this difficult and controversial topic.

What seems to be intuitively beneficial is leading a healthy lifestyle where diet and exercise play a key role. The impact of different diets and exercises, and the more extreme, pharmacological and surgical therapies for weight control and their impact on morbidity and overall mortality are being studied worldwide.

Summary Points

- There is a clear association between obesity and total and CV mortality.
- There is controversy regarding which anthropometric measure of obesity better predict total and CV mortality.
- BMI association with total and CV mortality is conflicting as it has shown that overweight subjects might have better survival and fewer CV events.
- Anthropometric measures of obesity that take into account central obesity, such as WC and especially WHR appear to better predict total and CV mortality than BMI alone.
- Although body fat is the gold standard definition of obesity, little is known regarding its impact on mortality. However, body fat and lean mass appear to play a key role in predicting mortality.

Key Points

Anthropometric measures of obesity in predicting total and cardiovascular mortality.

1. BMI association with total and CV mortality is controversial, as it follows a U-shape association with lowest mortality in overweight subjects.
2. Measures of central obesity, such as WC and WHR appear to better predict total and CV mortality but this remains to be proven.
3. Despite body fat being the gold standard to define obesity, little is known regarding its relationship with mortality. However, data suggests that body fat increases mortality while lean mass is related to improved survival.

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Chapter 22
Body Fat Measurement by Air Displacement Plethysmography: Theory, Practice, Procedures, and Applications

Mauro E. Valencia and Rosa C. Villegas-Valle

Abstract The importance of measuring body composition has increased because of the need to evaluate changes in nutritional status that can affect body reserves differentially. These changes can be detected only by using valid body composition measurement techniques. Air displacement plethysmography (ADP) has proved to be a valid method for determining body composition in adults and children. ADP measures body volume using a subtraction technique in which body volume equals reduction in the volume of a chamber resulting from the introduction of the individual into the chamber. There are two versions of the plethysmograph, one for adults and children, the BOD POD, and another version for infants, the PEA POD. Both versions correct the raw body volume measurement for the isothermal effect of skin on air and thoracic gas volume. The body volume is then converted to mass and density relationships for body fat and fat-free masses, and body fat percentage is calculated. In both formats, ADP has good reliability in terms of body volume and fat percentage and has been validated against three-compartment (3C) and four-compartment (4C) models. It has also been used to develop body composition prediction equations for methods like bioimpedance analysis (BIA) and anthropometry in a wide range of populations. Among other applications, ADP has been applied successfully to determine the relationship between body size and adiposity, to evaluate intervention programs based on diet or physical activity, and in athletes, to evaluate body composition changes related to training in different sports.

Abbreviations

2C, 3C, 4C	Two-, three-, and four-compartment models
% fat	Percentage of fat mass
ADP	Air displacement plethysmography
BIA	Bioimpedance analysis
BMI	Body mass index
CV	Coefficient of variation
D_2O	Deuterium oxide
DXA	Dual X-ray absorptiometry
FFM	Fat-free mass

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_22,

HW	Hydrostatic weighing, hydrodensitometry
SAA	Surface area artifact
SD	Standard deviation
SEE	Standard error of the estimate

22.1 Introduction

The importance of measuring body composition has increased because of the need to evaluate changes in nutritional status that can affect body reserves differentially. Individuals can gain or lose body fat, fat-free mass (FFM), bone mineral mass, or cellular mass components as a result of disease, overeating, sports, or undernutrition (anorexia nervosa), or as a result of nutritional intervention programs. These changes can be detected only by using valid body composition measurement techniques. In addition, the worldwide epidemic of obesity and its association with chronic disease has also contributed to the need to study body composition and the distribution of body components. The definition of obesity based on body size has been challenged in the context of different populations because of the different relationships of percent (%) body fat at the same body mass index (BMI) levels (Gallagher et al. 2000). Therefore, a definition of obesity based on body composition terms could help to clarify this issue.

22.2 Measurement of the Density of the Body

Air displacement plethysmography (ADP) is a valid method for determining body composition compared with hydrodensitometry and the four-compartment (4C) model in adults (Demerath et al. 2002; Fields et al. 2002), in elderly adults (Alemán-Mateo et al. 2007), and in babies (Ellis et al. 2007). Body density measurement by hydrostatic weighing (HW or hydrodensitometry) originally outlined by Behnke et al. (1942) uses Archimedes' principle to determine body volume by measuring an individual's weight in water compared with that in air (Fig. 22.1). This procedure requires the person to be submerged completely under water, exhaling maximally to measure the residual lung volume (V_r). This V_r has been commonly measured using the O_2-dilution method of Wilmore (1969), with nitrogen analyzers.

In spite of having been a reference standard for many years, HW is time consuming, laborious, and difficult to perform in the elderly, disabled, obese, and in infants. To overcome these limitations, alternative methods to HW that measure whole-body volume have been developed, including ADP, acoustic plethysmography, helium displacement, photogrammetry, and the more recent 3-dimensional photonic scanning and sulfur hexafluoride dilution (Fields et al. 2002). Some of these methods have unsatisfactory reliability and validity because of technical and practical problems (McCrory et al. 1998). This chapter focuses on ADP, which measures body volume by a subtraction technique in which body volume is equal to the reduction in chamber volume caused by the introduction of the individual to be measured. The main features of the method are described in Table 22.1.

The earliest attempts to use ADP yielded results that were not very useful for measurement of body composition. The volume measurement errors were high, and body fat changes ranged from 20% to 32%, mainly because of difficulties with temperature, pressure, and relative humidity in the enclosed chamber (Gnaedinger et al. 1963). Later, Gundlach and Visscher (1986), in an effort to

Fig. 22.1 Measurement of hydrostatic weight (courtesy of INCAP, Guatemala). This figure shows a person being introduced in a water tank to calculate body density by the hydrostatic weight method, while the technician prepares for the measurement of residual lung volume (courtesy of INCAP, Guatemala)

Table 22.1 Important features of air displacement plethysmography (ADP) by the BOD POD

1. Solid physical principles are the basis of this method
2. It has been validated against its predecessor, hydrodensitometry, for determining body volume and body density, including the corrections for lung volume
3. There have been many reliability studies both in the calibration procedure with phantoms and humans, and repeated measurements taken with respect to volume, density, and percent body fat.
4. The validation has been done against other reference methods like isotopic dilution, DXA, and the 4C Model
5. It is a potential reference for validating field methods like BIA and anthropometry through the development of age–sex–ethnicity-specific algorithms for the estimation of fat mass and fat-free mass.
6. It is useful in a wide range of populations: from infants to the elderly, malnourished and obese individuals, athletes, and patients under different conditions, and/or diseases.
7. With proper training, it is fast and easy to perform

This table lists some important characteristics of air displacement plethysmography (ADP) by the BOD POD, referring to its general uses and advantages
Abbreviations: *DXA* dual X-ray absorptiometry; *4C* four-compartment model; *BIA* bioimpedance analysis

maintain isothermal and adiabatic conditions, measured ADP and compared it to HW in a group of 88 people. Although they experienced practical difficulties, the prediction of % body fat from ADP showed an $R^2 = 0.93$ and a standard error of the estimate (SEE) = 6.7%.

A new air displacement plethysmograph, the BOD POD (Body Composition System; Life Measurement Inc., Concord, California now a part of COSMED srl.Italy), has been recently developed and appears to overcome previous problems. There are two versions, the BOD POD for adults and children and the PEA POD for infants. For the BOD POD, a new pediatric option accesory for children as small as 12kg and between 2 and 6 years of age is now available (COSMED srl, 2011).

22.3 Description of the BOD POD and Principles of Operation

The BOD POD is based on physical principles to measure whole-body volume (V_b) of an individual. It uses the relationship between pressure and volume (the gas laws), to calculate the V_b, which, along with the measurement of body mass (M_b) permits calculation of body density (D_b) and subsequently the estimation of % body fat and FFM (Dempster and Aitkens 1995). Table 22.2 explains the main gas laws involved in the performance of the measurement.

The BOD POD is made out of fiberglass. There are two chambers, separated by a seat where the individual sits and the volume is measured. A door with an acrylic window is the entrance for the individual into the chamber and closes tightly by a series of electromagnets that reduce the sensation of being in a closed environment. Instruments, circuits, valves, air circulation system, pressure transducers, and other electronic devices are located in the rear chamber. Figure 22.2 shows the main system components of the BOD POD.

Table 22.2 Key facts in air displacement plethysmography (ADP): the gas laws

Boyle's Law states that the pressure of a fixed amount of gas maintained at constant temperature (isothermal condition) is inversely proportional to the volume of the gas (Chang 2000). Thus, a quantity of air compressed under isothermal conditions will decrease its volume in proportion to the increasing pressure, or

$$P_1 / P_2 = V_2 / V_1$$

where P_1 and V_1 represent one paired condition of pressure and volume and P_2 and V_2 represent a second condition. In contrast to isothermal conditions, under adiabatic conditions, air is more compressible. Poisson's Law describes the relationship between pressure and volume under adiabatic conditions as

$$(P_1 / P_2 = V_2 / V_1)^{\gamma}$$

where γ is the ratio of the specific heat of the gas at constant pressure to that at constant volume (Sly et al 1990). The value of γ is approximately 1.4 for air and 1.3 for CO_2 (Daniels and Alberty 1967).

The system maintains the equivalency of gas composition in the two chambers and constancy of the γ in the pressure–volume relationship.

This table explains the basic concepts of the gas laws involved in the accurate measurement of body volume by air displacement plethysmography (ADP)

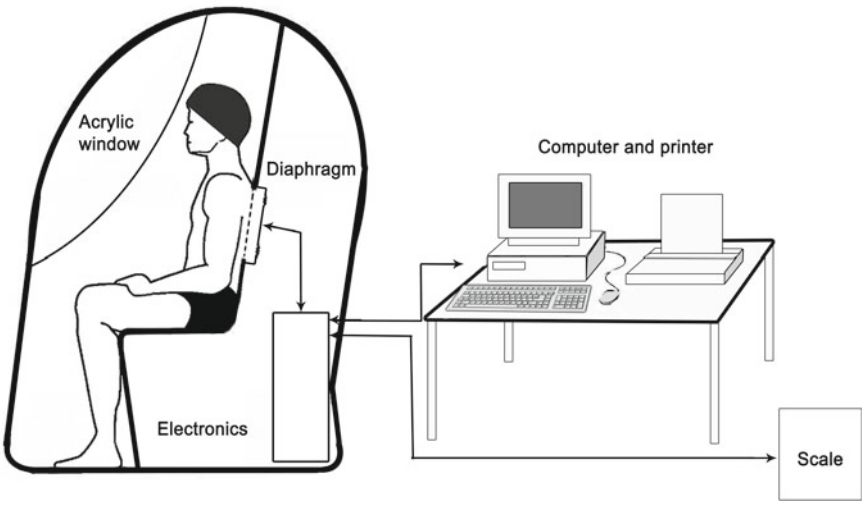

Fig. 22.2 Main system components of the BOD POD (Life Measurement Inc., Concord, CA). The figure shows the general system components of the BOD POD (Life Measurement Inc., Concord, CA), including the fiberglass chambers and electronic components. It also shows the position of the individual inside the equipment for the measurement of body density (adapted from Dempster and Aitkens 1995 under permission of Wolters Klower Health, Lippincot Williams & Wilkins, Baltimore, MD, USA)

The body volume is measured through an air displacement method. A moveable diaphragm mounted on a common wall separates the external and internal chambers. This diaphragm is controlled by a computer integrated into the system and oscillates to produce complementary volume perturbations (approximately 350 mL) in the two chambers that are equal in magnitude but opposite in sign. These volume perturbations lead to small complementary pressure fluctuations in the two chambers of approximately ±1 cm H_2O.

The results from the pressure fluctuations allow calculation of the chamber's air volume. After this, the individual enters the chamber and the same procedure is repeated. The volume of the chamber is reduced and the raw body volume (V_{br}) is calculated by difference:

$$V_{br} = (\text{Empty chamber volume}) - (\text{Chamber volume with individual inside.})$$

22.4 Practical Methods and Techniques

22.4.1 Calibration, Corrections, and Technical Aspects of the Measurement

Calibration of the BOD POD is done by a two-point system measuring the pressure of the ratio of the empty test chamber and the chamber with a 50-L cylinder. After the calibration procedure, the unit is ready for measuring people.

The difference in the behavior of gases under isothermal and adiabatic conditions is important for the accurate measurement of volumes by plethysmography. When an individual enters the chamber, air close to the skin and clothing will not maintain adiabatic conditions, but air in the lungs is maintained at body temperature (isothermal conditions). Air under these circumstances is more compressible than that under adiabatic conditions, and hair, clothing, and skin can show an apparent negative volume while measured in the chamber. To eliminate the effects of clothing and hair, the person must wear minimal and tight clothing (bathing suit), and the hair must be compressed with a swimming cap. Finally, to account for an apparent negative volume caused by the isothermal effects of the skin, a surface area artifact (SAA) is computed automatically and applied for this correction (Dempster and Aitkens 1995).

As in HW, residual gas volume in the lungs must be accounted for. In ADP, thoracic gas volume (V_{TG}) (volume of air in the lungs and air trapped in the thorax) is measured as a part of the procedure. Because the individual is breathing normally, the variable of interest is the average V_{TG}. This technique is similar to the plethysmographic measurement of V_{TG} used in pulmonary function testing (Ruppel 1995).

As Dempster and Aitkens (1995) described, the measurement of V_{TG} in the BOD POD includes the use of a single-use disposable filter and tubing attached to a port in the front chamber that passes to a breathing circuit housed in the rear chamber. With the door open, the person, with a nose clip attached, connects to the system and proceeds with quiet tidal breathing. The door is then closed. Pressure transducers in the two chambers monitor the person's body volume change due to breathing, producing a real-time record of tidal breathing. After 2–3 cycles, the airway is occluded at approximately average lung volume (mid-exhalation), at which point the individual puffs against the closed airway at about 1 Hz, producing pressure changes in the lungs that are measured by a transducer in the breathing circuit. During this occlusion, airflow is essentially zero, so there is little difference between pressure in the alveoli and the airway. Time-correlated analysis of airway pressure and tidal breathing record yields V_{TG} at the point in the breathing cycle when the airway is occluded. The V_{TG} at occlusion is

$$V_{TG} = \left(m / 1.4\right) - \text{dead space of the breathing apparatus}$$

where m is a slope and the constant 1.4 may be interpreted by considering the air in the thorax (mainly lungs) as isothermal while air in the chamber is adiabatic. As such, V_{TG} would be overestimated by 40% if m were not divided by 1.4.

A complete test involves measurement of the uncorrected body volume, computation of the surface area artifact (SAA), and measurement of V_{TG}. The latter two items serve to correct the original measurement of body volume (V_{br}) as follows:

$$V_b(L) = V_{br}(L) - \mathrm{SSA}(L) + 40\% V_{TG}(L)$$

where V_b (L) is the corrected body volume.

It is important to mention that the equipment can also predict V_{TG} with the entered data for the individual based on gender, age and height (Crapo et al. 1982; Fields et al. 2004).

22.4.2 Measurement Procedure

The measurement of V_b by the BOD POD begins with the calibration of the equipment with a "phantom" of previously known volume. After the calibration is completed, the person is weighed wearing tight clothing and swimming cap. Then the individual sits inside the chamber and remains still, and the measurement of V_b is performed by duplicate. The V_{TG} is either measured using a plastic tube attached inside the instrument and a nose clip, or predicted by the equipment. The total time of the measurement is approximately 15 min. Figure 22.3 shows an explanatory sequence for the measurement procedure in the BOD POD.

22.5 Reliability

Reliability is a general term denoting repeatability or consistency between ≥2 measurements. The reliability of the BOD POD in measuring the body volume of inanimate objects is reported to be very good. Twenty consecutive measurements of a 50.039-L aluminum cylinder resulted in a mean ± SD, (standard deviation) volume of 50.027 ± 0.00127 L and a corresponding coefficient of variation (CV) of 0.025% (Dempster and Aitkens 1995).

Reliability in terms of % of body fat has also been explored. Fields et al. (2002) reported mean within-subject CVs for % body fat ranging from 1.7% to 4.5% within a day and from 2% to 2.3% between days. According to their review, these CVs are within the range of those measured previously by HW and dual X-ray absorptiometry (DXA).

Reliability of body volume measurements compared to hydrostatic weighing should be compared based on the combined measurements of body volume and lung volumes rather than on estimating the lung volume. Dewit et al. (2000) and Wells et al. (2000) reported that the precision of V_b in children aged 7–14 years was 0.07 and 0.08 L in the two studies, respectively, which was similar to the precision in adults in the same studies (0.07 and 0.11 L, respectively). In our laboratory, we tested the reproducibility of the ADP system using duplicate measurements in 91 adults. The duplicate measurements were both performed during the same session, with duplicated mean body density measurements of 1.0292 ± 0.019 and 1.0296 ± 0.019 and a mean difference in body density of 0.00007. In terms of % body fat, the technical error of measurement was 0.066% fat units, assessed as $\left(\sum d^2 / 2n\right)^{1/2}$, where d is the difference between repeated measurements and n is

Fig. 22.3 Sequence for the measurement of body volume using ADP (courtesy of CIAD, Mexico). (**a**) The instrument is calibrated before a series of measurements using a known volume or "phantom." (**b**) The individual is weighed in the calibrated scale. Note that the person is wearing tight clothing and a swimming cap, with no jewelry. (**c**) After a second calibration with the phantom, the individual enters the instrument and sits still. The measurement starts after closing the chamber and is performed twice. (**d**) To measure the lung volume, the person is instructed to breathe normally through the tube attached inside the instrument. The measurement is performed twice after the chamber is closed. The instrument will then calculate the final results

the number of paired repeated measurements (Macias et al. 2007). In another study (Ramírez et al. 2009) involving 60 children 6–14 years of age with a 4C model using the BOD POD, we found that the mean V_b within individuals was 0.0212 L and 0.23% fat (data not shown in that paper).

22.6 Validation Studies and Body Composition Prediction Equations

Just as HW once served as a reference method, ADP with the BOD POD is becoming a single-body composition reference method, especially thanks to the validation studies that have compared ADP to 3C and 4C models (Durenberg-Yap et al. 2001; Alemán-Mateo et al. 2007). In these multicompartment models, total body water was determined by deuterium oxide (D_2O) dilution and bone mineral content by DXA. Among these studies is a wide variation of age groups in both male and female individuals from children to the elderly, in ethnicity (Caucasians from North America and Europe, Latinos from Mexico, and Asians from Japan, Malaysia, and India), and in nutritional status, including individuals with overweight and obesity.

In obese individuals, ADP by the BOD POD has proved to be valid for measuring D_b compared with HW. Ginde et al. (2005) measured a wide range of individuals (n = 123; 42.4–190.2 kg) of which 70 were obese (BMI: 30.4–38.8) and 10 were very obese (BMI: 40.6–58.4). ADP was found to be accurate for measuring % body fat by D_b, with no significant bias attributable to the method up to a BMI of 58.4.

The BOD POD has also been used based on its own merits in multicompartment models to develop body composition prediction equations, using either bioimpedance analysis (BIA) (Macias et al. 2007) or anthropometry (Huerta et al. 2007). These equations usually arise from cross-validated studies in which the main sample is randomly split into two groups; one for developing the algorithm and the other for validating it.

Example. In our laboratory, we developed a simple BIA equation:

$$\mathrm{FFM}\left(\mathrm{kg}\right) = 0.7374 * (\mathrm{Ht}^2 / R) + 0.1763 * (\mathrm{BW}) - 0.1773 * (\mathrm{Age}) + 0.1198 * (\mathrm{Xc}) - 2.4658$$

based on the BOD POD by a 2C model. This study included 155 men and women from northern Mexico, 20–50 years of age, from low, middle, and upper income levels. In the equation, Ht^2 is height in centimeters, R is resistance in ohms, BW is body weight in kilograms, age is in years, and Xc is reactance in ohms.

The mean values of FFM predicted by this new BIA equation and measured by ADP in the validation sample were 48.57 ± 10.9 kg and 48.43 ± 11.3 kg, respectively. The limits of agreement, defined as mean ± 2 SD, were from -6.56 to + 4.82 kg of FFM. The new BIA equation based on a 2C model method was accurate, precise, and free of bias. The prediction-validated equation can be used to assess body composition and nutritional status in populations having anthropometric and physical characteristics similar to this sample.

22.7 Validity of Equations Based on Anthropometry to Estimate Body Fat in Older Adults

With the same ADP approach using the BOD POD, we also developed a prediction equation to estimate body fat mass from anthropometry in the healthy elderly using a 4C model as the criterion method. This study included 202 participants, 60 years of age and over. The measurements of total

body water, bone mineral content, and body density were included in the 4C model equation. The best model included body mass, sex, and the calf and triceps skinfold thicknesses, with an $R^2 = 0.85$ and a SEE of 3.2. The new equation was accurate and precise as well as free of significant bias in men and women together or separately. This equation can be a good option to estimate fat mass in elderly men and women with similar physical characteristics and ethnicity to participants in this study for use in clinical and epidemiological applications in this age group (Huerta et al. 2007).

$$\text{Fat mass (kg)} = (0.165 \times \text{Calf SFT}) + (0.355 \times \text{Biceps SFT}) + (0.521 \times \text{Body weight}) - (6.054 \times \text{Sex}) - 13.171$$

where SFT is skinfold thickness and for sex, female = 0 and male = 1.0.

22.8 New Developments: The Use of Plethysmography in Infants

Recently, a new ADP system has been developed for use in infants because of the need for body composition methods that help researchers clarify the link between infant development and childhood obesity. This system is called PEA POD (Life Measurement Inc., Concord, California, USA). The main features of this method are presented in Table 22.3.

22.9 Principles of Operation and Design

As described by Urlando et al. (2003), the PEA POD operation principles are based on Boyle's Law and Poisson's Law (described in Table 22.2), similar to the BOD POD system. Although the main components of the system are the same, the physical design of the apparatus differs.

The main system components of the PEA POD are shown in Fig. 22.4. All the system components are all placed in a moveable cart. These components are either located in the bottom section (reference chamber, calibration volume, electronic components, central process unit, and printer) or on the top of the cart (test chamber, scale, and monitor).

The PEA POD has two chambers (test and reference), both constructed with the same material, design, and volume (37 L). Both chambers are connected by a manifold that houses the volume-perturbing diaphragm, which is placed between the chambers and thus prevents their direct contact.

Table 22.3 Important features of air displacement plethysmography (ADP) for infants (PEA POD)

1. Solid physical principles are the basis of this method
2. It has been validated against tissue phantoms and against 4C models in vivo.
3. The lung volume is not measured; it is estimated based on previous work (Stick 1996; Stocks et al. 1996; National Center for Health Statistics 2000)
4. There are very few studies both in the calibration procedure with phantoms and humans with repeated measurements with respect to volume, density, and percent body fat.
5. Useful in a wide range of infant behaviors: awake, crying, asleep, etc.
6. Very fast and easy to perform with proper training

This table lists some important characteristics of air displacement plethysmography (ADP) by the PEA POD, referring to its general uses and advantages

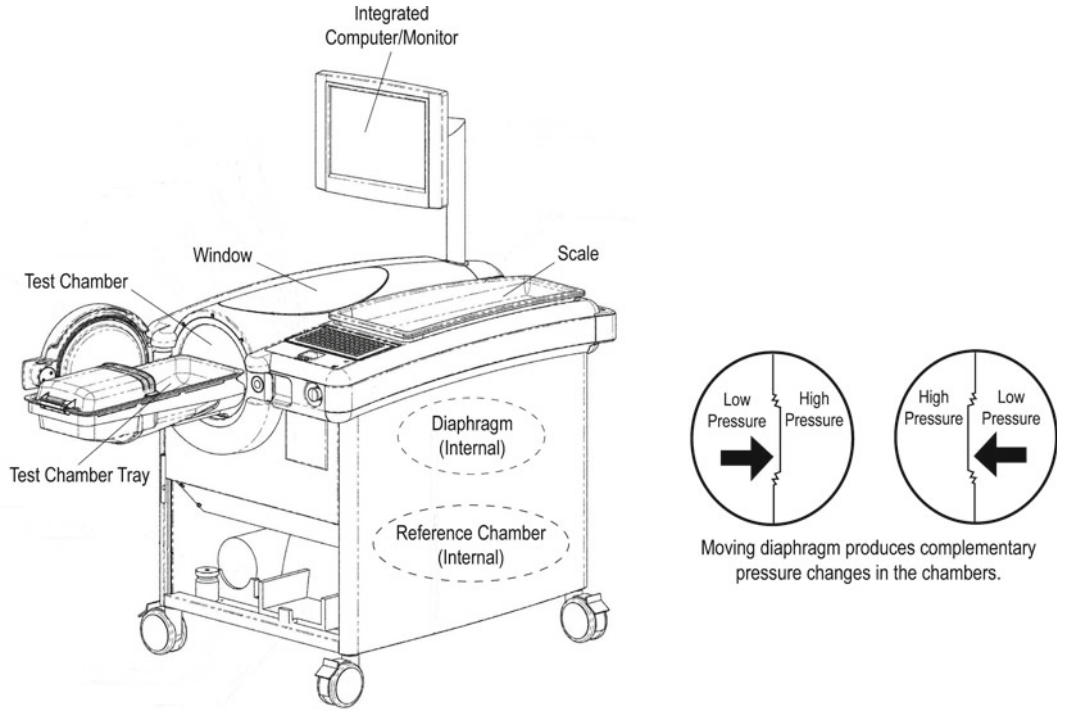

Fig. 22.4 General design and operation of the PEA POD Body Composition System (Used under license of Life Measurement Inc., Concord, CA, USA). The figure shows the general mechanical and electronic system components of the PEA POD (Life Measurement Inc., Concord, CA), mounted in a moveable cart, as well as an schematic representation of the pressure changes that occur in the chambers as the equipment performs the calibration or measurement

The test chamber consists of an acrylic cylinder containing a sliding plastic tray where the infant is placed. A pneumatic valve (calibration valve) connects the test chamber with the calibration volume container. Electromagnets close the aluminum door of the chamber during the calibration and test. A special characteristic of the test chamber is that it has a heating system to maintain a constant temperature between 31°C and 37°C.

As with the BOD POD, when the system is operating, the diaphragm creates equal volume changes in both chambers, but opposite in sign. These perturbations change the pressure in the chambers less than ±0.5 cm H_2O and make it possible to maintain a linear relationship between pressure and volume.

22.10 Practical Methods and Techniques

22.10.1 Corrections and Technical Aspects of the Measurement

Every measurement is corrected automatically for the isothermal behavior of air near the infant and inside the lungs. As in the BOD POD, the correction for the air near the infant is the SAA and is the result of the difference between the volume measured by the PEA POD and the actual volume of an object or person.

For the air inside the lungs, the thoracic gas volume (V_{TG}) of infants is predicted based on previous work (Stick 1996; Stocks et al. 1996; National Center for Health Statistics, 2000). As with the BOD POD, 40% of the V_{TG} is added to the infant's body volume measured by the PEA POD, accounting for the higher compressibility of air under isothermal conditions. Similar to what happens with larger individuals in the BOD POD, without this correction, the lung volume would be overestimated by 40%, which would therefore underestimate the person's volume. Each correction represents approximately 1.5% of the final volume of the individual (V_b).

The V_b is then calculated as follows:

$$V_b(L) = V_{br}(L) - \mathrm{SSA}(L) + 40\% V_{TG}(L)$$

where V_{br} corresponds to the raw volume directly measured by the apparatus.

In ADP testing, hair and clothes can cause a significant difference in the final fat percentage results. In the PEA POD, baby oil has been used to flatten the hair of infants closer to their heads, and the measurement has been performed without clothes (Ma et al. 2004; Ellis et al. 2007).

22.10.2 Measurement Procedure

The PEA POD accommodates infants ranging in size from 2.2 lbs (1 kg) to 17.6 lbs (8 kg) (Life Measurement Inc. 2009). Figure 22.5 summarizes the measurement sequence of body volume by ADP in the PEA POD. The first step of the actual measurement is the weighing of the infant to the nearest 0.1 g. At the same time, the volume of the chambers is calibrated automatically. This two-point calibration is made while the calibration valve is opened and closed, and the pressure changes are registered. The calibration lasts 50 s, although some have reported up to 2 min (Ma et al. 2004).

After the calibration, the test chamber door opens, the infant is placed in the sliding tray, which is pushed into the chamber, and the door is closed. When the measurement begins, air is exchanged between the chamber and the environment, and the pressure changes are collected. After 2 min, the door opens and the test is completed. This procedure is performed twice. The mean of the two measurements is used to calculate % body fat if the two volume measurements are within 5 mL of each other, or 0.25% of the mean of the two measurements, whichever is larger. If this requirement is not met, a third measurement is taken.

It has been observed that the behavioral state of the infant (quiet, alert, awake and active, crying, etc.) does not affect the fat % estimate (Ma et al. 2004).

22.11 Accuracy and Precision

Regarding the measurement of weight, it has been reported that the mean values of repeated measurements differ by ≤0.1 g to the actual mass values (Urlando et al. 2003), with a precision of 0.12% CV (Sainz and Urlando 2003). Regarding the precision of the volume measurement, reported mean SDs and CVs have varied from 1.7 to 2.3 mL and 0.03–0.08%, respectively, for several known volume levels (Urlando et al. 2003). A study performed in tissue phantoms found that in the repeated measurement of fat %, the SDs ranged from 0.2% to 1.7% for several fat percentages (Sainz and Urlando 2003), and in humans the mean within-subject SD and CV were 0.7% body fat and 7.9%, respectively (Ellis et al. 2007).

Fig. 22.5 Sequence for the measurement of body volume in infants using ADP (used under license of LMI Inc., Concord, California). (**a**) The infant is weighed, and at the same time, the volume of the chambers is calibrated automatically. (**b**) The test chamber door opens; the infant is placed in the sliding tray, and pushed into the chamber. (**c**) The measurement begins when the door is closed. After 2 min, the door opens and the test is completed. This procedure is performed twice. (**d**) The acrylic window allows the infant to be observed at all times. The behavioral state of the infant (quiet, alert, awake and active, crying, etc.) does not affect the fat % estimate (Ma et al. 2004)

The accuracy of the fat % results from ADP has been compared with several other body composition methods, in frozen animal tissue and in humans. The comparison of the ADP with chemical analysis of bovine tissue phantoms found that both methods gave virtually the same result for fat %, with a mean CV of 3.21% and 3.50%, respectively, in a range of fat percentages (Sainz and Urlando 2003). Another study performed in humans compared the PEA POD with D_2O dilution to calculate % fat. The mean difference and SD between the two methods, –0.07 ± 3.30% body fat, was not significant, and the differences were not related to body mass (Ma et al. 2004). Moreover, the comparison of infant ADP with a 4C model showed that the PEA POD estimates for % body fat were not significantly different from the values obtained with the 4C reference model (Ellis et al. 2007).

22.12 Reliability

The reliability of the PEA POD has also been evaluated. The mean difference in % body fat between days (–0.5 ± 1.21) and within days (0.16 ± 1.44) was not significant (Ma et al. 2004).

22.13 Future of the Method

Only a few studies have used the PEA POD to measure body composition in infants; however, it is in good agreement with the 4C model. Because the ADP has been used extensively in other populations and the PEA POD presents good accuracy, precision, and reliability, more studies could be useful to confirm that the infant ADP is not only easy to perform but also reliable and convenient in this population group.

22.14 Calculation of Body Density and % Body Fat by ADP

Using the corrected volume measured by the apparatus (V_b), the whole-body density (D_b), either in the BOD POD or PEA POD, is calculated using the following formula (Urlando et al. 2003):

$$D_b = M_b / V_b$$

where M_b is the body mass.

Then, the V_b is converted into:

$$M_b / D_b = M_f / D_f + M_{ffm} / D_{ffm}$$

where M_f is the fat mass, D_f is the density of the fat mass, M_{ffm} is the fat-free mass, and D_{ffm} is the density of fat-free mass. In adults, D_{fm} is mostly constant (approximately 1.100 g/mL) (Sopher et al. 2005). Because D_{fm} changes during growth, the PEA POD uses specific values for age and gender (Butte et al. 2000), which are shown in Table 22.4.

The fat percentage is then calculated as follows:

$$\%\text{fat} = (M_f / M_b)(100)$$

22.15 Application of ADP to Other Areas of Health and Disease

The worldwide obesity epidemic has brought about the necessity for looking at the nature of the disease beyond body size (BMI), which is most commonly used for the definition and classification of obesity. Different populations can show important differences in body fat content at the same body size, a phenomenon that can be related to ethnicity, environment, or both.

Intervention programs based on diet and/or physical activity for tackling overweight and obesity is probably one of the most practical applications of ADP. By contrast, malnutrition recovery in conditions like anorexia nervosa or other types of malnutrition can use this method to monitor changes in time.

Table 22.4 Fat-free mass (FFM) density according to age ($n = 76$) (adapted from Butte et al. 2000) under permission of WOHers Kluwer Health, Lippincot Williams & Wilkins, Baltimore, MD, USA).

Age (mo)	FFM density (g/mL)
Boys	
0.5	1.054 ± 0.006
3	1.061 ± 0.005
6	1.062 ± 0.004
9	1.066 ± 0.004
12	1.068 ± 0.005
18	1.072 ± 0.004
24	1.077 ± 0.005
Girls	
0.5	1.053 ± 0.005
3	1.060 ± 0.006
6	1.062 ± 0.006
9	1.066 ± 0.006
12	1.070 ± 0.005
18	1.072 ± 0.005
24	1.073 ± 0.005

Values are mean ± SD

Table 22.3 shows the densities of fat-free mass (FFM) according to age, and separated by sex ($n = 76$). Note that the density of FFM increases with age (adapted from Butte et al. 2000). Values shown are means ± standard deviation.

It is not easy to study body composition in infancy with a scientifically solid methodology. Alternatives like isotopic dilution by D_2O or oxygen-18 have to be analyzed by isotope ratio mass spectrometry (IRMS), which is not readily available to many hospital facilities as ADP could be. There are practically no studies of D_2O dilution in infants using Fourier transform infrared spectroscopy (FTIR). Also, the application of BIA and anthropometry estimation methods has its own technical difficulties and insufficiently validated algorithms for the calculation of FFM and fat mass components. The PEA POD can be a simple noninvasive and rapid method for evaluating body composition changes in time as indicators of nutritional status in infants that either by primary or secondary cause can be malnourished or require intervention for recovery. ADP in infants has been more recently used to evaluate the accuracy of some fetal parameters calculated from ultrasound (2D and 3D) for prediction of body fat percentage in newborns. The PEA POD is well tolerated by the infant. They do not have to be asleep, and there is no problem if they are crying during the procedure. Results are immediately available and the procedure can be repeated as needed. The PEA POD has shown good agreement with the 4C model.

There is a lot of interest in using ADP to evaluate changes in body composition in relation to the effect of training in different sports. It has also been used to measure the effect of several types of exercise on body fat loss, either total or regional, and to measure the effect of different supplements during training. In addition, ADP is useful in determining if the methods commonly used to measure body composition in athletes are accurate enough to assess changes over time due to training.

ADP has also been applied in the evaluation of body composition in patients suffering from different diseases. For example, it has been used to validate other methods of measuring body fat in pediatric cancer patients (White et al. 2008) and to evaluate body composition in patients with Huntington disease (Gaba et al. 2005).

Summary Points

- Valid body composition measurements help evaluate changes in body fat, fat-free mass, bone mineral mass, or cellular mass as a result of changes in nutritional status, exercise, or disease.
- Air displacement plethysmography (ADP) measures body volume by a subtraction technique in which body volume is equal to the reduction in the volume of a chamber caused by the introduction of the individual.
- Derivation of body volume, along with measurement of body mass, permits calculation of body density and subsequently the estimation of percent fat and fat-free mass.
- The final volume measured by the equipment is corrected for the effect of air near the skin and for the thoracic lung volume (air contained in the lungs).
- Two types of apparatus (plethysmographs) are available to date: the BOD POD for children and adults and the PEA POD for infants up to 17.6 lb (8 kg).
- The measurement of humans in the BOD POD involves the calibration of the apparatus with a "phantom" of known volume, weighing of the individual, duplicate measurement of body volume, and measurement (or prediction) of lung volume. The total time of the measurement is approximately 15 min.
- Measurement in the PEA POD involves the simultaneous weighing of the infant and calibration of the equipment. The infant is then placed on a sliding tray and pushed inside the chamber, where the body volume is measured twice.
- ADP has been extensively validated against 3C and 4C models in a wide range of populations (from infants to the elderly), and is reliable and accurate.
- Body composition prediction equations for field methods like bioimpedance and anthropometry have been developed with ADP.
- Applications of ADP include evaluation of changes in body composition due to intervention or training programs based on diet or physical activity, to evaluate associations between fetus size and newborn adiposity, and to evaluate the effect on body composition of supplements or drugs in patients suffering from different diseases.

Acknowledgments We thank the Centro de Investigacion en Alimentacion y Desarrollo (CIAD, A.C.) (Research Center for Food and Development) in Hermosillo, Mexico, for providing the equipment and facilities for the illustration of the BOD POD human measurement procedure. We specially thank Erika Ibarra and Alma Robles, for their assistance and participation in the photographic procedures, and Aida Espinosa for her assistance with drawings and graphics. We thank Cruz Teros, official photographer of the University of Sonora for taking the pictures of the BOD POD measurement procedure. We also thank Manuel Ramirez and Karen Schlosser from the Instituto de Nutricion de Centro America y Panama (Institute of Nutrition of Central America and Panama, INCAP) in Guatemala City, Guatemala, for providing the photographs of the hydrostatic weight measurement. Thanks also to Life Measurement Inc. (LMI), California, USA, for allowing us to use their images.

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Chapter 23
Selected Applications of Bioelectrical Impedance Analysis: Body Fluids, Blood Volume, Body Cell Mass and Fat Mass

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Abstract This chapter is intended as a practice-oriented complement to the introduction of the basic concepts of bioimpedance measurements in the chapter *Use of bioelectrical impedance: general principles and overview*. The present chapter focuses on selected applications of bioelectrical impedance analysis (BIA) for body composition analysis in health and disease. Various techniques and models are introduced in detail and summarized in a discussion about the potentials and limits of BIA. The chapter begins with a brief overview of the historical developments of BIA applications. The following section introduces a range of body composition applications such as measurements of intra- and extracellular water as well as fat mass, body cell mass, and blood volume. In addition to discussing the role of the basic BIA model in these applications, recent alternative developments that show promise for future research are addressed wherever applicable. This includes a discussion underlying the developments from single-frequency to multi-frequency BIA to finally bioimpedance spectroscopy (BIS). It also covers the potential advances of purely descriptive models that are statistically derived compared to rather explanatory, biophysical models that do not rely on calibrations of the target quantity by regression techniques. The most popular approach of the latter is the use of Hanai's mixture theory and its original approach plus its most recent advances are therefore discussed in detail. This is written in an accessible way, so that also the novice reader will be provided with a basic understanding of the technique to implement it in future applications. The chapter finally discusses the potentials and limits of the applications and models introduced, gives an outlook for future research, and concludes with recommendations regarding the use of BIA/BIS in practice.

Abbreviations

Latin letters (boldface letters denote complex numbers)

A	Area (m^2)
BCM	Body cell mass (kg)
BIA	Bioelectrical impedance analysis
BIS	Bioelectrical impedance spectroscopy
BM	Body mass (kg)

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_23,

BMI	Body mass index ($kg \cdot m^{-2}$)
ECW	Extracellular water (L)
f	Frequency (Hz)
f_c	Characteristic frequency (Hz)
FFM	Fat free mass (kg)
FM	Fat mass (kg)
%FM	Percentage fat mass (%)
H	Height (m)
ICW	Intracellular water (L)
l	Length (m)
L	Liter
R	Resistance (Ω)
R_0	Resistance at zero frequency (Ω)
R_∞	Resistance at infinite frequency (Ω)
R_e	Extracellular resistance (Ω)
R_i	Intracellular resistance (Ω)
TBW	Total body water (L)
V	General volume (L)
X_c	Capacitive reactance (Ω)
Z	General impedance (magnitude) (Ω)

Greek letters (boldface letters denote complex numbers)

ρ	Resistivity (Ω·m)
Ω	Ohm

23.1 Introduction

As early as 1888 the French psychiatrist Vigouroux suggested that bioimpedance measurements of the clinically ill might provide interesting diagnostic information. However, it was not until half a century later that the technique first made the transition from theory into practice. In 1929 Lueg and Grassheim demonstrated the first clinical application of bioimpedance analysis. They were able to show that electro-cardiographic changes in myxedema were partly due to modifications in the electrical properties of the skin and that these changes were related to the basal metabolic rate in both hypo- and hyperthyroid states. A few years later, Brazier (1935) improved the technique and provided a rapid and easy method for monitoring thyroid function based on measurements of phase angle. During these early studies, some of the major problems of bioimpedance monitoring such as stray cable capacitance, polarization potentials between electrodes or tissue interfaces, and surface conduction already became transparent. To minimize the errors due to polarization effects of the electrode–skin interface, Horton and Van Ravensway (1935) introduced a tetrapolar electrode arrangement which is still used today in a similar way. Nearly 25 years later Nyboer achieved measuring physiological and pathological volume changes in body segments based on continuous bioimpedance monitoring. Since the 1960s, electrical bioimpedance research has developed in several areas. In 1962, the Frenchman A. Thomasset demonstrated the potential of the technique to determine total body water. In the following years, his research group managed to differentiate intra- and extracellular fluid volumes using high and low frequencies (Jenin et al.1975; Thomasset 1963). Almost at the same time Hoffer (1969) compensated for the weakness of the bipolar technique

employed by Thomasset, by slightly modifying the tetrapolar arrangement originally suggested by Horton and Van Ravensway. This approach was then extended by Nyboer (1981) to quantifying fat-free mass and fat mass, which is still one of the most widely used applications today. In fact, its portability, quick and easy operation, financial attractiveness, and non-invasive nature affirm that his method is one of the most widely used techniques for determining body composition. Furthermore, the technological explosion of computers and electronics and the appearance of a number of commercial instruments have substantially supported the expansion of bioelectrical impedance applications in a number of clinical settings, including the assessment of hydration during dialysis (Chertow et al. 1997), the determination of nutritional status (Barbosa-Silva et al. 2003), abdominal fat (Scharfetter et al. 2001), body cell mass (De Lorenzo et al. 1997), skeletal muscle mass (Janssen et al. 2000) and blood volume (Siconolfi et al. 1996), the prediction of survival in human immunodeficiency virus-infected patients (Ott et al. 1995), the quantification of muscular activity during exercise (Cornish and Fallah 2001), and the assessment of neuromuscular disease (Tarulli et al. 2005).

23.2 Body Fluids

Based on the relationships underlying the basic biophysical model of BIA (for details see the chapter *Use of bioelectrical impedance: general principles and overview*), Thomasset (1962) first presented the potential of bioimpedance measurements for determining total body water (TBW). Since then an overwhelming number of regression equations have been published which relate bioimpedance and sometimes additional covariates such as anthropometry, age, and gender to different body fluid compartments. An overview of published regression equations is provided by Baumgartner (1996) and more recently by Kyle et al. (2004a, b). These types of equations can be classified as either single- or multi-frequency methods, whereas the latter usually employ two to four frequencies. To differentiate multi-frequency methods from approaches employing a much higher range of frequencies (between 15 and 500), the term bioimpedance spectroscopy (BIS) is commonly used.

23.2.1 Single-Frequency BIA

Single-frequency methods most commonly employ frequencies at 50 kHz. Impedance (Z) or resistance (R) corrected for conductive length (l), is then used to predict TBW. This is the simplest implementation of the basic biophysical model underlying bioimpedance measurements. The major criticism pertaining to single-frequency bioimpedance measurements at 50 kHz is that only a portion of the intracellular space is measured (Cornish et al. 1993; Matthie et al. 1998; Schoeller 2000). In fact, full penetration of the extra- and intracellular compartments requires frequencies of 10 MHz (Schwan 1957). Consequently, the strong relationship between TBW and bioimpedance indices at 50 kHz might be due to the high intercorrelations between extracellular water (ECW), intracellular water (ICW) and TBW in normal hydration states (Van Marken Lichtenbelt et al. 1994; De Lorenzo et al. 1997; Gudivaka et al. 1999; Schoeller 2000). Interestingly, some studies also suggested that reactance (X_c) obtained at 50 kHz is useful for estimating ECW (Lukaski and Bolonchuk 1988; McDougall and Shizgal 1986). However, according to Segal et al. (1991) it is likely that this finding is a function of the linear dependence between ECW and TBW in the samples studied. Furthermore, since the ratio between ECW and ICW is tightly regulated and the two compartments reflect TBW, any single-frequency measurement in the β-frequency range (frequency spectrum between a few kHz and 100 MHz) will predict ECW, ICW,

or TBW equally well during normohydration. Given that the characteristic frequency (f_c) can vary substantially between individuals – average frequencies ranging between 30 kHz and 60 khz with values up to 130 kHz have been reported for healthy adults (Baumgartner 1996; De Lorenzo et al. 1997; Matthie et al. 1998; Ward and Stroud 2001) – different amounts of volume of the extra- and intracellular compartments are measured. Furthermore, disruptions in the ratio of ECW to ICW or basically any changes in intracellular resistance (R_i), extracellular resistance (R_e) or membrane capacitance (C_m) can affect f_c. Thus, f_c varies not only between, but also within individuals, and the respective measured volume fractions can be highly variable (Matthie et al. 1998). This might at least in part explain the population specificity as well as the poorer performance of single-frequency measurements in subjects with illness and/or obesity or generally when fluid status is altered (De Lorenzo et al. 1997; Matthie et al. 1998; Gudivaka et al. 1999; National Institutes of Health 1996; Schoeller 2000).

23.2.2 Multi-Frequency BIA

A number of remedies have been suggested to address the drawbacks underlying single-frequency measurements. A frequently employed approach is to measure *Z* or *R* at relatively high frequencies (200–500 kHz) and assume that both the extra- and intracellular compartments are penetrated entirely. Usually, this approach is coupled with an additional measurement at relatively low frequencies (1–5 kHz) and thus allows the separation of fluid compartments. This method is usually referred to as multi-frequency BIA and was first introduced by Thomasset and colleagues (Jenin et al. 1975). At low frequencies, the current is assumed to flow through the extracellular space only, and the resulting *Z* or *R* is regressed against water determined by ECW-specific dilution tracers, yielding a prediction algorithm for the extracellular fluid compartment. In contrast, at high frequencies, *Z* or *R* is supposed to reflect both the extra- and intracellular compartments and can therefore be used to determine TBW. Finally, ICW can then be derived by subtraction of ECW from TBW. Yet, if f_c changes, the problem of measuring different water volumes still remains (Matthie et al. 1998). Extending the lower and higher frequency limits poses technical problems. Even if measurements at very low frequencies (< 1 kHz) and at very high frequencies (> 5 MHz) were possible, the limiting resistances of ECW and TBW would not be reached as relaxation mechanisms in living tissue (delay in polarization of the cell membrane or between tissue interfaces) would prevent the impedance locus (see chapter *Use of bioelectrical impedance: general principles and overview* for details) to reach the x-axis (Jaffrin and Morel 2008). To overcome these difficulties and extrapolate resistance at zero and infinite frequency, bioimpedance spectroscopy can be employed.

23.2.3 Bioimpedance Spectroscopy

An extension of the high–low frequency approach is to extrapolate resistance at zero frequency (R_0) and infinite frequency (R_∞) by fitting measured data to the Cole equation (see chapter *Use of bioelectrical impedance: general principles and overview* for details). The advantage is that R_0 and R_∞ are independent of f_c, and any errors related to inconsistent f_c are removed. However, it should be noted that R_∞ is not a measure of TBW, but rather two fluid compartments with different electrical resistivities. Using R_∞ for the determination of TBW requires the resistivity of TBW (ρ_{tbw}) to be constant across fluid compartments. However, the resistivity of ECW (ρ_{ecw}) differs from the resistivity of ICW (ρ_{icw}) by a factor of 3–4. Hence, ρ_{tbw} can be significantly altered, simply when the ratio of ECW to ICW changes, even though ion concentration and other influences remain constant (Matthie et al. 1998).

A straightforward alternative for removing the error related to assuming a constant ρ_{tbw}, in cases when fluid distribution is altered, is to determine intracellular resistance (R_i) and extracellular resistance (R_e) separately (for details on determining R_i and R_e see the chapter *Use of bioelectrical impedance: general principles and overview*), and subsequently employ compartment-specific resistivities for separately determining ECW and ICW. Presently, BIS is performed using measurements from 15 to 500 frequencies ranging between 1 kHz and 1 MHz. Given that each measurement as well as fitting by Cole-Cole modeling are not without error and BIS instruments are still relatively expensive, the use of impedance at four frequencies for the derivation of resistance at zero and infinite frequencies has also been suggested (Ward et al. 2006). Irrespective of the number of frequencies employed, once R_i and R_e have been determined regression analysis can be used to derive prediction equations for ICW and ECW. Finally, TBW can be calculated as the sum of ICW and ECW.

23.2.4 Use of Hanai's Mixture Theory

A general drawback of regression equations is, however, that they are based on statistical rather than causal relationships, and are therefore highly population-specific. Specifically, the underlying biophysical model does not account for the non-linear effect of the mixture of non-conductors and conductors in human body tissue. Therefore, Van Loan and coworkers (1993) introduced the application of Hanai's mixture theory to whole-body bioimpedance measurements. This approach is based on Hanai's mixture theory which describes the effects on conductivity of a suspension of non-conductive spheres in a conducting medium (Hanai 1968). Originally, this theory was developed by Maxwell (1873) for dilute suspension of spherical particles. Hanai later extended the theory to high-volume fractions. Hanai's theory corrects the actual resistivity of a suspension for its non-conducting spheres. The apparent resistivity is therefore given by

$$\rho_a = \frac{\rho_0}{(1-c)^{3/2}} \quad (\Omega \cdot \mathrm{m}). \tag{23.1}$$

where ρ_a (Ω·m) is the apparent resistivity, ρ_0 (Ω·m) is the actual resistivity, and c (dimensionless) is the volumetric concentration of non-conducting spheres of the suspension. With regard to bioimpedance measurements the resistivity of blood can therefore be modeled as non-conducting particles, i.e. red blood cells, in the ECW which increase resistance as the current must flow around the cells (see also Fig. 3.7 in chapter *Use of bioelectrical impedance: general principles and overview*). Similarly, fat and bones can be thought of as non-conducting tissues assuming that they draw negligible current (Jaffrin and Morel 2009). An extensive theory of applying Hanai's model to bioimpedance measurements been described elsewhere (De Lorenzo et al. 1997).

23.2.4.1 Determination of ECW

At low frequency the volume fraction c for extracellular fluid is given by

$$c = 1 - \frac{V_{ecw}}{V_{wb}}. \tag{23.2}$$

where V_{ecw} (m^3) is the extracellular fluid volume, and V_{wb} (m^3) is the volume of the body. V_{wb} can be obtained by dividing body mass (kg) by mean whole-body density (δ_{wb}), which is assumed to be a constant (≈1.05 kg·m^{-3}). Combining (23.1) and (23.2) with regard to ECW yields to ECW) and substituting pa,ecw for pa and pecw for p0 (yields)

$$\rho_{a,ecw} = \rho_{ecw}\left(\frac{V_{wb}}{V_{ecw}}\right)^{3/2} \quad (\Omega \cdot m). \tag{23.3}$$

where $\rho_{a,ecw}$ (Ω·m) is the apparent resistivity of ECW, and ρ_{ecw} (Ω·m) is the resistivity of ECW. Resistance R can be expressed as

$$R = \frac{\rho l^2}{V} \quad (\Omega). \tag{23.4}$$

where ρ (Ω·m) is resistivity, V is volume (m^3), and l (m) is length. In order to account for the geometrical relations of the body, De Lorenzo et al. (1997) calculated a dimensionless correction factor K_{wb} for whole-body measurements, scaling the relative proportions of the leg, arm, and trunk. Details for the derivation of K_{wb} are given by De Lorenzo et al. (1997). Adding K_{wb} to (23.4) and substituting height H (m) for general conductor length yields

$$R = \frac{K_{wb}\rho H^2}{V_{wb}} \quad (\Omega). \tag{23.5}$$

Substituting $\rho_{a,ecw}$ for ρ and R_e for R in (23.5), yields

$$R_e = \frac{K_{wb}\rho_{ecw}H^2V_{wb}^{1/2}}{V_{ecw}^{3/2}} \quad (\Omega). \tag{23.6}$$

and solving for V_{ecw} yields

$$V_{ecw} = \left(K_{wb}\rho_{ecw}\frac{H^2}{R_e}V_{wb}^{1/2}\right)^{2/3} \quad (m^3). \tag{23.7}$$

V_{wb} can be replaced by δ_{wb} ($kg \cdot m^{-3}$) and BM (kg), yielding

$$V_{ecw} = \left(K_{wb}\rho_{ecw}\frac{H^2BM^{1/2}}{R_e\,\delta_{wb}^{1/2}}\right)^{2/3} \quad (m^3). \tag{23.8}$$

It should be noted that ρ_{ecw} and H are often expressed in Ω·cm and cm, respectively. Similarly, deltawb is expressed as kg/L or kg/cm^3. Hence, simple calculation of the units shows that the formula needs to be corrected by 10^{-2} (kg/dm^3) or 10^{-3} (kg/cm^3). Considering this unit correction factor and rewriting (23.8) according to De Lorenzo et al. (1997) finally gives

$$V_{ecw} = k_{ecw}\left(\frac{H^2\sqrt{BM}}{R_e}\right)^{2/3} \quad (dm^3), \tag{23.9}$$

with

$$k_{ecw} = 10^{-3}\left(\frac{K_{wb}^2\rho_{ecw}^2}{\delta_{wb}}\right)^{1/3} \tag{23.10}$$

23.2.4.2 Determination of ICW

Applying the Hanai theory to bioimpedance measurements at high frequencies, the volumetric concentration c is given by

$$c = 1 - \frac{V_{ecw} + V_{icw}}{V_{wb}}, \tag{23.11}$$

where V_{icw} (m^3) is the intracellular fluid volume.

Based on equation 23.1 the apparent resistivity of TBW $\rho_{a,tbw}$ ($\Omega \cdot m$) can be calculated as

$$\rho_{a,tbw} = \rho_{tbw}\left(\frac{V_{wb}}{V_{ecw} + V_{icw}}\right)^{3/2} = \rho_{tbw}\left(\frac{V_{ecw} + V_{icw}}{V_{wb}}\right)^{-3/2} \quad (\Omega \cdot m) \tag{23.12}$$

Assuming that the mean ρ_{tbw} is dependent on the volumes of ECW and ICW and their resistivities ρ_{ecw} and ρ_{icw} it follows that

$$\rho_{tbw}\left(V_{ecw} + V_{icw}\right) = \rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}, \tag{23.13}$$

Accordingly, mean ρ_{tbw} is given by

$$\rho_{tbw} = \frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)} \quad (\Omega \cdot m). \tag{23.14}$$

and can be used to replace ρ_{tbw} in (23.12). Hence,

$$\begin{aligned}\rho_{a,tbw} &= \left(\frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)}\right)\left(\frac{V_{ecw} + V_{icw}}{V_{wb}}\right)^{-3/2} \\ &= \frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)^{5/2}}V_{wb}^{3/2} \quad (\Omega \cdot m).\end{aligned} \tag{23.15}$$

Rewriting (23.4) with regard to high-frequency measurements gives

$$R_{tbw} = \frac{K_{wb}\rho H^2}{V_{wb}} \quad (\Omega). \tag{23.16}$$

where R_{tbw} (Ω) is the resistance of total body water. Replacing $\rho_{a,tbw}$ for ρ yields

$$R_{tbw} = \frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)^{5/2}}V_{wb}^{1/2}K_{wb}H^2 \quad (\Omega). \tag{23.17}$$

Since R_{tbw} can be assumed equal to infinite resistance (R_∞), R_{tbw} can be replaced by infinite resistance using intracellular resistance R_i and extracellular resistance R_e (see chapter *Use of bioelectrical impedance: general principles and overview* for details). Thus,

$$\frac{R_iR_e}{R_i + R_e} = \frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)^{5/2}}V_{wb}^{1/2}K_{wb}H^2. \tag{23.18}$$

Substituting (23.6) for R_e in the numerator of the left-hand side of (23.18) gives

$$\frac{\left(\frac{\rho_{ecw}}{V_{ecw}^{3/2}}V_{wb}^{1/2}K_{wb}H^2\right)R_i}{R_e + R_i} = \frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)^{5/2}}V_{wb}^{1/2}K_{wb}H^2, \tag{23.19}$$

and after simplification

$$\frac{R_i}{R_e + R_i}\left(\frac{\rho_{ecw}}{V_{ecw}^{3/2}}\right) = \frac{\rho_{ecw}V_{ecw} + \rho_{icw}V_{icw}}{\left(V_{icw} + V_{ecw}\right)^{5/2}}. \tag{23.20}$$

Finally, (23.20) can be rearranged as

$$\left(1 + \frac{V_{icw}}{V_{ecw}}\right)^{5/2} = \left(\frac{R_e + R_i}{R_i}\right)\left(1 + \frac{k_\rho V_{icw}}{V_{ecw}}\right), \tag{23.21}$$

Where k_ρ is a dimensionless parameter given by ρ_{icw}/ρ_{ecw}. Eventually, V_{icw} can be calculated by an iterative procedure. k_{ecw} in (23.10) and k_ρ in (23.21) can be obtained analytically but are usually derived statistically using tracer dilution reference methods. De Lorenzo et al. (1997) reported values of 0.306 and 0.316 for k_{ecw} and 3.82 and 3.4 for k_ρ in men and women, respectively. Assuming values of 4.3 and 1,050 kg·m^{-3} for K_{wb} and δ_{wb}, respectively, corresponding actual resistivities become 40.3 Ω·cm for men and 42.3 Ω·cm for women. These values are close to that of saline (Jaffrin and Morel 2008). It should be noted that the actual resistivities, which should be clearly distinguished from apparent resistivities, are also sometimes reported as reference values. Generally, conversion from one to the other is possible via (23.1), but then the concentration of nonconductive material should be known, which is determined by the ratios between the fluid volume compartments (see 23.2 and 23.11). Frequently, resistivities for ECW and ICW are not explicitly reported, but lumped into the k_{ecw} and k_ρ terms.

23.2.4.3 Hanai's Second Generation Mixture Theory

Matthie (2005) recently argued that the above-mentioned determination of V_{icw} is based on the assumption that the relationship between ρ_{tbw} and the V_{ecw} to V_{icw} ratio is linear. As he suggests that the effect of changes in the V_{ecw} to V_{icw} ratio are highly nonlinear due to the three- to fourfold higher resistivity of V_{icw}, a new V_{icw} equation was proposed taking into account the mixture of two conducting fluids, termed the second-generation mixture theory equation. Since at low frequencies it is still assumed that the relationship between impedance and V_{ecw} involves a simple nonlinear mixture effect between two spaces (conductor and non-conductor), the Vecw-equation (see equation 23.8) remains unchanged. For V_{tbw} and V_{icw}, however, it is now suggested that an additional mixture effect needs to be accounted for due to the nonlinear relationship between V_{ecw}, V_{icw}, and non-conductors (Matthie 2005). Accordingly, the resistivity of total body fluid ptbw is given by

$$V_{icw} = V_{ecw}\left\{\left(\frac{\rho_{tbw}\left(R_e + R_i\right)}{\rho_{ecw}R_i}\right)^{2/3} - 1\right\} \quad (m^3). \tag{23.22}$$

where V_{icw} (m^3) is the intracellular fluid volume, V_{ecw} (m^3) is the extracellular fluid volume, R_i (Ω) is intracellular resistance and R_e (Ω) is extracellular resistance, and ρ_{ewc} (Ω·m) and ρ_{tbw} (Ω·m)are the mean resistivities of the extracellular and total body fluid volume, respectively.

$$\rho_{tbw} = \rho_{icw} - \left(\rho_{icw} - \rho_{ecw}\right)\left(\frac{R_i}{R_e + R_i}\right) \quad (\Omega\cdot m). \tag{23.23}$$

where ρ_{icw} (Ω·m) and ρ_{ecw} (Ω·m) are the resistivities of V_{icw} and V_{ecw}, respectively. As the calculation for V_{ecw} (see equation 23.8) remains unchanged, V_{tbw} can be expressed in SI units as

Table 23.1 Variation of key parameters underlying Hanai modeling across different studies

Authors	Sample		k_{ecw}		k_ρ	
	n (men/women)	Subjects	Men	Women	Men	Women
Van Loan (1993) in De Lorenzo et al. (1997)	24 (10/14)	Healthy adults	0.306	0.316	3.82	3.40
Armstrong et al. (1997)	13	Healthy adults	0.337		2.905	
Gudivaka et al. (1996)	6 (3/3)	Healthy adults	0.338		2.968	
Van Marken Lichtenbelt et al. (1997) cited in Ellis and Wong (1998)	20 (10/10)	Healthy adults and GH-deficiency patients	0.245	0.238	6.408	6.469
Moissl et al. (2006)	78 (37/41)	Healthy adults	0.289	0.289		
Moissl et al. (2006)	42 (21/21)	Healthy adults	0.292	0.292		
Moissl et al. (2006)	32 (18/14)	Patients with imbalanced fluid status	0.3163	0.3163		
Xitron (Xitron Technologies 2001)			0.3068	0.2991		
Ellis and Wong (1998)	73	Healthy adults	0.348		3.264	
Ellis and Wong (1998)	14	Healthy adults	0.339		3.234	
Ellis and Wong (1998)	469 (172 boys/215 girls; 49 men/33 women)	Healthy children and adults	0.370	0.358	3.032	2.694
Ellis et al. (1999a)	347 (202/145)	Children aged 4–18 years	0.330	0.324	3.05	3.03
Cox-Reijven and Soeters (2000)	45 (5/40)	Overweight adults	0.3304	0.3003	2.827	3.026
Baarends et al. (1998)	37 (23/14)	COPD patients	0.2608	0.2577		

Listed are the parameters reported in various studies for k_{ecw} and k_ρ used to obtain estimates of TBW, ECW, and ICW by Hanai modeling. k_{ecw} and k_ρ are statistically derived from regression techniques. While k_ρ is a dimensionless parameter given by ρ_{icw}/ρ_{ecw}, k_{ecw} comprises the resistivity of ECW, whole-body density as well as a shape factor scaling the relative proportions of the leg, arm, and trunk. Most notably k_{ecw} varies between 0.238 and 0.370, and k_ρ can be as low as 2.827 and as high as 6.469. Accordingly, despite its appeal the Hanai approach might also suffer from the same drawbacks as regression-based estimations because different populations might also require very specific parameter values. Thus, the accuracy of estimations will largely depend on choosing the correct parameters

$$V_{tbw} = \left(\frac{\rho_{tbw} K_{wb} H^2 \sqrt{BM}}{\sqrt{\delta_{wb}} R_\infty} \right)^{2/3} \quad (m^3). \tag{23.24}$$

where R_∞ (Ω) is infinite resistance. The second-generation mixture equation has been shown to be superior compared to the original version (Matthie 2005). Further validation studies in different populations and under different conditions are, however, needed to confirm these findings.

23.2.4.4 Limitations and Future Directions of Hanai's Mixture

A quite recent advancement of the use of mixture theory for bioimpedance applications is to correct the parameters of the Hanai equation for differences in body composition by the body mass index (Moissl et al. 2006). This idea is related to the assumption that body density, resistivity, and the shape factor are not constant across diverse populations. In fact, the often observed differences in resistivity (and regression weights) between men and women might simply be an expression of gender-related differences in body composition. Consequently, various authors have suggested different values for

resistivity (ρ_{ecw} and ρ_{icw}), body geometry correction factor (K_{wb}) and whole-body density (δ_{wb}) related to their sample under study. Table 23.1 gives an indication of the range of parameter values employed in bioimpedance modeling using Hanai's mixture theory.

It is shown that k_{ecw} varies between 0.238 and 0.370, and k_{ρ} can be as low as 2.827 and as high as 6.469. Furthermore, it is worth noting that Ellis and Wong (1998) observed a high degree of variation between subjects for both k_{ecw} and k_{ρ} in a large sample of 469 healthy men and women, ranging in age between 3 and 29 years. Using tracer dilution techniques they reported coefficients of variation for k_{ecw} and k_{ρ} exceeding 19% and 25%, respectively. This dispersion by far exceeds the limits generally considered for defining constants in body composition analysis (Wang et al. 1992). In a subsequent reanalysis of the pediatric subsample (subjects aged 3–18 years only), the authors found that the coefficients of variations k_{ecw} and k_{ρ} were only about ±8%, when estimates of fluid volumes were derived from dual-energy X-ray absorptiometry (DEXA) and total body potassium counting (Ellis et al. 1999a). In spite of methodical aspects underpinning the reliability of dilution techniques that might have inflated the observed variability, it is apparent that ρ_{ecw} and ρ_{icw} used to calculate k_{ecw} and k_{ρ}, as well as the body geometry correction factor (K_{wb}) and whole-body density (δ_{wb}), might not be constant across age and gender. At least some of these differences might be associated with body composition. This is also supported by findings indicating that fluid volume estimations are affected by body composition (Carter et al. 2005). Furthermore, Cox-Reijven and Soeters (2000) observed that body mass index (BMI) is negatively correlated to k_{ecw}. Given this inverse relationship, it is unlikely that the body density and shape factor might account for this observation, as both these factors would be expected to be positively associated to BMI. In addition, since body density (δ_{wb}) varies relatively little between subjects, typically ranging between 0.95 and 1.1 kg·dm^{-3} (Keys and Brozek 1953) the impact on k_{ecw} is substantially less compared to the body geometry correction factor (K_{wb}) or ρ_{ecw}. This is also in line with the finding by Moissel et al. (2006). They found that replacing the fixed constant of 1.05 kg·m^{-3} by the true body density as determined by air displacement plethysmography did not decrease the variation in k_{ecw}. Further support attributing the variation of k_{ecw} to ρ_{ecw} and ρ_{icw} is given by Cox-Reijven and Soeters (2000), who reported that both ρ_{ecw} and ρ_{icw} are highly correlated to BMI ($r = -0.641$ and -0.683 for ρ_{ecw} and ρ_{icw}, respectively). In summary, given these findings the idea to adjust resistivity for body composition seems to be clearly appealing. Yet, it remains to be established whether this can be effectively achieved by the use of the BMI. In summary, it should be kept in mind that strictly speaking, the Hanai model is only valid for blood but not for other tissues. In addition, application of the model assumes that the body consists of five cylindrical segments with homogeneous electrical properties. While this may be true for the arms and legs, the trunk is clearly anisotropic (see also chapter *Use of bioelectrical impedance: general principles and overview*). These discrepancies can be corrected by different shape factors, fluid resistivities and body densities. Accordingly, when applying the Hanai model one needs to be aware of the pitfall of simply shifting from population-specific regression equations to population-specific resistivities, body densities and shape factors.

23.2.5 Alternative Approaches

Another suggestion to alleviate the problems of single-frequency bioimpedance approaches was proposed by Cornish et al. (1993). This approach is based on the fact X_c is maximal midway between R_0 and R_∞ at f_c. In particular, they hypothesized that since R at f_c is defined as $(R_0 + R_\infty)/2$ and given that R_0 as well as R_∞ are proportional to ECW and TBW, the same water volumes (or

proportion of water volumes relative to R_∞ and R_0) should be measured across and within individuals. However, the problem of assuming a constant ρ_{tbw} still remains. Thus, any single-frequency measurement including R at f_c as well as R_∞ is prone to errors as long as ρ_{tbw} is assumed to be constant.

Finally, Piccoli et al. (1994) suggested a qualitative evaluation of body hydration based on the measurements of R and X_c at 50 kHz. The principal component of this graphical method is the RX_c graph, which plots X_c vs. R standardized for height, respectively, and compares their resulting impedance vector with bivariate tolerance limits obtained in reference populations. According to Piccoli and colleagues, the impedance vector reflects body hydration. Basically, a shortening and downsloping of the impedance vector is assumed to indicate fluid overloading, while a lengthening and steepening is attributed to fluid removal. Thus, a comparison of the impedance vector with 50%, 75%, and 95% tolerance limits allows the distinction between different hydration levels between subjects. If the subject's impedance vector lies within the 75% tolerance ellipse, the authors suggest that normal hydration can be assumed and regression equations for estimating body fluids can be applied with confidence.

A similar approach employing phase angle spectrum analysis has been suggested by Chumlea et al. (1994, 1998). The basic idea is to plot the phase angle (φ) as a function of frequency, and compare and describe differences among individuals in levels of hydration. The difficulty with using φ or the RX_c-graph is that they are directly related to fluid distribution. However, as already indicated by Löfgren et al. (1951) and outlined by De Lorenzo et al. (1997), changes in body fluid distribution affect f_c, which, in turn changes X_c and φ. Since changes in f_c can be related to R_e, R_i, and C_m, or any combination of them (De Lorenzo et al. 1997), X_c and φ are affected by all these elements. Thus, it remains questionable to attribute the change in X_c or φ to unique alterations in body fluids only.

23.3 Fat Mass

23.3.1 Conventional Approach

The majority o f bioimpedance models for the estimation of body fat rely on the determination of FFM and the computation of fat mass (FM) by subtraction. Since BM is the sum of FM and FFM and FFM can be related to R and conductor length according to (23.4), percent FM (%FM) can be calculated as

$$\%\mathrm{FM} = 100\left(1 - \rho_{\mathrm{ffm}}\frac{H^2}{R\ \mathrm{BM}}\right)\quad(\%). \tag{23.25}$$

where ρ_{ffm} (Ω·m) refers to resistivity of FFM, R (Ω) to resistance, H (m) to height and BM (kg) to body mass. However, most %FM prediction equations are based on multiple regression analysis that lumps the best predictors into a single prediction algorithm without a sound physical basis. A review of the equations is provided by Kyle et al. (2004a, b). Some studies have also suggested regressing the impedance index directly against FM or %FM. This approach, however, clearly lacks physical meaning and any predictive potential is likely to be due to the association between height and/or weight and FM rather than by the assumption that the impedance index accounts for a substantial amount of variance in FM or %FM.

23.3.2 A Specific Resistivity Approach to Determine Segmental FM

To provide a straightforward estimate of FM that does not rely on statistical relationships, and has clear physical meaning, Fuller and coworkers (1999, 2002a, b) suggested a model for determining segmental fat mass taking into consideration that the flow of current might not be limited to skeletal muscle tissue and blood. Accordingly, the basic biophysical bioimpedance model can be extended by taking into account that the introduced current is not only drawn by skeletal muscle, but also by fat, neurovascular, bone, and skin tissue. Hence, after some algebraic rearrangement skeletal muscle volume ($V_{seg,sm}$) can be computed as

$$V_{seg,sm} = \frac{l_{seg}^2}{R_{seg,tot}} - \frac{V_{seg,tot}}{\rho_{fat}} + \frac{V_{seg,neu}}{\rho_{fat}} + \frac{V_{seg,bo}}{\rho_{fat}} + \frac{V_{seg,sk}}{\rho_{fat}} - \frac{V_{seg,neu}}{\rho_{neu}} - \frac{V_{seg,bo}}{\rho_{bo}} - \frac{V_{seg,sk}}{\rho_{sk}}\left(\frac{\rho_{sm}\rho_{fat}}{\rho_{fat} - \rho_{sm}}\right) \quad (m^3) \tag{23.26}$$

where $R_{seg,tot}$ (Ω) is the total segmental resistance. Values for ρ_{fat}, ρ_{neu}, ρ_{bo}, ρ_{sk}, and ρ_{sm} at 50 kHz are assumed to be respectively. Analogously, an estimate of segmental fat volume ($V_{seg,fat}$) is given by

$$V_{seg,fat} = V_{seg,tot} - V_{seg,sm} - V_{neu} - V_{seg,sk} - V_{seg,bo} \quad (m^3). \tag{23.27}$$

where the subscripts tot, sm, neu, sk, and bo refer to total tissue, skeletal muscle, neurovascular, skin, and bone tissue, respectively. $V_{seg,tot}$, $V_{seg,sm}$, $V_{seg,neu}$, $V_{seg,sk}$ and $V_{seg,bo}$ are calculated as the product of their respective segmental area (A_{seg}) and segment length (l_{seg}). $A_{seg,tot}$ is determined from measurements of circumference. $A_{seg,sk}$ is approximated by measurements of circumference and by assuming a skin thickness of 0.16 cm for men and 0.12 cm for women. In addition, it is assumed that neurovascular tissue contributes about 1% to total $A_{seg,tot}$, and $A_{seg,bo}$ can be approximated by about 6 cm^2. Hence, (23.27) can be rewritten as

$$V_{seg,fat} = V_{seg,tot} - V_{seg,sm} - V_{seg,tot} \times 0.01 - V_{seg,sk} - 0.0006 l_{seg} \quad (m^3). \tag{23.28}$$

Fuller and colleagues tested for leg and calf sections in both children and adults. While for skeletal muscle volume, the approach seemed to outperform anthropometry, the superiority was less clear for fat tissue. In addition, both methods showed substantial deviations for individual measurements as indicated by large limits of agreement. The authors suggested that part of the error regarding BIA could be attributed to disparities between the locations for circumference measurements and electrode positions, the violation of the assumption that the cross-sectional areas of the tissue are uniform, and uncertainties about the resistivities. The latter pertains to skeletal muscle in particular, as it has a substantial impact in the equations presented above. In addition, it should also be noted that the approach is based on a single-frequency measurement and generally any criticism that has been raised concerning such approaches for fluid volume estimations (see Sect. 23.2.1) also pertain to any other body compartment. In conclusion, it seems as if this approach seems to be the most advantageous for skeletal muscle volume determinations and it will be interesting to see how further research can address the choice and the development of resistivity constants.

23.3.3 A Three-Compartmental Model of Body Mass and Segment Resistivity to Predict Whole-Body Fat Mass

Another interesting approach for determining fat mass of the total body using segmental measurements and anthropometry has been suggested by Biggs et al (2001). Given its innovative character

and potential it will be presented in detail. Basically, the model assumes that both skeletal muscle and fat are conductive, while the remaining tissues such as bone, ligaments, and tendons are non-conductive. Thus, total mass (BM_{tot}) of the body can be described as the sum of the following distinctive masses by

$$BM_{tot} = BM_{con} + BM_{non} = BM_{sm} + BM_{fat} + BM_{non} \quad (kg). \tag{23.29}$$

where BM refers to mass (kg) and the subscripts sm, fat, and non denote skeletal muscle, fat, and non-conductive tissue, respectively. Furthermore, the total cross-sectional area for any specific body segment ($A_{seg,tot}$) is given by

$$A_{seg,tot} = A_{seg,con} + A_{seg,non} = A_{seg,sm} + A_{seg,fat} + A_{seg,non} \quad (m^2). \tag{23.30}$$

where A is the cross-sectional area (m^2), and the subscripts con, non, sm, and fat indicate conductive and non-conductive, skeletal muscle and fat, tissue, respectively. Accordingly, the conductive path can be modeled by two resistors in parallel, one representing the muscle compartment, the other indicating the fat compartment. Based on Kirchhoff's law, total resistance ($R_{seg,tot}$) of any body segment can be calculated as

$$\frac{1}{R_{seg,tot}} = \frac{1}{R_{seg,sm}} + \frac{1}{R_{seg,fat}} \quad (\Omega^{-1}). \tag{23.31}$$

where $R_{seg,sm}$ (Ω) and $R_{seg,fat}$ (Ω) refer to the resistance of skeletal muscle and fat tissue, respectively.

Given the relationship between resistance, length, area, and resistivity, (23.31) can be rewritten as

$$\frac{1}{R_{seg,tot}} = \frac{A_{seg,sm}}{\rho_{sm} l_{seg}} + \frac{A_{seg,fat}}{\rho_{fat} l_{seg}} \quad (\Omega^{-1}). \tag{23.32}$$

where ρ_{sm} (Ω·m) and ρ_{fat} (Ω·m) are the resistivities of skeletal muscle and fat, respectively, and l_{seg} (m) refers to the conductor length. Arranging the right-hand side term on a common denominator yields

$$\frac{1}{R_{seg,tot}} = \frac{A_{seg,sm}\rho_{fat} + A_{seg,fat}\rho_{sm}}{\rho_{sm}\rho_{fat} l_{seg}} \quad (\Omega^{-1}). \tag{23.33}$$

According to (23.30), $A_{seg,sm}$ can be replaced by the term $A_{seg,con} - A_{seg,fat}$. Hence, (23.33) can become

$$\frac{1}{R_{seg,tot}} = \frac{A_{seg,con}\rho_{fat} - A_{seg,fat}\rho_{fat} + A_{seg,fat}\rho_{sm}}{\rho_{sm}\rho_{fat} l_{seg}} \quad (\Omega^{-1}). \tag{23.34}$$

For clarity, $A_{seg,fat}$ can be grouped so that

$$\frac{1}{R_{seg,tot}} = \frac{A_{seg,con}\rho_{fat} + A_{seg,fat}\left(\rho_{sm} - \rho_{fat}\right)}{\rho_{sm}\rho_{fat} l_{seg}} \quad (\Omega^{-1}). \tag{23.35}$$

Multiplying (23.35) by he right-hand side denominator gives

$$\frac{\rho_{sm}\rho_{fat} l_{seg}}{R_{seg,tot}} = A_{seg,con}\rho_{fat} + A_{seg,fat}\left(\rho_{sm} - \rho_{fat}\right) \quad (\Omega \cdot m^3). \tag{23.36}$$

and solving for terms with $A_{seg,fat}$ yields

$$A_{\text{seg,fat}}\left(\rho_{\text{sm}}-\rho_{\text{fat}}\right)=\frac{\rho_{\text{sm}}\rho_{\text{fat}}\,l_{\text{seg}}}{R_{\text{seg,tot}}}-A_{\text{seg,con}}\rho_{\text{fat}}\quad(\Omega\cdot\text{m}^3). \tag{23.37}$$

Dividing both sides by $A_{\text{seg,con}}$, and then by $(\rho_{\text{sm}} - \rho_{\text{fat}})$ gives

$$\frac{A_{\text{seg,fat}}}{A_{\text{seg,con}}}=\frac{\rho_{\text{sm}}\rho_{\text{fat}}\,l_{\text{seg}}}{A_{\text{seg,con}}R_{\text{seg,tot}}\left(\rho_{\text{sm}}-\rho_{\text{fat}}\right)}-\frac{\rho_{\text{fat}}}{\left(\rho_{\text{sm}}-\rho_{\text{fat}}\right)}. \tag{23.38}$$

The left-hand side in (23.38) can be extended by l_{seg}, which gives

$$\frac{A_{\text{seg,fat}}\,l_{\text{seg}}}{A_{\text{seg,con}}\,l_{\text{seg}}}=\frac{V_{\text{seg,fat}}}{V_{\text{seg,con}}}=\frac{V_{\text{seg,fat}}}{V_{\text{seg,fat}}+V_{\text{seg,sm}}}\equiv Q_{\text{seg}}. \tag{23.39}$$

where V is the volume (m^3), and the subscripts sm, fat, and con refer to skeletal muscle, fat, and conductive tissue of the body segment, respectively. Thus, Q_{seg} can be understood as a fat quotient as it relates the segmental fat to the sum of fat and skeletal muscle. Substituting Q_{seg} for the left-hand side in (23.38), allows the calculation of the fat quotient Q_{seg} for an arbitrary number of body segments from measurements of resistance, length, and circumference.

$$Q_{\text{seg}}=\frac{\rho_{\text{sm}}\rho_{\text{fat}}\,l_{\text{seg}}}{A_{\text{seg,con}}R_{\text{seg,tot}}\left(\rho_{\text{sm}}-\rho_{\text{fat}}\right)}-\frac{\rho_{\text{fat}}}{\left(\rho_{\text{sm}}-\rho_{\text{fat}}\right)}. \tag{23.40}$$

Biggs et al. (2001) suggested deriving ρ_{sm} by nonlinear parameter estimation. Results in a calibration sample (n = 10) yielded an average value of 1.37 ± 0.11 Ω·m, which was not significantly different from values for muscle and blood determined ex vivo. ρ_{fat} (50 Ω·m) was taken from the literature data (Foster and Schwan 1989). $A_{\text{seg,con}}$ can be determined as follows. First, $A_{\text{seg,tot}}$ is simply calculated as

$$A_{\text{seg,tot}}=\frac{C_{\text{seg}}^2}{4\pi}\quad(\text{m}^2). \tag{23.41}$$

where C_{seg} (m) refers to the segmental circumference. Given that the area of any object generally scales with the square of its length (McMahon and Bonner 1983), $A_{\text{seg,non}}$ can be estimated from segment length squared after adjusting for different tissue compartments by a scaling coefficient (k_{a}). Hence,

$$A_{\text{seg,non}}\cong k_{\text{a}}l_{\text{seg}}^2\quad(\text{m}^2). \tag{23.42}$$

where l_{seg} (m) is the segmental length. k_{a} can be derived from converting the length of a typical upper-leg segment to a cross-sectional area approximating the shaft of an adult femur (Biggs et al. 2001). These computations were based on data for upper-leg cross-sections by Netter (1989). Subsequently, $A_{\text{seg,con}}$, can be calculated from the difference of $A_{\text{seg,tot}}$ and $A_{\text{seg,non}}$.

After obtaining the fat quotient Q_{seg} for different body segments such as the upper arm, lower arm, trunk, upper leg, and lower leg, these estimates can be combined to quantify total body %FM. Combining the body segments, however, requires that the body segments are weighted according to volume. This is achieved by first computing total conductive volume ($V_{\text{tot,con}}$) as the sum of all conductive volumes of each segment ($V_{\text{seg,con}}$).

$$V_{\text{tot,con}}=V_{\text{seg-1,con}}+\ldots+V_{\text{seg-n,con}}=A_{\text{seg-1,con}}l_{\text{seg-1}}^2+\ldots+A_{\text{seg-n,con}}l_{\text{seg-n}}^2\quad(\text{m}^3). \tag{23.43}$$

where the subscripts -1 and *n* refer to the first and *n*th segment, respectively. The weighing factors (w_{seg}) of each segment can then be calculated as

$$w_{\text{seg-n}} = \frac{V_{\text{seg-n,con}}}{V_{\text{tot,con}}}. \tag{23.44}$$

Finally, the overall fat quotient can be derived from

$$\hat{Q}_{\text{tot}} = w_{\text{seg-1}} Q_{\text{seg-1}} + \ldots + w_{\text{seg-n}} Q_{\text{seg-n}}. \tag{23.45}$$

Irrespective of whether $\hat{Q}_{\text{tot}}$ is obtained for single or multiple body segments, they need to be converted to %FM. This is achieved as follows. According to (23.39), $\hat{Q}_{\text{tot}}$ can be expressed as

$$\hat{Q}_{\text{tot}} = \frac{V_{\text{tot,fat}}}{V_{\text{tot,fat}} + V_{\text{tot,sm}}} = \frac{\frac{BM_{\text{fat}}}{\delta_{\text{fat}}}}{\frac{BM_{\text{fat}}}{\delta_{\text{fat}}} + \frac{BM_{\text{sm}}}{\delta_{\text{sm}}}}. \tag{23.46}$$

where $V_{\text{tot,fat}}$ (m^3), $V_{\text{tot,sm}}$ (m^3), δ_{fat} ($kg \cdot m^{-3}$) and δ_{sm} ($kg \cdot m^{-3}$) refer to total whole-body volume and density of fat and skeletal muscle, respectively. After simplification by finding a common denominator, (23.46) can be rewritten as

$$\hat{Q} = \frac{BM_{\text{fat}} \delta_{\text{sm}}}{\delta_{\text{sm}} BM_{\text{fat}} + \delta_{\text{fat}} BM_{\text{sm}}}. \tag{23.47}$$

According to (23.29), BM_{sm} can be expressed as

$$\text{BM}_{\text{sm}} = \text{BM}_{\text{tot}} - \text{BM}_{\text{fat}} - \text{BM}_{\text{non}} \quad \text{(kg)}. \tag{23.48}$$

Thus, substituting BM_{sm} in (23.47) yields

$$\hat{Q} = \frac{\text{BM}_{\text{fat}} \delta_{\text{sm}}}{\delta_{\text{sm}} \text{BM}_{\text{fat}} + \delta_{\text{fat}} \left(\text{BM}_{\text{tot}} - \text{BM}_{\text{fat}} - \text{BM}_{\text{non}}\right)}. \tag{23.49}$$

Multiplication with the right-hand side denominator and distribution of Q over terms give

$$\hat{Q}\delta_{\text{sm}} \text{BM}_{\text{fat}} + \hat{Q}\delta_{\text{fat}} \text{BM}_{\text{tot}} - \hat{Q}\delta_{\text{fat}} \text{BM}_{\text{fat}} - \hat{Q}\delta_{\text{fat}} \text{BM}_{\text{non}} = \text{BM}_{\text{fat}} \delta_{\text{sm}}. \tag{23.50}$$

Regrouping terms containing BM_{fat} and factoring lead to

$$\hat{Q}\delta_{\text{fat}} \text{BM}_{\text{tot}} - \hat{Q}\delta_{\text{fat}} \text{BM}_{\text{non}} = \text{BM}_{\text{fat}} \left(\delta_{\text{fat}} \hat{Q} + \delta_{\text{sm}} \left(1 - \hat{Q}\right)\right) \tag{23.51}$$

For clarity, the right-hand side terms in brackets are replaced by K. For isolation of BM_{fat} both sides are then divided by K.

$$\frac{\hat{Q}\delta_{\text{fat}} \text{BM}_{\text{tot}}}{K} - \frac{\hat{Q}\delta_{\text{fat}} \text{BM}_{\text{non}}}{K} = \text{BM}_{\text{fat}} \quad (kg). \tag{23.52}$$

Subsequently, both sides are divided by BM_{tot}, giving

$$\frac{\hat{Q}\delta_{\text{fat}}}{K} - \frac{\hat{Q}\delta_{\text{fat}} \text{BM}_{\text{non}}}{K \text{BM}_{\text{tot}}} = \frac{\text{BM}_{\text{fat}}}{\text{BM}_{\text{tot}}}. \tag{23.53}$$

Then, common terms can be factored out on the left-hand side and multiplied by 100 to convert proportion to percent:

$$100\frac{\hat{Q}\delta_{\text{fat}}}{K}\left(\frac{1-\text{BM}_{\text{non}}}{\text{BM}_{\text{tot}}}\right)=100\frac{\text{BM}_{\text{fat}}}{\text{BM}_{\text{tot}}}=\%\text{FM}\quad(\%).\tag{23.54}$$

Finally, K can be again substituted back, so that

$$100\frac{\hat{Q}\delta_{\text{fat}}}{\delta_{\text{fat}}\hat{Q}+\delta_{\text{sm}}\left(1-\hat{Q}\right)}\left(\frac{1-\text{BM}_{\text{non}}}{\text{BM}_{\text{tot}}}\right)=100\frac{\text{BM}_{\text{fat}}}{\text{BM}_{\text{tot}}}=\%\text{FM}\quad(\%).\tag{23.55}$$

δ_{fat} (900 kg·m^{-3}) and δ_{sm} (1,340 kg·m^{-3}) are assumed to be fixed and taken from the literature data (Brozek et al. 1963). Since the mass of any object generally scales with the cube of its length, BM_{non} can be estimated as

$$\text{BM}_{\text{non}}\cong k_{\text{m}}H^3\quad(\text{m}^3).\tag{23.56}$$

where k_{m} is a constant which scales the non-conductive compartment with subject height H (m) cubed. The value of k_{m} (3.90 ± 1.37) was also derived from parameter estimation in a calibration sample.

Biggs et al. (2001) determined fat quotients according to (23.40) for trunk and upper and lower arm and leg, respectively. The best prediction accuracy for %FM was achieved by simply combining Q obtained from the upper arm and upper leg. The root mean square error for FM was 2.65 kg and approaches the error inherent to the reference method, i.e. densitometry (Biggs et al. 2001). Furthermore, the values of the two calibrated parameters, i.e. ρ_{sm} and k_{m} are well in agreement with data theoretically expected based on the data obtained in vitro, substantiating the validity of the model. In addition, it is noteworthy that the sample under study comprised 21 men and 9 women aged 21–44 years from a variety of ethnic backgrounds. The subjects included descendents from North America, Asia, Middle East, Europe, and Africa. Accordingly, the model might not require population-specific adjustments as its accuracy might not be limited by age, gender, and ethnic background. It could be argued that the estimation of the scaling coefficient k_{a} in (23.42) is prone to substantial error. However, it should be noted that the impact of k_{a} on %FM is rather marginal. Biggs et al. (2001) showed that increasing or decreasing k_{a} changed the root mean square error of %FM about 0.02-fold. In summary, a unique feature of the approach is that each parameter of the model is inspired by a real physical parameter instead of lumping a variety of predictors such as age, weight, gender, and the resistance index into a multiple regression equation. In addition, the estimated parameters in fact show reasonable agreement with tissue properties measured in vitro, thus independently substantiating the biophysical validity of the model. The model therefore seems to be very promising. Future research should address testing the validity of the model in larger cohorts with a variety of body composition levels and different hydration states. Such research should also address the relevance of using multi-frequency BIA and BIS to quantify the potential error underlying single-frequency BIA (see also Sect. 23.2.1).

23.3.4 Local Fat Tissue Measurements

Another innovative approach that provides a rather direct determination of FM was proposed by Ward and associates (Elia and Ward 1999). The so-called electronic skinfold caliper is supposed to provide estimates of skinfold thickness at specific body sites by measuring Z via both a tetrapolar

and bipolar electrode arrangements. The difference between the two is assumed to be the combined Z of skin and subcutaneous adipose tissue and can therefore be used to compute skinfold thickness if the resistivities of skin and subcutaneous adipose tissue are known. Correlations with skinfold thickness measured by using a caliper yielded correlations as high as 0.94 with a standard error of the estimate (SEE) of 4.3%. The major advantage of this technique is an improved intra- and inter-observer reliability as well as the application of skinfold measurements in very obese subjects in whom measurements of skinfold by anthropometry may be difficult or impossible. This approach seems to be promising, and needs to be investigated in further studies. A similar technique was extensively investigated by Scharfetter (1999) for assessing abdominal fatness. By positioning voltage-sensing electrodes in close vicinity of current injecting electrodes, it was also assumed that measured voltage potentials mainly reflect the subcutaneous fat layer. Z was highly and significantly correlated with subcutaneous fat-layer thickness determined by magnetic resonance imaging ($r = 0.992$). Since the narrowest prediction intervals were obtained at 50 kHz, and no differences were found for the regression models between men and women at this frequency, the authors concluded that 50 kHz is well suited for this technique (Scharfetter et al. 2001).

23.4 Body Cell Mass

Body cell mass (BCM) represents the active metabolic component of the body and is thus an important component of body composition. BCM consists of intracellular fluid and solids. Hence, bioimpedance can also be expected to be associated with BCM. Lukaski et al. (1985) reported that the l^2/R at 50 kHz was highly related to total body potassium. Similarly, Pietrobelli et al. (2002) found arm potassium content to be highly related to arm impedance adjusted for a segment length. There was a slight trend for prediction accuracy to increase with frequency with the best model fit obtained at the highest frequency measured (300 kHz).

In addition to covariates such as age, gender, and anthropometry, some authors have also reported X_c to be highly related to BCM (Kotler et al. 1996; Gudivaka et al. 1999; Dittmar and Reber 2001). A clear theoretical explanation for the inclusion of X_c in predicting BCM is, however, lacking. Moreover, the zero-order correlation between fat-free mass (FFM) and X_c is as low as 0.23 (Kyle et al. 2001). It seems as if the predictive potential of X_c is only achieved when X_c is expressed as its parallel equivalent (Kotler et al. 1996; Lukaski 1996; Gudivaka et al. 1999). However, transforming measured series X_c to parallel X_c shows that the latter is inherently related to series R, which itself is associated with ICW due to the interdependence between TBW and ICW (see Sect. 23.2). Irrespective of the use of R and/or X_c for the estimation of BCM, it should be considered that analogue to the determination of body fluids, any prediction based on a single-frequency measurement will be prone to errors associated with assuming a constant characteristic frequency and/or a constant resistivity (Matthie et al. 1998). At least theoretically, a straightforward alternative is therefore to first determine ICW based on R_i and the use of Hanai's mixture theory, and subsequently derive BCM by dividing ICW by an assumed cell hydration (Wang et al. 2004).

23.5 Blood Volume

Siconolfi and coworkers (1994, 1996) suggested a technique termed bioelectrical response spectroscopy (BERS) to estimate blood volume (V_{bl}). Based on multiple regression analysis V_{bl} is predicted from resistance, capacitance, inductance, height, and body mass.

$$V_{bl} = 591.607 + 55.292 \times \left\{ 2.584 + 0.379 \times \left(\frac{l^2}{R_{tot}} \right) + 0.168 \times BM \right\}$$
$$+ 6.011 \times 10^{-6} \times \left(\frac{l^2}{L} \right) - 2.308 \times 1010 \times C \quad (mL). \tag{23.57}$$

where l (cm) is the height, R_{tot} (Ω) is the total resistance of the body and theoretically similar to R_{∞}, BM (kg) is the body mass, L (H) is the inductance, and C (F) is the capacitance. According to the authors, correlation coefficients exceeding 0.92, low SEE (>7.7%), and Bland–Altman comparisons between V_{bl} determined by BERS and V_{bl} measured by a radioactive dilution technique (^{125}I-albumin) verified the validity of the new approach. Though the results of this technique seem to be promising, a number of researchers have raised concerns both about the inclusion of an inductor in the underlying biological electrical equivalent circuit (Gluskin 2003; Riu 2004) and the viability of modeling total circuit resistance as suggested by Siconolfi and coworkers (Ward et al. 1999). Stahn et al. (2004) therefore also investigated the potential of conventional whole-body impedance measurements to predict V_{bl}. It was found that blood volume, erythrocyte volume, and plasma volume were highly associated with impedance (r = 0.89, 0.87, 0.85 for blood, erythrocyte, and plasma volume, respectively). In spite of these promising findings, substantiating the findings by Siconolfi and coworkers (1994, 1996), it should be noted that measurements were obtained in a sample of young, healthy men and women (n = 67). Consequently, given tightly regulated fluid compartments, the results are to some extent simply a reflection of the underlying relationship between body size and blood volume. This could be confirmed by statistically correcting the influence of body mass, the correlations were reduced to 0.65, 0.60, and 0.57 for blood, plasma, and erythrocyte volume, respectively. Nonetheless, impedance seems to be independently related to hematological parameters, and might also explain to some extent the relationships found between bioimpedance and measures of physical work capacity (Varlet-Marie et al. 1997) and cardiorespiratory fitness (Varlet-Marie et al. 2003; Stahn et al. 2006, 2008)

23.6 Concluding Remarks

23.6.1 Lack of a Single Dominant Approach

Since the introduction of bioimpedance for measuring body fluids in the 1960s, a number of approaches and applications have been extensively investigated. Due to the complexity of assumptions underlying all bioimpedance techniques and concomitant error sources, a clear superiority of a single technique remains uncertain and is still being discussed (Hannan et al.1994, 1998; Paton et al. 1998; Ward et al. 1998; Ellis et al. 1999b; Schoeller 2000).

For instance, segmental measurements have not always shown to be superior to whole-body measurements. The segmental approach might therefore only reveal its full potential in subjects with altered fluid distributions (Thomas et al. 2003). Similarly, BIS seems to be advantageous over single- and multi-frequency BIA only when the relationship between ECW and ICW is changed. In fact, in a review study by Martinoli et al. (2003) it was observed that multi-frequency BIA was more accurate for estimating TBW than BIS. Furthermore, the benefit of additional modeling compared to BIS through the use of Hanai's mixture theory remains unclear.

The reasons for these observations are multifold. First, it should be noted that all approaches, some more, some less, violate the basic biophysical model underlying BIA and BIS. The human body is

neither an isotropic conductor, nor is its cross-sectional area always homogeneous. In addition, the tissues are neither fully aligned in parallel, nor is the current distribution uniform. Another grave simplification is that the FM draws negligible current and therefore does not significantly contribute to bioimpedance. In obese subjects, however, body geometry, the increased amount of adipose tissue and hydration of the latter might all affect bioimpedance measurements (Baumgartner et al. 1998). These alterations might explain the often observed overestimations of FFM in people with moderate to severe obesity. For these reasons, in addition to account anthropometrically for excess fat mass (De Lorenzo et al. 1999), new biophysical models distinguishing the separate contribution of adipose tissue, muscle, and body fluids have been proposed (Van Kreel et al. 1998; Fuller et al. 1999; Zhu et al. 2005). Furthermore, intra- and interindividual variations in the hydration of non-adipose and adipose tissue might further bias the relationship between bioimpedance and FFM. This led to a huge collection of regression equations, and the accuracy of BIA might often depend on the choice of the correct equation. Moreover, multiple regression analysis is often employed to allow for additional predictors expected to improve prediction accuracy. This, however, will further decrease equation stability across different populations. For instance, whereas age might generally be inversely related to TBW and FFM, this relationship might be less prevalent in older subjects engaging in regular physical activity, thus leading to underestimations of TBW and FFM, when regression equations are employed that additionally use age as a covariate.

The idea to replace these purely statistical, descriptive bioimpedance models by an explanatory, biophysical approach using Hanai's mixture theory is certainly appealing. Yet, it should be noted that the same violations underpinning BIA also pertain to Hanai modeling. In addition, neither R_i nor R_e are directly measured, but approximated by a fitting algorithm. Even assuming well-fitted predictions, errors in R_i can be high since it is the difference between $R_¥$ and R_0 and therefore errors involved in each parameter will affect R_i. Furthermore, Hanai's theory was originally based on suspensions of cells. It is, however, highly questionable to apply this theory to the entire human body including adipose tissue and bone. Finally, the existence of several different values for the parameters of the Hanai equation highlights the vulnerable point of the approach. Presently, it seems as if the choice of resistivity, shape factor, and body density depends on the investigators' preference rather than experimental data. As a result, the discussion will simply shift from sample-specific regression equations to sample-specific resistivity constants.

23.6.2 Validity and Reliability of Bioimpedance Measurements for Body Composition Analysis

Irrespective of the controversy of the best bioimpedance model, the majority of studies support the use of bioimpedance measurements for the determination of body composition. BIA seems to be reasonably valid and reliable (for a review of reliability studies see chapter *Use of bioelectrical impedance: general principles and overview*). Correlations between l^2/Z (l^2/R) and *FFM*, and between l^2/Z (l^2/R) and TBW exceed 0.9 in most studies. Kushner (1992) reviewed five studies for TBW and eight studies for FFM reporting regression models solely based on l^2/R. The unstandardized regression coefficients were quite similar between equations with coefficients of variation (CV) of ≈5% for TBW, and 7% for FFM. Furthermore, a single study seemed to substantially bias the results. Recalculating CV for the remaining seven studies reduced the variation to less than 3%. The small variation between regression coefficients indicates that different investigators obtained similar relationships between independent and dependent variables in samples diverse in age (0.4–83 years), underpinning the empirical stability of the model. Furthermore, dividing the mean regression coef-

Table 23.2 Key points on the accuracy of selected bioimpedance applications in health and disease

	Health		Disease	
	R^2	SEE	R^2	SEE
FFM	**0.86** (0.71–0.97)	**2.75** (1.6–3.9)	**0.81** (0.26–0.94)	**2.7** (1.9–3.3)
TBW	**0.87** (0.41–0.97)	**2.3** (0.9–3.8)	**0.77** (0.53–0.94)	**2.1** (0.8–3.4)
ECW	**0.78** (0.39–0.92)	**1.6** (0.9–2.2)	**0.76** (0.54–0.89)	**1.5** (0.7–2.4)
ICW	**0.73** (0.20–0.93)	**1.8** (0.9–3.5)	**0.51** (0.32–0.77)	**1.7** (1.4–1.9)

Data are reported as mean values (bold) and ranges (in brackets). Estimates are based on validation studies since 1990 as reported by Kyle et al. (2004a, b) and cover a variety of instruments of bioimpedance models, including single- and multi-frequency BIA, BIS, and Hanai modeling. Data for healthy subjects include children and the elderly between 12 and 94 years as well as studies where hydration was altered. Data for 'Disease' cohorts include a broad range of disease, including cancer, COPD, HIV, cirrhosis, congestive heart failure, hemodialysis patients, and different surgical patients
R^2 coefficient of determination; *SEE* standard error of the estimate

ficient for TBW by the generally assumed hydration constant of 0.73, yielded a value expected that from the slope of the FFM equations (0.82 for FFM equation vs. 0.89 for expected regression coefficient). Reported precision in terms of prediction errors expressed as SEE usually range between 0.8 and 3.8 L for TBW, 0.7–2.4 L for ECW, 0.9–1.9 L for ICW, 1.6–3.9 kg for FFM, 1.71–1.73 kg for BCM, and 1.9–5% for %FM. Accuracy expressed as total error (TE) combining SEE with the residuals observed in cross-validation samples are similar, ranging between 1.59 and 4.79 kg for FFM and 0.23–3.3 L for TBW. The small differences between SEE and TE further substantiate the validity of BIA models. However, in spite of the similarity of regression equations solely based on l^2/Z (l^2/R) in healthy subjects, the diversity of published prediction equations during disease and states in which the fluid compartments are altered highlight the importance of choosing appropriate equations for individual subjects. Optimal accuracy will only be achieved for a given subject if the employed prediction equation was validated for subjects comparable to the subject being assessed.

A confounding difficulty of all validation studies is that the so-called gold-standards used as a reference are not error-free, and therefore restrict the degree of precision and accuracy that can be achieved.

According to Houtkooper et al. (1996) prediction error (SEE) for FFM of 2.0–2.5 kg in men and 1.5–1.8 kg in women is considered as ideal with an actual error of up to 1.8 kg. Hence, precision increases if the dependent variable is determined by a multi-compartment model.

Recently, the feasibility of BIA to determine FFM and TBW was confirmed in a representative multicenter study (Sun et al. 2003). The total sample consisted of 1,829 ethnically diverse men and women, who were split into a validation (n = 1,304) and cross-validation sample (n = 525). Whereas TBW was measured by deuterium dilution, FFM was obtained from a four-compartment model. SEE was 3.6 and 2.6 L for TBW and 3.7 and 2.8 kg for FFM for men and women, respectively. TE slightly increased to 4.2 and 3.2 L for TBW and 4.5 and 3.4 kg for FFM for men and women, respectively. These data are summarized in Table 23.2.

Considering the size and characteristic of some of the samples underlying these validation studies (e.g., n = 1,829 ethnically diverse men and women in Sun et al. 2003), the results can be considered as excellent and confirm the potential of bioimpedance measurements in determining body composition as repeatedly reported in recent years (for review see Kyle et al. 2004a, b). Finally, it should be considered that a confounding difficulty of all validation studies is that the so-called gold standards used as a reference are not error-free, and therefore restrict the degree of precision and accuracy that can be achieved. In a recent review Armstrong reports the accuracy of

TBW by isotope dilution to be within 1% and 5%. For the Reference Man this corresponds to an absolute error of 0.42–2.1 L. Thus, the criterion method also contributes to the error observed for the new method. According to Lohman (1992) this contribution ranges between 20% and 50% as long as accuracy and precision of the reference method exceed 1%, respectively. Thus, the actual errors reported for BIS applications might actually be much smaller. Consequently, in comparison to isotope dilution the accuracy of 0.23–3.3 L for TBW based on bioimpedance measurements can be considered as very good, if not excellent.

Finally, precision needs to be taken into account to assess the usefulness of a technique. Dilution techniques have a precision of 1–4%, depending on the analytical method employed (Schoeller 2005). It is, however, not clear whether those values also include subject preparation and tracer administration or refer to repeated sample collection and analysis only. Even considering ideal conditions with a precision of 1.5% for TBW and ECW, respectively, the error for ICW will be as large as 2.5% as the errors are propagated if ICW is calculated from the difference of TBW and ECW (Schoeller 2005). In contrast, under ideal conditions the variation for repeated measurements of bioimpedance during a single testing session has been reported to be lower than 1% (Elsen et al. 1987; Turner and Bouffard 1998). While the intraindividual variability obviously increases over days or weeks to about 1–4% (see Chap. 3), a corresponding inflation of errors due to biological variation is expected for dilution techniques or any other body composition method. Accordingly, though any systematic bias might confound absolute estimations of body composition by bioimpedance techniques, they might well be sensitive to detecting small changes in body composition, and particularly fluid volumes. Consequently, at least under standardized conditions the technology might be most useful for determining changes in fluid volumes and body composition.

23.6.3 Final Notes

It should be noted though that the validity of bioimpedance rises and falls with the quality control of its performance. Its main advantages such as accessibility, non-invasiveness, low costs, and ease of operation might sometimes mask the complexity underlying the measurement. Each measurement should therefore precisely follow standardization procedures in accordance with ESPEN guidelines (Kyle et al. 2004b). Awareness for these aspects is promoted by a basic understanding of the raw data obtained from bioimpedance measurements and the biophysical model underlying BIA (see also Chap. 3). Furthermore, valid results will only be obtained if the bioimpedance models (i.e. regression equations or Hanai parameters) are carefully chosen in accordance with the subjects under study. In healthy subjects this minimally implies consideration of gender, age, and race, but might include factors such as physical activity levels or degree of obesity. Additionally, in the clinical setting, the type of disease might also be taken into consideration by the choice of specific regression equations. Cautious interpretation is even more important when hydration and/or electrolyte balance is altered. This particularly pertains to subjects in which body composition and/or body shape are at the extremes such as in highly obese people or in subjects with abnormal limb length to height ratios. Presently, bioimpedance measurements cannot be recommended in these situations. Further validation studies will show whether specific regression equations are needed for these conditions. The general concept of an explanatory biophysical model using Hanai's mixture theory is certainly promising and needs to be further investigated. It would be clearly extremely valuable to develop a universal model that can be applied for a range of populations, hydration states, and clinical conditions. Future research will show if, and to what extent, mixture theory can reveal the true underlying potential of bioimpedance applications.

Summary Points

- Technological advances and the commercial availability of instruments have promoted the use of bioimpedance measurements in various clinical and research settings. Applications include the determination of whole-body hydration and body composition, abdominal fat, predicting survival in human immunodeficiency virus-infected patients, monitoring muscular activity during exercise, and the assessment of neuromuscular disease.
- BIA is presently one of the most widely used techniques for determining body composition.
- Most BIA instruments perform measurements at a single frequency of 50 kHz. As only a portion of the intracellular space is penetrated at this frequency, any body composition estimations of this approach are based on a constant ECW to ICW ratio.
- Multi-frequency (at least one high and one low frequency) as well bioimpedance spectroscopy (BIS), i.e. the measurement of up to 500 frequencies, and the subsequent extrapolation of resistance at zero and infinite frequencies have been proposed to overcome the drawbacks associated with single-frequency measurements and to differentiate TBW, ECW, and ICW.
- Due to substantial differences between the resistivity of ICW and ECW, BIS has been extended by the use of Hanai's mixture theory. This approach determines the resistances of ICW and ECW separately, and employs fluid compartment specific resistivities to obtain estimates of ICW and ECW.
- Further advantage of the Hanai approach is that it is based on an explanatory, biophysical model compared to purely statistically derived descriptive models relying on multiple regression analysis.
- Given the complexity of assumptions underlying all bioimpedance techniques, models, and their concomitant error sources, a clear superiority of a single technique remains to be established.
- BIA/BIS should only be performed under highly standardized conditions. In addition, regression equations or respective model parameters need to be carefully chosen with regard to the physiologic characteristics of the subject under study.
- If hydration and/or electrolyte balance is altered, results need to be interpreted with caution. This pertains particularly to the highly obese populations as well as subjects with abnormal body shapes and/or abnormal limb length to height ratios. Currently, the use of BIA/BIS under these conditions cannot be recommended in the clinical setting.

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Chapter 24
Physiological Basis of Regression Relationship Between Body Mass Index (BMI) and Body Fat Fraction

David G. Levitt, Dympna Gallagher, and Steven B. Heymsfield

Abstract The body mass index (BMI) is the standard parameter for predicting body fat fraction (fat weight/total weight) and for classifying degrees of obesity. A large number of regression relations have been derived for predicting fat fraction from BMI. These regressions usually include age, sex and ethnicity. Most of these regressions are based on standard linear or non-linear fits. A recent approach is described in which the regression equation is derived from a physiological model of body composition. This model assumes that obese subjects can be represented by the sum of a standard lean reference subject plus an extra weight that has a constant adipose, bone and muscle fraction.

The optimal regression parameters are derived by fitting the equations to a large data set of three compartment (density and total body water) measurements of body fat. The data were collected at the New York Obesity Research Center, Body Composition Unit as part of ongoing studies. A total of 1,356 subjects were included, with a *BMI* range of 17–50 kg/m^2 for males and 17–65 for females.

There are large age and sex dependences of the regression relations. No significant difference was found for Caucasians, Blacks and Hispanics (excluding Puerto Ricans). Asians and Puerto Ricans have significantly different regressions. For the highly obese subjects (*BMI* > 45 kg/m^2), the non-linear physiological regression provides a significantly better prediction of fat fraction than the standard linear regression.

Abbreviations

BMC	Bone mineral mass
BMI	Body mass index
2C, 3C, and 4C	2-, 3-, and 4-compartment model of fat measurement
DXA	Dual energy X-ray absorptiometry
MSR	Mean square residual error
TBW	Total Body water

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_24,

24.1 Introduction

The body mass index (BMI), defined as weight (kg)/height $(m)^2$, is the closest universal indicator of body fat in the social sciences (Burkhauser and Cawley 2008). Although the limitations of BMI as a predictor of body fat are well recognized (Prentice and Jebb 2001; Garn et al. 1986), BMI has become widely accepted because of its simple dependence on commonly measured parameters. A large number of regression relations relating body fat fraction (fat weight/total weight, dimensionless) to BMI has been published (see Table 24.9 for a partial listing). Although the accuracy of the prediction is clearly improved by adding other measurements to the regression relation (e.g., skinfold thickness (Goel et al. 2008)), this review will be limited to a discussion of the dependence of the body fat fraction on the standard parameters, namely BMI, age, sex, and ethnicity. In addition, only the adult regression relations (≥18 years) will be considered (Table 24.1).

24.2 Physiological Models of Body Composition

Until recently, these regression relations were regarded simply as mathematical fits to the data (either linear or non-linear). However, if one wants to extend the regression to the highly obese (i.e., $BMI > 45$), it is important to use an expression that has the correct physiological relationship between BMI and body fat. Another advantage of using a physiological regression relation is that it becomes possible to interpret the regression parameters in terms of body composition, and to analyze the assumptions in the model.

In a recently described physiological model (Levitt et al. 2009), it has been assumed that the total body weight is equal to the sum of the standard lean reference subject (W_0) and the additional weight (W_1) of the obese subject, with each component, respectively, having fat weight F_0 and F_1, with fat fractions f_0 and f_1:

$$W = W_0 + W_1 = \frac{F_0}{f_0} + \frac{F_1}{f_1} \tag{24.1}$$

The additional weight W_1 includes the extra adipose tissue plus the additional muscle and bone, etc., that is required to support this extra adipose tissue. Assuming that W_0 scales as the square of the height ($W_0 = bH^2$), using $BMI = W/H^2$ and defining $BMI_0 = W_0/H^2$, (24.1) is solved for the total body fat fraction:

$$\begin{aligned} F = F_0 + F_1 = f_0 W_0 + f_1 W_1 = f_1 W + W_0 \left(f_0 - f_1\right) \rightarrow \\ \text{Fat Fraction}\left(BMI\right) = \frac{F}{W} = f_1 + \left(f_0 - f_1\right)\frac{BMI_0}{BMI} \end{aligned} \tag{24.2}$$

Table 24.1 Key features of Body Mass Index (BMI) regression equations

1. The *BMI* is defined as weight(kg)/height $(m)^2$
2. The regression equation predicts the body fat fraction given the subject's *BMI*, age, and ethnicity
3. A regression is derived based on a physiological model of body composition. This non-linear equation provides predictions of fat fraction at high *BMI* that are more accurate than the standard linear regressions
4. The *BMI* regression relations provide predictions of fat fraction that are within about ± 0.05 of the true value. The predicted fat fraction significantly overestimates the true fat fraction for subjects with very low fat fractions

This table lists the important features of the BMI, including how it is defined, its physiological basis, and its validity

Two different regression models will be considered. For Model I, it is assumed that the standard reference state is the zero-fat condition ($f_0 = 0$):

$$\text{Fat Fraction I}(BMI) = f_1 - f_1 \frac{BMI_0}{BMI} \tag{24.3}$$

For Model II, it will be assumed that lean subjects, who have a *BMI* less than the standard lean reference value of BMI_0, have a constant fat fraction of f_0:

$$\text{Fat Fraction II}(BMI) = \begin{cases} f_1 + (BMI_0 / BMI)[f_0 - f_1] & BMI >= BMI_0 \\ f_0 & BMI < BMI_0 \end{cases} \tag{24.4}$$

The fat fraction for Model II (24.4) depends on three adjustable parameters: (1) BMI_0, the *BMI* of the lean reference subject; (2) f_0, the fat fraction of the lean reference subject; and (3) f_1, the fat fraction of the extra weight in obese subjects.

It can be seen from (24.3) and (24.4) that the fat fraction has a non-linear dependence on *BMI*, with the fat fraction asymptotically approaching f_1 as *BMI* tends to infinity. For simplicity, it will be assumed that the age dependence is linear, and the age-dependent regression will be included only for Model I:

$$\text{Fat Fraction I}(BMI, \text{Age}) = f_1 - f_1 \frac{BMI_0}{BMI} + c\ \text{Age} \tag{24.5}$$

The regression dependence on sex and ethnicity will be implemented simply by deriving separate regression parameter sets for different conditions. Finally, the non-linear relations will be compared with the commonly used linear regression:

$$Fat\,Fraction(BMI, Age) = a + b\,BMI + c\,Age \tag{24.6}$$

Both the linear (24.6) and non-linear (24.5) age-dependent regressions depend on the three adjustable parameters.

For comparison, these BMI regression relations will be compared with the regression, where height and weight are regarded as independent variables.

$$\text{Fat Fraction}(\text{Height}, \text{Weight}, \text{Age}) = a + b\text{Height} + c\ \text{Weight} + d\,\text{Age} \tag{24.7}$$

This regression has four adjustable parameters.

24.3 Measurement of Body Fat Fraction

In order to estimate the regression parameters, it is necessary to have accurate measurements of the fat fraction over a wide range of *BMI* and age. Although the most commonly used method is dual-energy X-ray absorptiometry (DXA), this approach cannot be used for the highly obese subjects ($BMI > 45$) because they are too large to fit the commonly available scanner tables. In addition, the DXA software has not been calibrated for highly obese subjects, and there is evidence that DXA underestimates the body fat in obese subjects (Das et al. 2003; Evans et al. 1999; Schoeller et al. 2005; Strauss et al. 2003; Valentine et al. 2008). Thus, DXA is not a suitable approach for calibrating the regression parameters for a *BMI* range that includes the highly obese.

Table 24.2 Age (years) and *BMI* (kg/m^2) distribution for subjects in different ethnic groups

Ethnic	Male/Female	N	Age range; ave. (SD)	*BMI* range; ave. (SD)
Caucasian	Male	234	18–97; 39.9 (18.3)	18.59–50.3; 25.6 (4.3)
	Female	355	18–90; 45.97 (18.0)	17.07–65.75; 25.05 (6.34)
Black	Male	124	20–86; 48.6 (17.0)	17.27–41.9; 26.2 (3.9)
	Female	233	18–88; 50.15 (17.5)	17.07–61.02; 29.04 (6.48)
Hispanic	Male	30	20–74; 37.5 (17.4)	20.08–47.9; 26.6 (5.4)
	Female	57	20–87; 42.18 (16.8)	18.84–57.46; 27.31 (7.70)
Asian	Male	59	28–89; 53.3 (18.1)	17.79–30.25; 23.9 (3.0)
	Female	61	26–88; 54.26 (17.5)	17.18–28.44; 21.73 (2.83)
Puerto Rican	Male	105	20–79; 47.0 (14.9)	18.41–41.7; 27.3 (4.7)
	Female	98	20–85; 46.99 (15.5)	19.8–43.5; 28.48 (5.0)

The age, *BMI*, and sex distribution of the subjects used for most of the analysis discussed here

The gold standard method is the 4-compartment (4C) approach, which uses DXA to measure bone mineral content (BMC) along with measurements of body density by underwater-weighing- or air-displacement plethysmography and of total body water (TBW) by isotope dilution. Because of the stated limitations with DXA, BMC cannot be measured and one is limited to using the 3C model (Siri 1993). This requires an assumption for the value of D_{res}, the average density of the sum of the protein, glycogen, and the bone and soft-tissue minerals (determined from 4C measurements on normal weight subjects) (Silva et al. 2005). Because one cannot make 4C measurements on obese subjects, there is no information about the value of D_{res} here, and, by necessity, it is assumed in the 3C method that D_{res} is constant, independent of the fat fraction. Other studies have used 2C approaches based on either body density or TBW. These measurements are obviously somewhat less reliable than the 3C methods.

In this review, much of our focus will be on regression relations derived from fitting the 3C fat fraction measurements determined from ongoing clinical studies at the New York Obesity Research Center at St. Luke's-Roosevelt Hospital, New York (Levitt et al. 2009). This is the largest single set of 3C measurements over the widest *BMI* range currently available. The subjects were all ambulatory adults, age 18 years or over, without any clinically significant diagnosed medical conditions. A total of 1,356 subjects were included, with a *BMI* range of 17–50 kg/m^2 for males and 17–65 kg/m^2 for females. Table 24.2 summarizes the age and BMI distribution for the different ethnic groups. This is the same data set that was used in a recent publication (Levitt et al. 2009). That publication provides the details of the fat measurement methodologies and the statistical analysis. Recently, Mills et al. (2007) presented a detailed statistical analysis of the body fat–BMI relationships for a data set that includes much of the data used here.

24.4 Sex, Age, and Ethnic Dependence of BMI Versus Body Fat Fraction

Although numerous studies have clearly demonstrated the age, sex, and ethnic dependence of the relation between body fat fraction and *BMI*, the commonly used BMI calculators freely available on the Internet usually ignore this dependence. Although regression relations that directly include age will be derived below, the importance of this dependence can be more clearly seen by grouping the subjects into fixed age and BMI groups.

Tables 24.3 (males) and 24.4 (females) show the dependence of fat fraction on age for two or three different *BMI* ranges for Caucasians. The subjects in the different age brackets have been grouped so that they have nearly identical average *BMI* values and, thus, differences in fat fraction between the

Table 24.3 Caucasian males: dependence of fat fraction on age (years) for two *BMI* ranges

BMI range	Ave. age (year) (SD)	Age range	Ave. BMI	Ave. Fat Fraction	N
18–24	21.86 (2.44)	18–25	22.19 (1.08)	0.1193 (0.046)	29
	29.94 (2.36)	26–33	22.12 (1.34)	0.134 (0.048) (NS)	32
	52.83 (19.42)	34–84	22.39 (1.31)	0.173 (0.057) ($p < 0.01$)	30
24–44	25.94 (2.66)	21–30	27.64 (4.00)	0.188 (0.084)	47
	38.17 (5.07)	31–48	27.42 (3.96)	0.211 (0.072) (NS)	48
	66.25 (10.69)	49–97	27.93 (3.41)	0.284 (0.075) ($p < 0.01$)	47

Comparison of the fat fraction for males with similar BMI, but different ages

Table 24.4 Caucasian females: dependence of fat fraction on age (years) for three BMI ranges (the p value refers to comparison to the youngest age group)

BMI range	Ave. age (SD)	Age range	Ave. BMI	Ave. fat fraction	*N*
17–22	24.95 (3.41)	18–30	20.00 (1.38)	0.219 (0.045)	42
	38.04 (5.87)	30–49	20.60 (1.07)	0.241 (0.056) ($p < 0.05$)	42
	63.32 (11.18)	49–89	20.55 (1.01)	0.298 (0.053) ($p < 0.01$)	40
22–25.9	26.14 (4.72)	18–33	23.30 (1.03)	0.26 (0.049)	43
	39.12 (4.91)	33–51	23.45 (1.05)	0.30 (0.055) ($p < 0.01$)	41
	68.12 (10.47)	52–88	24.12 (1.15)	0.36 (0.059) ($p < 0.01$)	39
26–56	34.94 (6.198)	21–45	31.19 (6.12)	0.408 (0.074)	36
	54.0 (4.69)	46–61	31.72 (5.89)	0.428 (0.056) (NS)	35
	70.49 (6.87)	62–90	29.36 (2.68)	0.414 (0.053) (NS)	35

Comparison of the fat fraction for females with similar *BMI*, but different ages

Table 24.5 Ethnic dependence of BMI versus fat fraction for males as a function of age (years) and BMI (the p value refers to comparison to Caucasians)

	N	Age range (ave.)	BMI range (ave.)	Ave. fat fraction (SD)
Caucasian	106	28–54 (36.4)	20–34 (25.59)	0.189 (0.072)
Black	70	20–52 (36.5)	20–34 (26.33)	0.195 (0.073) (NS)
Puerto Rican	55	20–52 (37.5)	20–34 (26.13)	0.214 (0.064) ($p < 0.05$)
Caucasian	163	20–52 (31.5)	20–34 (25.02)	0.170 (0.073)
Hispanic	24	20–52 (31.0)	20–34 (26.04)	0.191 (0.071) (NS)
Caucasian	94	28–54 (35.6)	20–30 (24.68)	0.175 (0.065)
Asian	35	20–52 (36.6)	20–30 (23.97)	0.212 (0.069) ($p < 0.01$)

Fat fraction for males of different ethnic groups with similar age and BMI

groups is a direct measure of age dependence. For males, age dependence is dramatic and nearly linear, with the subjects in the oldest age group having about 50% more fat that those in the youngest with the same *BMI*. For females, the age dependence is not quite as large and is more complicated (non-linear). For subjects in the two lower *BMI* ranges, there is a roughly linear increase in fat fraction with age, with the oldest subjects having about 35% more fat than the youngest with the same *BMI*. However, there is no significant age dependence of the fat fraction for obese females in the highest *BMI* range (26–56). The sex dependence of the fat fraction is obvious from comparing Tables 24.3 and 24.4, with the fat fraction in females nearly 0.1 greater than men for the same value of *BMI*.

Tables 24.5 (males) and 24.6 (females) describe the ethnic dependence of the fat fraction for Caucasians, Blacks, Hispanics (not including Puerto Ricans), Puerto Ricans, and Asians. The age

Table 24.6 Ethnic dependence of BMI versus fat fraction for females as a function of age (years) and *BMI* (the *p* value refers to comparison to Caucasians)

	N	Age range (ave.)	*BMI* range (ave.)	Ave. fat fraction (SD)
Caucasian	129	20–57 (37.4)	22–34 (25.42)	0.321 (0.071)
Black	95	20–52 (37.8)	20–34 (26.57)	0.328 (0.074) (NS)
Hispanic	37	20–60 (36.1)	20–34 (25.40)	0.311 (0.09) (NS)
Puerto Rican	41	20–52 (35.7)	20–30 (26.18)	0.348 (0.058) ($p < 0.05$)
Caucasian	153	23–53 (35.41)	17–25 (21.72)	0.257 (0.061)
Asian	35	23–53 (36.7)	17–28 (21.25)	0.282 (0.066) ($p = 0.07$)

Fat fraction for females of different ethnic groups with similar age and *BMI*

and *BMI* ranges of the different ethnic groups have been selected so that the average age and *BMI* are similar to that for Caucasians and, thus, any difference in fat fraction is an indication of ethnic dependence. There is no significant difference among Caucasians, Blacks, and Hispanics and, in the following analysis, these subjects will be grouped together. This differs from some other studies that have found significant differences between Blacks and Caucasians (Ortiz et al. 1992; Schutte et al. 1984; Gallagher et al. 2000a; Deurenberg et al. 1998). There is a clear difference between Asians and Caucasians, with Asians having a fat fraction that is about 0.03 greater than Caucasians with the same average *BMI* and age. This is a consistent observation for Asians (Gallagher et al. 2000a; Deurenberg et al. 1998). This study group (Table 24.2). had a large Puerto Rican population that was distinguished from other Hispanics, and Puerto Ricans have a significantly different *BMI* versus fat fraction relation, with an average fat fraction about 0.025 greater than Caucasians with the same average age and *BMI*.

24.5 Comparison of Age-Independent Linear and Non-linear Regressions

Three different forms of the relationship between fat fraction and *BMI* are described above: the standard linear regression and the two non-linear regressions (Model I, (24.3) and Model II, (24.4)). Figures 24.1 (males) and 24.2 (females) compare these three regression relations for Caucasians, Blacks, and Hispanics (all ages). The scatter plot of the experimental fat fraction around the value predicted by the regression relation provides a graphic indication of the quality of the regression relation. The large scatter seen in Figs. 24.1 and 24.2 partially results from the fact that all ages are included in this plot. As seen in Figs. 24.3 and 24.4, if the age range is limited, the scatter is significantly reduced. A quantitative measure of the scatter is provided by the mean square residual error (MSR), which is defined as the sum $(X_{\text{model}} - X_{\text{exp}})^2/N$, where X_{model} and X_{exp} are the predicted and experimental fat fraction, respectively. The square root of MSR provides an estimate of the average error. Table 24.7 lists the values of the regression parameters and MSR for the three regression relations for the different age ranges.

For males, the simple linear regression provides a good fit to the data, and no significant improvement in the fit (i.e., decrease in MSR) is provided by the non-linear models (see Figs. 24.1 and 24.3 and Table 24.7). For females, where some have a *BMI* as high as 65 kg/m^2, the non-linear regression clearly provides a better fit than the linear regression for the highly obese (Figs. 24.2 and 24.4), with MSRs for the non-linear Models I and II, which are about 25% less than for the linear regression. For females, there is no significant difference in MSR between Models I and II.

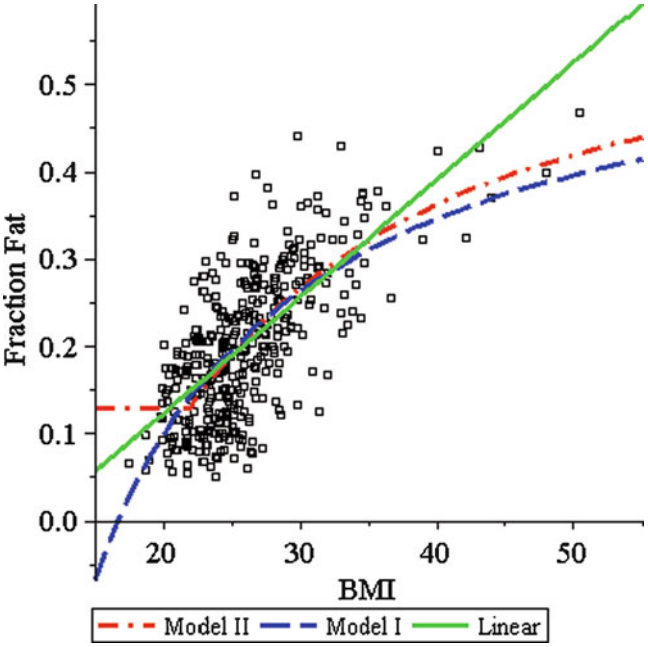

Fig. 24.1 Plot of the fat fraction as a function of *BMI* for Caucasian, Black, and Hispanic males of ages 18–89 years. The least-square fits to the data of the linear and the non-linear Models I and II are shown. The three lines show the fat fraction as a function of *BMI* predicted by the different regression relations for males. There is no significant difference in the accuracy of the different predictions

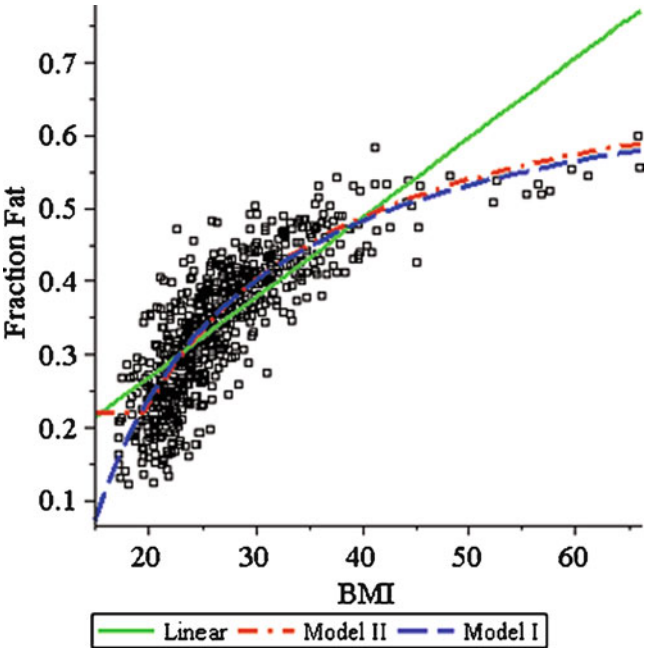

Fig. 24.2 Plot of the fat fraction as a function of *BMI* for Caucasian, Black, and Hispanic females of ages 18–90 years. The least-square fits to the data of the linear and the non-linear Models I and II are shown. The three lines show the faction fat as a function of *BMI* predicted by the different regression relations for females. The non-linear regressions (Models I and II) provide significantly better predictions, especially for the highly obese females

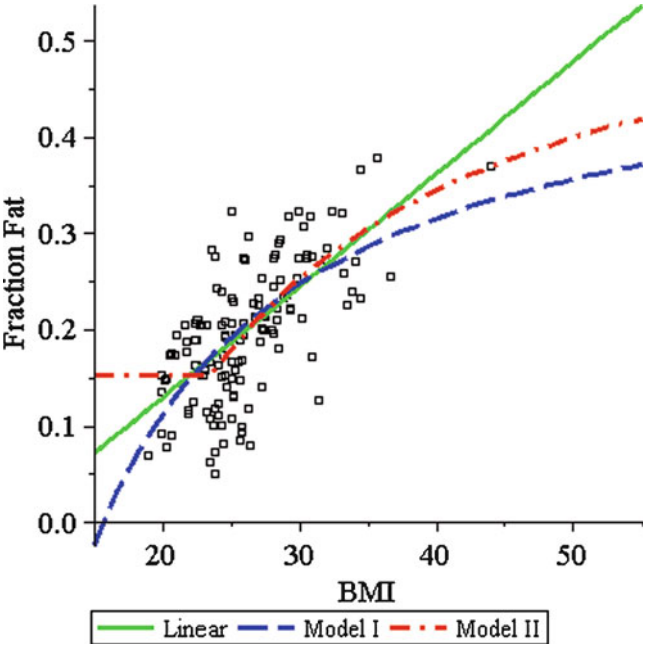

Fig. 24.3 Plot of the fat fraction as a function of *BMI* for Caucasian, Black, and Hispanic males of ages 32–50 years. The least-square fits to the data of the linear and the non-linear Models I and II are shown. This plot is similar to that of Fig. 24.1 except that only subjects in the age range 32–50 years are included

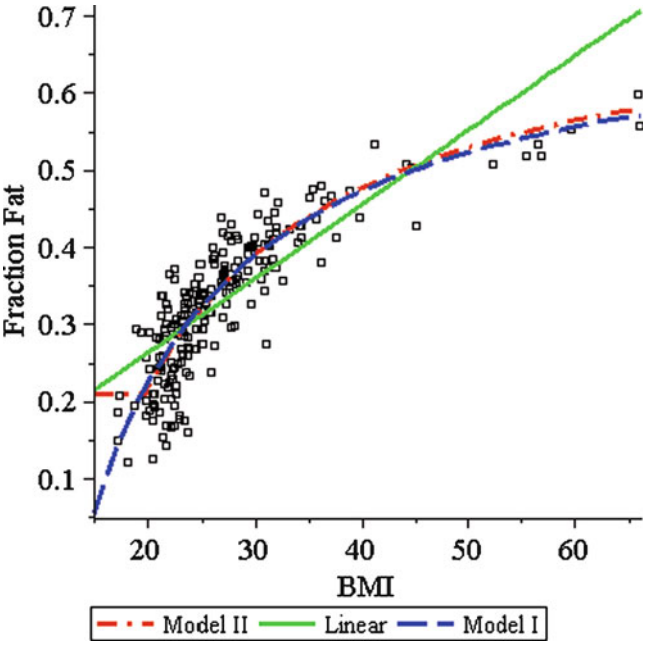

Fig. 24.4 Plot of the fat fraction as a function of *BMI* for Caucasian, Black, and Hispanic females of ages 32–50 years. The least-square fits to the data of the linear and the non-linear Models I and II are shown. This plot is similar to that of Fig. 24.2 except that only subjects in the age range 32–50 years are included

24.6 Comparison of Age-Dependent Linear and Non-linear Regressions

One approach for including age dependence in the regression is to use small age intervals and derive different sets of regression parameters for each interval (as was done in Table 24.7). However, this is complicated and it is simpler to directly include the age in the regression. Ideally, one would like to include age in a way that is based on the effects of age on the basic physiological model described

Table 24.7 Regression parameters and mean square residual error (MSR) for Caucasian, Black, and Hispanic subjects

	Linear			Model I (24.3)			Model II (24.4)			
Subjects	a	b	MSR	f_1	BMI_0	MSR	f_1	f_0	BMI_0	MSR
Male: 18–89	–00.145	0.0134	0.0038	0.594	16.71	0.00385	0.647	0.129	22.00	0.00377
Male: 18–31	–0.201	0.0134	0.00273	0.543	19.39	0.00315	0.706	.118	23.78	0.00261
Male: 32–50	–0.133	0.0119	0.00303	0.505	16.54	0.00312	0.619	0.153	23.54	0.00281
Male: 51–89	–0.126	0.0136	0.00310	0.628	16.28	0.00299	0.661	0.167	21.43	0.00283
Female: 18–90	+0.0494	0.0109	0.00351	0.728	13.50	0.00276	0.745	0.220	19.65	0.00272
Female: 18–31	–0.00685	0.0116	0.00237	0.695	13.99	0.00225	0.774	0.214	21.30	0.00181
Female: 32–50	+0.0700	0.00963	0.00306	0.723	13.86	0.00212	0.737	0.208	19.71	0.00209
Female: 51–90	+0.106	0.0101	0.00225	0.681	11.57	0.00210	0.682	0.249	18.28	0.00210

Parameters and error for the three regression equations used to predict fat fraction from *BMI* for subjects in different age ranges

Table 24.8 Comparison of linear and non-linear regression expressions for predicting body fat fraction from *BMI* and age

		Linear (24.6)				Non-linear model I (24.5)			
Subjects	±Age	a	b	c	MSR	BMI_0	f_1	c	MSR
Male Caucasians	No	–0.166	0.0141	–	0.00404	17.20	0.624	–	0.00409
	Yes	–0.218	0.0129	0.00207	0.00263	19.15	0.500	0.00194	0.00287
Male Caucasian	No	–0.145	0.0134	–	0.00380	16.71	0.594	–	0.00385
+Hispanic+Black	Yes	–0.206	0.0127	0.00182	0.00270	18.73	0.496	0.00172	0.00288
Male Asian	Yes	–0.156	0.0126	0.00169	0.00201	15.72	0.438	0.00169	0.00212
Male Puerto Rican	Yes	–0.155	0.0119	0.00163	0.00189	17.84	0.536	0.00150	0.00188
Female Caucasian	No	0.0409	0.0113	–	0.00391	13.50	0.739	–	0.00314
	Yes	–0.0240	0.0104	0.00186	0.00281	14.39	0.635	0.00151	0.00244
Female Caucasian	No	0.0494	0.0109	–	0.00351	13.50	0.728	–	0.00276
+Hispanic+Black	Yes	–0.0160	0.0104	0.00169	0.00260	14.37	0.642	0.00132	0.00222
Female Asian	Yes	–0.0903	0.0153	0.00122	0.00137	12.38	0.573	0.00122	0.00140
Female Puerto Rican	Yes	0.0718	0.00919	0.000947	0.00159	12.82	0.639	0.000737	0.00142

Parameters for the linear and non-linear regression relations for the entire subject base (all ages), with and without and a linear age-dependent term

above. However, due to lack of such information, age is usually added as a linear term in the regression (see (24.5) and (24.6)). This is clearly an approximation because, as described above, the effect of age in females is non-linear (see Table 24.4).

Two different age-dependent regressions are considered: the standard linear (24.6) and the non-linear Model I (24.5). Table 24.8 summarizes the results of fitting these two equations to the New York Obesity Research Center data set (Levitt et al. 2009). The regression relations with and without the addition of the linear age term are listed. The ethnic dependence of the regression is incorporated by deriving separate sets of regression coefficients for each of the ethnic groups that differed significantly from Caucasians (see Tables 24.5 and 24.6).

Adding age dependence clearly improves the prediction of the regression relation, decreasing MSR by about 25%. The differences between the MSR for the linear and non-linear regressions are small. For males, the linear regression is slightly better, whereas for females with their larger *BMI* range, the non-linear regression is significantly better (e.g., an MSR of 0.00222 for non-linear vs 0.0026 for the linear regression). Also, the MSR when Caucasians, Blacks, and Hispanics are grouped is no worse than when the Caucasian regression is used separately, supporting the above conclusion that there is no significant difference among these three ethnic groups.

MSR provides a quantitative measure of the accuracy of the prediction of fat fraction from the regression relation, with the square root of the MSR being an approximate measure of the error in the prediction. For example, for female Caucasians, Blacks, and Hispanics, the square root of the MSR for the non-linear regression is 0.047 (units of fat fraction, dimensionless). That is, the error in the predicted fat fraction is 0.047 for the entire age and *BMI* range. Another way to visualize this error is as a scatter plot of the values of error in the predicted fat fraction. Figures 24.5 (males) and 24.6 (females) show plots of this error for the linear (24.6) and non-linear (24.5) regression as a function of the subject's BMI for Caucasian, Black, and Hispanic subjects. For males (Fig. 24.5), there is a small tendency for the predicted fat fraction at high *BMI* to be overestimated by the linear regression and underestimated by the non-linear regression. For females (Fig. 24.6), the linear regression dramatically overestimates the fat fraction at high *BMI* (>40), whereas there is no significant correlation of the error with *BMI* for the non-linear regression. Figures 24.7 (males) and 24.8 (females) show similar plots of the error as a function of the subject's true (experimental) fat fraction. For males, there is an obvious correlation of the error with fat fraction, with the predicted fat fraction overestimating the true experimental value at low fat fractions and underestimating it at high fat fractions. For females, the linear regression again overestimates the fat fraction at low fat values, whereas at high fat values, there are very large positive and negative errors. There is clearly less systematic error in the non-linear regression predictions for females.

Although the main focus of this review is *BMI* regression relations, the results for *BMI* in Table 24.8 were compared with the linear regression in which height, weight, and age were regarded as independent parameters (24.7). For Caucasian, Black, and Hispanic males, the MSR for this four-parameter regression was 0.00270, identical to that for the three-parameter *BMI* linear regression (24.6). For Caucasian, Black, and Hispanic females, the MSR for this four-parameter regression was 0.00260, identical to that for the three-parameter *BMI* linear regression and not as good as the non-linear three-parameter *BMI* regression (24.5). It is surprising that the addition of another independent parameter does not improve the prediction. This comparison provides additional support for the validity of the *BMI* as an indicator of fat fraction.

24.7 Accuracy of the *BMI* Regression Predictions of Fat Fraction

The accuracy of the prediction of body fat fraction from the *BMI* is graphically illustrated in Figs. 24.5–24.8, which show the scatter plots of the age-dependent regression error in fat fraction as a function of either *BMI* (Figs. 24.5 and 24.6) or experimental fat fraction (Figs. 24.7 and 24.8). The overall average error in the fat fraction (estimated from the square root of the RMS, Table 24.8) is 0.052 for men and 0.047 for women. As shown in Figs. 24.7 and 24.8, there is a systematic bias in the *BMI* estimate of fat fraction, with the regression overestimating the fat fraction for subjects with very low fat fractions. This probably results, in part, from the very low fat fractions in athletes, who commonly have higher muscle mass fractions than the general population.

A basic assumption underlying the use of *BMI* is that weight scales as height^N, where $N = 2$. In 2005, a large, extensive review of the height versus weight relationship found an average value of N of 1.92 for males and 1.45 for females. A recent study (Heymsfield et al. 2007) looked at the scaling of weight, adipose mass, skeletal mass, etc., with height, and found that weight scaled as 1.94, whereas fat mass scaled as only 1.43. One factor that was not considered by these analyses is that, according to the physiological model described above, it is only W_0, the weight of the lean reference subject, and not the total weight, that is assumed to scale as height^2. As a test of this

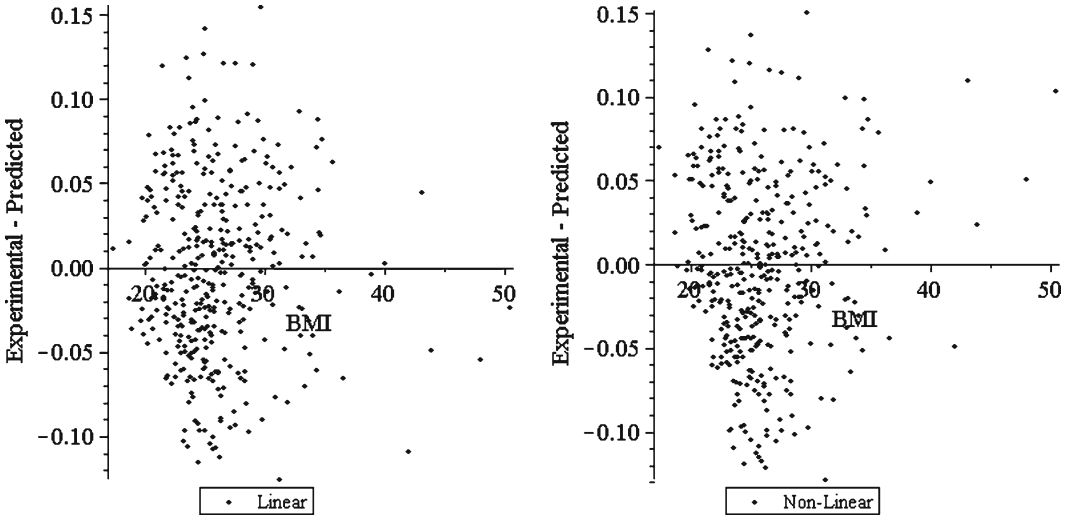

Fig. 24.5 Plot of the error in the fat fraction predicted from the age-dependent linear and non-linear regression equations (experimental vs predicted) as a function of *BMI* for Caucasian, Black, and Hispanic males. The scatter in the points represents the error in the fat fraction predicted by the linear (*left*) and non-linear (*right*) regression as a function of the subjects' *BMI*

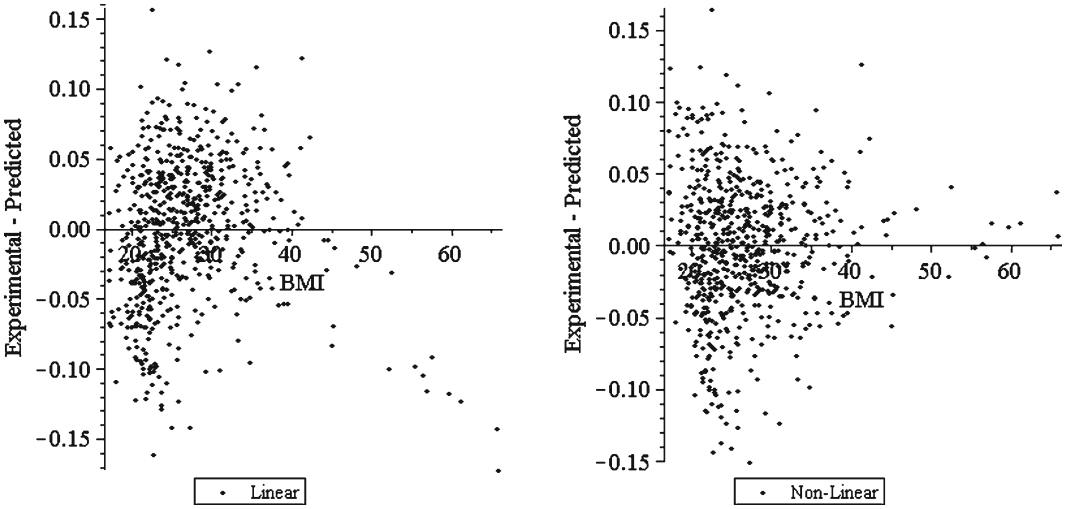

Fig. 24.6 Plot of the error in the fat fraction predicted from the age-dependent linear and non-linear regression equations (experimental vs. predicted) as a function of *BMI* for Caucasian, Black, and Hispanic females. The scatter in the points represents the error in the fat fraction predicted by the linear (*left*) and non-linear (*right*) regression as a function of the subjects' *BMI*

assumption, Fig. 24.9 shows a log–log plot of height versus weight for the lean males (fat fraction < 0.15) and females (fat fraction < 0.24) in the subject data set used in this analysis. This assumes that these subjects are representative of the hypothetical lean reference subject. For both males and females, the average value of N is close to 2 (1.96 for males and 1.95 for females), in support of this basic assumption.

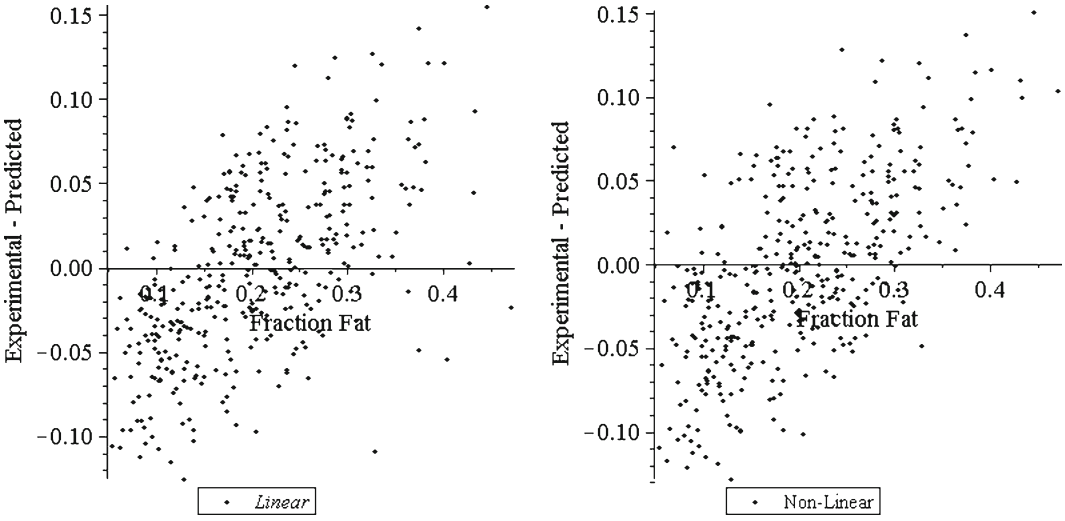

Fig. 24.7 Plot of the error in the fat fraction predicted from the age-dependent linear and non-linear regression equations (experimental vs. predicted) as a function of experimental fat fraction for Caucasian, Black, and Hispanic males. The scatter in the points represents the error in the fat fraction predicted by the linear (*left*) and non-linear (*right*) regression as a function of the subjects' fat fraction

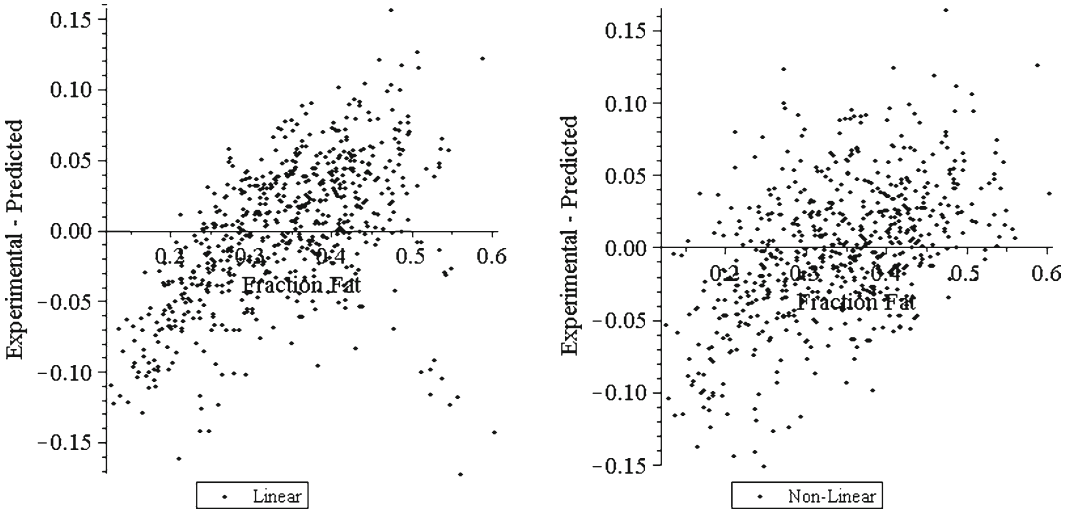

Fig. 24.8 Plot of the error in the fat fraction predicted from the age-dependent linear and non-linear regression equations (experimental vs. predicted) as a function of the experimental fat fraction for Caucasian, Black, and Hispanic females. The scatter in the points represents the error in the fat fraction predicted by the linear (*left*) and non-linear (*right*) regression as a function of the subjects' fat fraction

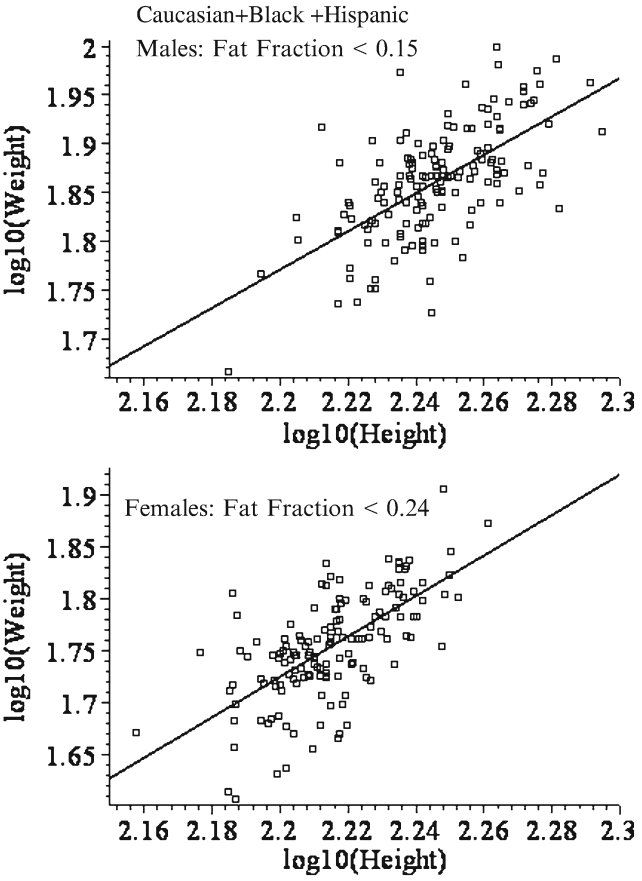

Fig. 24.9 Log–log plot of height versus weight for lean Caucasian, Black, and Hispanic males (*top panel*) and females (*bottom panel*). The line is the least-squares linear fit. Test of the assumption in the non-linear model that weight scales as the square of the height of lean subjects

24.8 Summary of Recent Regression Relations

Table 24.9 lists some recent *BMI* regression relations and compares them with the regression results discussed here (Levitt et al. 2009). Two of these regressions (Gallagher et al. 2000a, 1996) are based on a subset of the data used in the present analysis. These regressions are plotted in Figs. 24.10 (males) and 24.11 (females), assuming an age of 40 years.

As can be seen in Figs. 24.10 and 24.11, for the *BMI* range of 25–35 kg/m^2, all the regressions are quite similar. The major differences occur when the regressions are extrapolated to very large *BMI* values, beyond the data range that was used to derive all the regressions except the one discussed here (Levitt et al. 2009; see Table 24.2). It is when applying these regressions to the very obese (up to *BMI* equal to 65 for females) that the non-linear form of the equation becomes important. For the two physiologically based relations derived here ((24.3) and (24.4), the fat fraction asymptotically approaches the fat fraction of the extra weight (f_1) as *BMI* approaches infinity. In contrast, for the linear regression, the fat fraction becomes greater than 1 at very high *BMI*, which is impossible. Both Jackson et al. (2002) and Larsson et al. (2006) use a non-linear regression formed by adding a term that varies as the square of the *BMI*. This arises simply from the standard curve fitting approach to non-linear data. This quadratic term is also non-physiological, as it predicts a decrease in fat fraction at large *BMI* values, as can be clearly seen in Fig. 24.11.

Table 24.9 Summary of recent *BMI* regression equations used to predict percent body fat for men and women. If the study found ethnic differences, only the Caucasian regression is listed

Reference	Regression equation		*BMI* range	Method
	Men (*N* subjects)	Women (*N* subjects)		
Levitt et al. (2009)			<65	3 Comp
Linear	0.0127BMI + 0.00182 age – 0.206 (388)	0.0104*BMI* + 0.00169 age – 0.0160 (645)		
Non-linear	0.496 – 9.29/BMI + 0.00172 age (388)	0.642–9.23/*BMI* + 0.00132 age (645)		
Gallagher et al. (2000a)	0.516 – 8.64/*BMI* + 0.0012 age (192)	0.637 – 8.64/*BMI* + 0.0012 age (225)	<35	4 Comp
Gallagher et al. (1996)	0.0140*BMI* + 0.00177 age – 0.2252 (214)	0.01591*BMI* + 0.00096 age – 0.1166 (290)	<35	4 Comp
Jackson et al. (2002)	0.0376 *BMI* – 0.0004BMI^2 – 0.478 (296)	0.0435 *BMI* – 0.0005BMI^2 – 0.462 (359)	<45	Body density
Deurenberg et al. (1998)	0.0129*BMI* + 0.002 age – 0.193 (1976)	0.01294*BMI* + 0.002 age – 0.08 (2516)	<36	Variety
Larsson et al. (2006)	0.0189*BMI* – 0.2817 (274)	0.0386*BMI* – 0.000344BMI^2 – 0.495 (357)	<45	DXA

Comparison of different regression relations recently used to predict fat fraction from *BMI* and age

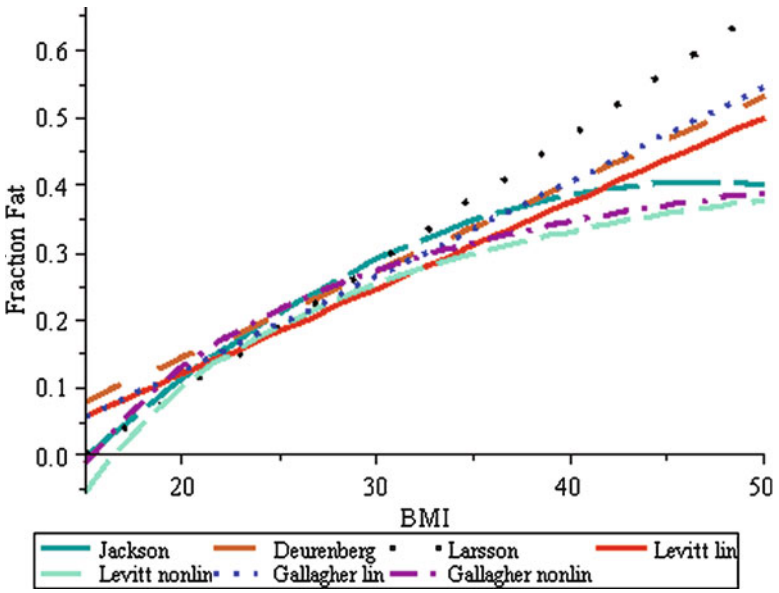

Fig. 24.10 Plot of the regression relations listed in Table 24.9 for men, age 40 years. Comparison of the different regression relations that have been recently proposed for predicting fat fraction from *BMI* for males

If the regression will be applied to the highly obese, then the non-linear form (24.3), (24.4) or (24.5) is clearly superior (this is the same form that was used by Gallagher et al. (2000a)). This is clearly seen in the data for females (Fig. 24.2), where the non-linear form diverges from the linear for $BMI > 45$ and the RMS of the non-linear relation is about 25% less than the linear for the entire female data set. For males (Fig. 24.1), the *BMI* does not reach high enough values in this data set to make the non-linear relation superior to the linear relation, with only two men having a $BMI > 43$.

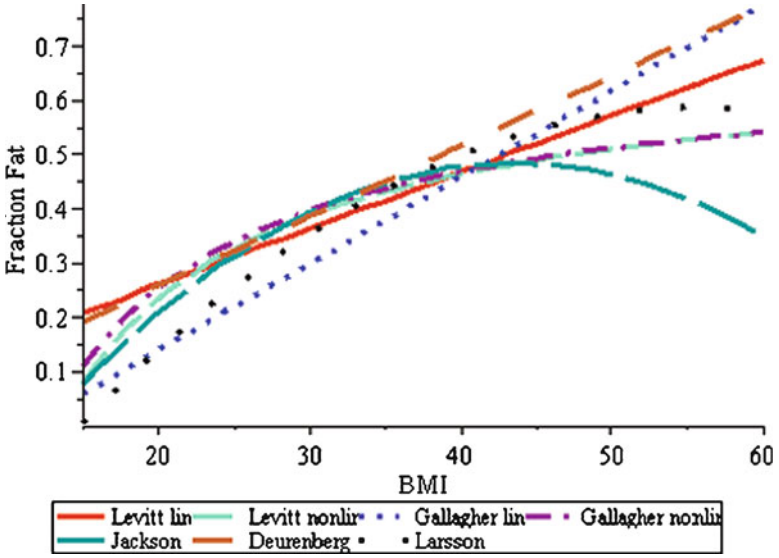

Fig. 24.11 Plot of the regression relations listed in Table 24.9 for women, age 40 years. Comparison of the different regression relations that have been recently proposed for predicting fat fraction from *BMI* for females

24.9 Applications to Other Areas of Health and Disease

An advantage of using a physiological model for BMI is that the regression parameters provide information about the body composition of both normal and highly obese subjects. The basic assumption used in the derivation of the physiological regression relations (24.3) and (24.4) is that, as a subject with a given height gains weight, the extra weight has a constant, fixed composition, with a fat fraction f_1. This is clearly an approximation because one would expect that, in severe obesity, as the subject becomes increasingly sedentary, there should be accompanying changes in both bone and muscle mass along with other pathological changes (Oppenheimer et al. 2006). However, the good fit of Model II for a *BMI* range of 17–65 (Fig. 24.2) suggests that this is an approximately valid supposition. For the two-parameter regression (Model I, (24.3)), the parameters correspond to BMI_0 (the *BMI* of the lean reference subject) and f_1 (the fat fraction of the extra weight). For the three-parameter regression (Model II, (24.4)), which is probably the most realistic, the parameters are BMI_0, f_1, and f_0 (the fat fraction of the lean reference subject). The values of these parameters for the different age ranges for men and women are listed in Table 24.7.

For males, the fat fraction of the lean reference subject is 0.129 and the fat fraction of the extra weight is 0.647. For females, the corresponding values are 0.22 and 0.745. Combining these results with body density measurements and some additional assumptions about body composition, one can estimate that the composition of the extra weight in men is 4.2% bone, 20% muscle, and 75.8% adipose, whereas in women it is 3.67% bone, 9.74% muscle, and 86.5% adipose (Levitt et al. 2009). This estimate of about 10% muscle in the extra weight for women is less than estimates of about 17%, based on direct MRI measurement of changes in muscle mass after dieting and weight loss (Gallagher et al. 2000b).

Summary Points

- The regression relation between body mass index (BMI) and fat fraction (fat weight/total weight) has a strong dependence on age. For males, subjects in the age range of 34–84 years have about 50% more fat than 18–25-year olds with the same *BMI*.
- The non-linear physiological regression relation should be used in place of the standard linear regression for highly obese subjects ($BMI > 45$ kg/m^2).
- The *BMI* regression relations provide predictions of fat fraction that are within about ±0.05 of the true value. The predicted fat fraction significantly overestimates the true fat fraction for subjects with very low fat fractions.
- For Caucasians, Blacks, and Hispanics, the following regression relations provide good estimates of fat fractions for a *BMI* range of 17–65 kg/m^2:

  Males: fat fraction = 0.496 – 9.29/*BMI* + 0.00172 age
  Females: fat fraction = 0.642 – 9.23/*BMI* + 0.00132 age

- Asians have a fat fraction that is about 0.03 greater than Caucasians for the same *BMI* and age and different regression equations should be used:

  Males: fat fraction = 0.438 – 6.885/*BMI* + 0.00169 age
  Females: fat fraction = 0.573 – 7.097/*BMI* + 0.00122 age

Acknowledgments This study was supported in part by National Institutes of Health Grants PO1-DK-42618 and P30-DK-26687, and RR24156.

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Chapter 25
Relationship Between Physical Measures of Anthropometry and Bioimpedance Measures

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Abstract The purpose of this chapter is to compare the results of body composition obtained by anthropometry and by Bioelectrical Impedance Analysis (BIA). A brief review of the physical and biological bases of BIA is conducted and the main types of devices on the market are described. They are classified according to the range of frequencies (single or multiple frequencies) and the number of electrodes (bipolar, tetrapolar, octopolar). BIA equations for use in children and adults according to age and sex are offered and the statistical methods for checking agreement between the results obtained by BIA and by anthropometry. This point is illustrated with examples from two studies conducted by the authors. The first one corresponds to 106 young adults that were analyzed simultaneously by anthropometry, two BIA bipolar analyzers (OMRON BF-306 and LAICA EP1340) and one tetrapolar BIA analyzer (Holtain BC). The second example is based on a sample of 86 schoolchildren analyzed by anthropometry and a BIA tetrapolar device (Bodystat 1500).

The bipolar monitors, also called regional, produce results that depend on fat distribution in the individual. This means that results vary depending on fat location in the upper or lower segment of the body. In contrast, a tetrapolar analyzer offers values which are independent of the localization of fat deposits. The final result is a better match between fat percentage obtained by type scale BIA analyzer and anthropometry in females and between type hand BIA analyzer and anthropometry in males. Tetrapolar devices are more accurate in the paediatric age.

Abbreviations

BIA	Bioelectrical impedance analysis.
DEXA	Dual-Energy X-Ray Absorptiometry
FFM	Fat free mass
FM	Fat mass
ICC	Intraclass correlation coefficient
TBW	Total body water

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_25,

25.1 Introduction

One of the methods used to evaluate nutritional status is body composition analysis. Several models can be established according to the number of elements into which the total weight is divided. One of the simplest and classic models is the bicompartmental model, which describes the body as the sum of two factors, the fat mass and the lean body mass. More complex models distinguish five or six compartments (Heymsfield et al. 1996; Pietrobelli and Tato 2005).

This fragmentation is determined by several indirect procedures, but one of the most commonly used is the anthropometric technique. Depending on the number of components to be estimated, different variables such as lengths, diameters, circumferences, skinfold thickness, weight and height are used. These measures are implemented in a mathematical formula that usually changes depending on ethnicity, gender, and age (Bellisari et al. 2007).

Another method for the analysis of body composition, called BIA (bioelectrical impedance analysis), was subsequently added. This technique was developed around the middle of the twentieth century, when it was shown that changes in impedance were associated with changes in blood volume (Nyober et al. 1940). At this time, apparatuses to determine body composition began to be used. Among the first were devices with electrodes arranged in a bipolar fashion – left hand and right foot (Thomaset et al. 1963). Then, Hoffer et al. (1969) used four electrodes using one or several frequencies. Finally, in the 1980s, several instruments became available in the market. Currently available devices are simple to operate and cheap and easy to transport; through an integrated program, these instruments are used to calculate the different body fractions immediately.

Anthropometry and BIA are two different means for analyzing body composition, and it is necessary to know how closely the results are correlated, and to what extent they may be equated. This chapter aims to establish the agreement that exists between these two analytical methods, which are now in use for nutritional status assessment.

25.2 BIA: Physical and Biological Bases

Impedance (Z) is defined as the response with which a cylinder filled with liquid opposes the passage of an electric current. For a cylindrical conductor of length L and cross section S, to which a potential difference is applied between its ends – at a particular intensity – the impedance is given by the following expression:

$$Z(\Omega) = \rho(\Omega \cdot \mathrm{m}) L(\mathrm{m}) / S(\mathrm{m}^2)$$

The resistivity (ρ) is a constant of proportionality that depends on the shape and size of the electric conductor. From this formula, we can ascertain the cylinder volume based on the impedance:

$$V(\mathrm{m}^3) = \rho(\Omega \cdot \mathrm{m}) L^2(\mathrm{m}^2) / Z(\Omega)$$

The BIA technique was developed by considering the human body as an irregular cylindrical conductor. If the above expression is interpolated to the case of humans, we can calculate the individual total body water (TBW) as follows (Houtkooper et al. 1996):

$$\mathrm{TBW}(\mathrm{m}^3) = \rho(\Omega \cdot \mathrm{m}) \mathrm{Height}^2(\mathrm{m}^2) / Z(\Omega)$$

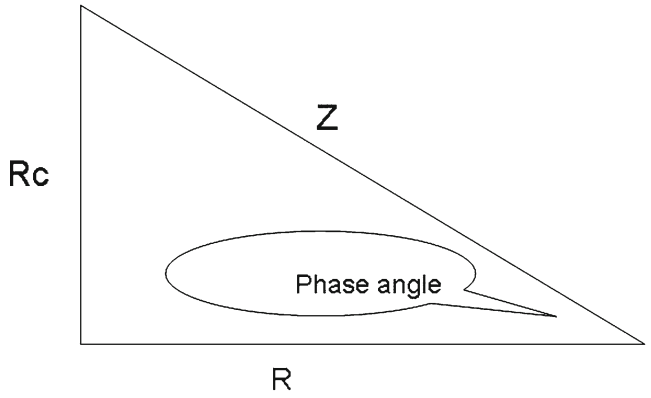

Fig. 25.1 Geometric relation among resistance (*R*), reactance (*Rc*), and the phase angle

The correlation between impedance (*Z*), resistance (*R*), and reactance (*Rc*) is observed in Fig. 25.1 (Brazier 1935). The reactance *Rc* varies with frequency. At very high or very low frequencies, Rc tends to zero and *Z* equals *R*. However, at intermediate frequencies,

$$Z = (R^2 + \mathrm{Rc}^2)^{1/2}$$

$$\text{Phase angle} = \operatorname{arctg}(\mathrm{Rc} / R)$$

The resistance *R* measures the opposition of biological materials to the flow of electric current and depends on both the physical nature and the section of the conductor. Consequently, if we accept that the human body consists of the sum of several cylinders connected in series, those that correspond to the extremities have a lower cross section than the trunk and, thus, the resistance will be higher in the former than in the latter.

Rc is determined either by the dielectric properties of tissues or by the temporary accumulation of charges on cell membranes, as the latter behave as capacitors. From an electrostatic viewpoint, this means that the lipid bilayer prevents the passage of alternating current. If frequency is high, the current will cause a change in polarity in membranes, pass through them, and flow through both the extra- and intracellular liquids. Conversely, if we apply a low-frequency current (50 kHz), it will only flow through the extracellular water and cannot go through cell walls.

25.3 Types of Body Composition Analyzers

We can apply two criteria of classification, which are interrelated: first, according to analyzers which operate at one or more frequencies and, second, according to the number of electrodes which are placed on the individual. The analyzers can be single frequency, for example when these use a single-frequency range (50 kHz). These were breakthrough devices but have the disadvantage that they are incapable of measuring intracellular water. However, analyzers that work with various frequencies (e.g., 50, 100, and 200 kHz) can measure the water both inside and outside cells.

Depending on the number of electrodes that are placed on the individual, analyzers can be bipolar (two electrodes), tetrapolar (four electrodes), and octopolar (eight electrodes). In the bipolar case,

there are two possibilities: one where both electrodes are placed on the so-called upper body and the device is held with both hands, and the other where electrodes are placed on the lower body, that is, on the feet (these are called scale type).

With tetrapolar analyzers, it is necessary to control electrode location and follow certain instructions (Lukaski et al. 1985; Callejo 2007). Thus, all electrodes should be placed on the right side, and of the two that are receptors, one is on the wrist (halfway between the ulnar and radial epiphysis) and the other is located on the ankle (between the medial and lateral malleolus). Similarly, transmitters are located 4 cm from receptor, in the direction of the phalanges.

The individual must be lying horizontally, with arms and legs open at angles of approximately 10–15°. Other factors, such as room temperature, the individual's hydration status, and the menstrual cycle phase, must also be controlled (Callejo 2007).

Octopolar analyzers use eight electrodes, two of which are placed on each foot and the other two are placed on each hand. This technique (often called segmental) also determines the body composition of each individual segment of the body, namely the trunk, the right arm, the left arm, the right leg, and the left leg.

25.4 BIA Equations

In the literature, multiple regression equations have been reported that vary depending on the characteristics of the population analyzed for age, sex, ethnicity, body mass index, etc., and the analyzer used. In these equations, *TBW* and *FFM* were calculated from the value of *Z* or *R* (*Rc* is usually ignored), although most use the resistance. Tables 25.1 and 25.2 show some of the equations recommended by Houtkooper et al. (1996) and Ellis (2000) to calculate, respectively, the TBW and the FFM. The devices used to develop these equations are tetrapolar (except in the work of Boulier et al. 1990, where bipolar device was used) and single frequency at 50 kHz. Also, many formulations have used the so-called impedance index (height^2/resistance (Ht^2/R)) discussed earlier. Table 25.3 contains some formulas recommended by Bray et al. (2001), especially for children.

From *TBW*, *FFM* is calculated using the Siri (1961) equation:

$$\text{TBW} = \text{FFM} \times 0.73$$

Table 25.1 BIA regression equations for TBW (From Houtkooper et al. (1996) and Ellis (2000))

	Age (years)	
Author	*N*	Equation TBW
Kushner and Schoeller (1986)	17–66	0.5561 Ht^2/*R* + 0.0955 Wt + 1.726 (both sexes)
	40	
	20	0.382 Ht^2/*R* + 0.105 Wt + 8.315 (females)
	20	0.396 Ht^2/*R* + 0.143 Wt + 8.399 (males)
Kushner et al. (1992)	2–67	0.593 Ht^2/*R* + 0.065 Wt + 0.04 (both sexes)
	116	
Lukaski and Bolonchuck (1988)	20–73	0.372 Ht^2/*R* + 3.05 sexes + 0.142 Wt – 0.069 age + 4.98 (both sexes)
	53	
Lukaski and Bolonchuck (1988)	20–73	0.374 Ht^2/*R* + 0.151 Wt – 0.083 years + 2.94 sexes + 4.65 (both sexes)
	57	

sex = 1 (male) and 0 (female)
Ht height (cm), *Wt* weight (kg), *R* resistance, *Age* decimal age

Table 25.2 BIA regression equations for FFM (From Houtkooper et al. (1996) and Ellis (2000))

Author	Age (years) N	Equation FFM (kg)
Lukaski et al. (1986)	18–50	0.821 H^2/R + 4.97 (females)
	67	
	47	0.827 H^2/R + 5.21 (males)
Segal et al. (1988)	17–62	0.00108 H^2 – 0.02090 R + 0.23199 Wt – 0.06777 age
	498	+ 14.59453 (females)
	1069	0.00132 Ht^2 – 0,04394 R + 0.30520 Wt – 0.16760 Edad + 22.66827 (males)
Gray et al. (1989)	19–74	0.00151 Ht^2 – 0.0344 R + 0.140 Wt – 0.158 age
	62	+ 20.387 (females)
	25	0.00139 Ht^2 – 0.0801 R + 0.187 Wt + 39.830 (males)
Boulier et al. (1990)	22–71	0.40 Ht^2/R + 0.64 Wt – 0.16 Edad + 6.37 – 2.71 Sexe
	202	(both sexes)
Van Loan et al. (1990a)	18–32	0.50 Ht^2/R + 0.37 Wt + 1.93 Sexes + 3.12 (both sexes)
	150	
Van Loan et al. (1990b)	18–32	0.53 Ht^2/R + 0.29 Wt + 1.38 Sexe + 4.40 (both sexes)
	150	
Lohman (1992)	18–30	0.476 Ht^2/R + 0.295 Wt + 5.49 (both sexes)
	153	

Sex = 1 (male) and 0 (female) excepting in Boulier et al. (1990) in which sex = 1 (male) and 2 (female)
Ht height (cm); *Wt* weight (kg); *R* resistance; *Age* decimal age

Table 25.3 BIA regression equations for FFM in children. (From Bray et al. (2001))

Authors	Age (years) sex	Equation FFM
Deurenberg et al. (1990)	7–9	FFM = 0.640 (H^2/R) + 4.83
	both sexes	
Deurenberg et al. (1990)	10–12 ♀	FFM = 0.483(H^2/R) + 0.221 (W) +
	10–15 ♂	0.1277(H) – 14.7
Deurenberg et al. (1990)	♀ >13	FFM = 0.258 (H^2/R) + 0.375 (W) + 6.3
	♂ >16	(sex) + 10.5 (H) – 0.164 (age) – 6.5
Deuremberg et al. (1990)	7–25	FFM = 0.438 × 104 (H^2/R) + 0.308 W
	both sexes	+ 1.6 sex + 7.04 H – 8.5
Goran et al. (1996)	6	FFM = 0.15 (Sub) + 0.36 (W) + 0.12 (Tri)
	both sexes	– 0.2 (H^2/R) – 2.3
Schaefer et al. (1994)	3–19	FFM = 0.65 × H^2/R + 0.68 × age (years) +
	both sexes	0.15
Cordain et al. (1988)	9–14	FMM = 6.86 + 0.81 × H^2/R
	both sexes	

Sex: 1 (males) and 2 (females)
W weight (kg), *H* height (m), *R* resistance (ohmnios), *Tri* tricipital skinfold (mm), *Sub* subescapular skinfold (mm)

25.5 Statistical Methods to Establish the Agreement Between BIA and Anthropometry

Anthropometry and bioimpedance are analytical methods that are based on different fundamentals. Various methods, devices, and BIA equations have been explained previously. It is therefore necessary to ascertain whether the results obtained by using different techniques and devices can be equated.

Table 25.4 Direct measures and composition estimators obtained by anthropometry, bipolar BIA, and tetrapolar BIA in a sample of Spanish youngsters (Marrodán et al. 2007)

	Males			Females		
Variables	Mean	SD	Máx.–Mín.	Mean	SD	Máx.–Mín.
Age (years)	21.48	3.11	31–18	20.59	2.48	32–17
Weight (kg)	76.58	11.98	105.5–51.1	58.10	8.33	92.4–42.0
Height (cm)	176.75	5.26	186.3–164.2	161.61	5.47	174.0–150.2
Triceps skinfold (mm)	9.81	6.57	33.2–3.0	14.82	5.06	33.0–6.4
Bíceps skinfold (mm)	5.66	2.39	11.2–2.4	7.96	3.33	19.0–2.2
Subescapular s. (mm)	12.45	5.67	31.0–5.6	12.33	5.19	31.2–4.0
Suprailiac s. (mm)	12.49	7.74	34.0–4.2	12.33	5.44	32.2–3.2
% Body Fat A	15.21	5.45	27.97–6.08	25.03	4.76	37.11–11.41
% Body Fat H	18.69	6.28	32.30–8.70	20.25	5.96	34.10–8.7
% Body Fat O	18.39	6.77	34.50–7.20	26.96	6.14	44.70–13.40
% Body Fat B	24.30	8.36	44.10–13.20	26.19	6.40	44.60–14.30
Fat Mass A (kg)	11.96	5.88	25.39–4.42	14.71	4.42	27.84–4.79
Fat Mass H (kg)	14.42	6.38	32.30–4.80	12.17	4.57	25.58–4.11
Fat Mass O (kg)	14.80	7.33	36.40–4.49	15.73	4.45	26.18–7.21
Fat Mass B (kg)	19.10	9.35	44.10–8.47	15.89	5.97	35.11–6.01
Fat Free Mass A (kg)	64.62	8.21	80.11–46.68	43.39	4.83	66.93–35.33
Fat Free Mass H (kg)	60.91	7.83	77.09–46.30	46.68	5.33	70.22–36.26
Fat Free Mass O (kg)	62.69	5.98	74.54–50.43	42.36	6.18	70.96–31.92
Fat Free Mass B (kg)	56.21	5.27	65.76–41.95	42.87	4.16	57.29–33.52

A Anthropometry; *H* Holtain; *O* Omron; *B* Scale

It is necessary to apply appropriate statistical tests to make this comparison. One of these is based on the intraclass correlation coefficient (*ICC*), calculated as follows:

$$\mathrm{ICC} = \left(\mathrm{SD}_{\mathrm{A}}^2 + \mathrm{SD}_{\mathrm{B}}^2 - \mathrm{SD}_{\mathrm{AB}}^2\right) / \left(\mathrm{SD}_{\mathrm{A}}^2 + \mathrm{SD}_{\mathrm{B}}^2 + \mathrm{X}_{\mathrm{AB}}^2 - \left(\mathrm{SD}_{\mathrm{AB}}^2 / n\right)\right)$$

In the above expression, SD_A, SD_B, and SD_{AB} are the standard deviations of the methods A (anthropometry), B (BIA), and the difference between both methods, respectively; X_{AB} is the mean of the differences between both methods and n the number of individuals. This coefficient has values between 0 and 1. It is considered that ICC higher than 0.75 indicates a close agreement between the two methods being compared, values between 0.4 and 0.75 indicate that the agreement is fair to good, and those less than 0.4 indicate the absence of concordance. Another method is the graphical model of Bland and Altman (1986) employed to visualize changes in the differences between the values obtained by anthropometry and BIA (*Y* axis), depending on the mean value obtained by applying both methods (*X* axis).

As an example, Table 25.4 shows the results of a comparative study in which the authors (Marrodán et al. 2007) analyzed, in 106 young adults, body composition by anthropometry and BIA. The equations used were those given by Durnin and Womersely (1974) for density and by Siri (1961) for fat percentage. Three BIA techniques were used: bipolar electrodes to the hands (OMRON BF-306 analyzer), bipolar electrodes to the feet (LAICA EP1340 analyzer), and tetrapolar BIA (Holtain BC analyzer).

In the male series, a greater fat percentage is obtained with all BIA analyzers than with anthropometry. The OMRON bipolar device and the tetrapolar device show very similar results. In the female series, the lowest mean value for fat percentage is obtained with tetrapolar BIA. Both bipolar devices show similar adiposity results and only slightly higher than those obtained by anthropometry.

Table 25.5 Intraclass correlation coefficient (ICC) for the percentage of fat obtained by anthropometry and the three techniques BIA (bipolar OMRON, bipolar scale LAIKA, and tetrapolar BODYSTAT)

	CCI males	CCI females
Anthropometry – Holtain	0.59	0.41
Anthropometry – Omron	0.73	0.54
Anthropometry – Scale	0.33	0.69

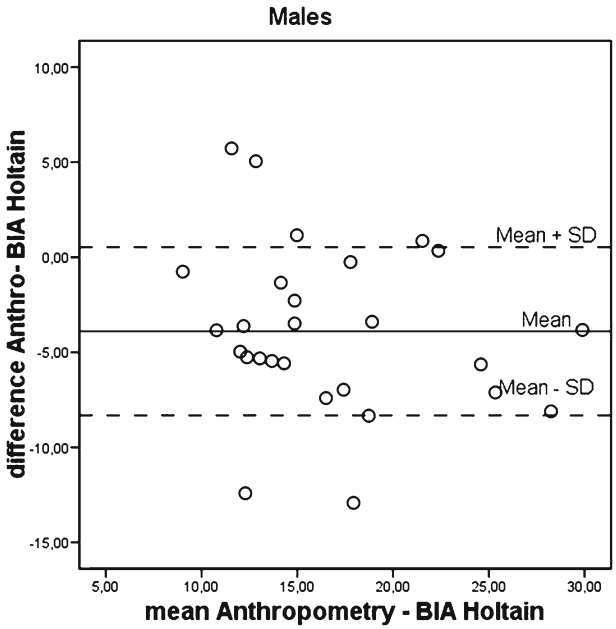

Fig. 25.2 Differences between anthropometry and BIA (Holtain) in males

Table 25.5 shows the intraclass correlation coefficients. The agreement between anthropometry and tetrapolar BIA was better in males. Comparing anthropometry and bipolar BIA, the correlation is higher with the hand analyzer OMRON in males, and with the scale type analyzer (LAIKA) in females. How can we explain these results? Bipolar monitors, also called regional monitors, produce results that depend on fat distribution on the subject analyzed. This means that these results vary, depending on whether the fat is situated on the upper or lower body. In contrast, the tetrapolar analyzer simultaneously evaluated both segments, producing values independent of the preferential location of fatty deposits. To clarify this, it must be borne in mind that, with age, men and women accumulate fat differently. Therefore, scales that take information from the electrodes placed on the feet better reflect the accumulation of fat in the legs, thighs, and buttocks of the female sex. The conclusion is a better match between the fat percentage obtained by BIA scales and the anthropometry in females. However, in males, where fat is deposited preferentially in the region of the thorax and abdomen, the results of fat percentage measured with the OMRON hand analyzer show better agreement compared to the anthropometric method.

The scatter plots resulting from using the Bland and Altman method show different trends according to sex and the BIA technique used. Figures 25.2–25.7 show that the general trend in differences between anthropometry and BIA is always negative for the male series. This means that the

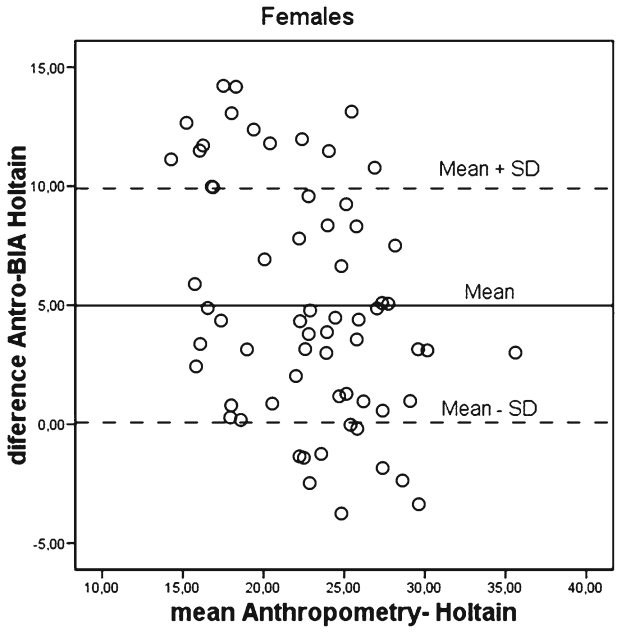

Fig. 25.3 Differences between anthropometry and BIA (Holtain) in females

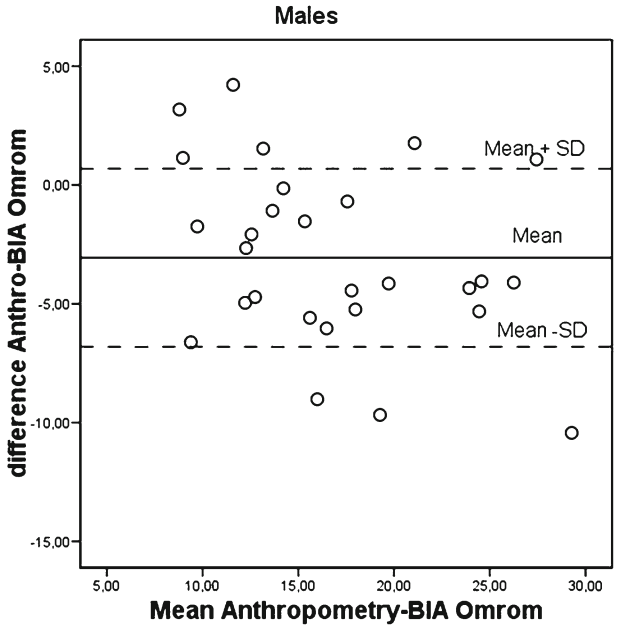

Fig. 25.4 Differences between anthropometry and BIA (OMRON) in males

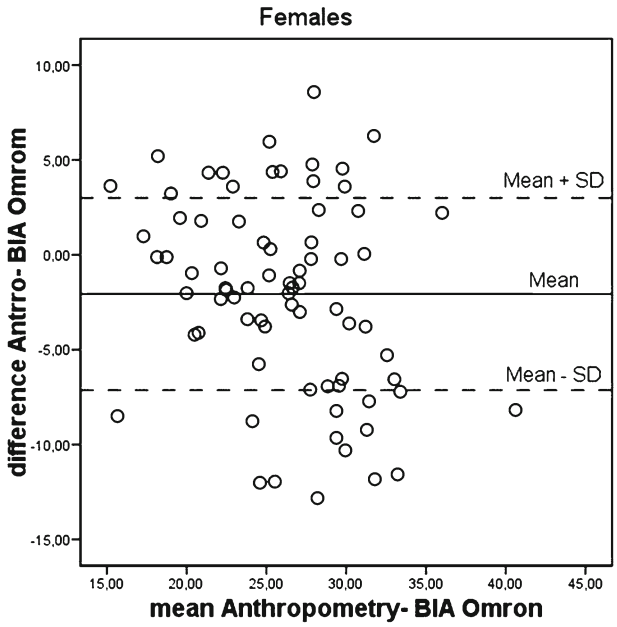

Fig. 25.5 Differences between anthropometry and BIA (OMRON) in females

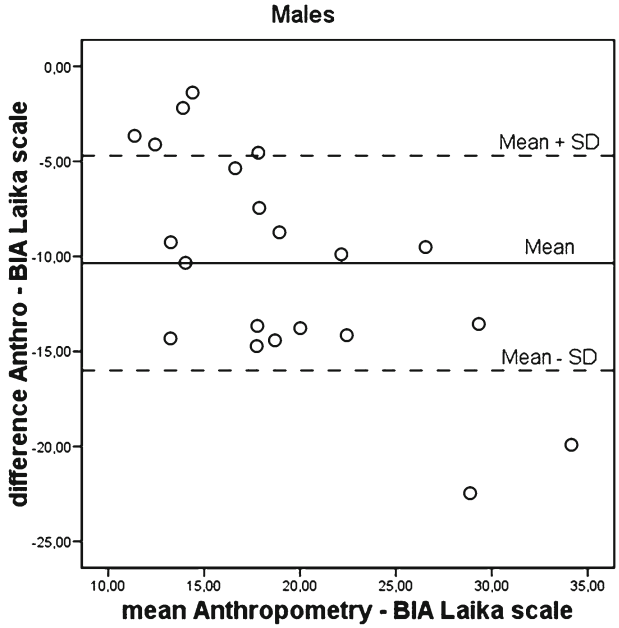

Fig. 25.6 Differences between anthropometry and BIA (LAIKA scale) in males

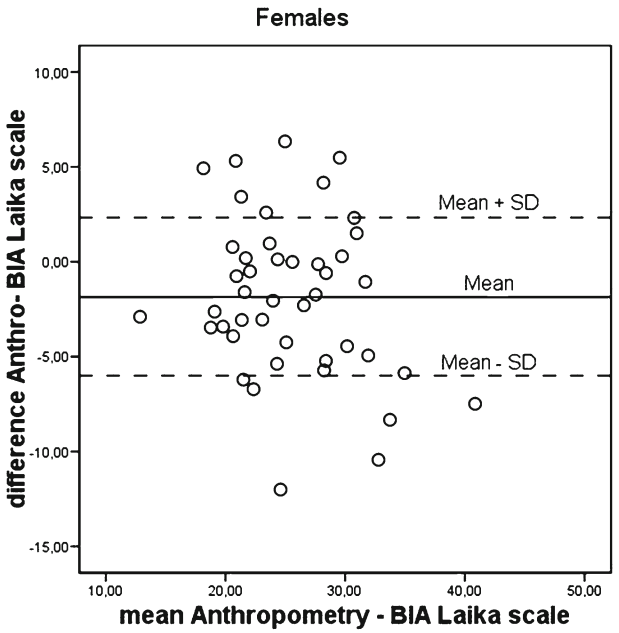

Fig. 25.7 Differences between anthropometry and BIA (LAIKA scale) in females

relative adiposity value is always higher in men when measured by a BIA technique. In the female series, the difference between anthropometry and tetrapolar BIA is usually positive. With bipolar analyzers, differences are close to zero, and take negative values only for higher fat percentages. This means that the tetrapolar analyzer usually offers lower fat percentage results than those obtained through anthropometry. With respect to bipolar devices, both offer adiposity values very similar to those calculated by the Siri equation (1961).

As a second example, results obtained by authors on analyzing body composition by anthropometry and tetrapolar BIA in 86 schoolchildren of both sexes are provided. The anthropometric equations used were those given by Durnin and Womersely (1974) for body density and by Siri (1961) for fat percentage. Tetrapolar BIA was applied using a Bodystat 1500 analyzer. This device directly provides the fat percentage value. It also provides the impedance value in ohms at a fixed frequency of 50 kHz, and this allows another estimate of fat percentage to be made by applying an equation. For this case, the Deurenberg et al. (1991) formula for fat free mass (FFM) was applied:

$$\mathrm{FFM} = 0.438 \times 10,000 \times \mathrm{H}^2 / \mathrm{I} + 7.04 \times \mathrm{E} + 0.308 \times \mathrm{W} + 1.6 \times \mathrm{S} - 8.5$$

H = height (m), W = weight (kg), I = impedance (ohms), S = sex (value 1 for males and 2 for females).

From this value, and knowing the total weight, fat mass (*FM*) was obtained.

Table 25.6 shows the results: first, with the Siri anthropometric equation (1961); second, with the BIA analyzer directly; and third, applying the BIA equation of Deurenberg et al. (1991) to the impedance value in ohms. Compared with anthropometry, BIA overestimated fat in the male series and slightly underestimated it in the female series. The values of ICC show that, between anthropometry and direct BIA, the correlation is very low in male series and is acceptable in female series. When using the Deurenberg et al. (1991) equation, the correlation increases: it is acceptable for the female series and good for the male series (Table 25.7).

Table 25.6 Body fat percentage obtained by different techniques in a sample of 86 Spanish children

	% BF males		% BF females	
Method	Mean	SD	Mean	SD
Anthropometry Siri (1961) equation	17.31	5.84	24.45	5.53
Direct-BIA	19.66	5.75	23.74	5.65
BIA Deuremberg et al. (1991) equation	24.14	9.28	22.11	7.13

Table 25.7 Agreement between anthropometry (Siri 1961) and BIA techniques in a sample of 86 Spanish children

	ICC males	ICC females
Siri-Direct-BIA	0.30	0.43
Siri-BIA Deuremberg et al. (1991) equation	0.73	0.50

The results obtained by the authors in the two cases described suggest that BIA underestimates body fat in relation to anthropometry in females, and overestimates it in males, both children and adults. The results alsoshow that there is better agreement between anthropometry and bipolar BIA with electrodes placed on the hand in males. In contrast, anthropometry correlates more consistently with the bipolar BIA technique with electrodes placed on the feet in females. Finally, agreement between methods decreases as the degree of adiposity of individuals increases.

Lukaski and Siders (2003) and Sun et al. (2005) report an overestimation of the body fat percentage obtained from tetrapolar BIA regarding anthropometry in both sexes. They also note, as does this study, that differences between methods are accentuated in cases of high fat percentage. According to experts such as Fors et al. (2002), the BIA method would have no validity in obese children with high fat rates. Rowe et al. (2006) also find that the correlation between anthropometry and whole-body bioelectrical impedance in children and adolescents decreases with increasing adiposity. However, Goldfield et al. (2006) arrive at opposite results, noting that the scale BIA or foot-to-foot method is appropriate for estimating body composition in obese adults and children, due to its great concordance with the DEXA (dual-energy X-ray absorptiometry) technique. Casanova et al. (2004), obtaining a high ICC between anthropometry and tetrapolar BIA between 6- and 14-year olds (ICC > 0.75) believe that BIA is an excellent diagnostic method. Rodríguez et al. (2008) also consider that tetrapolar BIA is an appropriate method to analyze body composition in children of normal weight and aged between 4 and 6 years. Although the results discussed are partly contradictory, almost all studies show that, despite the higher or lower correlation obtained, the BIA method is not interchangeable with DEXA and anthropometry takenas the benchmark method.

There are not many publications that compare different types of bioimpedance analyzers under the same measurement conditions. Nuñez et al. (1997) and Jart et al. (2000) contrasted the scale type analyzer with the four-electrode BIA technique and obtained different results, depending on the individual age range. Lukaski and Siders (2003) observed that bipolar type BIA analyzers usually underestimate the fat percentage compared to the DEXA technique taken as the gold standard. As in the present study, the correlation between the reference method (anthropometry and DEXA) and the scale is greater for females and, in contrast, there is a greater interrelation between the fat percentage results obtained by the OMRON hand analyzer in males. Other comparative research, such as Dittmar (2003), found significant individual differences in estimating relative adiposity measured by any kind of bipolar monitor (e.g., OMRON BF-302 and scale Tanita BF-538 y 101-A RLJ) and detected a remarkable influence of factors, such as age or gender.

25.6 Applications to Other Areas of Health and Disease

Today, body composition assessment is useful in the clinical, epidemiological, and sports domains. It is essential in the diagnosis and control of obesity and malnutrition. Its use is highly desirable in diseases that seriously affect the nutritional status, such as cancer and AIDS, among others. The analysis of body composition is also useful in situations that alter the balance of body fluids, such as in patients undergoing dialysis, have severe burns, etc. In addition, body composition is a fundamental tool in athlete selection, training monitoring, and exercise planning.

Anthropometry should be applied by trained and experienced personnel. In particular, the measurement of subcutaneous adipose skinfolds is relatively difficult for untrained professionals. Compared to anthropometry, BIA appears to be a simpler and faster method. However, it also has disadvantages. Not all BIA models incorporate in their software prediction formulas applicable in different population groups: children, adults, seniors, athletes, etc. On the other hand, only multiple-frequency analyzers can differentiate intracellular and extracellular water. Also, there are no reference values for all BIA analyzers. Given the above, researchers and health professionals should choose the BIA device that best fits their needs.

25.7 Conclusions

The main aim of this chapter was to compare multiple measurement techniques, devices, or equations to obtain body composition estimators, in a given sample. Several conclusions emerge from the results obtained in the two examples discussed together with the contributions from the literature.

BIA methods are acceptable enough to use in epidemiological studies of nutritional assessment. However, it is necessary to take several considerations into account. Bipolar monitors, also called regional monitors, produce results that depend on fat distribution in the individual. This means that the results vary, depending on fat location in the upper or lower segment of the body. In contrast, with a tetrapolar analyzer, both segments are evaluated simultaneously and this device offers values independent of the localization of fat deposits. The final result is a better match between fat percentage obtained by the scale type BIA analyzer and anthropometry in females and between the hand type BIA analyzer and anthropometry in males. Tetrapolar devices are more accurate in the pediatric age group.

The discrepancy of results at individual, ontogenetic, and gender levels, particularly with bipolar monitors, implies limitations for use in clinical diagnosis, as there are no appropriate standards for each population, gender, and age. It would therefore be highly desirable to develop standards that could be provided to professionals as a reliable benchmark when using any of the devices.

Summary Points

- The methods of bioelectrical impedance analysis (BIA) are increasingly used to estimate body composition. Nowadays, both BIA and anthropometry are used for this purpose. It is necessary, however, to know whether the results obtained by the two techniques are comparable.
- The basis of BIA is the least resistance to the passage of an electric current (low-intensity, low or medium frequency) of the fat-free mass (FFM) compared with adipose tissue or fat mass (FM).
- Single-bioimpedance analysis (S-BIA) devices have only one frequency (usually 50 kHz) for the induction of current. These analyzers allow us to distinguish fat mass from fat-free mass.

Multiple-biompedance analysis (M-BIA) devices use a broad spectrum of frequencies (1–1,500 kHz) and also enable us to differentiate the volumes of intra-and extracellular water.

- Numerous specific BIA equations for age, gender, population, and type of device have been published. Most of these formulas calculate total body weight (TBW) or fat-free mass (FFM) from the impedance index (HT^2/R).
- Intraclass correlation coefficient (ICC) and the graphic method of Bland and Altman are appropriate statistical tests for estimating the agreement between BIA and anthropometry. Also, these tests are useful for comparing results obtained by different types of BIA analyzers.
- BIA methods are useful for assessing body composition in both healthy subjects and patients. In some cases, M-BIA also measured the kinetics of body fluids. Therefore, BIA methods are a good tool in the medical field (clinical and epidemiological) and for monitoring sport.
- S-BIA devices are valid for population studies in adulthood. To study children and adolescents, it is necessary to use M-BIA. For clinical use, M-BIA devices (with four or eight electrodes) are recommended.

Key Concepts

- Anthropometric methods for the analysis of body composition are primarily based on the measurement of subcutaneous fat skinfolds. Bioimpedance analysis (BIA) is based on the resistance of body components to an electric current. Impedance is low in lean tissues, which are mainly composed of intracellular fluids and electrolytes. Impedance is high in fat tissue and is proportional to total body water. Anthropometry cannot assess the changes in hydration levels that the BIA methodology can detect.
- Anthropometry and BIA are two techniques that are used in the assessment of nutritional status. The results obtained by either procedure are comparable only if there is a significant degree of concordance between them. Appropriate statistical tests for this purpose are the intraclass correlation coefficient (ICC) and the Bland–Altman graphic method. A high ICC (>0.75) does not mean that the two methods are interchangeable.
- In adult females, relative adiposity measured by anthropometry shows better agreement with body fat percent assessed by single bipolar BIA (S-BIA) foot-to-foot. In adult males, relative adiposity measured by anthropometry shows better agreement with body fat percent assessed by single bipolar BIA (S-BIA) hand-to-hand. The results obtained by multiple BIA of four or eight electrodes (M-BIA) are independent of adiposity distribution of fat and fit better with anthropometry in both genders. In children, only M-BIAsare appropriate for assessing body composition.
- In BIA, low frequencies cannot pass through cell membranes and detect only extracellular water. High frequencies cross cell membranes and detect extracellular and intracellular water. S-BIA devices work at 50 kHz, but M-BIA operates at various frequency ranges: 5–200 kHz. These latest devices are best for clinical use in monitoring diseases that alter body hydration.

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Part V
Regions and Anatomical Areas of the Body: Head and Face

Chapter 26
Fetal Head Circumference as an Anthropometric Index

Emmanuel Stephen Mador, Josiah Turi Mutihir, and John Oluwole Ogunranti

Abstract The present chapter focuses attention on head circumference measurement – an anthropometric parameter – in growing fetuses using ultrasound machine. This is to provide information and glimpse into the nature of the growth velocity during fetal development and to suggest the need for its further studies in the future. Head circumference has been implicated in various conditions and is related to brain size, brain development, intelligence, maternal nutrition, ethnic group and race. It is also of interest in certain clinical conditions such as macrocephaly or indeed microcephaly. More importantly it is a clinical anthropological parameter, by which we determine variations from one location to another or one race or ethnic group to another. In the emerging field of sonographic or ultrasonic embryology, it is a vital tool in the diagnosis of congenital anomalies. When compared with rates in other studies we see differences, which can be explained on the basis of nature and nurture. Needless to say that head circumference follows a bell shaped pattern of growth known for neural tissues and correlates very well with fetal brain growth pattern. But its significance in early maturation of the brain, and its higher values for African babies when compared to other races necessitates the need for further understanding of racial or genetic factors that determine its growth and ipso facto, its relationship to intelligence. This review provides extensive data for head circumference of 13,740 African (Nigerian) fetuses and suggests that early maturation of head circumference in African children vis-a-vis European, is a genetic rather than nutritional factor. Postnatal development however is probably dependent on nutrition and environment rather than genes.

Abbreviations

AC	Abdominal circumference
BPD	Biparietal diameter
cm	Centimeter(s)
CRL	Crown-rump length
FL	Femur length
GSD	Gestational sac diameter
HC	Head circumference
IUGR	Intrauterine growth retardation
mm	Millimeter(s)

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_26,

N	Universal population
n	Sample size
OFD	Occipitofrontal diameter
SD	Standard deviation
SEM	Standard error of mean
TORCH	Acronym for toxoplasmosis, rubella, cytomegalovirus and herpes infection

26.1 Introduction

One of the most important measurements in the evaluation of fetuses is the circumference of the head because this parameter is related to intracranial volume and it permits an estimation of the rate of brain growth. Head circumference (HC) became a useful tool for researchers/anthropometrists in determining the characteristics of human intelligence since Galton (1988) and more so in recent times. In addition, just like growth charts used to monitor the adequacy of nutrition, it will become the anthropometric parameter of the future to determine the adequacy of the development of the brain and ipso facto, intelligence. Head circumference measurement in pregnancy using ultrasound has always been recognized as an established method of assessing fetal growth (Hadlock et al. 1982), dating pregnancies (Callahan et al. 2003), and in the detecting fetal abnormalities (Baker 2001; Woo 2006). It is one of the multiple fetal anthropometric parameters used in obstetrics and sonographic embryology. In this chapter, evidence for the utility of HC as an anthropological parameter (anthropometry), which has variational attributes between geographically separate communities and must require the procurement of normal average values for each community, is presented in an anthropological manner. Furthermore, the HC of contemporary growing fetuses in Nigeria is examined as a prelude to prescribing normal values of HC for the present generation of Nigerian (African) fetuses. Comparisons using HC values obtained in other parts of the world, as reported by previous investigators.

26.2 Head Circumference as an Anthropological Parameter

Physical (biological) anthropology has been the major natural scientific backbone of medical clinical anthropology, and it derives its inspiration from the sciences of Darwinism, Mendelian genetics, embryology, and anatomy. Physical anthropology has been applied differently in different populations. Biological anthropology has changed from the primitive man's basic knowledge to a variety of formidable data about man and his physical characteristics in various societies and places. Anthropometry is a major branch of biological anthropology, and HC is considered a basic feature of anthropometry, which is dependent on both environmental and genetic influences (of a polygenic inheritance nature rather than a simple Mendelian), as all other anthropometric parameters known to man. Head circumference was utilized earlier to denote proper development of the fetus. It remains one of the most important anthropometric parameters of biological anthropology. In estimating fetal weight during intrauterine life, HC is used in conjunction with other fetal parameters, such as biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL). Since Morley (1977) said, "weight charts…form the most convenient estimate of a fetus/child's nutrition and health…" it follows that Morley's approach forms a basis for implicating anthropometry in modern medical practice. It proves that physical anthropological characteristics such as HC can be highly valuable as health indicants or concomitants (Morley et al. 1968). Morley's approach to the study and utility of

weight in clinical practice (Morley 2001) has been examined and found to be a pioneering effort in clinical anthropology (Ogunranti 1987; Nwokoro et al. 2006). This science can be recognized as an applied branch of medical anthropology that has direct relationship with the clinical situation for diagnosis and treatment of patients.

With this definition of clinical anthropology, we just have to associate the clinical utility of HC and its anthropological attribute in order to understand the value of HC as a clinical anthropological parameter. Although the erstwhile approach to clinical anthropology is highly culturally oriented (Kleinman 1980; Ogunranti 1995; Rush 1996), we have formulated a revised form of clinical anthropology, which includes biological data as it affects the developing world (Ogunranti 1986; Rush 1996; Loustaunan and Sobo 1997; Martínez-Hernáez 2008). In view of this factor, one can relate Morley's approach to obtaining weight for clinical utility as a pathbreaking effort in clinical anthropology in general, and our endeavor in procuring normal values for HC in the growing fetus as another effort in clinical anthropology. Ogunranti (1994), taking the cue from Morley in the 1980s, suggested the need for a biologically oriented clinical anthropology, and provided considerable anthropometric data of Nigerians, which proved useful for them in the 1980s and 1990s (Ogunranti 1995).

26.3 Concept of Clinical Anthropology and Head Circumference

Clinical anthropology began as a discipline that recognized the input of medical anthropology in modern health care (Kleinman 1980; Rush 1996). Kleinman, in a series of writings, advanced arguments for the use of medical anthropological information in treatment and diagnosis of diseases in the Western setting. He described this as clinically applied medical anthropology. Medical anthropology, on the other hand, is a discipline that recognizes variation in human adaptive arrangements in relation to medicine and medical systems, and human confrontation with disease and illness (Landy 1977). It therefore recognizes variation in medical systems and medicine in different cultures (Janzen 2002; Martínez-Hernáez 2008). It is strongly linked to cultural modes of diagnosis and treatment of diseases. When such information related to cultural beliefs and attitudes toward sickness and the state of being unwell is applied to the treatment of a patient from a similar environment under the Western system, the technique islabeled as clinical anthropology (Ember 2004).

Our own extension of clinical anthropology has included biological anthropology, as variations do exist for data from culture to culture and community to community. Thus, if the HC of a fetus from Jos in North Central Nigeria is lower than the normal average value of the same for his age obtained at Edinburgh, we can look at the normal values of the Jos's fetuses in order to determine whether such a fetus is abnormal or not. This is the central thesis of biologically derived clinical anthropology, and the thrust of the present concept on anthropometry (Ogunranti 1995; Boixareu 2008).

26.4 Head Circumference as a Growth Parameter

Growth, which is a combination of multiplicative, auxetic, and accretionary parameters, measures the total increase in size of the whole organism. The phenomenon is studied by a growth chart in fetuses or in growing children. The most commonly used parameter to measure growth in the fetus includes BPD, HC, AC, and FL. The first idea about growth chart came from a child research project, which was instituted in New Castle, England. Tanner et al. (1966) prepared cross-sectional standards for weight (attained at each age in English boys and girls), which are widely used as standards today and as comparison figures all over the world. In the USA, extensive studies on height and weight were

conducted on children by Simmons (1944). This was followed by a larger survey, of white and black children, from 1970 to 1976 (Hamil et al. 1976). In Nigeria, the first longitudinal growth study was conducted in Imesi-Ile, Western Nigeria in 1959. Cunningham (1969) compared the growth charts derived from weight studies as compiled by Morley in 1959 for Imesi-Ile and a neighboring village of Oke-Imesi. Collis et al. (1962) obtained figures for 200 children of ages 1–8 years living around Ilesha in western Nigeria, and compared these with figures obtained in Pankshin, the Plateau State of Northern Nigeria. A recent study of Nwokoro et al. (2006) uses a modern approach as well as longitudinal study in western Nigeria.

Fetal growth is defined as the time-dependent changes in body dimensions that occur during the pregnancy. The growth rate of various parameters is rapid especially in the 1st and 2nd trimesters; the parameters change significantly with the advancement of pregnancy, and must be evaluated against the normal value at that age. Fetal anthropometry can be carried out by cross-sectional or longitudinal studies. For a cross-sectional study, fetuses are examined only once during the gestation period. This type of study can be performed over a small period of time, and the data are easier to collect and analyze statistically. A longitudinal study, on the other hand, is one in which a small number of fetuses are investigated serially, at least thrice during the course of pregnancy. This study necessitates that the same fetuses be scanned during the whole gestation, which increases the time needed for data collection considerably, and calls for high motivation on the part of both the mother and the investigator. The growth pattern in HC is the so-called neural growth that follows the pattern of brain growth. It is bell shaped as opposed to reproductive organ growth, which is sigmoid in shape.

26.5 Ultrasonic Embryology 1: Head Circumference as a Parameter of Dating Pregnancy

Ultrasonic embryology is an emerging field which studies the fetus to provide descriptive embryological data and the prediction or diagnosis of congenital anomalies by the application of ultrasound technology. Head circumference is a very useful parameter in ultrasonic embryology as it can be used to predict congenital anomalies as well as embryological dating and clinical staging/dating of pregnancy.

Multiple fetal anthropometric parameters are available to predict the gestational age. These include measurement of gestational sac, crown–rump length (CRL), fetal BPD, HC, occipitofrontal diameter (OFD), AC, and FL.

26.5.1 Frequently Used Parameters

Gestational Sac Diameter (GSD): The gestational or pregnancy sac is usually visible on ultrasound scan at about 5 weeks after the last missed period. The sac may be circular, oval, or even elliptical in shape, with an echogenic margin. An embryonic pole can usually be seen after 6 weeks, and the cardiac flicker is picked up with a real-time scanner (Palmer 1995). GSD has been reported as the first ultrasonic parameter to be used for confirmation of pregnancy.

Crown–rump Length (CRL): Crown–rump length is one of the most reliable ultrasonic anthropometric parameters, and is used in the first trimester. By 7 weeks, the embryo is clearly seen in the gestational sac, and its CRL can be measured in long axis. By this time, the yolk sac can be seen in relation to the

ventral surface of the embryo. The presence of the yolk sac is deemed to be an encouraging sign of fetal well-being, and it remains visible until about 10 weeks of gestation (Hadlock et al. 1992).

The CRL is utilized for estimation of gestational age up to the 11th week, with accuracy in 95% of cases within 2.7–4.7 days. After that, the curvature of the fetus affects the reliability of measurement; therefore, from the 12th week onward, the BPD is considered to be more accurate.

Biparietal Diameter (BPD): This parameter is used in the second trimester, from the 12th week onwards. It measures the maximum distance between the two parietal bones taken from the leading edge of the skull to the leading edge, that is, outer to inner (Hadlock et al. (1982). It can also be measured from outer to outer table of the skull. This axial plane passes through the widest portion of skull where the continuous midline echo of falx cerebri is broken by the cavum septum pellucidum with both the thalami enclosing the slit-like opening of the 3rd ventricle of the brain. Studies report that the growth of the BPD in the mid trimester is linear and rapid, and biological variation at each week of gestation is small. The measurement of BPD from 14 to 26 weeks predicts the correct duration of gestation to the extent of ±9 days in 95% of cases; however, the measurement of the parameter in second trimester (16–20 weeks) routine scan is performed in all good antenatal care centers.

At times, when the fetal head is short and wide (brachycephaly), or long and flattened (dolicephaly), the assessment of age from BPD may be under- or overestimated. Therefore, if the shape of the head appears brachycephalic or dolicephalic, the cephalic index should be calculated. If this is found to be beyond the normal range, the HC should be used to estimate age.

Head Circumference (HC): This parameter is used in the third trimester along with other parameters such as FL. It is measured at the same level at which the BPD is taken, using the ellipsoid mode of the machine, and adjusting the elliptical calipers to the outer margin of the skull table. The accuracy of this parameter is ±2–3 weeks, with 95% confidence interval.

Abdominal Circumference (AC): This ultrasonic fetal anthropometric parameter is less commonly used for the assessment of gestational age. It is, however, more frequently used for monitoring fetal growth, especially in the third trimester, and for estimating fetal weight. The AC is taken at a level where the umbilical vein enters the left branch of portal vein; alternatively, a scan at a slightly lower level, showing a short segment of the umbilical vein, may be taken. The outline of the abdomen should be as circular as possible. Until the 36th week of pregnancy, the HC is larger than the AC; the HC: AC ratio is therefore more than 1; but, after 36 weeks, the AC catches up with the HC, and then continues to grow at a faster rate, so that the ratio of HC to AC near term becomes less than 1 (Chang et al. 2003).

Femur Length (FL): Femur length is a very useful anthropometric parameter used in the second and third trimesters of pregnancy. It grows linearly throughout, and is best measured after 14 weeks of gestation. The diaphysis is measured from the greater trochanter above, to the lateral condyle below. The outer border of femur is straight and the inner border is curved normally. The accuracy of gestational age calculation by FL is within 6–7 days of menstrual age at 95% confidence level. These four parameters are most frequently used for the estimation of gestational age, and sometimes considered as the "gold standard," and they collectively assess the gestational age to the highest degree of accuracy.

26.5.2 Less Frequently Used Parameters

Parameters, less frequently used in the discipline of fetal anthropometry, include fetal transverse thoracic diameter, thoracic circumference, and measurement of long bones, orbit and lens dimensions, and fetal binocular distance. The thoracic diameter and circumference is specially used in assessment of fetal weight.

Fetal orbit, lens dimensions, and fetal binocular distance are used to predict gestational age. The variability (±2 SD) associated with predicting menstrual age using binocular distance is ±14 days between 14 and 27 weeks, and ± 24 days between 29 and 40 weeks, respectively (Tongsong et al. 1992).

Fetal long bones are also used for the assessment of gestational age, but are more frequently in use for detecting divergence from normalcy, for example, in suspected cases of skeletal dysplasias. Bones used for the estimation of gestational age include fetal humerus, radius, ulna, femur, tibia, and fibula (Chitty and Altman 2002). The correct evaluation of gestational age is possible every 2 weeks by assessing all these bones except femur, where evaluation is possible every week before 28 weeks and every 2 weeks after 28 weeks. These biometric parameters are rarely used, as some of these are technically difficult to measure. The size of the cerebellum and transverse cerebellar diameter is considered as a useful anthropometric parameter in estimating gestational age in the second trimester. Fetal clavicular measurement is used in evaluating gestational age and estimating fetal weight. Studies suggest that the gestational age in weeks is approximately equal to the length of the clavicle expressed in millimeters. Interclavicular distance in cases of breech presentation has an added benefit in assessing the capacity of pelvis of the mother for subsequent delivery.

Fetal liver and kidney, at times, are measured for fetal anthropometry (Konge et al. 2002)**.** Parameters such as fetal scapula, sacral length, fractional spine length, foot length, fetal ear length, and the fetal nasal bones are used for dating the fetus periodically. Fetal nasal bones are used, in addition, to detect cases of trisomy 21.

26.6 Ultrasonic Embryology 2: Head Circumference as an Established Method of Detecting Fetal Abnormalities

Limitation of growth potential in the fetus, called intrauterine growth retardation (IUGR), can be either symmetrical or asymmetrical (Table 26.1). Symmetrical growth retardation implies a fetus whose entire body is proportionally small, whereas asymmetrical growth retardation implies a fetus that is undernourished and directs most of its energy to maintaining growth of vital organs, such as the brain and heart, at the expense of the liver, the muscle, and the fat. A high fetal brain-to-liver ratio manifests asymmetrical growth retardation and whereas these organs cannot be directly measured, ultrasound circumference measurement of the fetal skull and the fetal abdomen at the level of the liver can be performed, and would appear to be a logical alternative. Ratios of fetal anthropometric parameters can be useful in screening for growth retardation (Deter et al. 1987), especially when it is asymmetrical. Ratios not involving head measurements tend to be relatively constant after 20 weeks of gestation, hence, can be useful in evaluating fetuses where the dates are uncertain. The ratios of body parameters commonly used for assessing fetal development include BPD to OFD ratio, HC to AC ratio, BPD to FL ratio, thoracic circumference to AC ratio, FL to HC ratio,

Table 26.1 Key features of intrauterine growth retardation (IUGR)

1. Limitation of growth potential in the fetus is called IUGR
2. IUGR can either be symmetrical or asymmetrical
3. Symmetrical IUGR implies a fetus whose entire body is proportionally small
4. Asymmetrical IUGR implies a fetus that is undernourished and is directing most of its energy to maintaining growth of vital organs, such as the brain and heart, at the expense of the liver, muscle, and fat
5. Ratios of parameters can be useful in screening for growth retardation, especially when it is asymmetrical

This table lists the key facts of IUGR, its classifications, and diagnosis

and FL to AC ratio. These ratios can be used in the diagnosis of congenital anomalies, such as Down syndrome, dwarfism, microcephaly, achondroplasia, arthrogryposis multiplex congenital, and congenital amputee.

26.6.1 Biparietal Diameter to Occipitofrontal Diameter Ratio (Cephalic Index)

Cephalic index is the ratio of the BPD of the skull to the OFD and can detect asymmetry in the skull during development (Abuhamad 1996).

The normal range is 74–83%; <74.9% indicates a dolichocephalic skull; from 75% to 79.9% a mesocephalic skull; and from 80% to 84.9% a brachycephalic.

26.6.2 Head Circumference to Abdominal Circumference Ratio

The HC to AC ratio is useful in detecting asymmetrical growth retardation (Chitkara et al. 2000). It varies over the gestational period. When measured by ultrasound, it can differentiate between symmetrical and asymmetrical fetal growth restriction. In symmetrical fetal growth that tends to occur after 28 weeks of gestation, the head to abdomen ratio is normal, but absolute values of AC and HC are low. Common causes of symmetrical growth in the human fetus include early intrauterine infections, such as rubella, toxoplasmosis, or cytomegalovirus, maternal anemia, malnutrition, or chronic blood pressure.

Asymmetrical fetal growth is one that occurs before 28 weeks of gestation. In this case, the head grows normally (and ipso facto the HC remains normal), but the body fails to catch up. Asymmetrical growth is common in congenital anomalies and TORCH infections.

26.6.3 Head Circumference and Nutrition

It is well established that the state of the maternal nutrition influences the nutrition and subsequent growth and development of the child (Kankeow 2007). If the need arises, the fetus is, to a certain extent, provided for at the expense of the mother. For example, when the maternal intake of iron, calcium, or phosphorous is inadequate, the fetus draws on her stores for its requirements. A severe reduction in protein intake, as during starvation, will lead to a lower-than-average weight, length, and HC in the newborn (Callahan et al. 2003). When starvation is sufficiently severe, it may result in sterility of the potential mother, but abortion and malformation do not appear to increase. Infants born to mothers on a good diet during pregnancy usually have, in general, superior health and vigor during early infancy, in comparison to infants of mothers on poor diets.

Although HC can be used to determine the adequacy of nutrition in the fetus and beyond, abdominal length and FLs are better indicators of fetal weight and nutrition than other parameters, to include HC. Whatever be the case, HC can also adjudge the level of fetal nutrition, and can be used in conditions or areas in which IUGR due to starvation or inadequate diet or indeed obesity are a problem. Such conditions have been implicated in studies on kwashiorkor and marasmus, and it has been

shown that post-marasmic children tend to have lower values of HC. This does not seem to affect children with kwashiorkor (Branko 2001) as discussed below.

26.7 Application to Other Areas of Health and Disease

26.7.1 Head Circumference and Microcephaly (Table 26.2)

Microcephaly is a neurological development disorder in which the HC is less than the 3rd centile for a person's age and sex. It may be caused by congenital anomaly, which appears at birth, or may develop postnatally. Microcephalin genes have been implicated in this anomaly. Those born with microcephaly have their HC either normal or reduced in size. They have been found to be of subnormal intelligence.

26.7.2 Head Circumference and Macrocephaly (Table 26.3)

Macrocephaly can be diagnosed if the HC is greater than the 97th centile. It therefore goes without saying that reference values and the use of such values to indicate micro- or macrocephaly would vary from one community to another (Mortimer et al. 2003).

The following conditions can be diagnosed from macrocephaly: autism, neurofibrosis type 1, tuberous sclerosis, Sotos syndrome, Fragile X syndrome, leukodystrophies, Weaver syndrome, Bulldog syndrome, Noonan syndrome, Costello syndrome, Canayan disease, glutaric aciduria type 1, cardiofaciocutaneous syndrome, megalencephalic leukoencephalopathy with subcortical cysts, and D-2 hydroxyglutaric aciduria.

Table 26.2 Key features of microcephaly

1. Microcephaly means a small brain enclosed within a small skull
2. Microcephaly may be caused by maternal heroin addiction or by rubella virus infection
3. Microcephaly is not a structural abnormality, but a severe slowing of the growth rate of the fetal head
4. Microcephaly diagnosis is usually made after 20 weeks of gestation
5. Many microcephalics die shortly after birth and individuals who survive are not only severely mentally retarded but are also dwarfed

This table lists the key features of the condition called microcephaly, which is related to HC measurement and can be diagnosed by it

Table 26.3 Key features of macrocephaly

1. Macrocephaly means a huge brain enclosed within a gigantic skull
2. Macrocephaly is not a structural abnormality but an acceleration of the growth rate of the fetal head
3. Macrocephaly diagnosis is usually made after 20 weeks of gestation
4. Macrocephalics have large head above the 97th centile for sex and age
5. It may be caused by enlargement of cranium or brain
6. When it affects the soft tissue, it may be caused by either abnormal proliferation of brain tissue or accumulation of abnormal metabolic materials

This table lists the key features of the condition called macrocephaly, which is related to HC measurement and can be diagnosed by it

26.7.3 Head Circumference and Growth Chart

Growth charts have been used extensively in the past to determine how normal the growth of a child or a fetus is (Morley 2001; WHO Child Gold Standard 2006). This is also possible using the HC, although weight and height had been used more than HC in community surveys. Growth charts are useful in making a pre-diagnosis of such conditions as Down's syndrome and Turner's syndrome, as the two conditions provide charts that deviate significantly from the norm.

26.7.4 Head Circumference and Intelligence

Variations in head size and brain volume are genetic and, since Galton, it has been customary to associate size of the head (and ipso facto size of brain), as measured by HC, with intelligence. Even the genes responsible for brain size (which is directly related to HC, cranial capacity, OFD, etc.) have been identified even though they vary from one continent to another, and require to be mapped. A 40% correlation between head size and intelligence quotient (IQ) has been found using MRI (magnetic resonance imaging) studies. Brain size, as determined by small size, is said to correlate positively with memory retention in old age and the onset of dementia. It has also been shown that HC is strongly correlated with brain volume, which presumably determines intelligence. Racial studies have shown a relationship between brain size and adult intelligence, but we do not have enough data to determine the situation before birth, which is different from that after birth (Mortimer et al. 2003). This study provides authoritative data on HC in African children with a population size of over 13,740 fetuses.

26.7.5 Miscellaneous Head Circumference Data

Abnormal HC have been implicated in such conditions as benzodiazepine ingestion in utero with its associated microcephaly and low intelligence, pachygyria and all its subdivisions, such as lissencephaly (smooth brain), polymicrogyria, and craniosynosotosis. Also, certain genes are implied in the development of autism and low HC (Gallagher et al. 2004).

A program called DENVER II has been designed to assist in ascertaining health status from such anthropometric parameters as height and weight, and also HC (Frankenburg et al. 1992).

26.7.6 Practical Methods and Technique

There are multiple fetal anthropometric charts for the prediction of gestational age from a given parameter, but no chart exists for the prediction of other fetal parameters using HC measurement.

26.8 Nigerian Head Circumference Studies

A total of 13,740 growing fetuses were studied in Jos, the capital of Plateau State. Plateau State derives its name from the geographical landscape that predominates in this part of the country. It has a population of 3,178,712 (2006 census). The state lies between latitude 7 and 11° north of the

Table 26.4 Mean fetal HC values (in mm) in a Nigerian population

GA (weeks, days)	Number of fetuses (*n*)	Mean HC	SD	SEM
12 to 12 + 6	49	80.9	10.5	1.5
13 to 13 + 6	384	94.1	9.6	0.5
14 to 14 + 6	371	108.6	11.8	0.6
15 to 15 + 6	351	122.5	13.8	0.7
16 to 16 + 6	505	133.0	9.7	0.4
17 to 17 + 6	427	146.1	10.9	0.5
18 to 18 + 6	446	162.1	23.5	1.1
19 to 19 + 6	282	169.4	15.2	0.9
20 to 20 + 6	553	180.7	12.7	0.5
21 to 21 + 6	400	193.0	11.7	0.6
22 to 22 + 6	398	201.9	11.3	0.6
23 to 23 + 6	478	212.7	13.9	0.6
24 to 24 + 6	520	225.8	13.3	0.6
25 to 25 + 6	388	238.7	14.0	0.7
26 to 26 + 6	511	249.3	15.2	0.7
27 to 27 + 6	432	260.0	15.4	0.7
28 to 28 + 6	548	269.1	13.3	0.6
29 to 29 + 6	484	274.2	23.3	1.1
30 to 30 + 6	625	284.9	17.0	0.7
31 to 31 + 6	523	292.2	14.9	0.7
32 to 32 + 6	583	299.5	14.7	0.6
33 to 33 + 6	516	306.9	12.9	0.6
34 to 34 + 6	744	314.6	15.0	0.6
35 to 35 + 6	739	318.8	13.5	0.5
36 to 36 + 6	599	324.9	14.7	0.6
37 to 37 + 6	532	330.9	13.7	0.6
38 to 38 + 6	481	337.6	15.1	0.7
39 to 39 + 6	525	342.9	14.4	0.6
40 to 40 + 6	252	345.2	14.1	0.9
41 to 41 + 6	72	349.6	11.8	1.4
42 to 42 + 6	22	347.4	23.6	5.5
Total	**13,740**			

This table gives the mean values of fetal HC measurements for each gestational age in weeks from 12 to 42 weeks' gestation together with their corresponding SDs and standard errors of mean

GA gestational age, *HC* head circumference, *SD* standard deviation, *SEM* standard error of mean, *mm* millimeter

Equator and longitude 7° east. Although located in the tropical zone, the climate of Plateau state is the nearest equivalent of a temperate climate in Europe and USA. The state has over 50 ethnic groups, each with a proud cultural heritage, with no single group large enough to claim majority. Nature has endowed this State with scenic beauty, coupled with an invigorating climate. People from all over the country like staying in Jos; that is why the State has been rightly described as a miniature Nigeria because it contains within itself almost, if not all, the various ethnic groups of Nigeria. The study population consisted of all women with uncomplicated pregnancy, who presented for routine ultrasound at the Centre for Reproductive Health Research, Jos, between December 1997 and April 2002. Every fetus was measured and included only once, so that a pure cross-sectional set of data was constructed. Table 26.4 shows the frequency distribution of fetuses scanned by gestational age, mean HC, standard deviation (SD), and the standard error of the mean (SEM) of HC measurements,

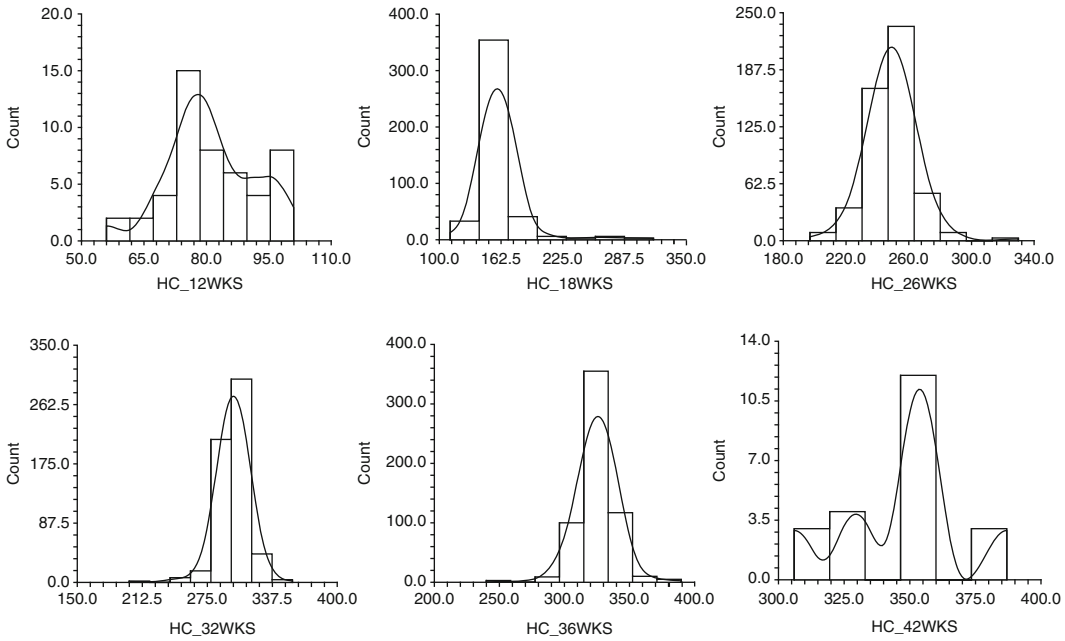

Fig. 26.1 Histograms of HC data at 12, 18, 24, 30, 36, and 42 weeks of gestation. This histograms show the distribution of the HC measurements at 12, 18, 26, 32, 36, and 42 weeks. At 12 and 42 weeks, the distribution is multimodal, whereas 18, 26, 32, and 36 weeks shows symmetrical distribution

carried out on the studied population. From this table, it can be seen that 75% of the fetuses scanned were above 21 weeks of gestation. At each gestational week, over 30 fetuses were examined, with the exception of week 42, where only 22 fetuses were examined. The test for normality is shown in Fig. 26.1 (histogram of HC data) and Fig. 26.2, which shows probability plot for 12, 18, 24, 30, 36, and 42 weeks. Martinez-Iglemicz's goodness of fit test carried out on the fetal HC measurements accepted normality of the data distribution. The geometric means of all sets of measurements are less than their arithmetic means, but greater than their harmonic means, indicating that all the values of fetal HC measurements were not identical. Also, Fig. 26.3 shows skewness of the HC data; Fig 26.4, kurtosis; Fig. 26.5, coefficient of dispersion of all individual observations plotted against gestational age. From these graphs, it can be seen that during the second trimester, the HC measurements were positively skewed, whereas during the third trimester, the measurements were negatively skewed, with wide variation at week 18. Also, the coefficient of dispersion is very high initially, but tapers down as it reaches higher gestational values (Fig. 26.5).

Figure 26.6 shows the scattergram of individual values obtained with the sample size of 13,740. It shows a few outliers, which are more around the latter part of the second trimester and the early part of the third trimester. In Fig. 26.7, mean HC is plotted against gestational age, with error bars showing SD. Mathematical modeling of data demonstrated that the best-fitted regression model (Fig. 26.8) to describe the relationships between HC and gestational age was the third order polynomial regression equation: $y = -0.0029x^3 + 0.0518x^2 + 13.136x - 78.198$, where y is the HC in millimeters, and x is the gestational age in weeks. Figure 26.9 shows mean values of HC in months plotted against gestational age. Values are in Table 26.5. There is a positive polynomial correlation between gestational age (in months) and HC (in millimeters), with a correlation coefficient of $R^2 = 0.9991$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the second order polynomial

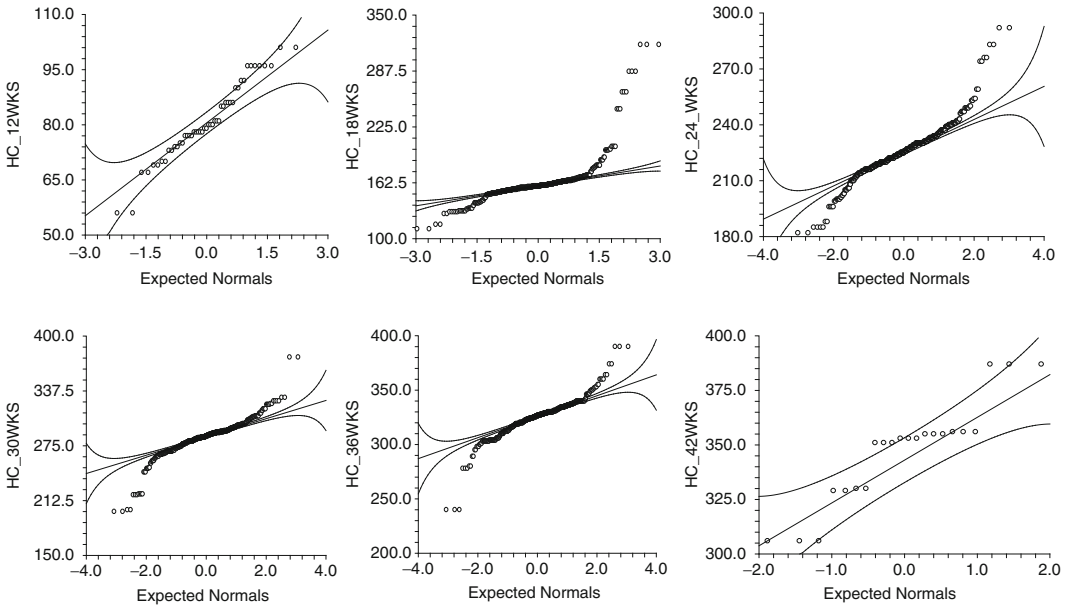

Fig. 26.2 Probability plot of HC data at 12, 18, 24, 30, 36, and 42 weeks of gestation. This probability plots gives a visual impression of whether the normality assumption is valid. They let one determine if the assumption is invalidated by one or two outliers (which could be removed), or if the data follow a completely different distribution

regression equation $y = -3.3238x^2 + 85.755x - 177.78$, where y is the HC in millimeters and x is the gestational age in months. Figure 26.10 shows the histogram of monthly data of HC whose values are also shown in Table 26.5. Figure 26.11 shows the histogram with population sizes for each of the 2nd and 3rd trimesters; see the data in Table 26.6.

26.8.1 Practical Methods and Technique

There are multiple fetal anthropometric charts for the prediction of gestational age using a given parameter, but no chart exists for the prediction of other fetal parameters using HC measurement. When fetal anthropometric parameters, such as BPD, OFD, AC, FL and weight, are plotted against HC, certain hidden relationships can be forced out. For example, Fig. 26.12 shows the relationship of HC with BPD. From the graph, it can be seen that there is a positive linear correlation between BPD and HC, with a correlation coefficient of $R^2 = 0.9997$ ($p < 0.0001$), in Nigerian fetuses. The relationship is best described by the linear regression equation $y = 0.2792x - 0.8656$, where y is the BPD in millimeters and x is the HC in millimeters. Figure 26.13 shows the relationship of HC with OFD, which depicts the regression equation of $y = 0.347 + 0.0528$; $R^2 = 1$; $p < 0.0001$. Figure 26.14 shows the relationship between cephalic index and HC. The relationship is best described by the fourth order polynomial regression equation $y = 1E\text{-}08x^4 + 1E\text{-}05x^3 - 0.0036x^2 + 0.5497x + 49.656$, where y is the cephalic index and x is the HC in millimeters; $R^2 = 0.7451$; $p < 0.0001$.

Other relationships can be calculated outside the skull. Figure 26.15 shows relationship between HC and AC. From the graph, it can be seen that there is a positive linear correlation between AC and

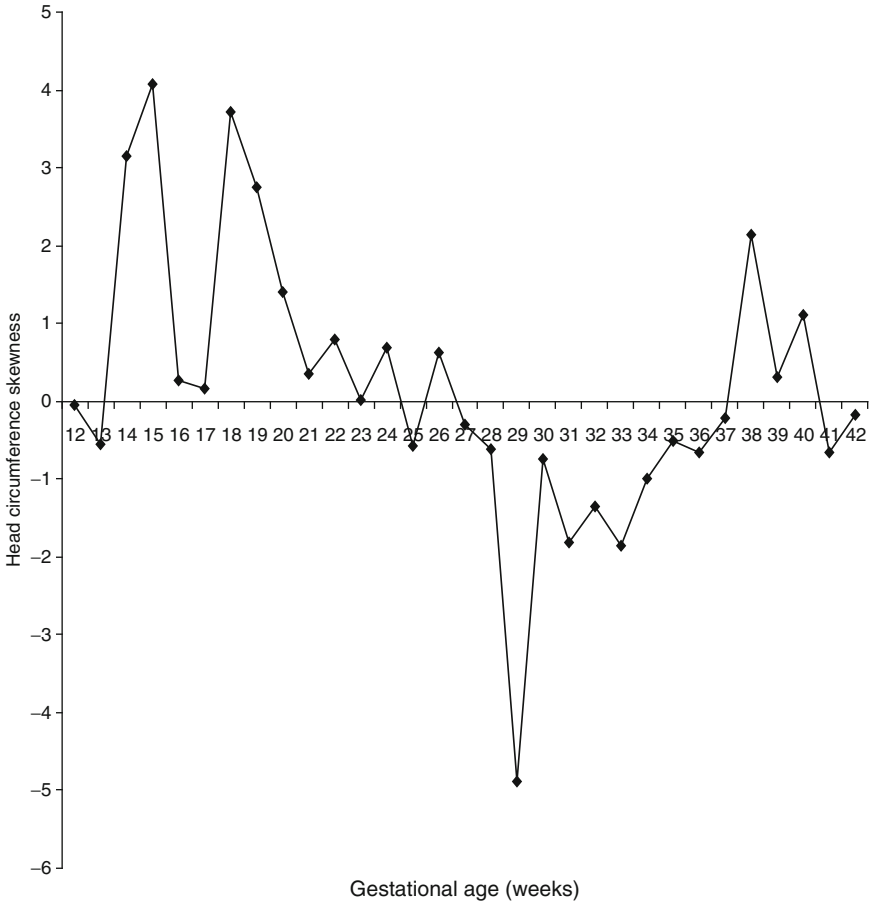

Fig. 26.3 Head circumference data of 13,740 fetuses subjected to skewness analysis at different gestational age ranging from 12 to 42 weeks. The figure shows that the distribution of HC measurements has a longer "tail" to the right of the central maximum than to the left or is skewed to the right from 13 to 24 weeks. From 25 to 37 weeks, the distribution has a longer "tail" to the left of the central maximum than to the right or is skewed to the left. By the time pregnancy reaches term, the distribution becomes skewed to the right before skewing again to the left, as from 41 weeks

HC, with a correlation coefficient of $R^2 = 0.994$ ($p < 0.0001$), in Nigerian fetuses. The relationship is best described by the linear regression equation $y = 1.0644x - 29.032$ where y is the AC in millimeters and x is the HC in millimeters.

Figure 26.16 shows the relationship between FL and HC. There is a positive power correlation between FL and HC, with a correlation coefficient of $R^2 = 0.9962$ ($p < 0.0001$), in Nigerian fetuses. The relationship is best described by the power regression equation $y = 0.046x^{1.2897}$, where y is the AC in millimeters and x is the HC in millimeters. Figure 26.17 shows the relationship between fetal weight, which is strongly correlated with fetal nutrition, and HC. The relationship is best described by the exponential regression equation $y = 57.144e^{0.012x}$, where y is the fetal weight in grams and x is the HC in millimeters.

When the relationship between HC and symphysio-fundal height was determined, it was found that there is a positive polynomial correlation between symphysio-fundal height and HC, with a correlation coefficient of $R^2 = 0.9954$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best

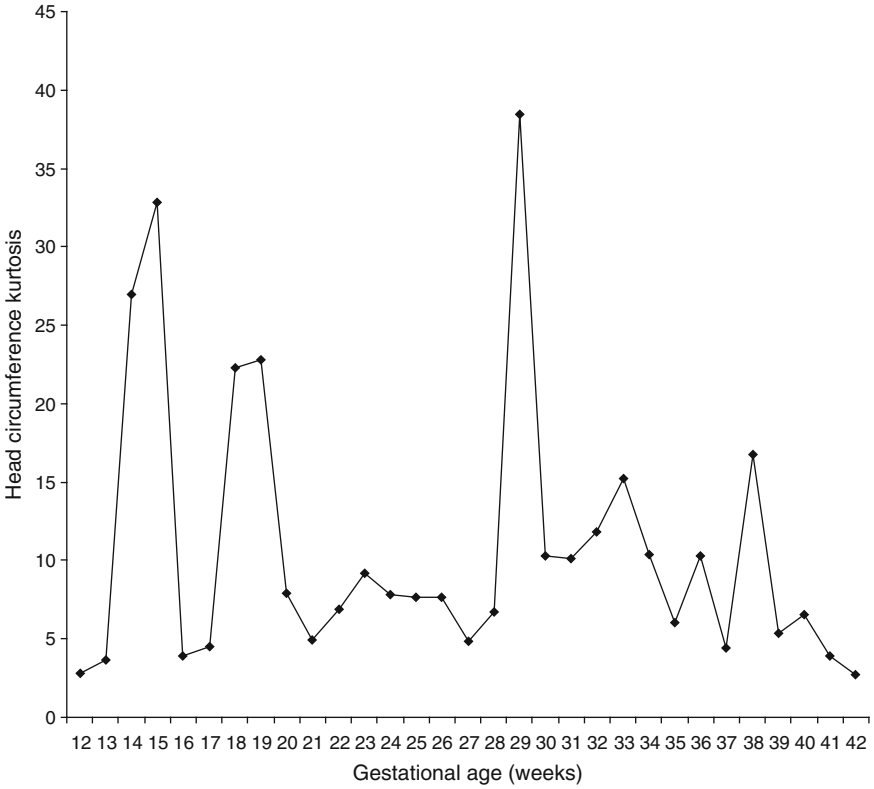

Fig. 26.4 Head circumference data of 13,740 fetuses subjected to kurtosis analysis at different gestational age ranging from 12 to 42 weeks. The figure shows that the kurtosis of HC measurement is leptokurtic at 14, 15, 18, 19, 29, 33, and 38 weeks of gestation, whereas, at 12, 13, 16,17, 20, 21, 22, 23, 24, 25, 26, 27, 28, 20, 31, 32,34, 35, 36, 39, 40, 41, and 42 weeks of gestation, the kurtosis is mesokurtic

described by the sixth order polynomial regression equation $y = –2E\text{-}05x^6 + 0.0037x^5 – 0.2533x^4 + 9.0473x^3 – 177.54x^2 + 1823.4x – 7544.3$, where y is the HC in millimeters and x is the symphysio-fundal height in millimeters; see Fig. 26.18.

Centile values for 3rd, 5th, 50th, 90th 95th, and 97th are plotted in Fig. 26.19. Table 26.6 shows obtained 3rd, 5th, 10th, 50th, 90th, 95th, and 97th centiles of HC at each week of gestation. In Fig. 26.20, they are smoothened into a growth chart, which can be utilized to determine growth and of course brain size development, strongly related to intelligence and wellness, using HC. Table 26.7 shows HC z-scores.

Figure 26.21 shows comparison graph between African (Nigerian) children and European children in the Kurmanavicius et al. (1999) study for 3rd, 5th, 50th, 90th, 95th, and 97th centiles. It is obvious from the comparison graph of Fig. 26.21 that African children maintain a lead over Europeans ones during the development of the skull and HC. When comparison graphs are broken into months (Figs. 26.22–26.28), it is clear that the European children catch up initially at 6 months but still decline till birth.

Figure 26.29 shows the growth rate of the measured fetal HC with a quadratic polynomial mathematical model predictive formula $y = 0.0008x^2 – 0.0095x + 2.1811$ ($R^2 = 0.721$; $p < 0.0001$), where y is the fetal HC growth rate in millimeters and x is the gestational age in weeks. It is clear from this graph that growth rate is much higher in the early stages of development than in the late stages that precede term.

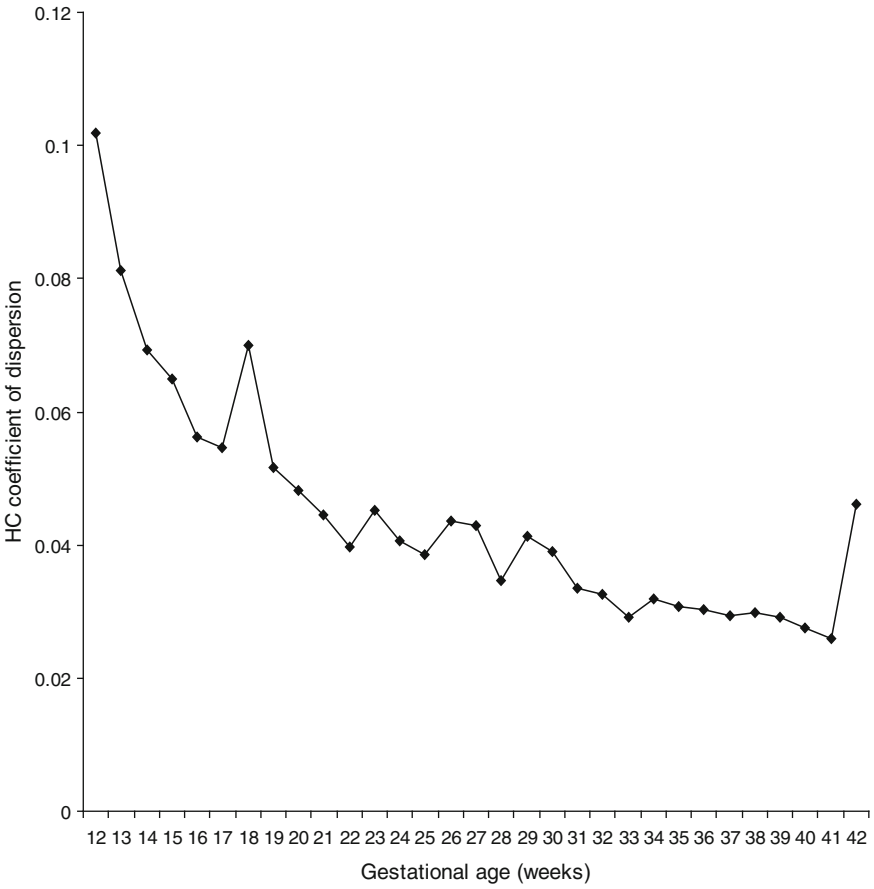

Fig. 26.5 Head circumference coefficient of dispersion in 13,740 fetuses of gestational ages between 12 and 42 weeks. Coefficient of dispersion of HC data of 13,740 fetuses at different gestational age shows a decrease in value as gestational age advances except at 18, 23, 25, 26, 29, 30, and 42 weeks where it peaks. *HC*: head circumference

Ultrasonic fetal anthropometry (Table 26.9) is of great interest in obstetric practice and early pregnancy science. It is helpful in the estimation of gestational age, especially in women who do not remember the dates of their last menstrual period, or whose fundal height on abdominal examination does not correspond to dates. The practice of assessing gestational age in early gestation is valuable in detection of growth aberration in later stages of pregnancy. In addition, fetal anthropometry distinguishes the normal from abnormal fetal structures. Ratios of these measurements calculated for each environment will assist in no small measure in diagnosing certain congenital anomalies, such as Down syndrome, congenital amputee, arthrogryposis multiplex congenita, achondroplasia, gastroschisis, exomphalos, anencephaly, and hydrocephalus. Naeye, as far back as 1973, wrote: "At present there seems to be no completely valid method available to determine normal fetal growth using measurements from neonates because there is no assurance that prematurely born neonates are normally grown." Naeye (1973) went on to say: "Ultrasound and other modalities may eventually solve this problem by providing accurate, sequential in utero measurements of normal fetuses." Regarding fetal length and body weight, was there, for example, a period of peak length velocity and peak weight velocity comparable to the adolescent velocity peaks of height and weight? Tanner (see Morley 2001) had suggested that fetal peak growth velocity in length occurs

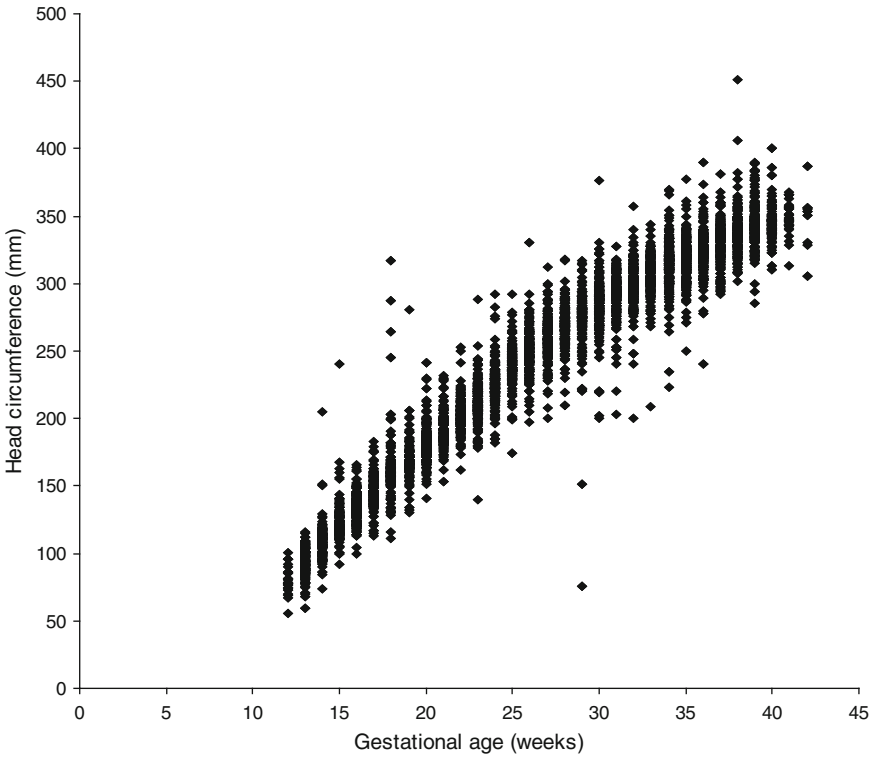

Fig. 26.6 Scattergram of 13,740 fetal head circumference (HC) measurements from 12 to 42 weeks of gestation. The scattergram in figure shows that there are very few bad data points or outliers in the HC measurements of 13,740 fetuses. The outliers are more from 26 to 42 weeks of gestation. This shows the pattern of growth recognized for neural tissue, which suggests growth of brain

around 20 weeks' gestation and in weight a good deal later – around 30 weeks' gestation. Prenatal measurement of fetal parameters, and estimated size and weights vary among different populations, depending upon their racial, demographic characteristics and nutrition. It is therefore important that fetal anthropometry be performed for local population, and local charts of normal anthropometry be constructed and followed for these populations and ethnic groups.

The standard of fetal ultrasound anthropometry was started after Willocks published, probably the first paper on fetal ultrasound cephalometry in 1964. Later, in 1968, fetal cephalometry was included in routine fetal anthropometric scans. Many reference charts and tables have been published since then. However, a number of these were produced using old ultrasound equipment with low spatial resolution in different ultrasound velocities compared with today's modern real-time scanners, which have not only led to the development of improved measurement techniques, but also provided us with multiple fetal parameters (Woo 2006). Several of these charts, however, have methodological flaws, falling short of the ideal attributes of gestational age-related reference curve design, namely non-identification of the statistical method of analysis, a supernormal data set, and inadequate account in variability of measurements with gestation, and failure to present scatter diagrams. In the publications of Altman and Chitty (1994), methodological guidelines were created for the construction of fetal biometry charts.

The final goal of fetal anthropometry is to allow the user to predict information concerning a fetus, and to authenticate how closely the fetus conforms to the prediction. While constructing the fetal anthropometry charts, the statistical justification of the sample size is as necessary as the selection of

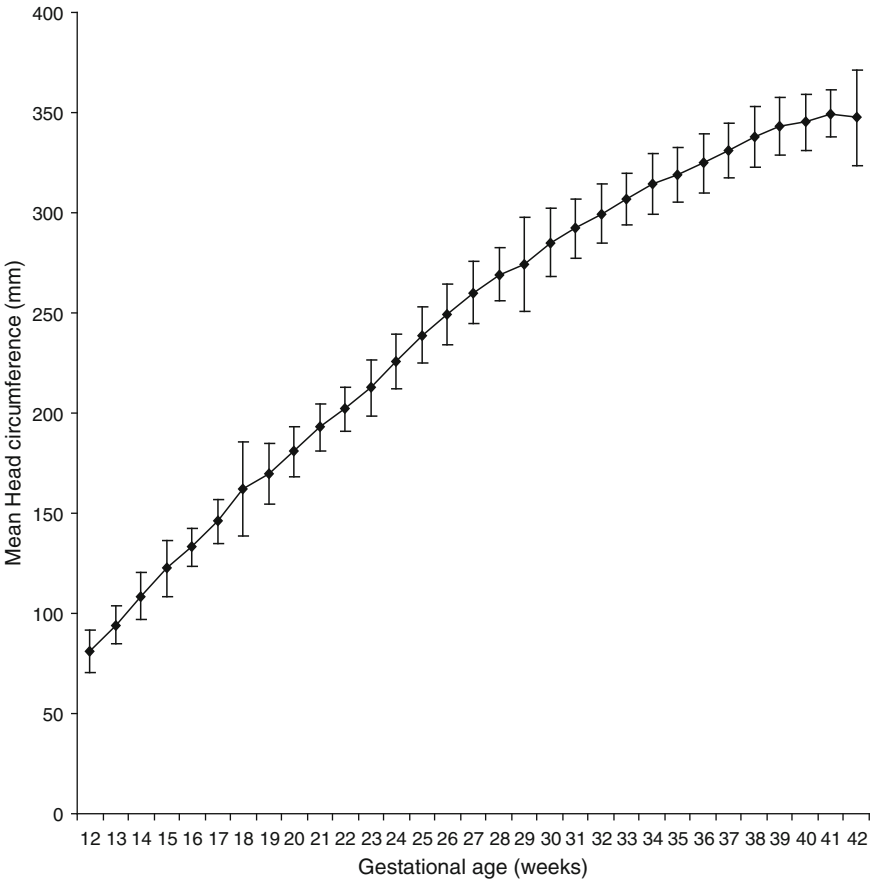

Fig. 26.7 Mean fetal head circumference values in 13,740 fetuses of women at different gestational ages between 12 – 42 weeks. The vertical bars show the values of ± SD. Mean and standard deviation go together like star and satellite. With the mean, we have some idea of the kind of numbers it represents, but the whole story is still a mystery. To clear up the mystery of the hidden numbers that made up a mean, the standard deviation is necessary. For example, the mean ± 1 standard deviation will include about 2 out of 3 numbers in the group while the mean ± 2 standard deviations will include about 95 out of 100 numbers in the group and the mean ± 3 standard deviations will include 997 numbers out of 1,000.

study design type, so that the results may subsequently be generalized to the whole population, or at least to the concerned ethnic group. Mean and SD values of the parameter(s) are computed. The smaller the SD, the less is the variability of the sample around the mean. The SD is also used to describe the statistical limits of "normality." These intervals are called confidence limits. Traditionally, the confidence limits are set at the 5th and 95th centiles. The values of 5th and 95th centiles suggest the lower and the upper limits of normal reference intervals respectively, or normal ranges for the selected parameter. Scattergrams are constructed and regression analysis is done, yielding a specific regression equation that enables one to predict the fetal gestational age, once the specific values of fetal parameter is known.

Fetal anthropometry studies reported from Iran, Oman, Cameron, Bangladesh, Pakistan, and Israel describe the uniqueness and specification of different fetal parameters for their own populations (Stein 1975). Ethnic variations have also been described. Therefore, anthropometric curves for one population may over- or underestimate the fetal age when used for another population with different demographic characteristics. Thus, the construction and use of biometric normograms specific for populations and ethnic groups is always recommended.

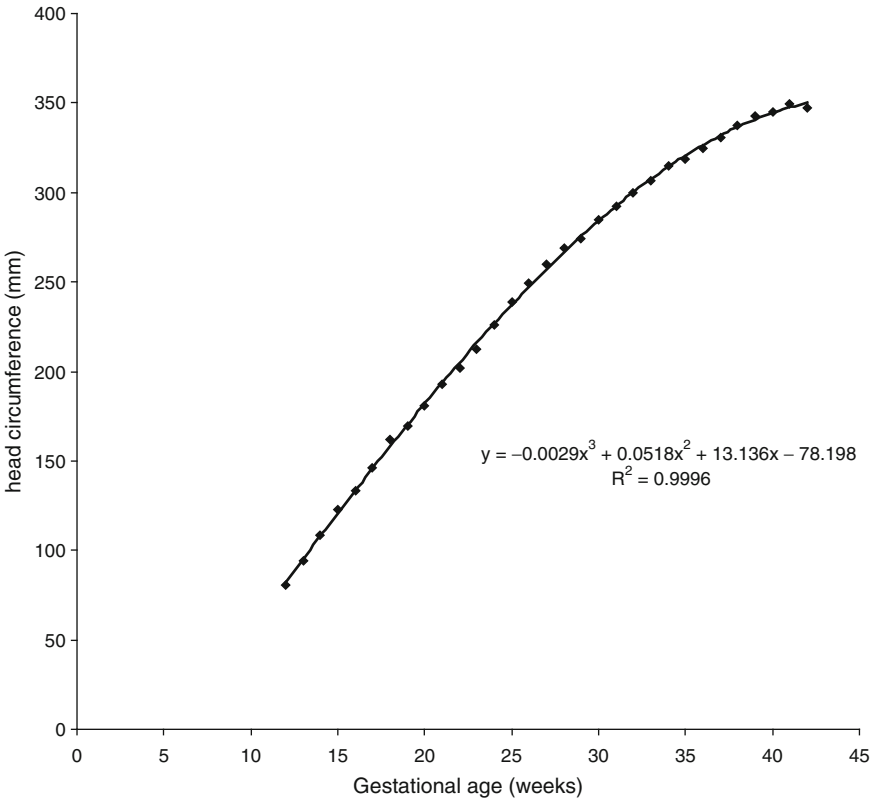

Fig. 26.8 Correlation and regression equation of mean HC values in 13,740 Nigerian fetuses plotted against gestational age in weeks. There is a positive polynomial correlation between gestational age and HC with a correlation coefficient of $R^2 = 0.9996$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the third order polynomial regression equation $y = -0.0029x^3 + 0.0518x^2 + 13.136x - 78.198$, where y is the HC in millimeters and x is the gestational age in weeks

26.9 Conclusion

We have presented mean values ± SD, centile charts, tables, and formulas for fetal HC in Africans derived from a very large sample size (13,740: probably the largest ever recorded) in a cross-sectional study. We have also shown how important these values are in the new and emerging field of ultrasonic embryology and, indeed, clinical anthropology. It is clear when we make comparison with studies in other racial groups such as that of Europeans that the African HC increases faster than that of the European fetus and is bigger than it at birth, on average. We conclude that there is a faster and shorter period of maturation of the skull and the brain, respectively in the African fetus than in the European fetus. We also conclude that modern studies, which implicate HC in intelligence, suggest that the well-known decline in HC in the African vis-a-vis other racial groups occurs after birth and

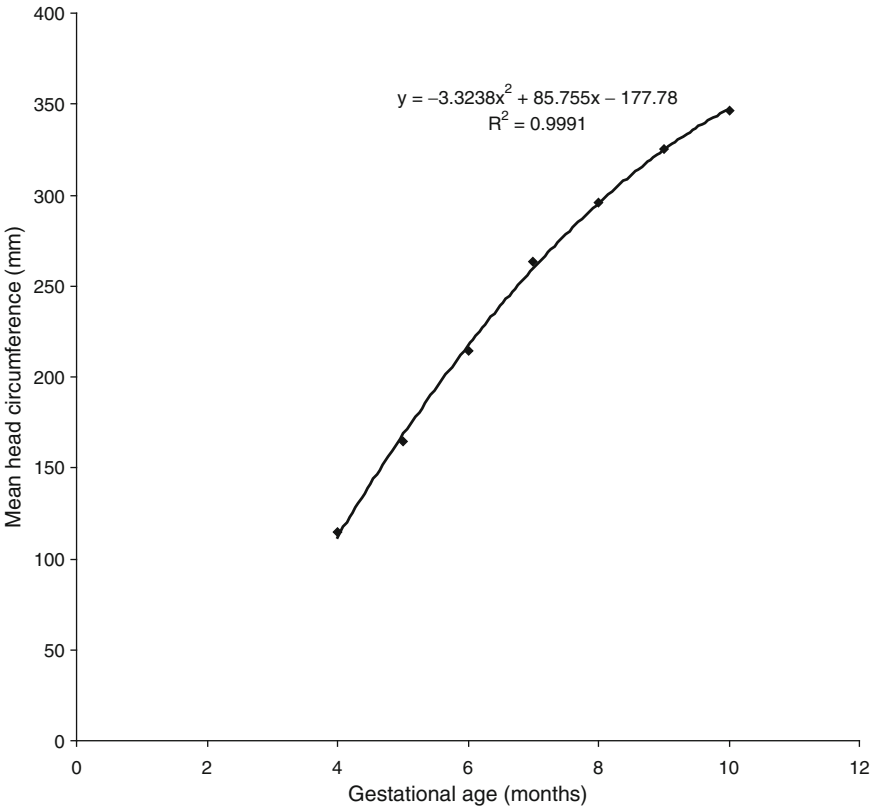

Fig. 26.9 Correlation and regression equation of mean HC values in 13,740 Nigerian fetuses plotted against gestational age in months. There is a positive polynomial correlation between gestational age and HC with a correlation coefficient of $R^2 = 0.9991$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the second order polynomial regression equation $y = -3.3238x^2 + 85.755x - 177.78$, where y is the HC in millimeters and x is the gestational age in months

not before it. We are equally aware that early maturation does not necessarily indicate better intelligence. However, we suggest that postnatal decline in velocity of growth of HC in the African is probably due to low nutrition, and that with improved diet, this seeming difference will be corrected. It is already well documented that postnatal nutrition contributes to the development of intelligence. The significance of nurture rather than nature has placed the African child at a disadvantage not only for HC but also for other well-known anthropometric parameters, such as height and even weight after birth. The future and intelligence of the growing African child is dependent on his nurture more than his nature and this may account for the spuriously low IQ frequently reported by some investigators in Africa. However, we also see that HC is not a good indicator of nutritional status in the fetus, nor is it well correlated with FL, AC, or cephalic index. The prospect for further studies on craniometry and HC measurements, especially in the postnatal human, seems promising, given the intelligence data, as intelligence is increasingly being implicated with these cranial measurements and would ultimately explain them.

Table 26.5 Monthly mean fetal HC values (in mm) in a Nigerian population

GA (months)	Fetuses (*n*)	Mean (mm)	SD	SEM
4	1,660	114.5	16.9	8.4
5	1,708	164.6	14.5	7.2
6	2,184	214.4	18.3	8.1
7	1,975	263.2	10.9	5.5
8	2,247	295.9	9.5	4.7
9	3,095	325.4	9.2	4.1
10	871	346.3	2.9	1.4
Total	13,740			

This table gives the mean values of fetal HC measurements from the 4th month of intrauterine life to the 10th month with their corresponding SD and SEM

SD standard deviation, *SEM* standard error of mean

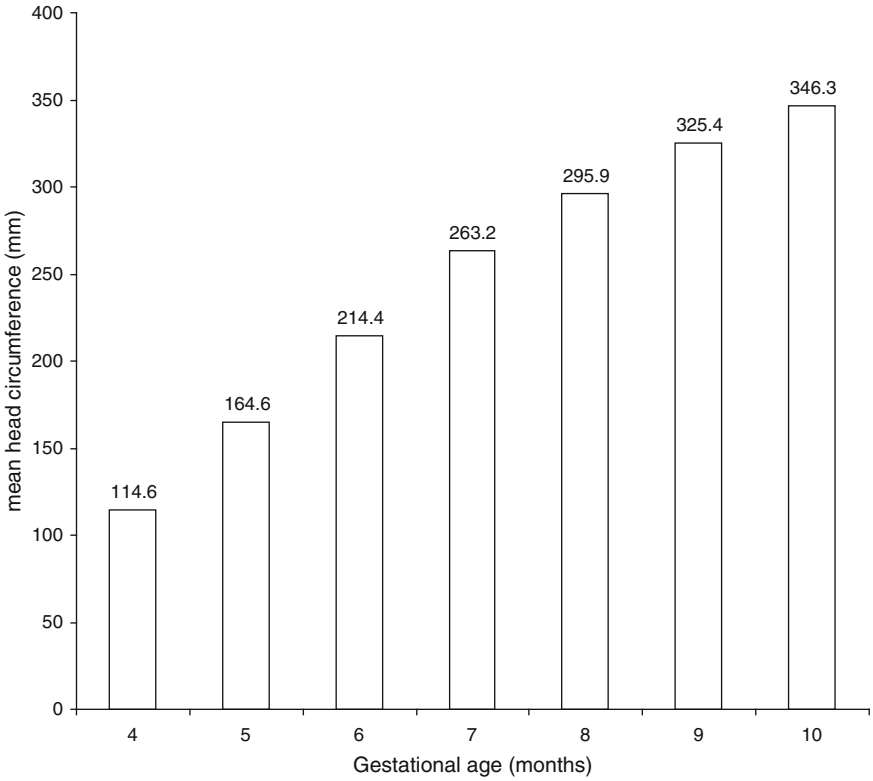

Fig. 26.10 Histogram showing mean HC values in 13,740 HC data of fetuses in women of gestational ages from 4 to 10 months. Histogram shows a steady rise of mean values from 4 to 10 months of gestation. Values shown are HC mean values (see Table 26.5)

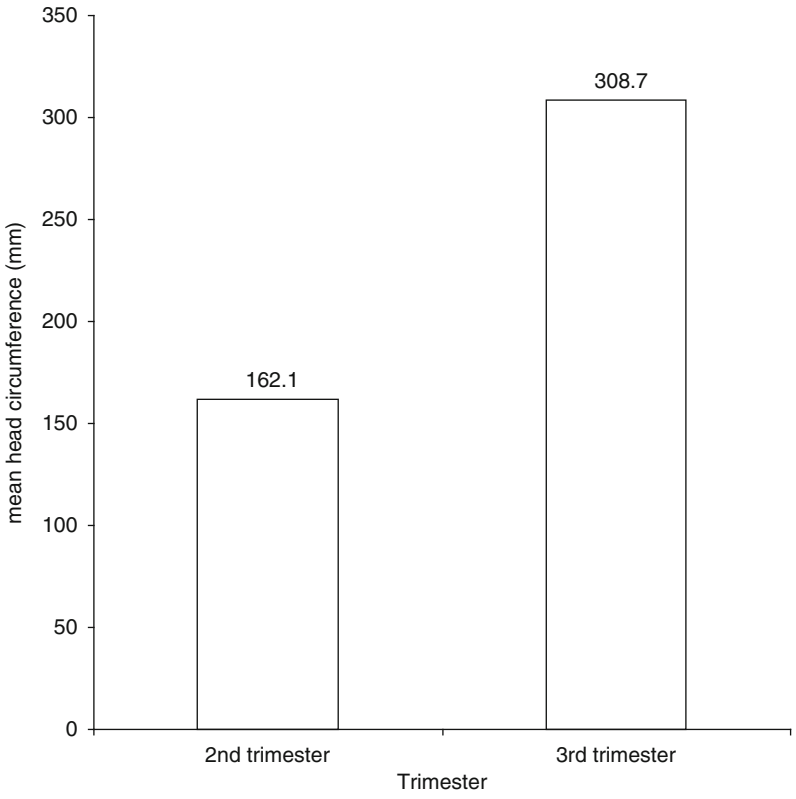

Fig. 26.11 Histogram showing mean HC values in 13,740 HC data of fetuses in women of gestational ages from 4 to 10 months divided into two trimesters. Mean HC show statistically significant higher value for third trimester (SD 32.6) when compared to second trimester (SD 49.7; $p < 0.001$). Values shown are HC mean values. SD: standard deviation (see Table 26.6)

Table 26.6 Mean values of fetal HC by Trimester

Trimester	Fetuses (*n*)	Mean	SD	SEM	Minimum	Maximum	Range
2nd	5,552	162.1	49.7	13.3	80.9	238.7	157.8
3rd	8,188	308.7	32.6	7.9	249.3	349.6	100.3
Total	13,740						

This table gives mean values of HC for 2nd and 3rd trimesters with their corresponding SDs, SEM, and range for each trimester

SD standard deviation, *SEM* standard error of mean

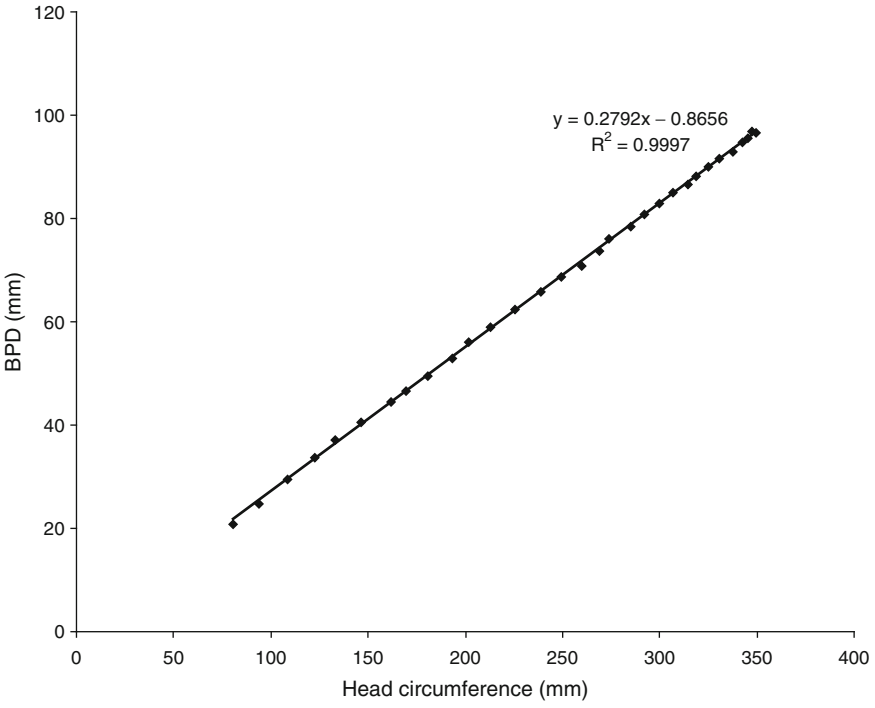

Fig. 26.12 Correlation and regression equation of mean biparietal diameter (BPD) HC values in 13,740 Nigerian fetuses plotted against HC. There is a positive linear correlation between BPD and HC with a correlation coefficient of $R^2 = 0.9997$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the linear regression equation $y = 0.2792x - 0.8656$, where y is the BPD in millimeters and x is the HC in millimeters. BPD: Biparietal diameter

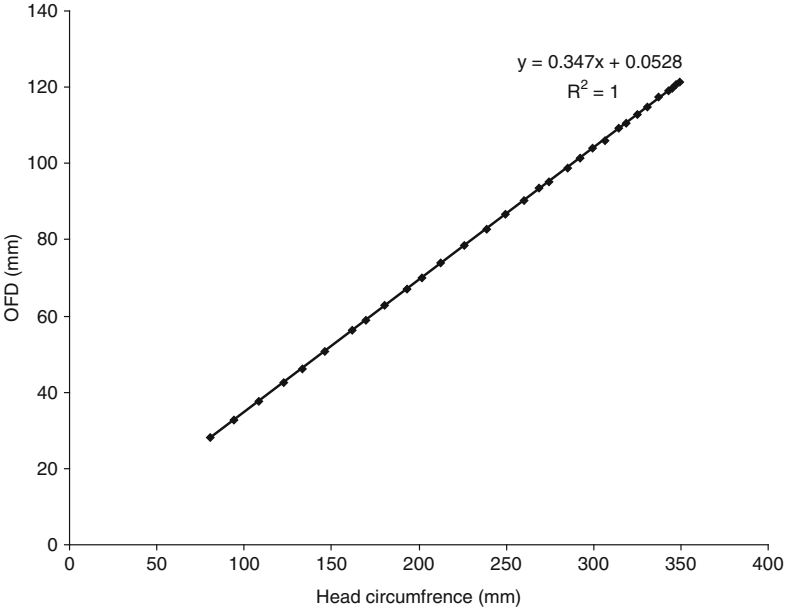

Fig. 26.13 Correlation and regression equation of mean occipitofrontal diameter (OFD)HC values in 13,740 Nigerian fetuses plotted against HC. There is a positive linear correlation between OFD and HC with a correlation coefficient of $R^2 = 1$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the linear regression equation $y = 0.347 + 0.0528$, where y is the OFD in millimeters and x is the HC in millimeters. OFD: occipitofrontal diameter

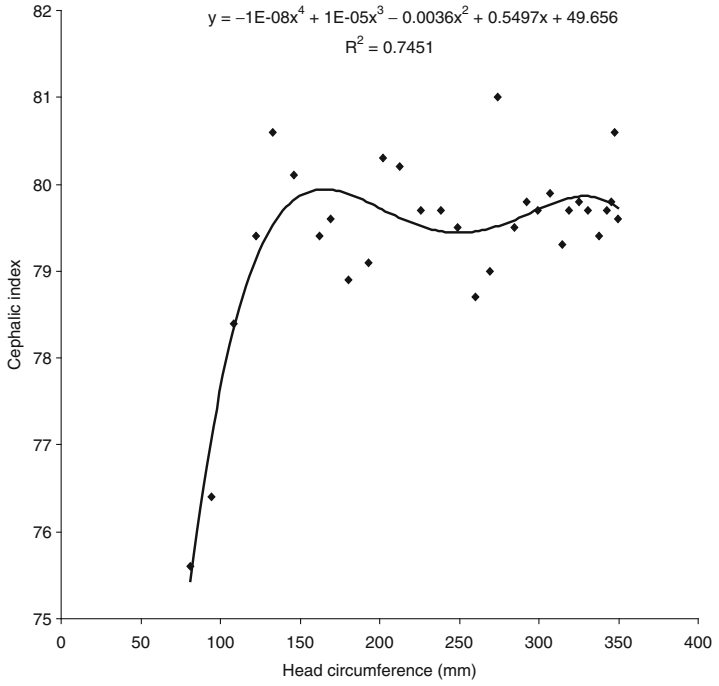

Fig. 26.14 Correlation and regression equation of mean cephalic index HC values in 13,740 Nigerian fetuses plotted against HC. There is a positive polynomial correlation between cephalic index and HC with a correlation coefficient of $R^2 = 0.7451$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the fourth order polynomial regression equation $y = 1E\text{-}08x^4 + 1E\text{-}05x^3 - 0.0036x^2 + 0.5497x + 49.656$, where y is the cephalic index and x is the HC in millimeters

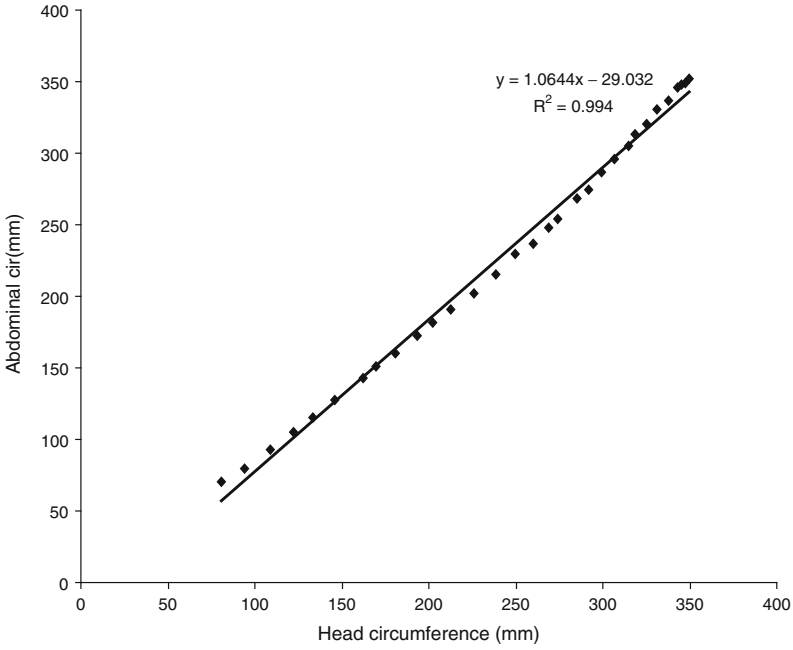

Fig. 26.15 Correlation and regression equation of mean AC HC values in 13,740 Nigerian fetuses plotted against HC. There is a positive linear correlation between AC and HC with a correlation coefficient of $R^2 = 0.994$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the linear regression equation $y = 1.0644x - 29.032$, where y is the AC in millimeters and x is the HC in millimeters

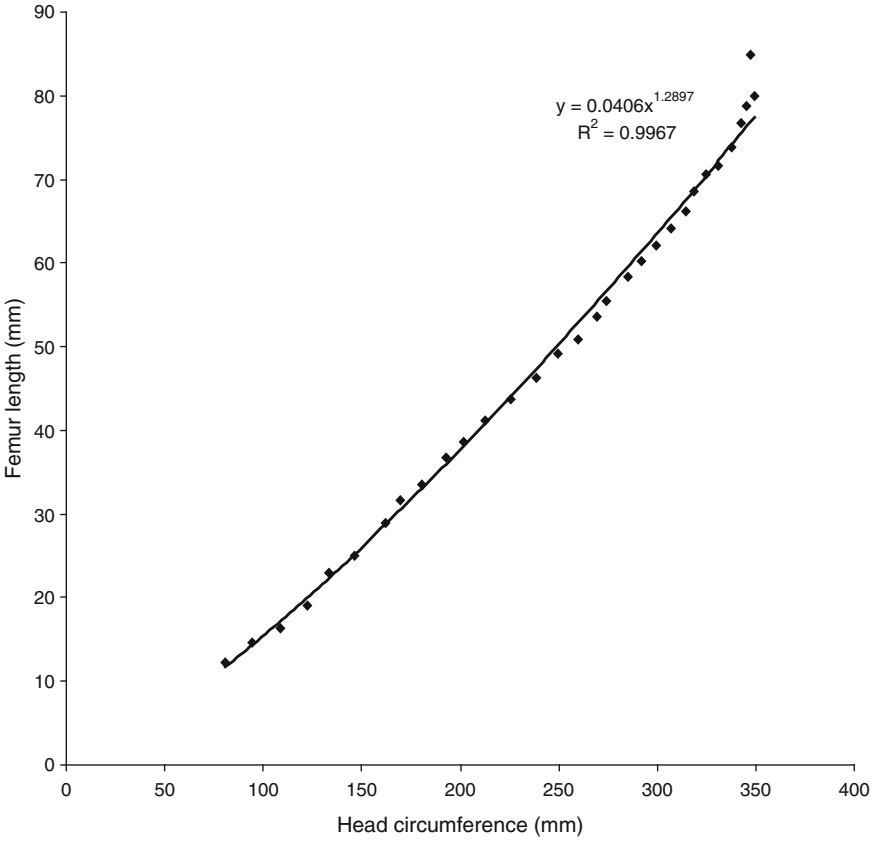

Fig. 26.16 Correlation and regression equation of mean against femur length (FL) HC values in 13,740 Nigerian fetuses plotted against HC. There is a positive power correlation between FL and HC with a correlation coefficient of $R^2 = 0.9962$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the power regression equation $y = 0.046x^{1.2897}$, where y is the AC in millimeters and x is the HC in millimeters

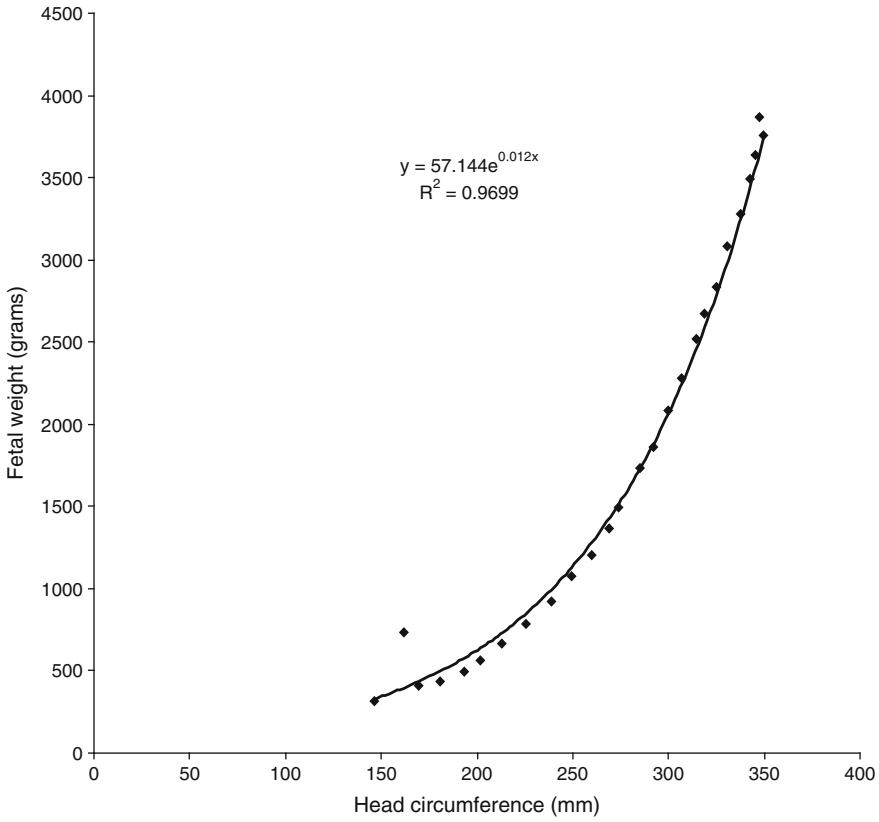

Fig. 26.17 Correlation and regression equation of mean fetal weight HC values in 13,740 Nigerian fetuses plotted against HC. There is a positive exponential correlation between fetal weight and HC with a correlation coefficient of $R^2 = 0.9699$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the exponential regression equation $y = 57.144e^{0.012x}$, where y is the fetal weight in grams and x is the HC in millimeters

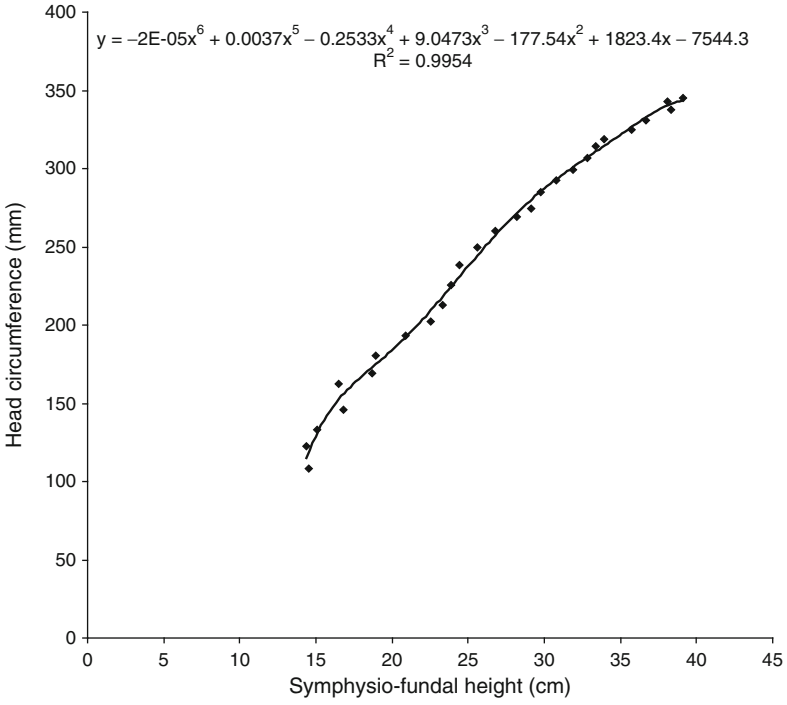

Fig. 26.18 Correlation and regression equation of mean HC values in 13,740 Nigerian fetuses plotted against symphysio-fundal height. There is a positive polynomial correlation between symphysio-fundal height and HC with a correlation coefficient of $R^2 = 0.9954$ ($p < 0.0001$) in Nigerian fetuses. The relationship is best described by the sixth order polynomial regression equation $y = –2E\text{-}05x^6 + 0.0037x^5 – 0.2533x^4 + 9.0473x^3 – 177.54x^2 + 1823.4x – 7544.3$, where y is the HC in millimeters and x is the symphysio-fundal height in millimeters

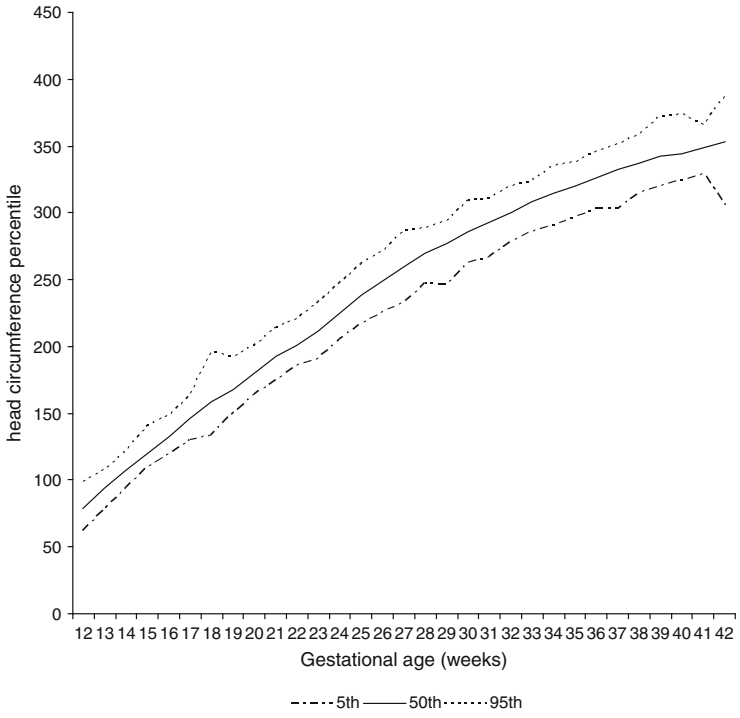

Fig. 26.19 Fifth, 50th, and 97th centiles for HC in 13,740 fetuses at different gestational ages from 12 to 42 weeks. Centile values plotted against gestational age from 12 to 42 weeks. The 5th, 50th, and 95th centiles showing a bell-shaped curve similar to that of the mean curve in Fig. 26.8

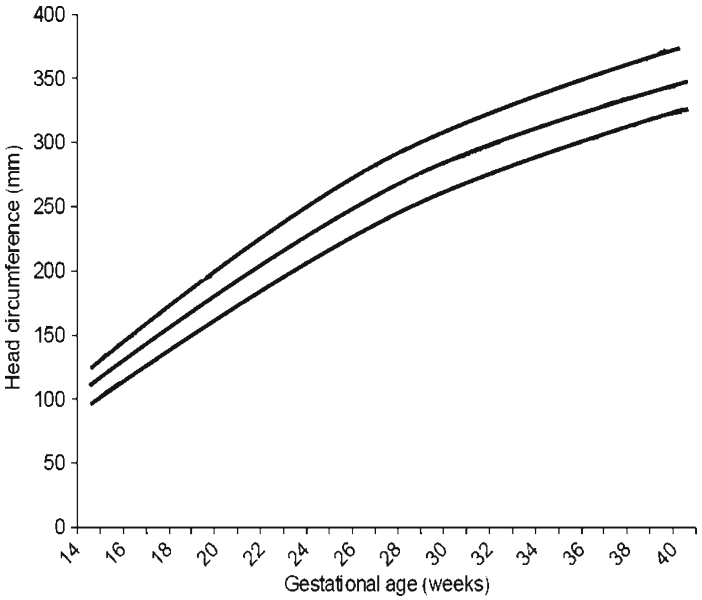

Fig. 26.20 Curves created from 3rd, 50th, and 97th fetal HC centiles. Chart using HC derived from data from 3rd, 50th, and 97th centiles. The curves can be used to monitor growth in a developing fetus to determine its growth velocity and pattern and can be used like other growth charts in this environment

Table 26.7 Centiles of fetal HC measurements

	Head circumference centiles (mm)						
Gestational age	3rd	5th	10th	50th	90th	95th	97th
12 to 12 + 6	56.0	61.5	69.0	79.0	96.0	98.5	101.0
13 to 13 + 6	75.0	78.0	82.0	94.0	106.0	108.0	109.0
14 to 14 + 6	92.2	94.0	96.0	108.0	118.8	122.0	126.0
15 to 15 + 6	104.6	110.0	111.0	120.0	134.0	141.0	155.4
16 to 16 + 6	116.0	119.0	121.0	133.0	145.0	149.0	151.0
17 to 17 + 6	122.7	130.0	135.0	146.0	159.0	163.0	170.0
18 to 18 + 6	131.0	134.0	146.0	159.0	172.2	196.2	203.0
19 to 19 + 6	140.0	150.0	156.3	168.0	183.0	191.9	200.5
20 to 20 + 6	160.0	164.0	169.0	180.0	195.0	201.0	210.0
21 to 21 + 6	171.0	175.0	181.0	193.0	206.9	214.0	222.0
22 to 22 + 6	181.0	186.0	190.0	201.0	215.0	220.1	223.0
23 to 23 + 6	183.0	191.0	199.0	212.0	227.0	233.0	239.6
24 to 24 + 6	200.0	205.0	214.0	225.0	239.9	247.0	250.0
25 to 25 + 6	206.4	216.5	225.9	238.0	253.0	261.7	265.0
26 to 26 + 6	220.0	226.0	232.2	249.0	265.0	272.0	279.0
27 to 27 + 6	230.0	232.7	240.3	260.0	278.0	287.0	292.0
28 to 28 + 6	243.0	247.0	255.0	270.0	284.0	289.0	292.0
29 to 29 + 6	229.2	246.3	260.0	277.0	290.0	294.0	302.0
30 to 30 + 6	250.0	262.3	269.0	286.0	300.0	309.0	315.4
31 to 31 + 6	253.0	267.0	276.0	293.0	309.0	311.0	314.3
32 to 32 + 6	274.1	279.2	284.4	300.0	316.0	320.0	322.0
33 to 33 + 6	280.0	286.0	293.0	308.0	321.0	324.0	328.0
34 to 34 + 6	286.0	290.5	300.0	315.0	330.5	335.0	340.0
35 to 35 + 6	291.2	297.0	301.0	320.0	333.0	338.0	340.8
36 to 36 + 6	301.0	303.0	306.0	326.0	339.0	346.0	351.0
37 to 37 + 6	300.0	302.7	312.3	333.0	344.7	351.0	358.0
38 to 38 + 6	310.9	315.0	320.0	337.0	352.0	359.0	364.0
39 to 39 + 6	318.0	320.3	326.2	342.0	359.0	372.0	378.0
40 to 40 + 6	323.0	324.3	330.0	344.0	360.0	373.5	382.5
41 to 41 + 6	316.0	329.0	335.0	348.5	366.0	366.0	367.6
42 to 42 + 6	306.0	306.0	306.0	353.0	387.0	387.0	387.0

This table gives the 3rd, 5th, 10th, 50th, 90th, 95th, and 97th centile values for fetal HC measured at different gestational age ranging from 12 to 42 weeks. For example, it can be seen from the table that the 10th percentile of HC at 18 to 18 + 6 weeks' gestation is 146 mm. This means that 10% of the fetuses at 18 to 18 + 6 weeks had a mean HC less than 146 mm, whereas 90% had a mean HC greater than 146 mm. Similarly, the 97th percentile with respect to HC at 39 to 39 + 6 weeks is 378 millimeters. Hence 97% of fetuses at 39 to 39 + 6 weeks had a mean HC less than 378 millimeters, whereas 3% had a mean HC greater than 378 mm

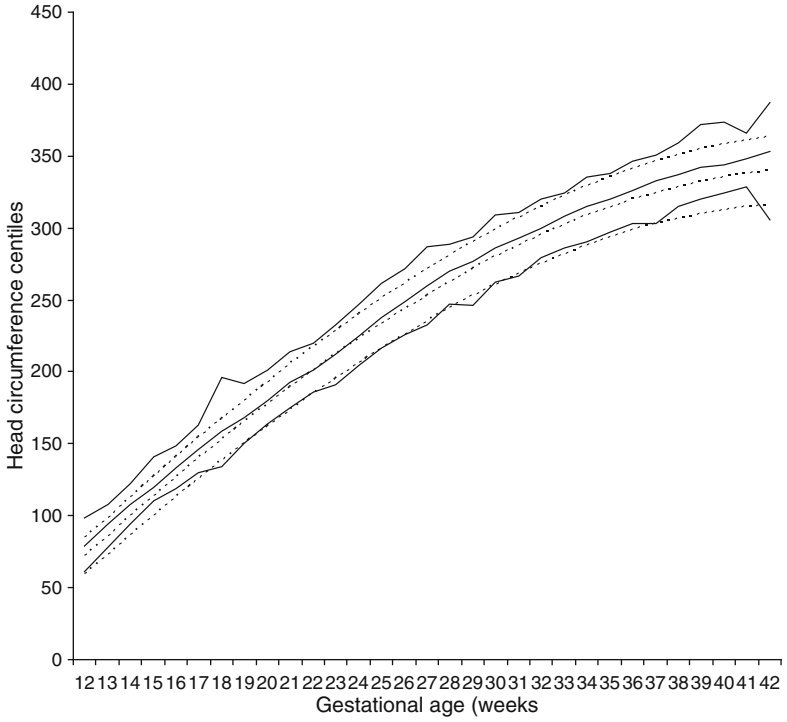

Fig. 26.21 Comparison between centile values of HC in African and European fetuses from 12 to 42 weeks of gestation. Comparison of African (Nigerian) HC 5th, 50th, and 95th centiles values in our study from 12 to 42 weeks of gestation (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed line*). The trend in the African shows consistently higher values when compared with the European values and more so in later years at the third trimester

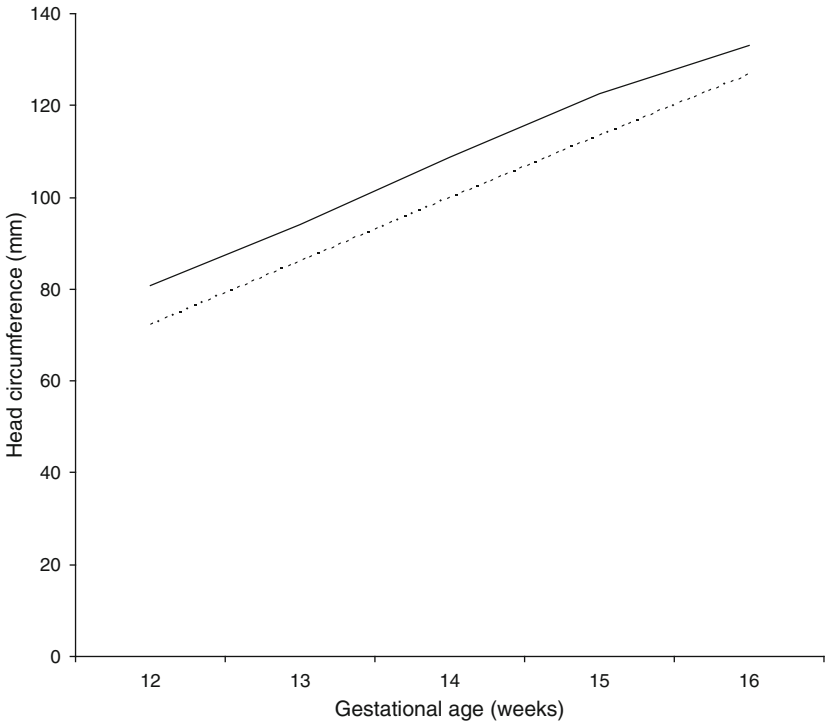

Fig. 26.22 Comparison between centile values of HC in African and European fetuses at 4 months (12–16 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 4 months (12–16 weeks of gestation) (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed line*). Values are consistently lower in Europeans than in African fetuses

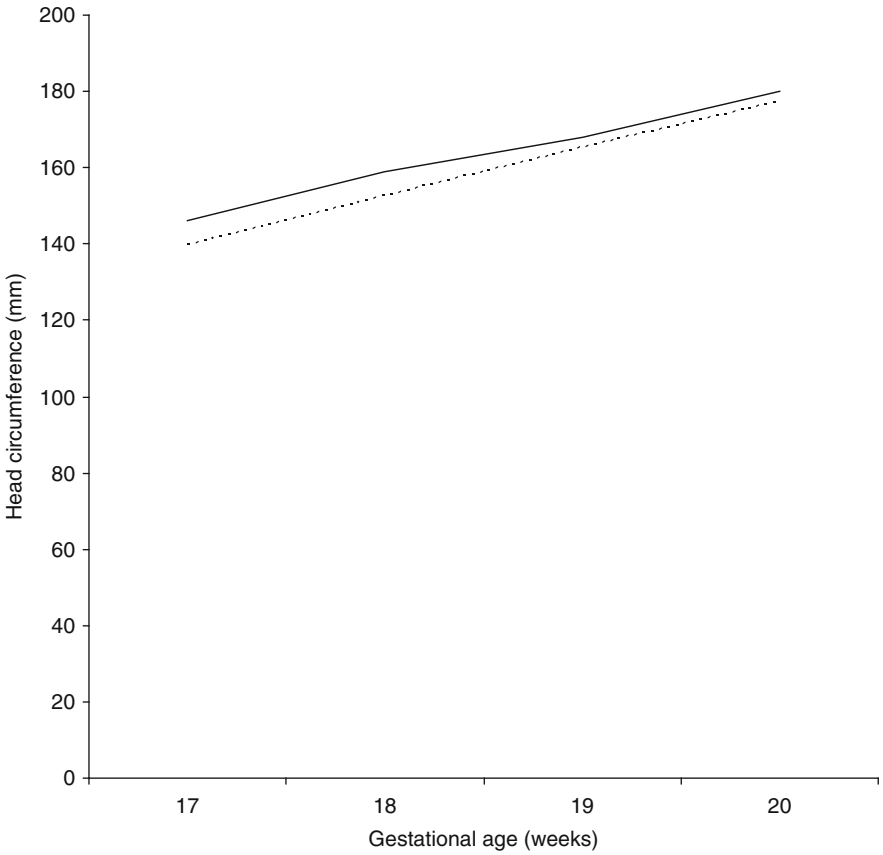

Fig. 26.23 Comparison between centile values of HC in African and European fetuses at 5 months (17–20 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 5 months (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed lines*). At 5 months, there is little difference in the values of European and African fetuses

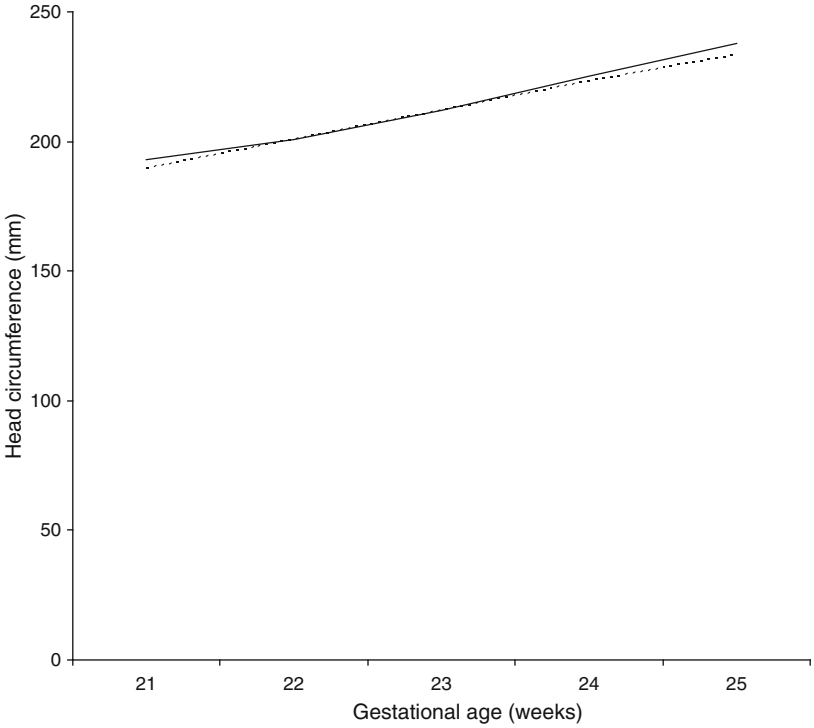

Fig. 26.24 Comparison between centile values of HC in African and European fetuses at 6 months (21–25 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 6 months (*solid lines*) with those of European – Kurmanavicius et al. (1999) (*dashed lines*). At 6 months, there is no difference at all in the values of European and African fetuses

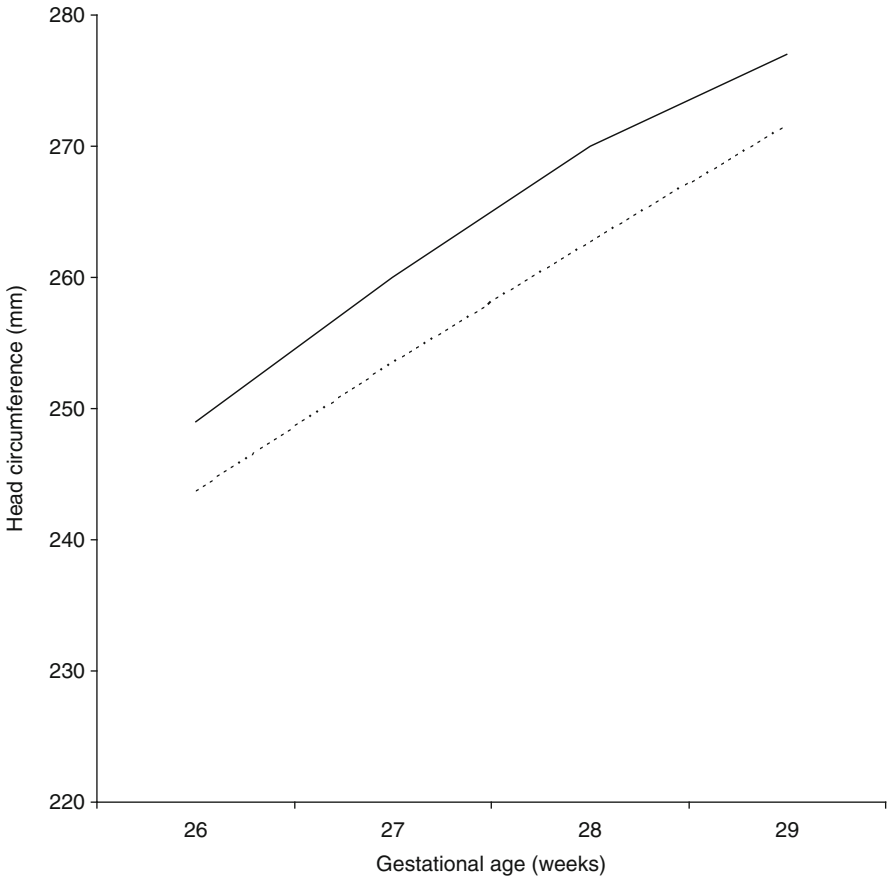

Fig. 26.25 Comparison between centile values of HC in African and European fetuses at 7 months (26–29 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 7 months (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed lines*). At 7 months, there is difference in the values of European and African fetuses

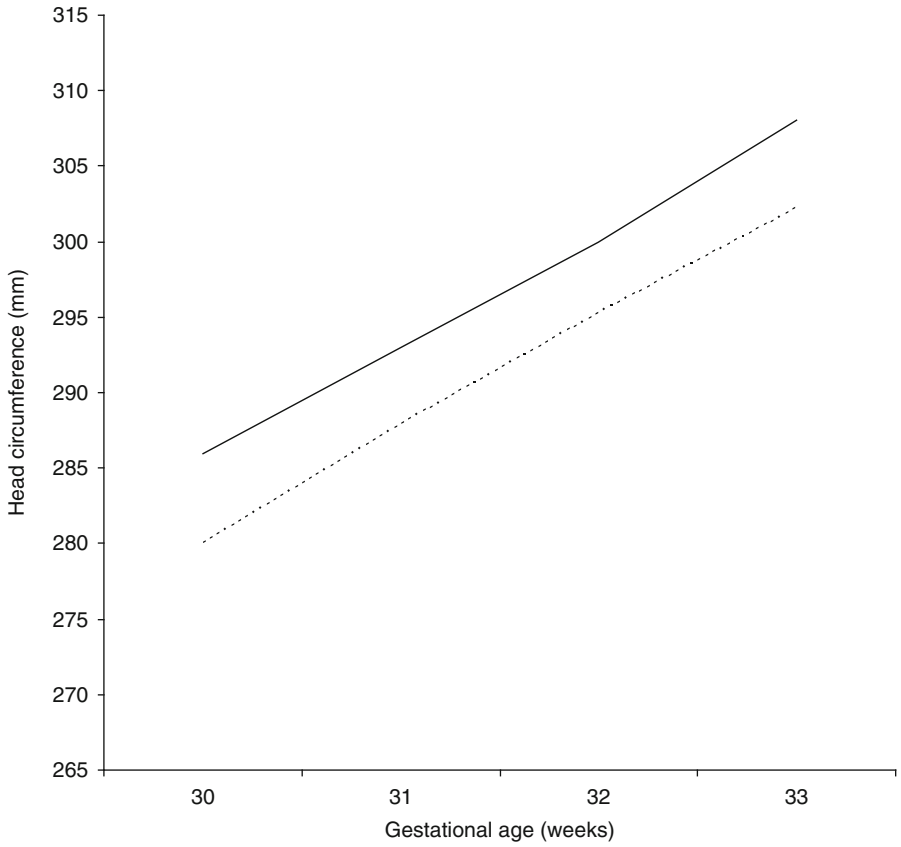

Fig. 26.26 Comparison between centile values of HC in African and European fetuses at 8 months (30–33 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 8 months (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed lines*). At 8 months, there is difference in the values of European and African fetuses

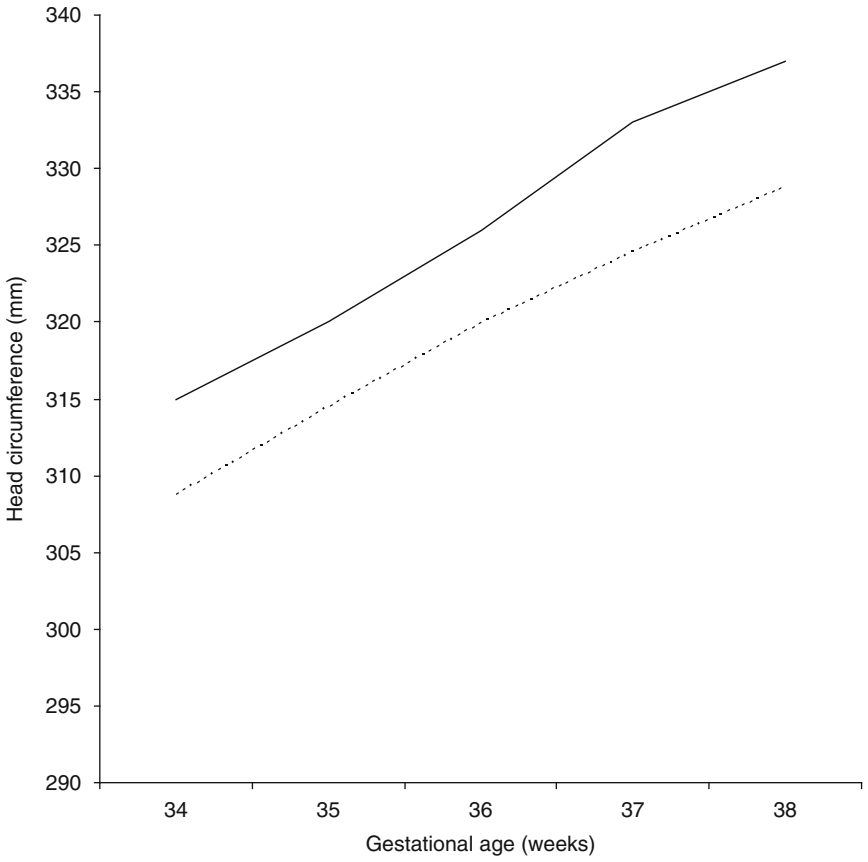

Fig. 26.27 Comparison between centile values of HC in African and European fetuses at 9 months (34–38 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 9 months (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed lines*). At 9 months, there is difference in the values of European and African fetuses, with African values being consistently higher than European ones

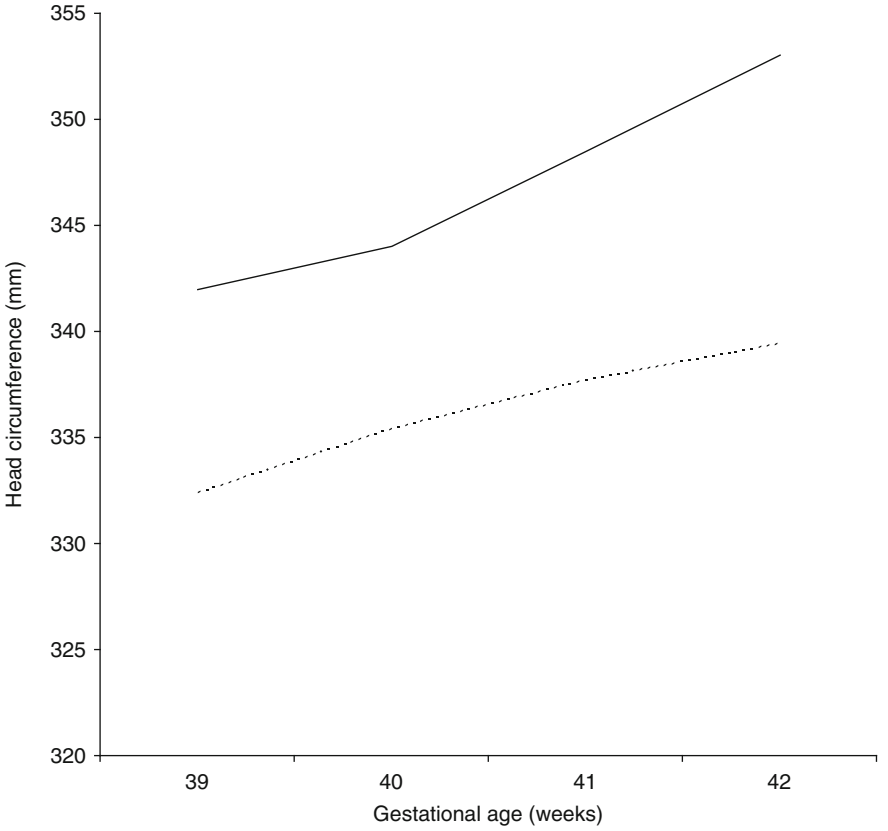

Fig. 26.28 Comparison between centile values of HC in African and European fetuses at 10 months (39–42 weeks) of gestation. Comparison of African (Nigerian) HC centile values in our study at 10 months (*solid lines*) with those of European fetuses – Kurmanavicius et al. (1999) (*dashed lines*). At 10 months, there is considerable difference in the values of European and African fetuses, with African values being consistently higher than European ones. The African values are highest over European ones at this month. It is obvious that, before birth, the African child is far more mature in HC than his European counterpart

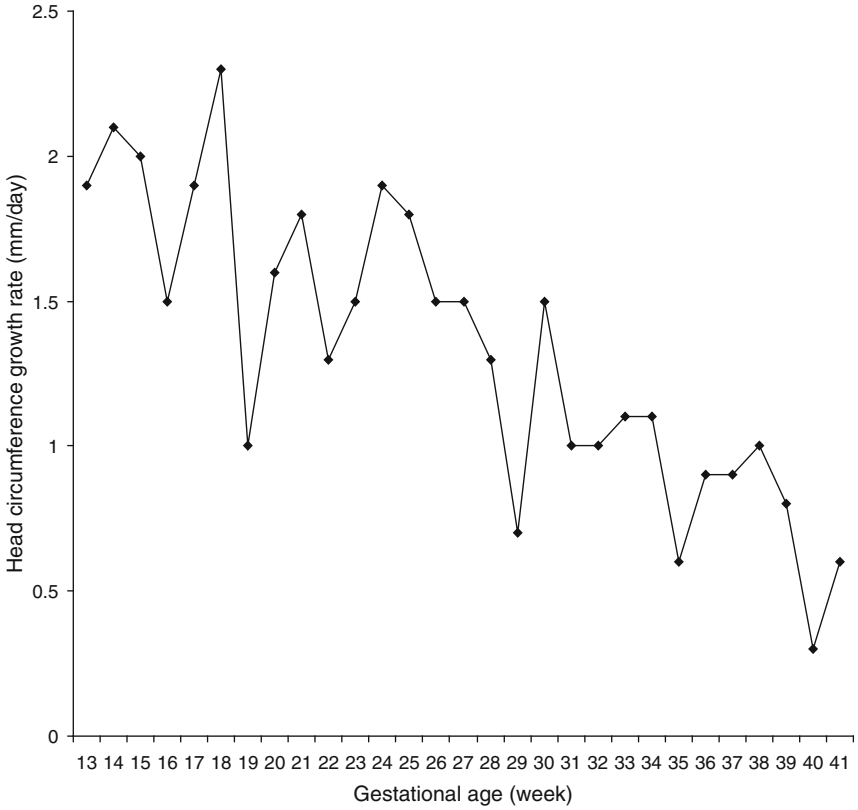

Fig. 26.29 Growth velocity pattern of head circumference in 13,740 Nigerian fetuses.Head circumference growth rate when compared to gestational age. It seems to fall from 12 weeks down to 41 weeks. Its pattern is similar to that of coefficient of dispersion of head circumference values in Figure 26.5

Table 26.8 Standard score (z-score) of HC measurements in 13,740 Nigerian fetuses ranging from 12 to 42 weeks of gestation

Gestational age	Fetuses (n)	Mean z-score
12 to 12 + 6	49	–2.14E-03
13 to 13 + 6	384	–1.46E-03
14 to 14 + 6	371	3.29E-03
15 to 15 + 6	351	–1.75E-03
16 to 16 + 6	505	–3.67E-03
17 to 17 + 6	427	1.35E-03
18 to 18 + 6	446	1.85E-03
19 to 19 + 6	282	–2.29E-03
20 to 20 + 6	553	–1.42E-05
21 to 21 + 6	400	–2.14E-04
22 to 22 + 6	398	–1.16E-03
23 to 23 + 6	478	8.13E-04

(continued)

Table 26.8 (continued)

Gestational age	Fetuses (*n*)	Mean *z*-score
24 to 24 + 6	520	2.31E-03
25 to 25 + 6	388	–2.50E-03
26 to 26 + 6	511	–3.48E-03
27 to 27 + 6	432	1.50E-04
28 to 28 + 6	548	2.63E-03
29 to 29 + 6	484	1.08E-03
30 to 30 + 6	625	2.87E-03
31 to 31 + 6	523	–4.62E-04
32 to 32 + 6	583	1.81E-03
33 to 33 + 6	516	–2.61E-03
34 to 34 + 6	744	–2.90E-03
35 to 35 + 6	739	–1.72E-03
36 to 36 + 6	599	1.58E-03
37 to 37 + 6	532	–1.89E-03
38 to 38 + 6	481	5.51E-05
39 to 39 + 6	525	–2.58E-03
40 to 40 + 6	252	4.50E-04
41 to 41 + 6	72	–3.77E-03
42 to 42 + 6	22	–1.56E-03
Total	**13,740**	

The *z*-score enables us to study head measurements in each gestational age and see how they compare on the same standard; taking into account the mean and SD of each gestational age. For example, HC measurements at 12 weeks are –0.002 SDs from the mean, whereas measurements at 14 weeks are 0.003 SDs from the mean. Again, from the above z-score table, it can be seen that the HC measurements at 20 and 38 weeks are 0.000 deviations from the mean

Table 26.9 Key facts of ultrasonic fetal anthropometry

1. Ultrasonic fetal anthropometry is a technique in sonographic embryology, which measures fetal parts
2. It uses focused, high-frequency sound waves to generate fetal images.
3. It is not invasive
4. Sound is the orderly transmission of mechanical vibrations through a medium
5. The number of these vibrations per second is the frequency (measured in hertz)
6. Audible sounds are in the range of 20–20 kHz
7. "Sound" above 20 kHz is described as ultrasound
8. Ultrasound allows detailed examination of fetal anatomy
9. It is safe for the patient, the fetus, and the sonologist
10. Ultrasonic fetal anthropometry is now the gold standard for assessing fetal growth
11. It involves measurement of BPD, HC, OFD, AC, FL, and fetal weight

This table lists the key facts of ultrasonic fetal anthropometry, the parameters measured using it, its safety, uses, and application in modern embryology

Summary Points

- This chapter provides extensive data for HC of 13,740 African (Nigerian) fetuses and suggests the early maturation of HC in African children vis-a-vis European children is a genetic rather than nutritional factor.
- Head circumference has been implicated in various conditions and is related to brain size, brain development, intelligence, maternal nutrition, ethnic group, and race.

- Head circumference is related to intracranial volume and permits an estimation of the rate of brain growth.
- Head circumference became a useful tool in determining the characteristics of human intelligence since Galton.
- Head circumference is a very useful tool in ultrasonic or sonographic embryology, as it can be used to predict congenital anomalies as well as embryological dating and clinical staging/dating of pregnancy.
- Limitation of growth potential in the fetus, called IUGR, can be either symmetrical or asymmetrical.
- Symmetrical growth retardation implies a fetus whose entire body is proportionally small.
- Asymmetrical growth retardation implies a fetus that is undernourished and is directing most of its energy to maintaining growth of vital organs, such as the brain and heart, at the expense of the liver, muscle, and fat.
- It is well established that the state of maternal nutrition influences the nutrition and subsequent growth and development of the child.
- Microcephaly is that neurological development disorder in which the HC is less than the 3rd centile for a person's age and sex.
- There is a positive polynomial correlation between gestational age (in months) and HC (in millimeters), with a correlation coefficient of $R^2 = 0.9991$ ($p < 0.0001$) in Nigerian fetuses.
- The relationship is best described by the second order polynomial regression equation $y = -3.3238x^2 + 85.755x - 177.78$, where y is the HC in millimeters and x is the gestational age in months.
- The African fetus' HC increases faster than that of the European fetus and is bigger than it at birth, on average.
- The interplay of nurture rather than nature has placed the African in a disadvantaged position not only for HC but also in other well-known anthropometric parameters, such as height and even weight after birth.
- The future and intelligence of the growing African is dependent on his nurture more than his nature and this may account for the spuriously low IQ frequently reported by some investigators in Africa.

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Chapter 27
Anthropometry of the Intracranial Volume

Bunyamin Sahin

Abstract Intracranial volume (ICV) is an important data to evaluate the premorbid brain size in pathological conditions. It is also one of the most important characters for determining the racial difference. Several methods have been proposed for the assessment of ICV. Some of them are used only for the macerated skulls and most of them are suitable both for the dry skulls and living subjects. The packing/filling method is the most accurate in vitro method for the measurement of ICV. The others are the craniometry and cephalometry methods predicting the ICV using the measures of length, width and height of the skull directly over the bony structure or lateral and antero-posterior roentgenograms. Finally, the stereological methods are the recently proposed techniques that provide unbiased estimation of the ICV. The requirement for the application of this method is an entire set of two-dimensional slices through the object, provided they are parallel, separated by a known distance, and begin randomly within the object, criteria that are met by standard magnetic resonance and computed tomography imaging techniques. In the presented section we discussed the methods for the assessment of ICV. The filling method seams to be the most accurate for the assessment of cranial capacity. However, it must be used on macerated skulls. Even though the craniometry and cephalometry are quick and easy to apply, the obtained values may not be accurate. The stereological techniques require much more time than the others. However, the obtained values are unbiased and the method could be applied for living subjects.

Abbreviations

CE	Coefficient of error
CI	Cephalic index
CT	Computed tomography
ICV	Intracranial volume
MR	Magnetic resonance

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_27,

27.1 Introduction

There is a close relation between the size of the head and the brain. Brain growth drives skull growth during childhood (Sgouros et al. 1999; Knutson et al. 2001). The intracranial volume (ICV) increases with age from birth throughout childhood. Maximum growth is achieved in the first 5 years (Piatt and Arguelles 1990–1991; Sgouros et al. 1999). At the age of 16–20 years, ICV reaches its final size and it is thought that ICV does not change its size thereafter (Knutson et al. 2001; Wolf et al. 2003). At about 20 years of age, the volume of the brain starts decreasing, whereas it is presumed that ICV remains constant (Rushton and Ankney 1995; Wolf et al. 2003). Experience has suggested that ICV remains stable even after brain atrophy. Thus, ICV is generally considered to be a more accurate indicator of mature brain volume than head size (Wolf et al. 2003). By combining measures of brain volume and ICV, investigators can infer how much reduction in volume has occurred since brain volume was at a maximum (Jenkins et al. 2000; Knutson et al. 2001). Alternatively, ICV measurements may provide reliable indications of the premorbid brain size in neurodegenerative diseases (Jenkins et al. 2000). For this reason, many studies focus on the assessment of ICV.

Several methods have been proposed for the assessment of ICV of macerated skulls. The packing/filling technique is the most accurate in vitro method for measuring ICV. Other methods such as the linear measurement of skulls and cephalometry are used to predict ICV using the measures of length, width, and height of the skull directly over the bony structure, or lateral and anteroposterior roentgenograms (Manjunath 2002a).

Finally, the recently proposed techniques include the stereological methods that provide unbiased estimation of ICV. The requirement for the application of this method is an entire set of two-dimensional slices through the object, provided they are parallel, separated by a known distance, and begin randomly within the object, criteria that are met by standard magnetic resonance (MR) imaging and computed tomography (CT) techniques (Acer et al. 2007; Sahin et al. 2007, 2008).

27.2 Application to Other Areas of Health and Diseases

The human brain varies widely in size (Knutson et al. 2001). There are several factors that contribute to this variation. Factors related to brain growth, such as gender and physical size, are thought to influence the maximal size of an individual's brain (Raz et al. 1998; Sgouros et al. 1999). Large variability in brain size related to age, sex, and body size makes it difficult to compare solely the brain volume among individuals. To calibrate these variations, the volume fraction between the brain and the intracranial cavity should be evaluated (Whitwell et al. 2001, Mazonakis et al. 2004b). Hence, ICV provides a more stable and accurate normalization factor for estimating volumetric changes at the onset of a disease (Eritaia et al. 2000).

Cranial capacity constitutes one of the most important characteristics for determining racial differences (Hwang et al. 1995; Manjunath 2002a, b). For this reason, the assessment of the accurate volume of the intracranial cavity is very useful for anthropometric studies.

27.3 Intracranial Volume Assessment Techniques

27.3.1 Filling Method

The ICV of the skull can be determined by filling skulls with water and subsequently measuring the quantity of water using a cylindrical measuring glass. For this purpose, ordinary balloons may be

introduced into the cranial cavity via the foramen magnum and filled with water under the pressure. After the filling process, water is poured into a measuring cylinder, and this volume is taken as a measure of the total ICV.

This method is one of the most satisfactory methods of measuring ICV of a dry skull. Acer et al. (2006) tested the accuracy of the method by measuring the cranial capacity ten times of the same cranium; the difference between all measurements varied between 5 and 10 cm^3.

However, the balloons which are lowered into the cranial cavity may burst when they touch the sharp bony structures in the skull base. The problem can be solved by using thicker balloons. Additionally, the procedure of filling the cranium with liquid may be controlled by using an apparatus that measures the pressure within the cranial cavity. This may make it possible to judge the course of filling and the point of termination (Manjunath 2002a).

27.3.2 Packing Method

Packing the skull with a flowing material and measuring its amount is another common method for the assessment of ICV. The filling materials may be small-sized lead shots, sand, seeds, grain, millet, lentil, etc. Before the packing, the holes of the skull should be sealed to protect the leakage of the packing material.

The packing material is poured into the skull through the foramen magnum by means of a funnel. After the introduction of half the material, some of the filling material is shaken front down to ensure the filling of the anterior cranial fossa. As further lead, they are poured and packed by fingers to fill the intracranial cavity entirely. The skull is turned upside down, the packing material is poured into a measuring cylinder, and the amount of the packing material is recorded as the total ICV (MacKinnon 1955).

27.3.3 Craniometry

Craniometry is the technique of measuring the bones of the skull. In this technique, linear distance is measured between a variety of defined cranial and mandibular landmarks (Standring 2005). Some special gadgets (e.g., caliper, head spanner, and measuring tapes) are used for the measurements (Fig. 27.1).

Generally, a measured distance is divided by another distance. Finally, some key indices, which are expressed as percentages, are obtained. The most frequently used index (the breadth/length index) is called the cranial index or cephalic index (CI) in living subjects. It was widely used by anthropologists in the early twentieth century to categorize human populations. Today, the index is only used to describe individuals' appearances and to estimate the age of fetuses for legal and obstetrical purposes. A skull with a CI below 75% is classified as dolichocephalic (long headed). If the CI ranges between 75% and 79.9%, it is classified as mesocephalic (moderate headed). Skulls with a CI greater than 80% are classified as brachycephalic (broad headed) (Standring 2005; http://en.wikipedia.org).

Several formulas have also been calculated to estimate cranial capacity from linear measurements of the length, breadth, and height of the cranium (in centimeters). The standard linear measurements for the craniometry are follows:

1. Maximum head length: The distance between the glabella and inion (*L*).
2. Maximum head breadth: The distance between the parietal eminences (*W*).
3. Auricular height: The distance between the external acoustic meatus and the highest point of the vertex (*H*).

Fig. 27.1 A head spanner and its usage for the measurement of the length and the breadth of a skull

The data obtained from the linear measures are treated with regression formulas proposed by many authors (MacKinnon et al. 1956; Manjunath 2002a; Williams et al. 1989). It should be reminded that all the proposed formulas are the driven from a collection of skulls with known volumes and measured distances. Therefore, the proposed formulas may be different between the races. Moreover, the formulas may change depending on the researches. For this reason, such formulas involve some inaccuracy. The most recently used formula for the prediction of ICV is given by Williams et al. (1989).

$$\text{Males}: \quad 0.337 \times L \times W \times H + 406.01\ \text{cm}^3 \tag{27.1}$$

$$\text{Females}: \quad 0.400 \times L \times W \times H + 206.60\ \text{cm}^3 \tag{27.2}$$

The craniometry measurements are repeated at least three times and the average is considered for the calculation. It is recommended that the same performer should be employed for a particular study.

27.3.4 Cephalometry

Cephalometry is the measurement of the linear distance between certain landmarks of skull from roentgenograms. It is another common method predicting ICV using measurements of length, width, and height of the skull directly over the bony structure on lateral and anteroposterior roentgenograms (Manjunath 2002a).

Cephalometric measurements can be done on any standard lateral and anteroposterior roentgenograms of the skulls. An iron bar with a known length must be placed next to the skull to set the magnification rate of the measurements on the roentgenograms. Nowadays, the digital roentgen machines provide a scale indicating the reduction or magnification rate of the images. Therefore, an iron bar may not be required in practice. The distance between certain landmarks is measured and recorded in centimeters. For this purpose, internal length (*L*), internal height (*Hi*), diameter from

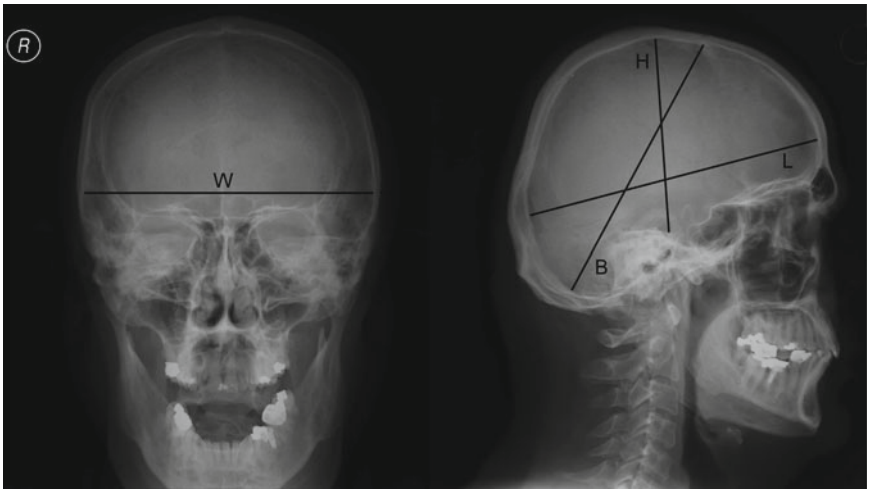

Fig. 27.2 Two standard anteroposterior and lateral cephalograms. Internal length (*L*), internal height (*H*), diameter from bregma to posterior cranial fossa (*B*), and width (*W*)

bregma to the posterior cranial fossa (*B*), and width (*W*) of the skulls on roentgenograms are measured (Fig. 27.2).The obtained data are used for the prediction of ICV by means of a regression formula.

ICV can be calculated using the formula proposed by Bergerhoff, as interpreted below (Sahin et al. 2007).

$$V = \left(\frac{L}{2}\right) \times \left(Hi + \frac{B}{4}\right) \times \left(\frac{W}{2}\right) \times 0.51 \times 8\ \text{cm}^3 \tag{27.3}$$

Published studies use different formulas for the estimation of ICV on roentgenograms, the most commonly used being the ellipsoid formula and MacKinnon's formula or its variations (Sgouros et al. 1999). MacKinnon (1955) was the first to demonstrate a method to estimate the cranial capacity using the cranial length measured on lateral roentgenograms. MacKinnon and his colleagues (1956) in their further studies derived a reliable method for estimating cranial capacity from roentgenograms. The internal lengths, heights, and some other data were measured and a prediction formula was proposed. This formula had been advanced and a new prediction formula based on the resemblance of the cranial cavity to an ellipsoid had been proposed.

A comparative and gold standard study carried out by Sahin et al. (2007) revealed that the volume prediction results obtained by anthropometry and cephalometry were statistically significantly different from the actual volume of skulls obtained by the water-filling method. However, the results of these two methods correlated well with the actual volume of skulls.

In addition to MacKinnon's formula and its variations, several formulas have also been constructed to indicate cranial capacity from length, width, and height of the cranium. However, such volume determinations may be considered to be inaccurate due to their dependence on linear measurements and due to the limited cephalometric landmark validity characterizing the skull radiographs. Various corrections do not entirely remove this inaccuracy (Williams et al. 1989; Sgouros et al. 1999; Mazonakis et al. 2004b).

This problem may be solved by proposing new formulas for different societies or nations. No one can, however, give the assurance that the normalized results are accurate, as the cephalometry method

obtains data from two-dimensional linear measurements. Since the third dimension is absent, these methods always fail to provide accurate information about the third-dimensional value, volume (Sahin et al. 2007).

27.3.5 Cavalieri Principle

Unbiased estimation of organs or structures can be done using the Cavalieri principle of stereological approaches (Cruz-Orive 1997; Roberts et al. 2000). The requirement for applying this method is an entire set of two-dimensional slices through the object, provided they are parallel, separated by a known distance, and begin randomly within the object – criteria that are met by standard sectional radiological imaging techniques. The section thickness of the images is multiplied by the cut surface area of the sections, and the total volume of the interested object is estimated. The cut surface areas of the sections can be estimated using planimetry and point-counting approaches, two methods for estimating volume based on the Cavalieri principle (Sahin and Ergur 2006).

Sectional imaging modalities have provided an opportunity for volumetric quantification of the intracranial cavity. Both CT and MR imaging may produce reliable measurements of ICV. Magnetic resonance imaging offers optimal soft-tissue contrast resolution and multiplanar capability without the use of ionizing radiation. However, CT imaging is still a powerful modality for central nervous system imaging and for subsequent routine ICV measurements because of the reduced scanning duration, its availability, and the detailed depiction of bony structures (Laughlin and Montanera 1998; Sugouros et al. 1999; Mazonakis et al. 2004b).

27.3.5.1 Point-Counting Method

The point-counting method consists of overlying each selected section with a randomly positioned, regular grid of test points. A test point is a plus-shaped line (+) and it is counted if a previously assigned corner of the intersection of the cross lines hit the object. After each superimposition, the number of test points hitting the structure of interest on the sections is counted (Fig. 27.3). Finally, the volume of the structure is estimated by multiplying section thickness, total number of points, and the area represented per point in the grid (Sahin and Ergur 2006). The unbiased estimator is written as follows:

$$V = t \times \frac{a}{p} \times \sum P \text{ cm}^3 \tag{27.4}$$

where t is the section thickness of consecutive sections, ΣP denotes the point counts and (a/p) represents the area associated with each test point, corrected for any change of scale in the images, as it is printed on the hardcopy films (Sahin et al. 2003b).

In the sectional radiological studies, the examined structures are reduced in size. Therefore, it is crucial to know the actual representative area for the points. The magnification or reduction correction may sometimes be tedious. Using the following formula for the scale correction of radiological images will solve the problem:

$$V = t \times \left(\frac{\text{SU} \times d}{\text{SL}} \right)^2 \times \sum P \tag{27.5}$$

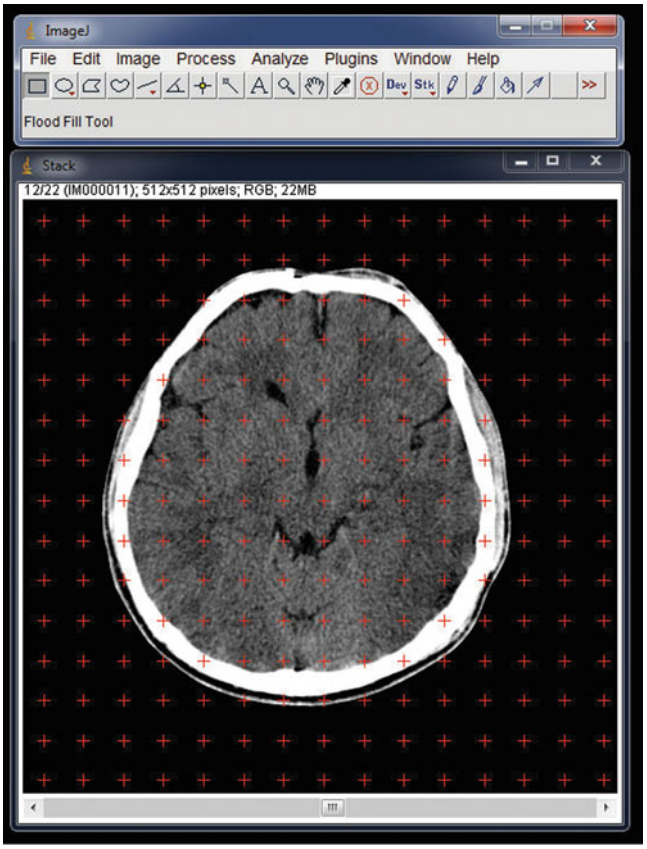

Fig. 27.3 A computed tomography (CT) scan in axial section. A transparent square-grid test system is superimposed randomly covering the entire image frame to estimate the section cut surface area

where t is the section thickness of consecutive sections, SU is the scale unit of the printed film, d is the distance between the test points of the grid, SL is the measured length of the scale printed on the film, and ΣP is the total number of points hitting the sectioned cut surface areas of intracranial space (Sahin and Ergur 2006).

27.3.5.2 Planimetry Method

Planimetry, which involves manually tracing the boundaries of objects of interest on images of sections, is the most commonly used technique. The sum of the measured areas of sections obtained by planimetry is multiplied by the section thickness, and the volume of the structure is estimated (Sahin and Ergur 2006).

The cross-sectional surface area of intracranial space can be measured by the planimetry method using free software. DicomWorks and ImageJ are found on the Internet for free. The latter is distributed by the National Institutes of Health, USA. The final release of the ImageJ has good tools for the estimation of surface area of the structures of interest.

Before the estimation, the scale of the image should be set in the software being used. Following the setting of the image size, the inner boundaries of the skull should be manually traced on each section using the mouse. If the region of interest is distinguished from the surrounding structures

Fig. 27.4 A CT scan in axial section. Inner boundaries of the skulls are manually traced on images to calculate the section cut surface area in the planimetry method

clearly, threshold processing of the program can be done. In this case, clicking on the surface of interest is enough to delineate its boundaries. Then, the software automatically calculates the number of pixels enclosed by the traced skull contours in each section and provides the cross-sectional area of the skull on a slice-by-slice basis (Fig. 27.4). The sum of the areas multiplied by the section thickness provides ICV. The planimetric volume estimation formula can be written as follows:

$$V = t \times \sum A \tag{27.6}$$

where t is the section thickness of consecutive sections and ΣA is the total sectional area of the consecutive sections (Sahin et al. 2003a).

27.4 Planimetry Versus Point Counting and Some Other Details on the Cavalieri Principle

The stereological approach allows the researcher to make appropriate changes on their sampling or estimating procedures. Therefore, the presented method provides a coefficient of error (CE) of estimation for each volume assessment. This way, a researcher can see the potential variability in any given volume measurement. When the CE is high, it can generate obvious problems in accuracy and

hence interpretation. These problems may arise if too few slices or too few points are used for volume estimation. The observer is eligible to change the spacing of points in the grid or the number of slices available in any CT study to obtain a reasonable CE value. It is also important to note that an appropriate grid size and the number of slices required for volume estimation of an object are crucial at the beginning; there is no need to calculate the CE value for repeated sessions (Sahin et al. 2003a). A CE value lower than 5% is in the acceptable range (Gundersen and Jensen 1987).

In the point-counting method, the CE of estimates can be evaluated by means of these consecutive two formulas.

$$\text{Noise} = 0.0724 \times \left(\frac{b}{\sqrt{a}} \right) \times \sqrt{n \times \sum P} \tag{27.7}$$

Noise gives information about the complexity of the examined cut surface area of the specimen. Calculation of the CE using these equations requires knowledge of the value of a dimensionless shape of coefficient $(b / \sqrt{a})$, which is equivalent to the mean boundary length of the profiles divided by the square root of their mean area, and which is a measure of the average shape of the profiles through the structure of interest on the sections. It can be determined using the diagram proposed by Gundersen and Jensen (1987). Five may be a good value for the estimation of ICV; *0.0724* is a constant; n is the total number sections, and ΣP is the total number of points hitting the sectioned cut surface areas of intracranial space.

The final step of the CE estimation is as follows:

$$\text{CE} = \left(\sum_{i=1}^{m} P_i \right)^{-1} \times \left[\text{Noise} + \left(\frac{1}{12} \times \left(\left(3 \times \sum_{i=1}^{m} P_i^2 - \text{Noise} \right) - \left(4 \times \sum_{i=1}^{m-1} P_i \times P_{i+1} \right) + \left(\sum_{i=1}^{m-2} P_i \times P_{i+2} \right) \right) \right) \right]^{1/2} \tag{27.8}$$

where, $i = 1, 2, \ldots, m$ is the number of sections, P is the number of point hitting the sectioned surface areas, Noise is the value obtained earlier, and the others are constants (Gundersen and Jensen 1987; Sahin et al. 2003b).

In the planimetry method, the CE of estimates may be obtained using the following formula:

$$\text{CE} = \left(\sum_{i=1}^{n} A_i \right)^{-1} \times \left[\frac{1}{12} \left(3 \sum_{i=1}^{n} A_i^2 - 4 \sum_{i=1}^{n-1} A_i A_{i+1} + \sum_{i=1}^{n-2} A_i A_{i+2} \right) \right]^{1/2} \tag{27.9}$$

where, $i = 1, 2, \ldots, m$ is the number of sections, A is the measured area of the sections using planimetry, and the others are constants. This formula allows the researcher to evaluate the area changes and the measured cut surface areas in the consecutive section series (Mazonakis et al. 2002; Sahin et al. 2008).

The stereological technique may be optimized by systematically sampling CT sections and by determining an optimum distance between test points of the grid. The counting of approximately 115 points on six to eight systematically sampled CT sections enables the determination of ICV with a CE below 5% in less than 3 min.

The combination of the optimized stereological technique with CT scanning gives the possibility of obtaining acceptable ICV estimations with minimal effort (Mazonakis et al. 2004b). Eritaia et al. (2000) reported that there is a positive relationship between the number of slices used to estimate ICV and the accuracy of that measurement. As the number of slices sampled decreased, ICV between

the estimated ICV and the actual ICV also decreased. In addition, the variance of the estimated ICVs increased. They also reported that ICV can be confidently traced using a 1/10 section sampling strategy, which should result in significant timesaving. This sampling strategy produced 5–10% difference between the estimated volumes. However, it reduced the time required for ICV measurement from 120 to 10 min with minimal loss of accuracy or reliability (Eritaia et al. 2000). Decreasing the number of examined slices by using systematic random sampling will decrease the required time period for the point-counting and delineation process.

Calculation of ICV, CE of estimates, and other related data may be obtained as a spreadsheet using Microsoft Excel for the point-counting and planimetry methods.

Good agreement is reported between results obtained with the point-counting and planimetry techniques, the former being 50% faster. As the point-counting method can be applied to any sets of printed CT images, this approach allows one to perform retrospective and prospective studies, without engaging the CT machines and their PC accessories. Moreover, the procedure of manually tracing boundaries of the intracranial cavity in all CT sections using planimetry is tedious and requires experience (Mazonakis et al. 2002; Sahin and Ergur 2006).

Intracranial volume measurements using CT scans have already been reported in the literature (Abbott et al. 2000; Wolf et al. 2003; Mazonakis et al. 2004b). Most of these attempts to determine ICV were carried out using the technique of manual planimetry (Lyden et al. 1994; Abbott et al. 2000; Mazonakis et al. 2004b). The studies reported that operator intervention was necessary to manually trace the intracranial cavity borders on CT sections. However, manual delineation of the intracranial cavity boundaries is a tedious and labor-intensive process. Point-counting estimations are based on the process of point counting and not on the user's skill in delineating the boundaries of the structure of interest (Mazonakis et al. 2004b). Most of the studies adopting the point-counting technique for organ volume estimations have mentioned that this volumetric approach is superior to the technique of planimetry (Mazonakis et al. 2002, 2004a).

Sahin et al. (2007) used point-counting and planimetry techniques to estimate ICV in a series of CT sections. The results obtained with these two methods were compared with each other and also with the results of other methods. Finally, the results of stereological estimates were compared with the actual volume of skulls to check the accuracy. Their findings revealed that there was no difference between the results of the point-counting and planimetry methods. The results of both stereological methods were, however, statistically significantly different from the actual volume of the skulls. Correlation analysis revealed that the results of point counting and planimetry not only correlated well with each other but also with the actual volume of the skulls. The systematic deviation from the actual volume for the point-counting and planimetry methods resulted in underestimation (Sahin et al. 2007).

Their results showed that increasing the CT section thickness can lead to a growing discrepancy between ICV measurements and the actual volume. This is mainly attributed to the influence of section thickness on the partial volume artifacts presenting on cross-sectional images. It is well known that partial voluming arises when a voxel contains different types of tissues. As a result, the reconstructed intensity ascribed to this voxel in the displayed CT image represents an intermediate value that does not correspond to any real tissue. The partial volume effect is more pronounced in thick sections and can considerably influence the accuracy of the obtained volume measurements (Nawaratne et al. 1997). To minimize this effect, the operator should select CT sections of sufficiently small thickness, thus securing constant attenuation characteristics across the imaging plane.

The problem of underestimation of the stereological methods probably originates from the effect of section thickness on the printed two-dimensional images (Sahin et al. 2008). There are restricted studies evaluating the effects of section thickness on the estimated volume of structures using CT and MR images (Emirzeoglu et al. 2005; Sahin and Ergur 2006). Sahin et al. (2008) evaluated the effect of

section thickness on the estimated ICV in CT imaging. Decreasing the slice thickness to less than 10 mm may decrease the under-projection effect of sectioned structures, which may result in a smaller degree of underestimation (Emirzeoglu et al. 2005; Sahin and Ergur 2006). They scanned the skulls with 2, 3, 5, 7, and 10 mm thicknesses. The volume of the cranial cavity was systematically overestimated in 2 mm-thick scanned sections compared with the actual value of ICV. A mean overestimation of up to 2.0% was found ($p < 0.05$). For section thicknesses of 3, 5, 7, and 10 mm, however, a systematic volume underestimation was observed ($p < 0.05$). The mean underestimation compared to the actual volume of the dry skulls was 2.2–8.5% and 2.6–7.0%, respectively. Ideally, CT scanning with 2.5 mm-thick slices will lead to an ICV estimation that does not deviate from the actual volume. Their study provides a simple mathematical formula that allows the user to calculate the deviation of the estimated ICV from the real volume, if the scanning thickness is different from the ideal (Sahin et al. 2008).

During the windowing of frames, different levels of settings to obtain best view are chosen. Windowing adjustments are related to the nature of scanned structure and the imaging technique. Moreover, Diederichs et al. (1996) showed that a proper windowing must be chosen to obtain maximum intensity projections. In living subjects, the skull is filled with brain, meninges, and cerebrospinal fluid. During the scanning, these structures absorb or reflect X-ray waves to different degrees. For these reasons, windowing parameters must be standardized in the comparative studies.

Summary Points

- The ICV gives information about how much reduction in volume has occurred since brain volume was at its peak. It provides a more stable and accurate normalization factor for estimating volumetric changes at the onset of a disease. It is one of the most important characteristics for determining racial difference.
- Several methods have been proposed for the assessment of ICV. The packing/filling method is the most accurate in vitro method for the measurement of ICV; the others are the craniometry and cephalometry methods. Finally, the stereological methods are the recently proposed techniques that provide unbiased estimation of ICV.
- In the water-filling method, ordinary balloons are inserted into the cranial cavity via the foramen magnum and filled with water under pressure. This method is one of the most satisfactory methods of measuring ICV of a dry skull, and is easy and simple. However, the balloon may burst when it touches the sharp bony structures in the skull base.
- In the packing method, the packing material is poured into the skull through the foramen magnum. As a second step, it is poured into a measuring cylinder and the amount of the packing material is recorded as the total ICV.
- In the craniometry method, the length, width, and height of the skull are measured and the obtained values are treated with the prediction formulas. The formulas may change depending on the race and researches. For this reason, such formulas involve some inaccuracy. Additionally, the same performer should be employed to avoid inter-observer variation.
- The breadth/length index is called the CI. It is only used to describe individuals' appearances and for estimating the age of fetuses for legal and obstetrical purposes. CI below 75% is a long head; that ranging between 75% and 79.9% is a moderate head; and that greater than 80% is a broad head.
- The first formula for the cephalometry was proposed by MacKinnon and his colleagues. For cephalometry, internal length, internal height, diameter from bregma to the posterior cranial fossa, and width of the skulls on roentgenograms are measured. The obtained data are treated with the several regression formulas for the estimation of ICV.

- In the Cavalieri principle, sectional radiological images are used for the estimation of volume. The cut surface areas of the sections are multiplied by the section thickness and the volume is estimated. Point counting and the planimetry are two methods for estimating the cut surface area of the sections.
- In the point-counting method, the volume of the structure is estimated by multiplying section thickness, total number of points, and the area represented per point in the grid.
- The point-counting method is practical and rapid. It does not require sophisticated gadgets. It is timesaving and ideal both for retrospective and prospective examinations.
- Planimetry involves manually tracing the boundaries of objects of interest on images of sections. The sum of the measured areas of sections obtained by planimetry is multiplied by the section thickness and the volume of the structure is estimated.
- Some of the following factors should be considered for the estimation of ICV using CT sections: increasing the CT section thickness can lead to decrease in ICV measurements; ideal section thickness is 2 or 3 mm – if the section thickness is different, some of the correction formulas can be used; standard and optimum windowing should be chosen.

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Chapter 28
Anthropometry and Numerical Simulations of a Child Head Model

Sébastien Roth, Jean-Sébastien Raul, and Rémy Willinger

Abstract During growth, a child's head undergoes different modifications in morphology and structure. This chapter presents an anthropometric study in terms of dimension compared to a mathematical method called "the scaling method" consisting of reducing the adult head model with a scaling coefficient to obtain a child head. A detailed sizes and shape analysis of brain contour in sagittal and frontal plans is proposed, for child head versus a scaled adult head. The superimposition of these contours allowed pointing to main differences. Numerical simulations performed with detailed child head model of Strasbourg University, and a scaled adult head finite element model, showed that reducing an adult finite element model to obtain a child head by scaling method does not seem to be realistic. Then, the anthropometry of child head is a fundamental aspect and the creation of specific finite element models of child head are necessary to investigate child injury mechanisms at a numerical level.

Abbreviations

FEM	Finite Element Model
YOC	Year-Old Child
MOC	Month-Old Child
CSF	Cerebrospinal Fluid

28.1 Introduction

According to epidemiological studies reported in several countries, traumatic brain injury (TBI) is a major cause of death and disability among the young paediatric population. The most frequent causes of TBI are vehicle traffic accidents, falls and mishandling (Viano et al. 1997). Determination of reliable injury criteria and tolerance limits is essential for understanding injury occurrence mechanisms and for development of protective devices. Investigations of these injuries use comprehension of dynamic behaviour of brain tissues. One of the ways to investigate head trauma is

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_28,

numerical methods. Indeed, comparing the gravity and type of lesions of the trauma with results of accident simulations can lead to correlate mechanical parameters with specific injuries.

Accident studies in the literature often highlight the gravity and type of lesions of the head/neck system at specific ages, and vary if the accident involves a child or an adult. Indeed, the response of a complex system such as the head is closely linked to the size, the geometry and the constitutive law of the brain and skull.

In order to comprehend head injuries better, many works have experimented using dummies or animals, leading to the definition of injury criterion, such as the HIC (Head Injury Criterion), which is the most commonly used one. However, even if this criterion can evaluate the gravity of a lesion, it cannot make a clear distinction between different injury mechanisms during an impact; this is because it is based on only linear acceleration, and mechanical parameters are not taken into account. Progress in computer science allows development of new methods and new ways in head/neck system studies in order to perform precise finite element (FE) simulations.

Several FE models of the adult head have been developed in the last few decades in order to simulate real-world head trauma with the aim of developing predictive tools for appearance of injuries.

In parallel to adult head studies, the biomechanics for child head injuries become increasingly important. Indeed, accidental free falls or mishandling, such as 'the shaken baby syndrome', are very specific accident cases, very different from adult cases, involve many children and need to be clearly understood. So, it seems very important to study very specific child injury mechanisms.

In this context, it appears very important to investigate the child head at a morphological, anthropometric level, in order to motivate the development of a specific FE model of the child head.

Biomechanical studies investigate the adult head with many criteria and tolerance limits that have been developed using different methods: dummies, finite element analysis, multibody analysis, etc. Some of these methods have been adapted to the child head without considering the consistency of scaling geometry or tolerance limit.

In a first step, a detailed study on child head evolution at a morphological and structural level will be made, with a specific question: 'Can a child head be considered as a scaled adult head?' One of the typical methods, called 'the scaling method', is described in this section and poses questions about its use, its limitations and its guidelines.

According to specific guidelines, specific FE models can be developed by taking into account the main features of the child head, according to the age (fontanels, sutures, diploe, etc.). These realistic models in terms of geometry need accurate material laws to be implemented in an FE code, in order to be a 'biofidelic' model, which can be used for accident reconstructions which are specific to child trauma.

28.2 Child Head Morphology and FE Analysis

28.2.1 Anatomical and Morphological Features of Child Head

We focus first on the morphology of paediatric head as a function of age, and its evolution during growth. At birth, the neurocranium (occipital, sphénoïdal, temporal, parietal and frontal bones) appear to be large relative to the size of the face, as it can be seen in Fig. 28.1. The size of the neurocranium represents approximately 25% of its future size, whereas the face represents only 10–15%. By the end of the second year, the neurocranium has reached approximately 75% of its future size. Growth of the neurocranium is directly related to genetic factors and expansion of the brain: at birth,

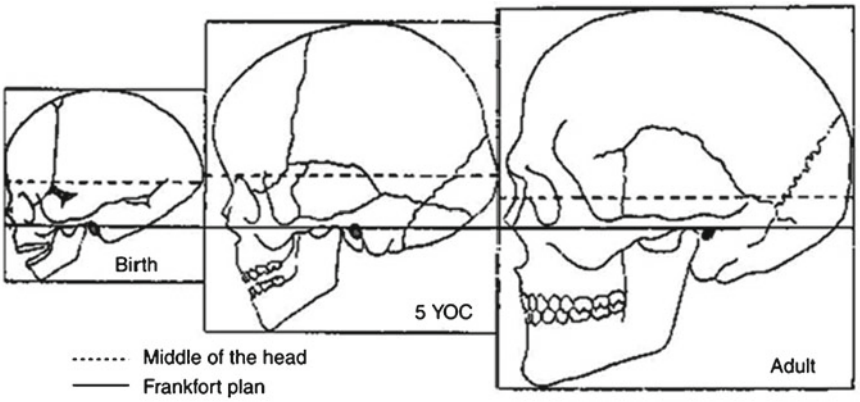


Fig. 28.1 Development of the skull and the face during the growth according to Izard (1950). The three heads are aligned along the Frankfort plane. One can notice the difference in growth of the neurocranium with respect to the face

the weight of the brain is approximately 370 g, reaching up to 1,300 g at the age of 6 years and up to 1,400 g at the age of 19 years.

During the first and early second years, growth of the vault is mainly obtained by ossification at apposed margins of bones, accompanied by some accretion and absorption of bone at surfaces.

Anteroposterior growth occurs at the coronal, sphénotemporal and lambdoid sutures.

Growth in height occurs at the frontozygomatic and squamosal sutures, pterion and asterion.

Growth in breadth occurs at the sagittal, sphenofrontal, sphenotemporal and occipitomastoid sutures and petro-occipital cartilaginous joints. The growth of the face is closely linked to muscular function. The teeth, the tongue and the masticatory muscles are in great part responsible for the growth of the face.

The three heads are aligned with the Frankfort plan in Fig. 28.1. One can notice the difference of growth of the neurocranium with respect to the face (Izard et al. 1950).

The sutures are relatively wide at birth, with large gaps where two or more sutures meet. These areas are called fontanels.

At birth, ossification is incomplete and some bone parts are still separated by fibrous tissue or cartilage.

The main sutures of the newborn are the sagittal suture (between the two parietal bones), coronal suture (between frontal and parietal bones), lambdoid suture (between parietal and occipital bone) and the two parietotemporal sutures (between temporal and parietal bones), as illustrated in Fig. 28.2.

The fibrous membrane, forming the cranial vault before ossification, is not ossified at the angle of the parietal bones, leaving six fontanels, including two median (anterior and posterior) and two lateral pairs (sphenoidal and mastoid).

The fontanels close earlier than the sutures. The first to be closed is the posterior fontanels at the age of 3 months. The sphenoidal fontanel and the mastoid fontanel close, respectively, at 5 and 18 months, whereas the anterior fontanel closes between the age of 24 and 36 months (Fig. 28.3).

After this qualitative analysis of structural aspects, a description of global skull geometry follows. The growth of the skull is closely linked to the growth of the brain. To illustrate the growth of the skull, contours of the brain in a sagittal plan, for different ages, are superimposed. Figure 28.4 illustrates the evolution of the morphology of the brain, which does not grow linearly with age.

As a consequence of brain growth, skull structures do not grow linearly either. Several works concerning size evolution or morphology, such as Dekaban (1977), Roche (1953), Lang and Bruckner (1981), and Lang (1983), have been reported. The authors reported measures of length characteristics during growth, as illustrated in Figs. 28.5–28.7.

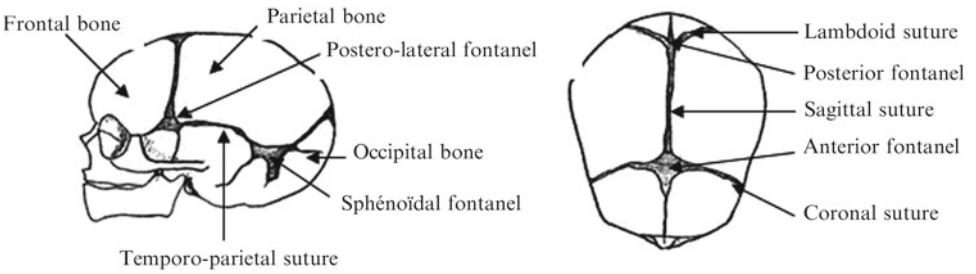


Fig. 28.2 Illustration of infant skull, cranial bone, sutures and fontanels

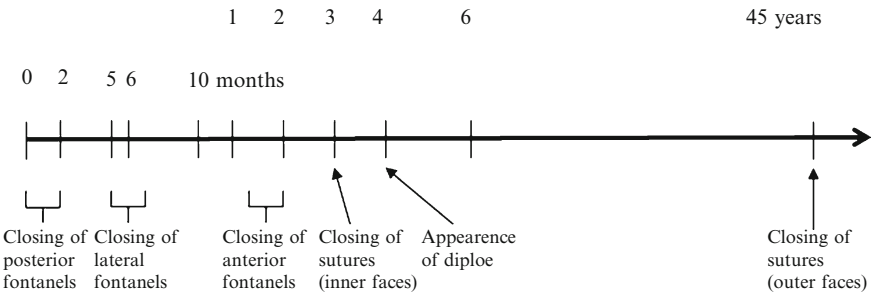


Fig. 28.3 Evolution of sutures and fontanels

Fig. 28.4 Brain morphology as a function of age in the sagittal plan

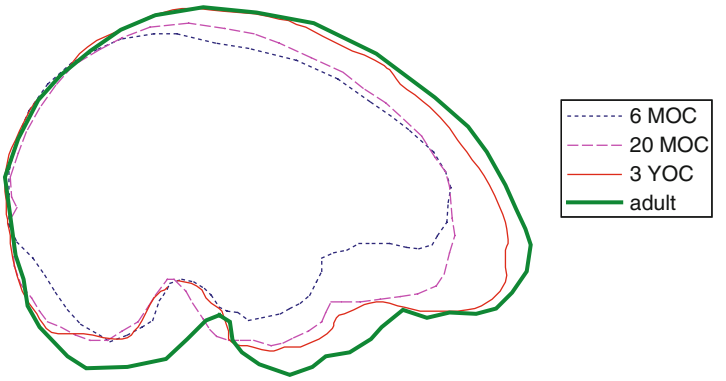
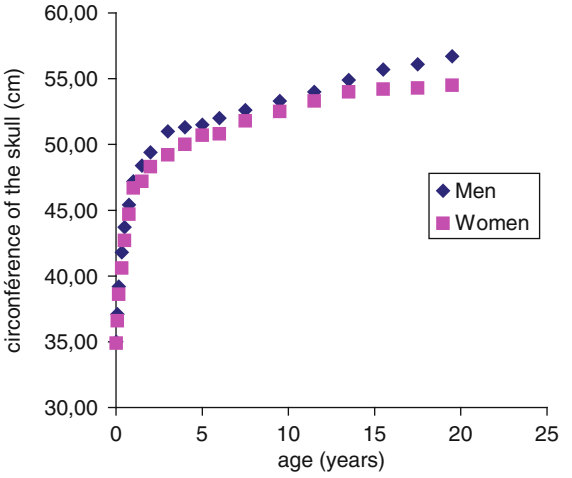


Fig. 28.5 Mean circumference of the skull according to Dekaban (1977) (men in *blue* and women in *pink*)



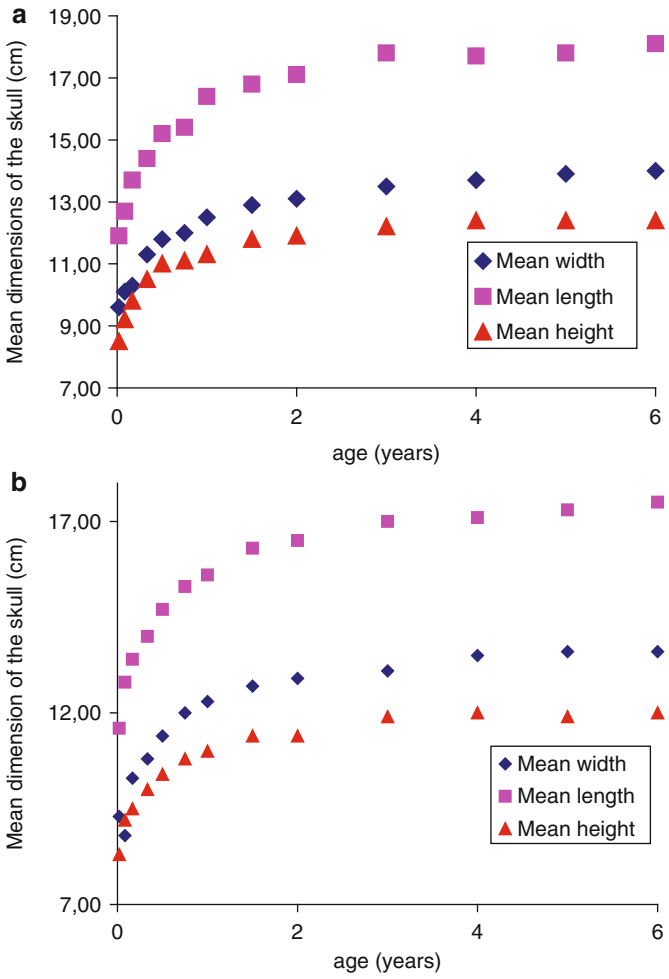


Fig. 28.6 Mean dimension of the skull for men (**a**) and women (**b**) according to Dekaban (1977) (width in *pink*, length in *blue* and height in *red*)

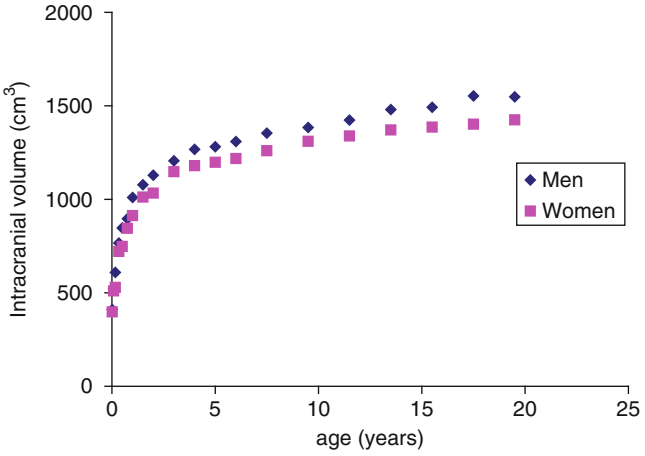


Fig. 28.7 Mean volume of the skull for men (*blue*) and for women (*pink*) according to Dekaban (1977)

Finally, several data on skull dimension of the child head have been collected, and give a first idea of the morphological evolution of the head during growth. These studies can lead (in the next chapter) to an evaluation of the validity of the scaling method, which is often used as an alternative because of the lack of paediatric data by reducing adult anatomy with a scaling coefficient. Indeed, scaling factors are applied to adult morphology in order to obtain child morphology. Are anatomical data reported in the literature coherent with data obtained with the scaling method?

The next paragraph explains child head growth at a morphological and anatomical level pointing out important aspects allowing giving recommendations and guidelines when using the scaling method.

28.3 The Scaling Method: Use, Limitations and Guideline

28.3.1 Definition

The finite element method (FEM) is typically used in biomechanics to understand the dynamic behaviour of a body part, especially of the head, for which a number of FE models have been developed in the last decades. Several anatomists have studied the evolution of skull dimension for males and females since birth. These studies gather a lot of information concerning skull diameters, volumes and characteristic dimensions (Roche 1953; Dekaban 1977), as described in the first paragraph. Based on characteristic dimensions, Mertz (1984) and Irwin and Mertz (1997) developed a method to obtain the child head geometry from the adult one. Because of the lack of studies concerning children, this scaling method seems to be an interesting way to study injury mechanisms for children. A series of coefficient are available in order to reduce mass and dimension of the adult head to obtain child head as reported in Table 28.1.

In parallel to these dimensional parameters, and as very few material constitutive laws are available, the scaling method has been extended to obtain material properties of tissues in children. This theory is based on existing elastic modulus of the skull found by Mc Pherson (1981) in newborn and 6-year-old children and by Hubbard (1971) in adults. A cubic spline was created to fit all the data, suggesting an extrapolation of the bone elastic modulus as a function of age. More recently, authors have studied material properties of children and have established the Young modulus of the skull as a function of age (Margulies and Thibault 2000; Jans et al. 1998). Figure 28.8 shows data obtained by the scaling method superimposed with recent experimentations.

It can be observed in this figure that new experimental data correlate well with those obtained with the scaling method at around 1 year of age. For further ages, more research is clearly needed. Concerning dimensions (length, width and height), is this method reliable in every case?

28.3.2 Comparison Between Anatomical Data and the Scaling Method

Based on experimental data in the literature (contributed by different anatomists named in the first paragraph), a comparison between anatomical data and those obtained with the scaling method is performed, as illustrated in Fig. 28.9.

Table 28.1 Scaling coefficients developed by Mertz (1984) and Irwin (1997)

		6 month old	12 month old	18 month old	3 year old	6 year old	10 year old
Head	$\lambda_x = \lambda_y = \lambda_z$	0.775	0.817	0.844	0.876	0.914	0.931

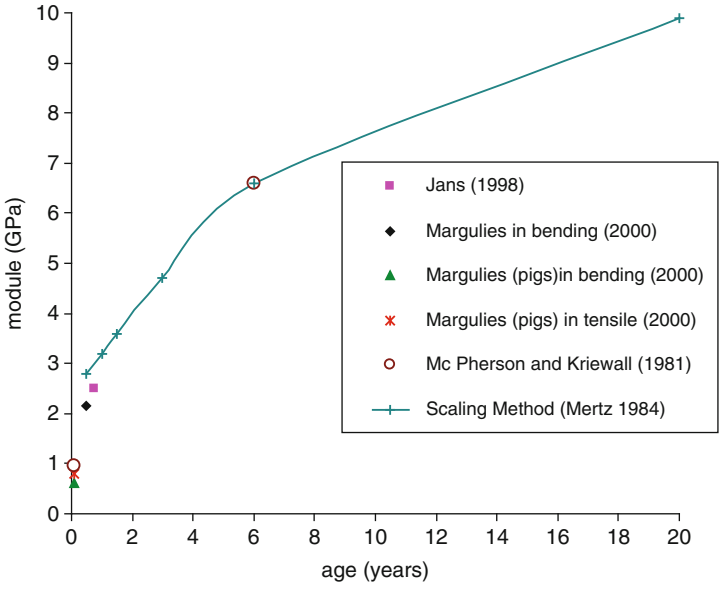


Fig. 28.8 Quasi-static Young modulus of the skull as a function of age: Experimental data and scaling method

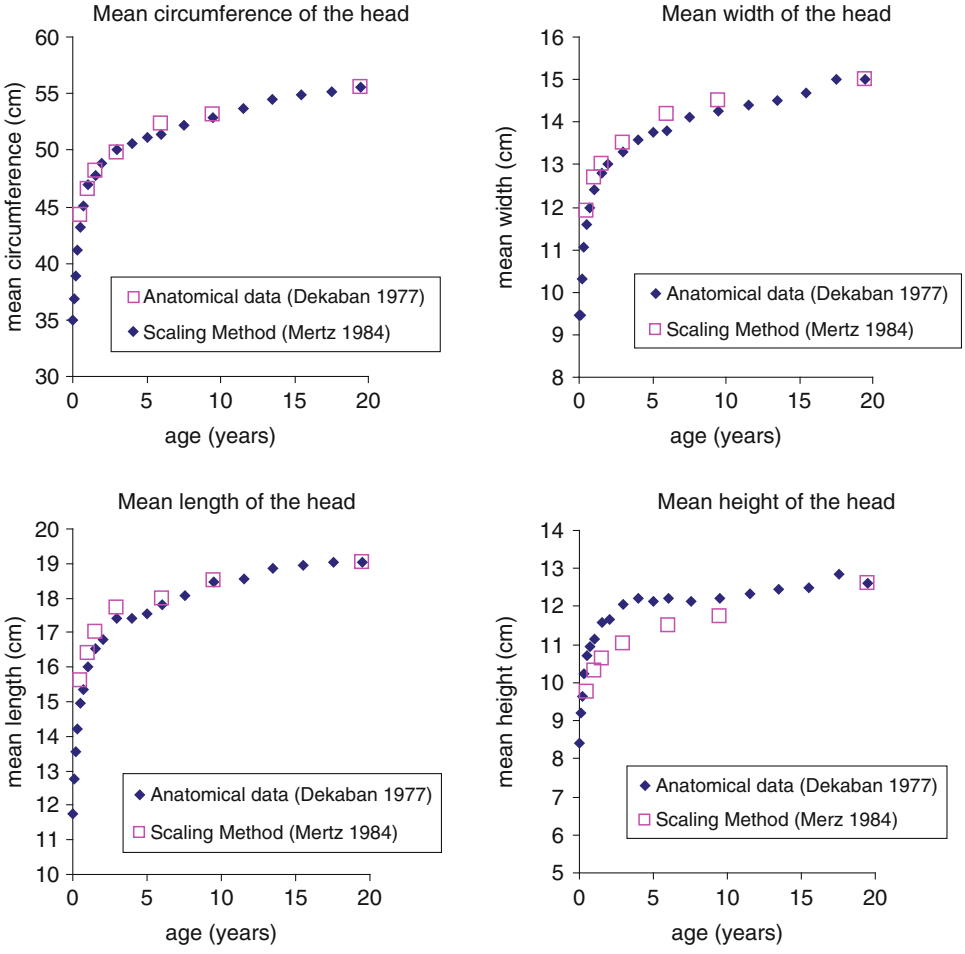


Fig. 28.9 Superimposition of the evolution of the skull circumference, width, length and height as a function of age: anthropometric study and scaling method

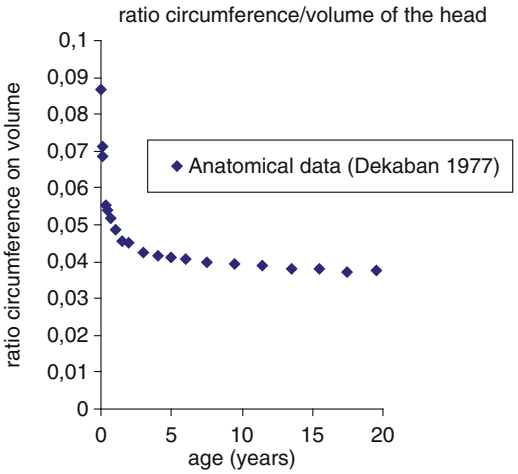


Fig.28.10 Ratio circumference of the head over volume of the head

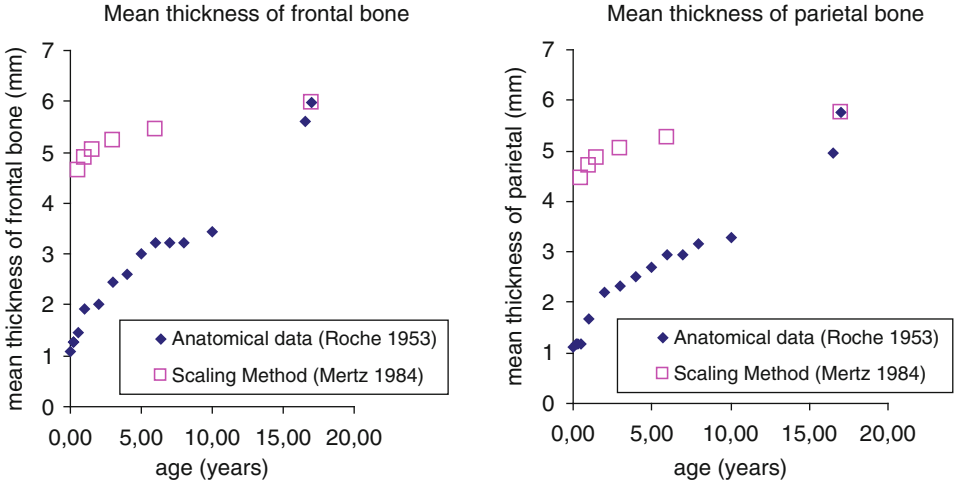


Fig. 28.11 Evolution of skull thickness as a function of age from anatomical study (Roche 1953) and Scaling Method

As far as skull height parameter is concerned, anatomical studies show rapid evolution from birth to 6 years, and stabilisation of the rope of the curve after 6 years of age. This phenomenon is not reproduced by the scaling method.

Figure 28.10 gives a shape parameter as it illustrates the evolution of the ratio of the circumference to head volume. A stabilisation of the curve after an age of 6 years can be observed illustrating that the child's head has a similar shape as an adult head after 6 years of age.

In addition to skull global geometry, skull thickness in frontal and parietal areas has also been reported in previous studies. Figure 28.11 reports data coming from anatomical data and from the scaling method. It can be observed that the thickness, both for parietal and frontal areas, is quite different between the anatomical studies and curves obtained with the scaling method.

In reality, bone thickness changes much more than the scaling method reports.

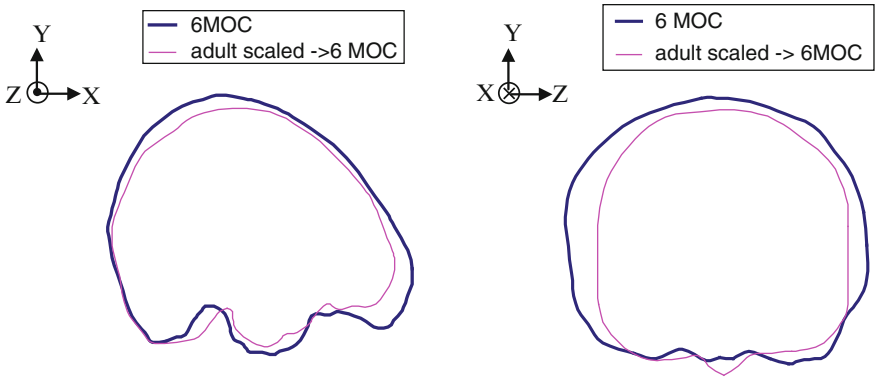


Fig. 28.12 Superimposition of brain's CT scan of a 6 MOC and a scaled brain's CT scan of an adult (sagittal and coronal plan)

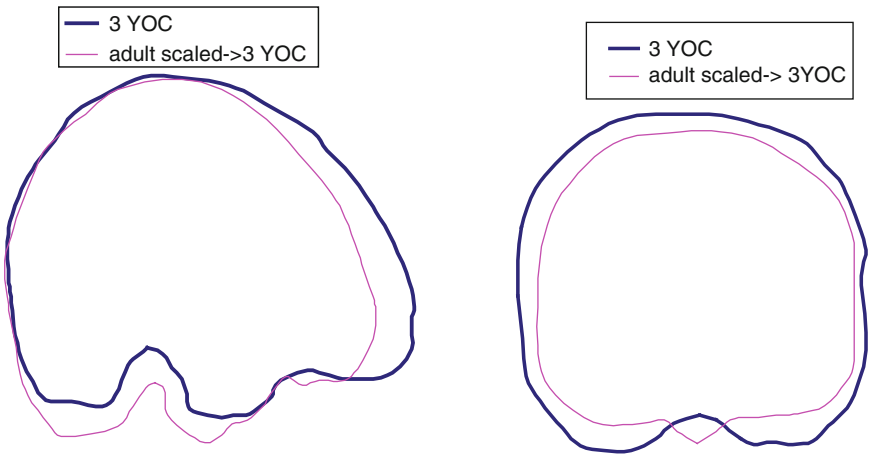


Fig. 28.13 Superimposition of brain's CT scan of a 3 YOC and a scaled brain's CT scan of an adult (sagittal and coronal plan)

Thus, evolution of dimensional parameters illustrated in Figs. 28.9–28.11 shows several limits, which seem to be important in morphological analysis. Indeed, as far as dimensional parameters are concerned, the age of 6 years seems to be a limit. After this critical age, a homothetic evolution until adulthood is observed. For a morphological analysis, we can conclude that the scaling method cannot be applied before 6 years of age because of too large a discrepancy between skull height and thickness.

As far as thickness is concerned, anatomical data show another limit. A large variation can be observed until 10 years of age, and a linear evolution of these parameters after this age until adulthood.

After this analysis of specific skull dimensions, global skull geometry is further investigated by superimposing CT scan slices of the brain obtained in a sagittal and coronal plan for an adult, a 3-year-old and a 6-month-old child.

Therefore, contours of the adult brain obtained from Fig. 28.4 are scaled down according to the Mertz method with appropriate coefficients, respectively, 0.775 and 0.876 for the 6-year-old and the 3-year-old child and superimposed with the scanned child geometry in Figs. 28.12 and 28.13.

Table 28.2 Structural aspect for the application of the scaling method

Structural aspect			
Age	Presence of fontanels	Presence of sutures	Presence of trabecular bone
Newborn	Yes	Yes	No
6 months	Yes	Yes	No
1 year	Yes	Yes	No
3 years	No	Yes	No
6 years	No	No	Yes
10 years	No	No	Yes
Adult	No	No	Yes

Table 28.3 Application field of the Scaling Method

Application Field of the Scaling Method				
	Global Geometry Level			Structural level
Age	D_x	D_y	D_z	■ Thickness of the skull ■ Fontanels and Sutures ■ Trabecular Bone
Newborn	No	No	No	No
6 months	No	No	No	No
1 year	No	No	No	No
3 years	No	No	No	No
6 years	Yes	Yes	Yes	No
10 years	Yes	Yes	Yes	Yes
Adult	/	/	/	/

It can be observed in these figures that the scaling coefficients applied to the geometry lead to a child geometry, which is quite far from the real geometry obtained by CT scans. Indeed, for the 6 MOC, differences between the real geometry and the scaled one in terms of area reach 11% and 17% in the sagittal and the coronal plan, respectively. For the 3 YOC, differences between the real geometry and the scaled one in terms of area reach 4% and 18% in the sagittal and the coronal plan, respectively.

Then, accurate child geometry is needed to obtain a realistic geometry of a 6-month-old or a 3-year-old child head model. Studying child brain injuries with physical or numerical models should be based on the creation of realistic and biofidelic models.

Based on evolution of dimensions, studies of morphology, limitations and guidelines for the use of the scaling method are summarised in Tables 28.2 and 28.3. In these tables, 'yes' in the application field of the scaling method means that the method can be applied.

28.3.3 Conclusion

Scaling methods are often used to obtain the geometry of a child head. They are frequently used for dummies, which use scaling factors to reduce an adult physical or numerical model to the appropriate size. Concerning this method, the present study has shown that skull length and width found by anatomical studies and with the scaling method seem to be in accordance; but, for the skull height,

discrepancies appear. Concerning the circumference/volume ratio, a stabilisation of the curve after the age of 6 years is observed, giving a limit of validity of the scaling method at this age. Concerning the skull thickness, anatomical studies and the scaling method allow observing that the thickness for parietal and frontal bones is drastically lower in anatomical studies compared to the scaling method. From a geometrical point of view, comparison between real head and scaled head has shown significant difference in terms of size and shape, especially at the base of the brain. Finally, from a detailed structural point of view, the child head changes widely during growth, with appearance of trabecular bone, and closing of sutures and fontanels. These important structural aspects are obviously not taken into account with the scaling approach.

28.4 Practical Methods and Techniques: Finite Element Modelling

28.4.1 FEM: A Way to Study Injury Mechanisms

Computer models are increasingly used in biomechanics as an alternative to complicated, practically unfeasible or unethical (human or animal) experiments. FEM is a mathematical method for solving complex physical problems; it is commonly used to investigate injury mechanisms. The finite element modelling technique offers the advantage of being able to model structures with complex shapes and complex mechanical behaviour, leading to the investigation of local behaviour such as local stresses or strains.

For a biomechanical application, such as child head injuries, this method can be very interesting and efficient for modelling injury mechanisms and developing injury criteria.

This method has been widely used for adult head biomechanics, and is beginning to be used for investigating child head injury criteria.

28.4.2 Adult FEMs

Finite element modelling is a widely used tool for investigating the dynamic response of the head under external loading. Presently, about a dozen three-dimensional FEMs of the adult head have been developed that include implementation of constitutive relationships of head components. Among these models, some have been used to simulate real-world accidents and to develop injury criteria based on mechanical parameters. Figure 28.14 and Table 28.4 illustrate these models, with the corresponding threshold for injury appearance.

28.4.3 Child Head FEM

Thus, finite element analysis of adult head has been investigated extensively. However, injury biomechanics applied to the paediatric population is still an emerging field, and only a few FEMs of child head are available in the literature. Only a brief description of models developed in the literature is provided in the present chapter.

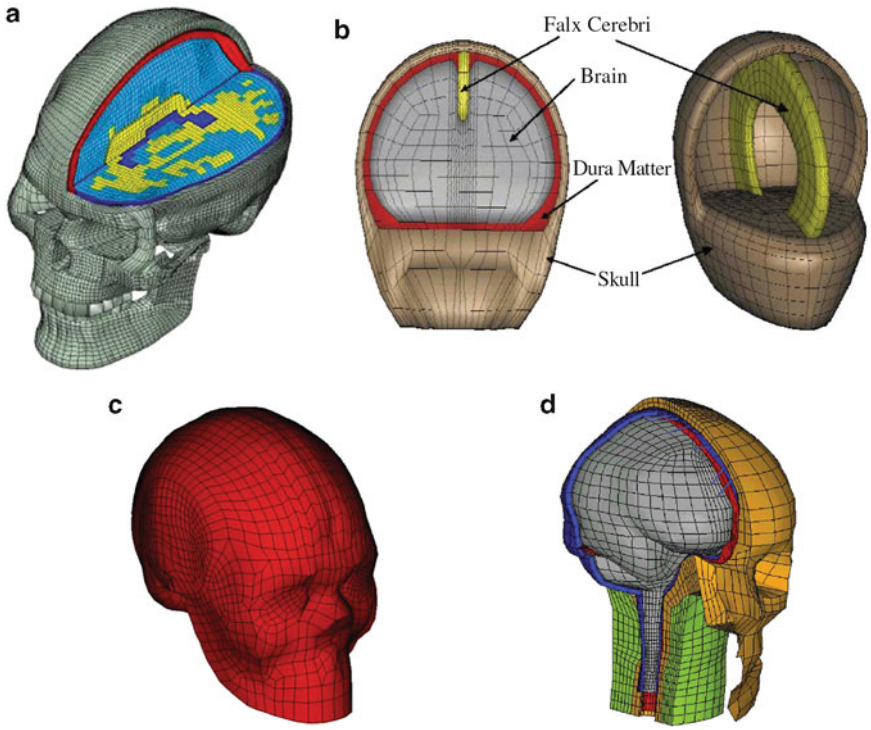


Fig. 28.14 Finite element models that predict injuries' appearances. Wayne State University (**a**) (Zhang et al. 2001), SIMon model (**b**) (Takhounts and Eppinger 2003), Strasbourg ULP98 model (**c**) (Kang et al. 1997) and KTH model (**d**) (Kleiven 2007)

Table 28.4 Adult FE model based Injury mechanisms and injury criteria

FE models	Diffuse Axonal Injuries	Contusion	SDH	Skull fracture
SIMon	CSDM[a] 55%	DDM[a] 7.2%	RMDM[a] 1	
WSUBIM	Strain rate: 19 s^{-1} Strain * Strain: 60 s^{-1}			
KTH	Brain first principal strain 0.21–0.26			
ULP	Brain Von Mises stress: 27 kPa for moderate 39 kPa for severe		CSF strain energy: 4.211 mJ	Skull strain energy: 833 mJ

[a]Cumulative strain damage measure (CSDM) is associated with the cumulative volume of brain tissue experiencing tensile strains over a predefined critical level. Dilatation damage measure (DDM) is proposed for the evaluation of brain injury that occurs as a result of dilatational stress states. Relative motion damage measure (RMDM) is related to brain motion relative to the interior surface of the cranium

28.4.3.1 Mc Pherson et al

Mc Pherson and Kriewall (1980) developed numerical models to investigate the effects of intra-uterine pressure on parietal bones during labour. This model focusses on skull deformation.

28.4.3.2 Prange et al

Prange et al. (1999) analysed the influence of the size, shape and the mechanical properties of the brain by modelling a coronal slice of a 1-month-old child head.

28.4.3.3 Margulies and Thibault

Margulies and Thibault (2000) developed a hemispheric model and studied the influence of mechanical properties and the structure of the head.

28.4.3.4 Lapeer and Prager

Lapeer and Prager (2001) developed a simplified numerical model of parietal bones to investigate the deformation of foetal skull subjected to uterine pressure during labour.

28.4.3.5 DeSantis Klinich et al

An FEM model of a 6-month-old child has been developed by DeSantis Klinich et al. (2002). They analysed the intracerebral response during simulation of real accidents.

28.4.3.6 Mizuno

Mizuno et al. (2004) developed an FEM of a 3-year-old child, by scaling down the THUMBS model AM50 of TOYOTA, according to the scaling method, using an appropriate coefficient. The material properties of the skull were also scaled down with coefficients of 0.8 and 1.6 for stress and strain, respectively.

28.4.3.7 Guan et al

Guan et al. (2006) developed a finite element model for a 6-month-old child using different types of mesh element to investigate the convergence of the models during a numerical simulation.

28.4.3.8 Coats et al

Coats et al. developed an FEM of the head for a 1.5-month-old infant to reproduce experiments on paediatric bone fracture. The authors compared results of the numerical simulations to experimental tests for different impacted surfaces, in terms of the fracture line. Replication of a number of falls helped find the tolerance limit for skull fracture for the newborn infant head.

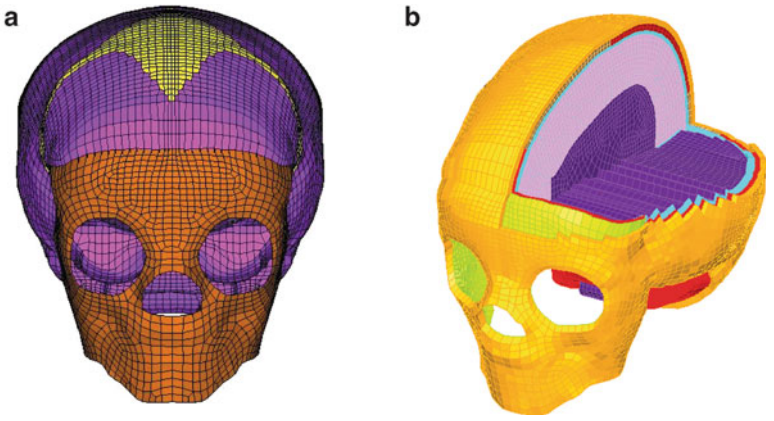


Fig. 28.15 UDS' FE model of a 6-month-old child (2007)

Table 28.5 Material properties for the 6 MOC UDS' model

	Young modulus (MPa)	Poisson ratio	Density (kg/m^3)
Membranes	31.5	0.45	1,140
Cerebrospinal fluid	0.012	0.49	1,040
Scalp	16.7	0.42	1,200
Skull	2,500	0.22	2,150
Sutures and Fontanels	1,500	0.22	2,150
Brain	$G(t) = G_\infty + (G_0 - G_\infty).e^{-\beta.t}$		
	$G_0 = 5.99 \times 10^{-3}$ MPa $G_\infty = 2.32 \times 10^{-3}$ MPa		
	$\beta = 0.09248$ s^{-1}		
	with a bulk modulus $K = 2{,}110$ MPa		

28.4.3.9 UDS Models

Several models have been developed at Strasbourg University.

A 6-month-old child head model is illustrated in Fig. 28.15, whose material properties are summarised in Table 28.5, and a 3-year-old-child head model is illustrated in Fig. 28.16, with material properties summarised in Table 28.6. The use of these models is described in Section 4 (Roth et al. 2007; Roth et al. 2008).

28.4.3.10 Anthropometric Point of View

The developed finite element models are based on CT scans of children and infants. They closely follow the anthropometry of the head at a specific age. As it was explained in the previous chapter, the child head undergoes modifications during growth. That's the reason why it is necessary to develop a model that reflects the accurate geometry of the head at a specific age. We will discuss in the next chapter the influence of this anthropometry at a numerical level by comparing a real geometry of the head to a head that has been scaled according to the scaling method.

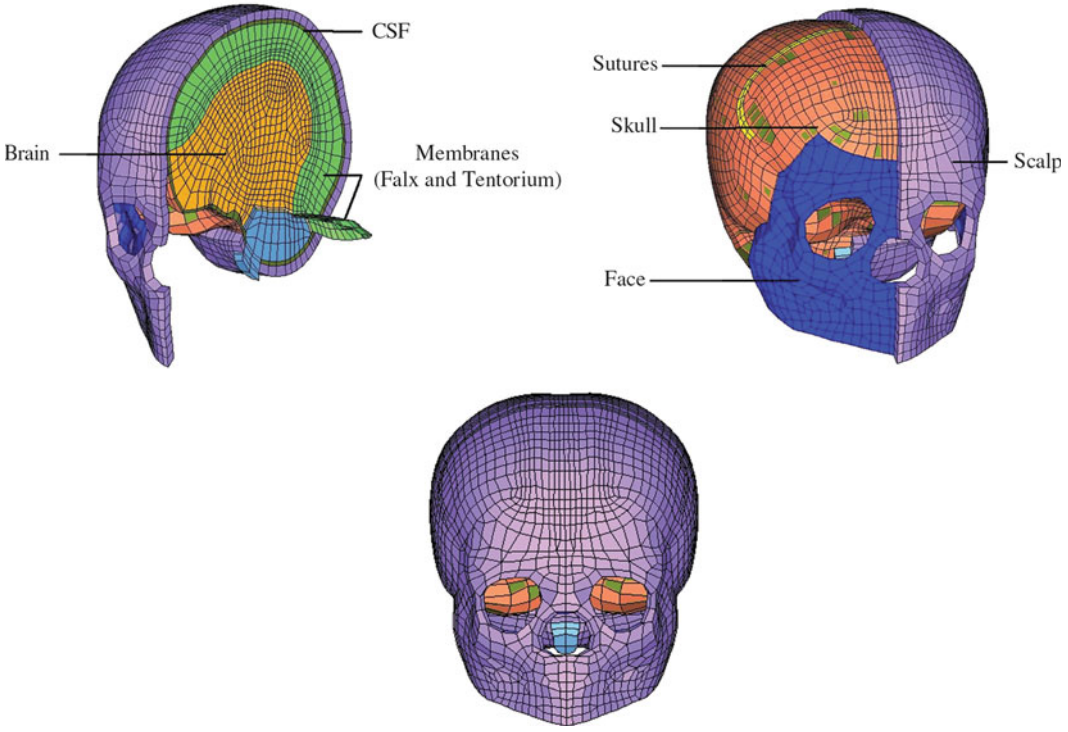


Fig. 28.16 UDS' FE model of a 3-year-old child (2009)

Table 28.6 Material laws used in the 3 YOC head model

	Young modulus (MPa)	Poisson ratio	Density (kg/m^3)
Membranes	31.5	0.45	1,140
Cerebrospinal fluid	0.012	0.49	1,040
Scalp	16.7	0.42	1,200
Skull	4,700	0.22	2,150
Sutures and Fontanels	1,500	0.22	2,150
Brain	• Viscoelastic law 1-mode relaxation (Shuck 1972)		

However, when looking at the evolution of some specific characteristic of the head during growth, especially the circumference/volume ratio, it appears that relative child skull geometrical parameters do not vary after the age of 6 years Even if a 6-year-old child head is slightly smaller than an adult head, its shape is similar to the adult one, as illustrated in Fig. 28.17.

Thus, the creation of a new finite element model of the head of a child older than 6 years does not seem to be useful, as the geometry is very similar in terms of shape to the adult head. In the contrast to younger children, using the scaling method to create a new model (older than 6 years) can be justified. For example, the creation of a 6-year-old finite element model of the head can be developed by

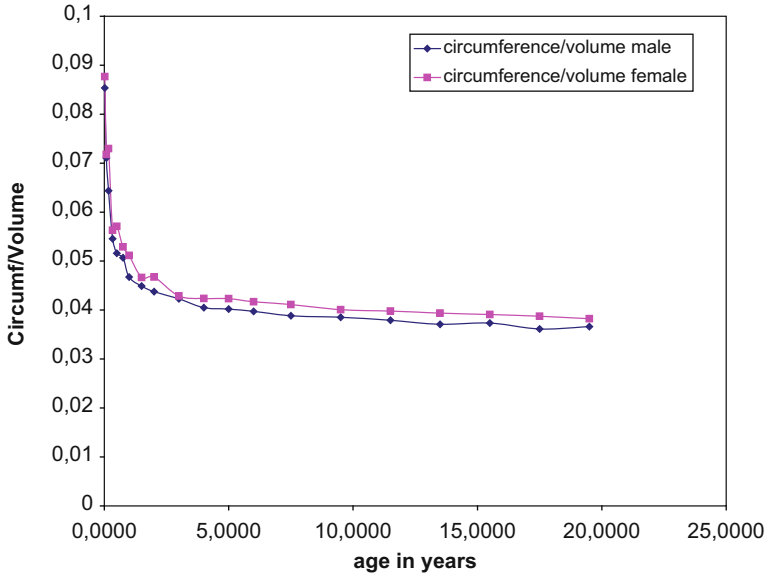


Fig. 28.17 Evolution of the ratio 'circumference/volume' during growth

scaling an adult FE model with the appropriate scaling coefficient ($\lambda_x = \lambda_y = \lambda_z = 0.914$, as suggested by Irwin and Mertz 1997).

28.4.3.11 Limitations of Child Head FE Model Development

The step after finite element development is the comparison of the response of the model to experimental data, as it was performed on adults' heads. However, due to ethical issues, very few data are available in the literature. The only data available are those from Prange et al. (2004) on newborns, which concern skull experimentations. However, it seems difficult to use Prange's experimentations on newborns to validate head measurements of older children.

The response of child brain tissues have not been published yet. Thus, for instance, the child head models cannot be validated, and their biofidelity in terms of mechanical response cannot be checked. However, it seems essential to study the child head at a mechanical level. Investigations on child injury mechanisms should not be avoided because of the lack of experimental data on the child head, as a large number of accident cases or mishandling involves children, infants or newborns.

28.4.4 Conclusion

Finally, this review on head biomechanics shows that the adult head has been widely studied at a numerical level with the development of biofidelic finite element models of the adult head. The responses of these models under dynamic loadings have been compared to experimental data in order to ensure their biofidelity. However, the state of the art concerning the child head is quite dif-

ferent. Indeed, due to ethical reasons, studies on the child head are more difficult. Therefore, the use of the finite element model seems to be an interesting way to study child injury mechanisms.

We will explain in the next paragraph the use of the finite element models developed by Strasbourg University in order to point out the importance of anthropometry (size, shape and morphology).

28.5 Numerical Response of Child Head FEM: Importance of the Anthropometry

28.5.1 The 3 YOC Head Model Versus the Scaled Adult Model

In order to investigate the influence of the geometry of the head on its mechanical response under impact, the new detailed 3 YOC finite element head model is compared to a previously developed

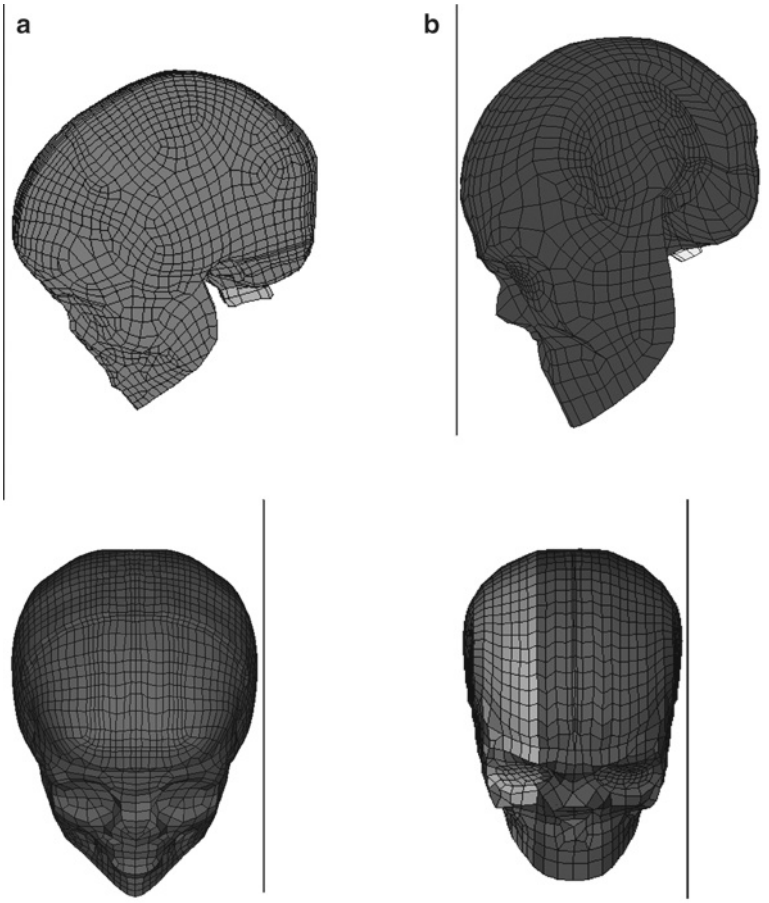


Fig. 28.18 Sagittal view of the detailed 3 YOC model (**a**) and the 3 YOC scaled-down adult head model (**b**) under frontal and lateral impact

Table 28.7 Inertia of both models, the real geometry and the scaled one

	Inertia of the real 3 YOC model (kg.m²)	Inertia of the 3 YOC Scaled down adult model (kg.m²)
I_{XX}	8.4×10^{-3}	1.3×10^{-2}
I_{YY}	7.1×10^{-3}	1.1×10^{-2}
I_{ZZ}	7.4×10^{-3}	9.8×10^{-3}

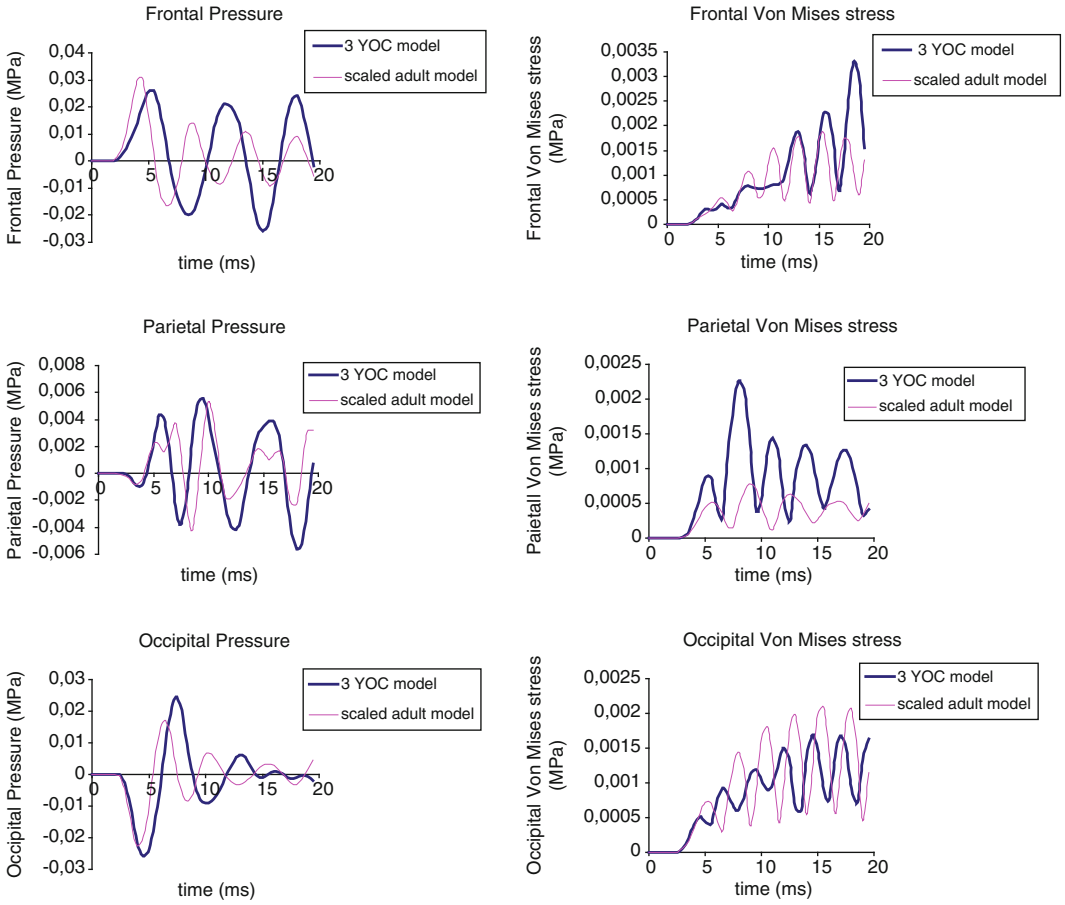


Fig. 28.19 Pressure and Von Mises stress computed with both model in different areas of the brain for a frontal impact

adult head finite element model (Kang and Willinger, 1997), which was scaled down with a 0.876 factor, according to Mertz (1984). The adult head model simulates closely the main feature of the adult head. A sagittal view of both models is displayed in Fig. 28.18.

The 3 YOC finite element model has a total mass of 2.9 kg, whereas the scaled adult head model has a total mass of 3.2 kg. Inertias of both models are listed in Table 28.7, and point out very significant differences (up to 35%). In order to analyse the influence of a child's head geometry, the response of the detailed model versus the scaled down adult head model in terms of intracranial field parameters are compared under similar impact conditions. Two impact cases were therefore simulated: a frontal one and a lateral one, both against a rigid wall at an initial velocity of 1 m/s in order to remain below the risk of skull rupture risk.

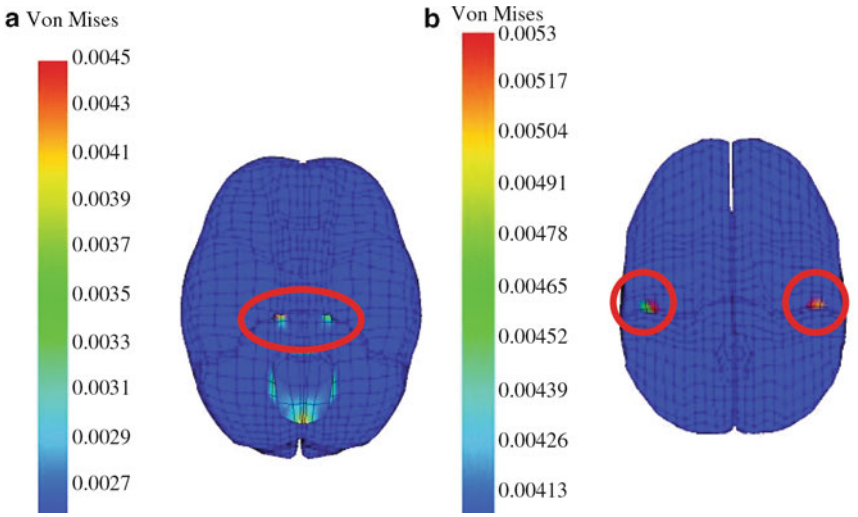


Fig. 28.20 Localisation of maximum Von Mises stress for the 3 YOC model (**a**) and the scaled adult model (**b**) at 13 ms under a frontal impact

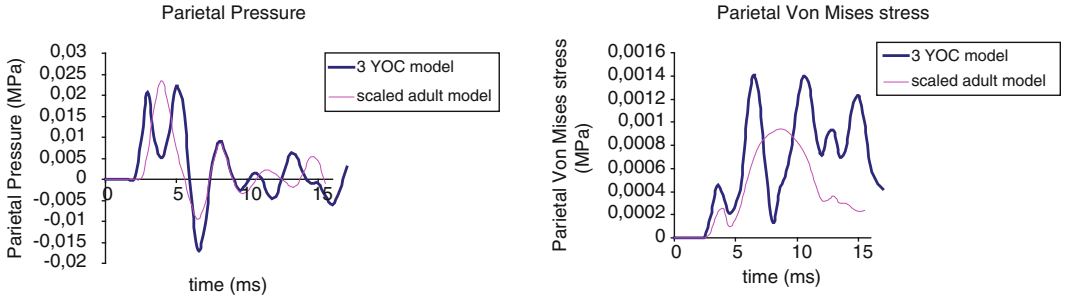


Fig. 28.21 Maximum Von Mises and pressure in the parietal area for a lateral impact

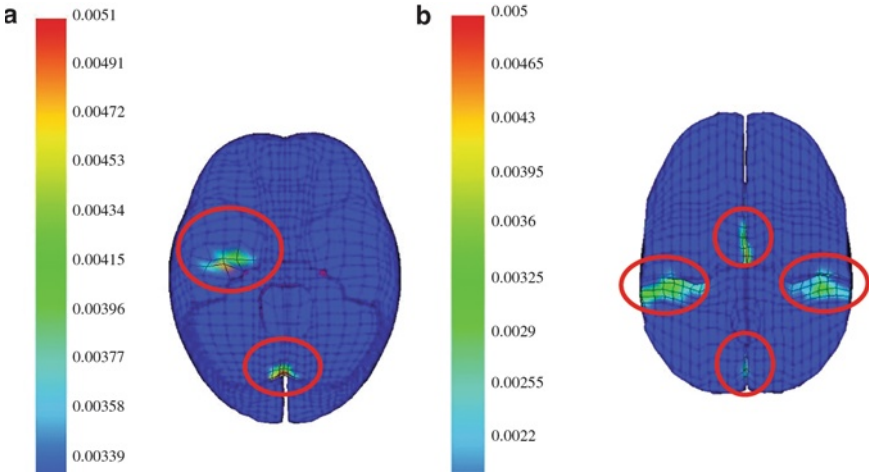


Fig. 28.22 Localisation of maximum Von Mises stress for the real 3 YOC model (**a**) and the scaled adult model (**b**) for a lateral impact

The face and the skull have the same constitutive law, as only the inertial effect of the face was considered for the present model. Facial impacts were not investigated.

With the above geometrical and mechanical properties, the responses of the detailed child head model versus the scaled-down adult head model were compared in terms of intracranial field parameters under similar impact conditions.

Models response in terms of intracerebral pressure and Von Mises stress are reported in Figs. 28.19–28.22 for both child head models successively under frontal and lateral impact. In terms of pressure, the maximum pressure seems to be equivalent for the two models. The 15% pressure difference is probably due to the slight mass difference between the two models. It can be observed in Fig. 28.19 that the shearing stress in the frontal area reaches 2.8 kPa with the real geometry, whereas it reaches 1.7 kPa with the scaled head model. In the parietal area, an important difference is observed, varying from 0.7 kPa for the scaled adult head to 2.3 kPa for the real geometry. This difference is less important in the occipital area. Furthermore, the localisation of maximum shearing stress is quite different for the two models, as illustrated in Fig. 28.20. Here, one can clearly see the influence of the geometry, in the light of the maximum stress localisation. For the scaled model, the maximum stress is located symmetrically at the posterolateral part of the inferior area of the temporal lobes, whereas it is located in the posteromedial part of the inferior area of the temporal lobes for the detailed 3 YOC head model. A similar investigation was performed under lateral impact, as illustrated in Fig. 28.18. Regarding pressure, the maximum in the impact area is of the same order of magnitude for both models and is, therefore, not reported. The responses obtained with the model based on the real geometry in terms of Von Mises stress are underestimated, compared to the scaled-down adult model (0.9 kPa against 1.4 kPa). Results are reported in Figs. 28.30 and 28.31, again in terms of pressure and shearing time histories, and shearing stress field for both models.

As for the frontal impact, the lateral impact leads to maximum stress in the temporal lobe for both models. Difference in terms of Von Mises stress and pressure can be observed between the two simulations (Fig. 28.21). In the new 3YOC model, an area of high stress is located opposite the impact side, at the inferior part of the temporal lobe. For the scaled adult model, areas of high stress are located in the middle of the brain and on the lateral part of the cerebellum, as illustrated in Fig. 28.22. For the 3 YOC brain, Fig. 28.22 shows that the brainstem is part of the maximum stress area, but this phenomenon is supposed to be an artefact due to the boundary condition at the brainstem level. Further investigations of this area would need a coupling of a neck model to the head model.

28.5.2 The 6 MOC Head Model Versus the Scaled Adult Model

In order to investigate the influence of the geometry of the head on the mechanical response, the UDS 6 MOC finite element model was compared with a previously developed adult head finite element model, which was scaled down with a scaling factor of 0.775. The new finite element model has a total mass of 2.2 kg, whereas the scaled adult head model has a total mass of 2.1 kg. The inertia of both models is listed in Table 28.8, and points out very significant difference on the *X*-axis (up to 19%). On the *Y*- and *Z*-axes, inertia is equivalent.

In order to analyse the influence of a child's head geometry, the detailed model versus the scaled-down adult head model responses in term of intracranial field parameters were compared under similar impact conditions. Three impacts were simulated: a frontal, a lateral, and an occipital impact against a rigid wall with an initial velocity of 1 m/s, as illustrated in Fig. 28.23.

Table 28.8 Inertia of both models, the detailed geometry and the scaled one

	Inertia of the detailed 6 MOC model (kg m²)	Inertia of the 6 MOC Scaled-down adult model (kg m²)
IXX	3.9×10^{-3}	4.8×10^{-3}
IYY	5.1×10^{-3}	5.5×10^{-3}
IZZ	4.6×10^{-3}	4.6×10^{-3}

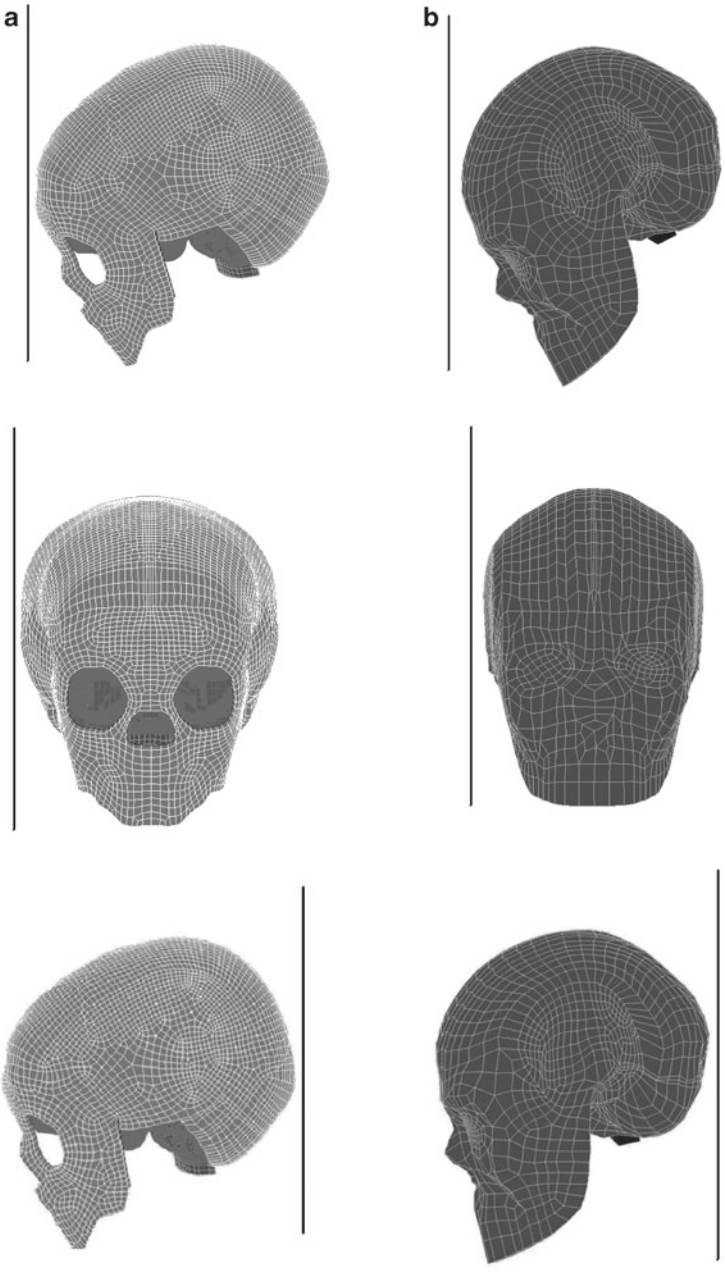


Fig. 28.23 View of the detailed 6 MOC model (**a**) and the 6 MOC scaled-down adult head model (**b**) under frontal, lateral impact and occipital impact

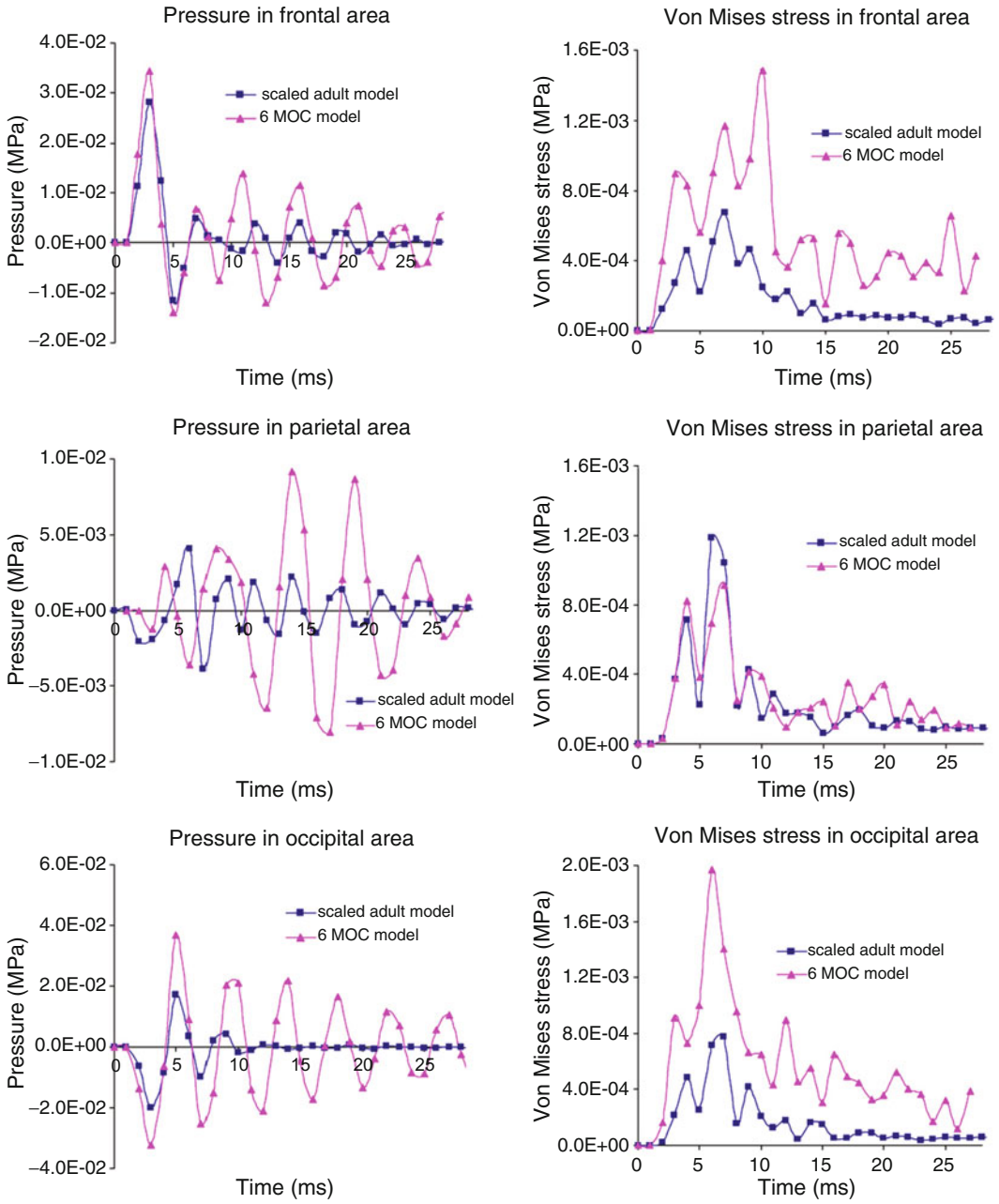


Fig. 28.24 Pressure and Von Mises stress computed with both model in different areas of the brain for a frontal impact

28.5.2.1 Frontal Impact

For frontal impact, the peak pressure in the frontal area for the new 6-month-old model and scaled adult model was 35 and 29 kPa, respectively (Fig. 28.24). In the occipital area, the difference of pressure was more important, and pressure reached 19 and 38 kPa for the 6-month-old model and for the scaled model, respectively. In the parietal area, pressure was 4 and 10 kPa for the 6-month-

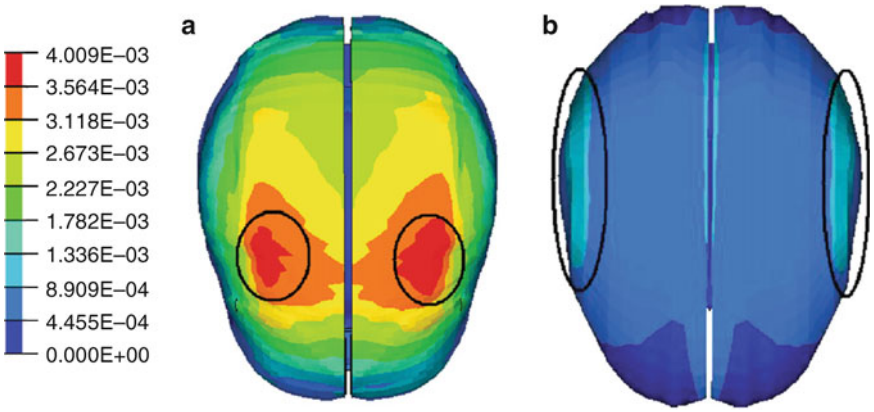


Fig. 28.25 Localisation of maximum Von Mises stress (MPa) in the brain for the 6 MOC model (**a**) and the scaled adult model (**b**) under a frontal impact

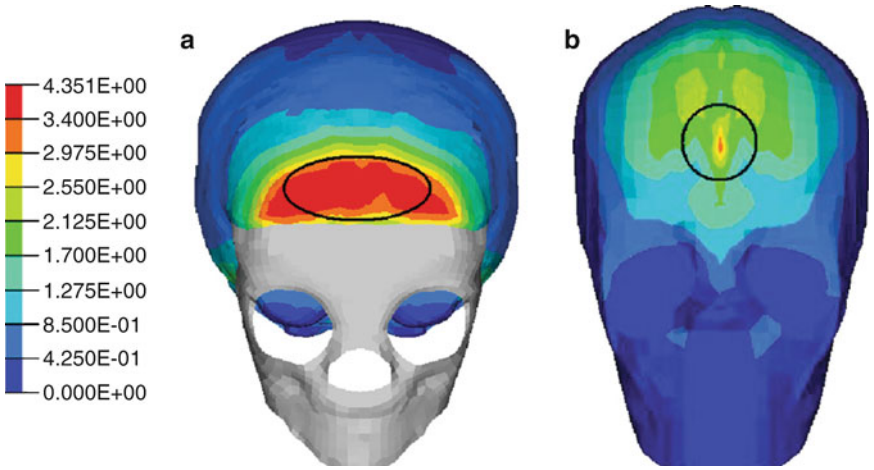


Fig. 28.26 Localisation of maximum Von Mises stress (MPa) in the skull for the 6 MOC model (**a**) and the scaled adult model (**b**) under a frontal impact

old model and the scaled model, respectively. It can be observed in Fig. 28.25 that the shearing stress in frontal area reached 1.6 kPa with the new detailed model, whereas it reached 0.65 kPa with the scaled head model. In the parietal area, Von Mises stress was 1.2 kPa for the scaled adult model and 0.95 kPa for the new detailed model. Also, a large difference of Von Mises stress was observed in the occipital area, being 0.8 for the 6-month-old model and 2 kPa for the scaled adult model. Furthermore, the localisation of maximum shearing stress was quite different for the two models, as illustrated in Fig. 28.25.

When comparing stresses in the skull, the maximum value was located at the impact area, but the distribution was quite different for both models, as illustrated in Fig. 28.26. Furthermore, maximum Von Mises stress was 3.7 and 4.4 MPa for the scaled adult model and the real model, respectively.

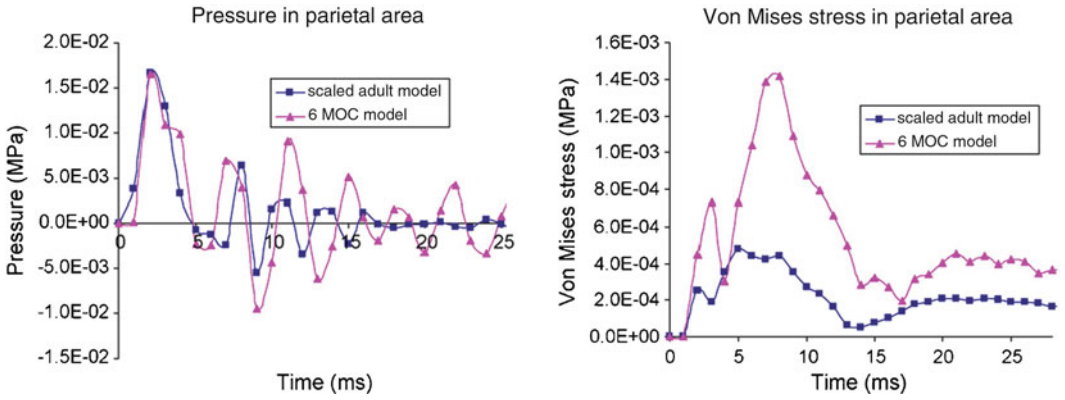


Fig. 28.27 Maximum Von Mises and pressure in parietal area for a lateral impact

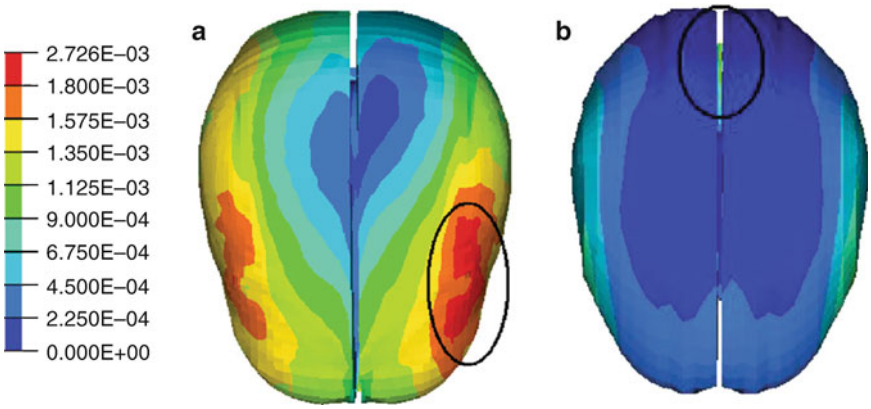


Fig. 28.28 Localisation of maximum Von Mises stress (MPa) in the brain for the 6 MOC model (**a**) and the scaled adult model (**b**) for a lateral impact

28.5.2.2 Lateral Impact

For the lateral impact, the maximum pressure in the impact area was of the same order of magnitude for both models. The response in term of Von Mises stress was 0.4 kPa with the scaled model and 1.4 kPa with the new detailed model, leading to an underestimation of 30% with the scaled model. Results are reported in Figs. 28.27 and 28.28 in terms of pressure, shearing time history and shearing stress field for both models. Similar to the frontal impact, the lateral impact led to different localisation of maximum shearing stress for the two models.

When comparing stresses in the skull, conclusions are the same as for frontal impact, as illustrated in Fig. 28.29. Maximum Von Mises stress was 3.9 and 9.4 MPa for the scaled adult model and the detailed 6-month-old model, respectively.

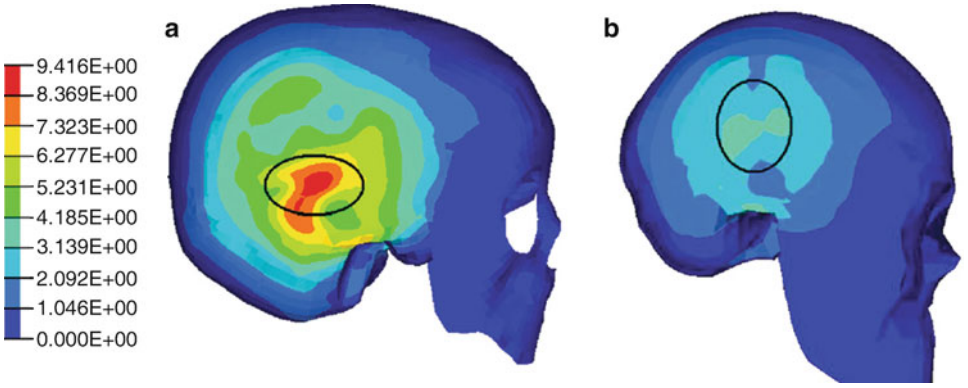


Fig. 28.29 Localisation of maximum Von Mises stress (MPa) in the skull for the 6 MOC model (**a**) and the scaled adult model (**b**) for a lateral impact

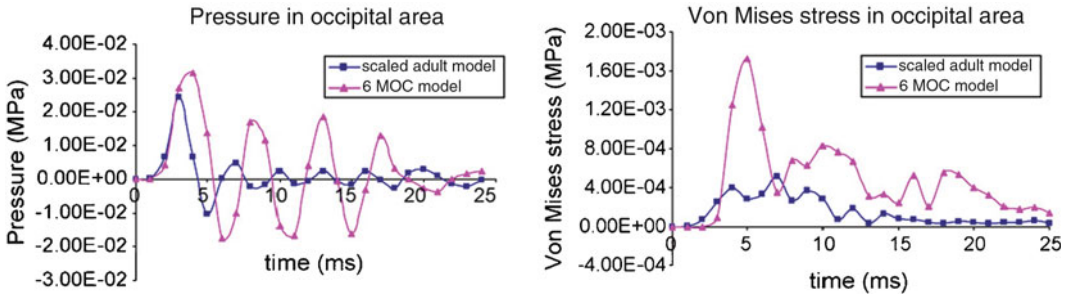


Fig. 28.30 Maximum Von Mises and pressure in the occipital area for an occipital impact

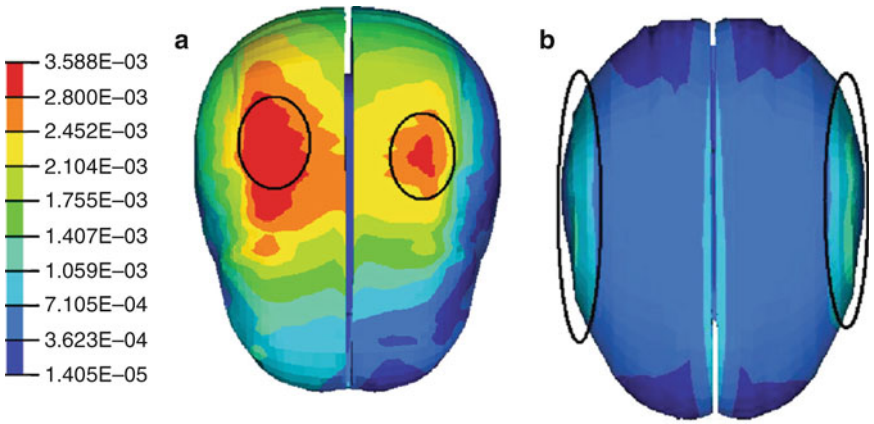


Fig. 28.31 Localisation of maximum Von Mises stress (MPa) in the brain for the 6 MOC model (**a**) and the scaled adult model (**b**) for an occipital impact

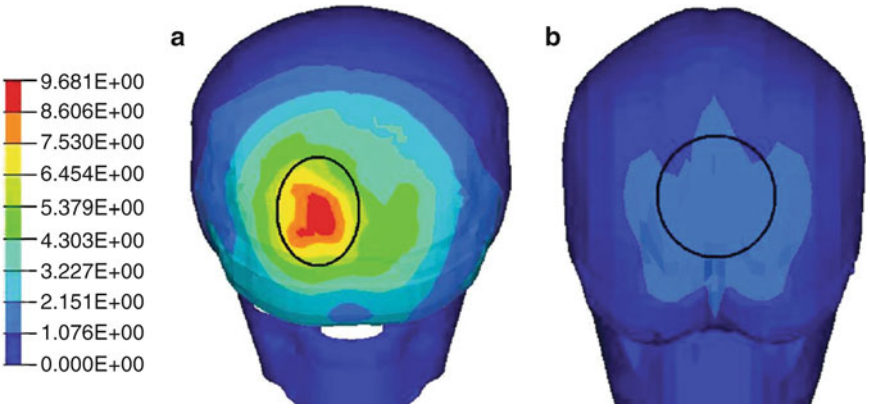


Fig. 28.32 Localisation of maximum Von Mises stress (MPa) in the skull for the 6 MOC model (**a**) and the scaled adult model (**b**) for an occipital impact

28.5.2.3 Occipital Impact

For the occipital impact, Fig. 28.30 shows Von Mises stress time history in the brain in occipital area, at 0.5 kPa for the scaled adult model and 1.8 kPa for the real geometry. Maximum stress was located at the same area as for frontal impact, as illustrated in Fig. 28.31. Stresses in the skull were located in the same area but were 2.3 and 9.7 MPa for the scaled model and the detailed model, respectively, as illustrated in Fig. 28.32.

Finally, morphological, structural and numerical analysis show the importance of the geometry: in order to analyse child head injuries, the creation of biofidelic models of the head appears to be necessary.

28.5.3 Conclusion

Finite element analysis, using realistic geometry, confirms the importance of morphology. Indeed, responses in terms of mechanical parameters are quite different because of the head shape. Furthermore, localisations of maximum stress did not appear in the same area of the brain for the realistic child head compared to the scaled adult head, showing again the importance of an accurate size and shape when performing finite element analysis. The UDS' finite element models (6 MOC and 3 YOC) have shown first interesting results in real-world head trauma reconstruction, and appear to be an interesting tool to study child injury mechanisms.

28.6 Child Anthropometry: Conclusion, Limitations and Prospects

After an anatomical, morphological and structural study, it appears that the child head cannot be considered as a scaled adult head, and that the scaling method commonly used in child head biomechanics has several limitations. The investigation of the child head goes through a precise study of the geometry of the head and specific attention to mechanical properties. Comparison between brain shape at a specific age (Figs. 28.4, 28.12, 28.13) pointed out significant differences in terms of anthropometry. These differences are also identified at a numerical level, which lead to the conclu-

sion that a finite element analysis of the child head can only be performed with a biofidelic model (with respect to size and shape) in terms of geometry. Differences in terms of mechanical parameters illustrate this important point.

Based on these conclusions and motivated by the need for brain trauma investigations among the paediatric population, finite element models of the child head begin to interest the biomechanics community. Indeed, more and more studies examine the child head in terms of numerical analysis. As an example, UDS' finite element models of the child head have been used to simulate complex head trauma configurations, as in the shaken baby syndrome.

Although this chapter summarises new findings in child biomechanics, they are only the first step in the comprehension of child head trauma. Indeed, development of child FEM needs realistic constitutive laws, which are rare in the literature. Even if some mathematical theory (scaling method) allows going further with material properties, experimentations on biological tissues are necessary. More studies are needed in order to improve the biofidelity of constitutive laws to be implemented in FE models. Another important limitation is the lack of experimental data for model validations. Indeed, ethical reasons prevent experiments on child tissues, and one cannot ensure the realistic response of a numerical model (as performed on adult FE models).

Finally, FE analysis is commonly used for real accident reconstruction in order to analyse mechanisms leading to neurological injuries or skull fractures of the adult head (Deck et al. 2008) and also for the paediatric population.

The development of realistic models needs the implementation of a correct constitutive law and also a correct geometry, based on anatomical evolution of the head and of the brain. Anthropometry is essential and infant and child heads (younger than 6 year-old) should not be considered as scaled adult heads. Sections of this chapter dealing with brain and skull evolution and numerical simulations have demonstrated this fundamental aspect.

Key Features of Finite Element Model

Finite element analysis is a numerical mathematical method, which consists of discretization of a continuous space and equations into finite subspace, in order to analyze structures at a local level (stress and strain). Both mesh and material properties are used in a Finite Element Code, to simulate a loading case. This powerful method is more and more used in several fields of mechanical engineering, such as crash field, and civil engineering. In the field of biomechanics, finite element method is used to simulate human body and biological structures in order to investigate their responses under loading case (static, dynamic, impact, etc.).

Summary Points

- During growth, a child's head undergoes different modifications in terms of morphology and structure. Great differences exist between adult and child head in terms of shape, size, and global morphology.
- A comparison between head shape for an adult and a child shows that child head (until the age of 6) cannot be considered as a scaled adult head.
- At a numerical level, a finite element analysis need precise geometry of child head in order to investigate head trauma, and scaling down an adult FE model of the head to obtain a child head is not recommended.
- A detailed geometry of the head is needed in order to investigate head trauma in paediatric population.

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Chapter 29
The Farkas System of Craniofacial Anthropometry: Methodology and Normative Databases

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Abstract LG Farkas created the first comprehensive craniofacial surface anthropometric atlas *Anthropometry of the Head and Face in Medicine* in 1981, and he has continued to develop new measurements and normative data through revision and updates of the atlas and published datasets. Trained in both plastic surgery and medical anthropology, Dr. Farkas created a meticulous measurement system that is based on the identification of anthropometric landmarks. Over the last 25 years he provided extensive hands-on training for clinicians and scientists in North America and around the world. This attention to detail is essential, since these procedures are painstaking and careful instruction is required.

The Farkas system of craniofacial anthropometry has found increasing application in medical and clinical genetics and in plastic and oral/maxillofacial surgery. Quantitative measurements have rendered the diagnosis of dysmorphic features both objective and reliable, a boon to geneticists and surgeons alike. Also, surgical planning has benefited from these metrics which are useful in the assessment of post-operative success. Both of these developments have been facilitated by the publication of the Farkas methods and norms, which continue to be expanded and updated. This craniofacial surface measurement system has become a popular standard reference, providing the most extensive normative database extant for North America.

Abbreviations

16p11.2	Human chromosome 16, short arm, band 11, sub-band 2
CT	Computed Tomography
IT	Information Technology
MRI	Magnetic Resonance Imaging
NIH	US National Institutes of Health
SD	Standard deviation
UCS	Unilateral coronal synostosis

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_29,

29.1 Introduction

This chapter provides an overview of Professor Farkas' system of craniofacial anthropometry, and the normative databases created from this methodology. Farkas' work on basic and clinical research, spanning a half century, generated the most comprehensive craniofacial measurement procedures to date. These methods have provided a framework for physical anthropology research, and have found application in a variety of disciplines such as medicine, including plastic surgery, oral/maxillofacial surgery, and medical and clinical genetics.

Farkas' craniofacial measurement system, as an alternative to subjective visual inspection (Holmes et al, 1987), is very much in the spirit of Lord Kelvin's call for quantification (Deutsch and Mulliken 2001): "I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts advanced to the state of Science, whatever the matter may be" (Thomson 1883). Though there had been earlier efforts to develop limited numbers of craniofacial anthropometric measurements (notably the pioneering efforts of Feingold and Bossert 1974), Farkas introduced remarkable complexity and breadth in formulating his methods and creating his normative databases.

LG Farkas provided these means of quantification by formalizing objective, reliable means of measuring craniofacial size and shape. He adapted classical measurement techniques and created novel anthropometric procedures to produce comprehensive anthropometric atlases of the human head and face. Below, we outline his methods, the compilation of his normative databases, and their use in a variety of disciplines. Finally, we describe how his direct measurement methods are now being extended to state-of-the-art digital morphometry.

29.2 The Farkas Atlases

The first atlas of measurements, *Anthropometry of the Head and Face in Medicine*, was published in 1981, with a revised atlas appearing in 1994. These surface measures were made with an array of direct anthropometric devices, many of them adaptations of classical instruments, such as sliding and spreading calipers, angle meters, and protractors. Additionally, he designed many instruments, tailor-made for specific classes of measurement (Farkas 1981), for example, a large double-sliding caliper with levels for projective measurements extending from the cranial vertex.

The 1994 atlas is a compendium of projective linear measurements, arcs, angles of inclination, and deviations, each connecting anthropometric landmarks that can be reliably identified (Fig. 29.1 and Table 29.1). This network of landmarks extends across single midline structures and paired measurements. Lateral asymmetries of these paired measurements are also enumerated as normative data. Additionally, in 1986, Farkas and Munro published norms for within-subject ratios of individual measurements in *Anthropometric Facial Proportions in Medicine*.

The most extensive norms in the Farkas atlases are for anthropometric measurements within the Caucasian North American population. Whereas the original 1981 atlas focused on Caucasian norms, the Farkas (1994) edition was expanded to include a broader age range of subjects, as well as samples of Chinese and African–American individuals. In this second edition, the norms included data for 2,326 Caucasian North American individuals, ranging in age from 1 year to adulthood. This edition of the atlas, *Anthropometry of the Head and Face*, has been called "a quantitative foundation… for the human head and face and their features…of obvious value to plastic surgeons, but also for

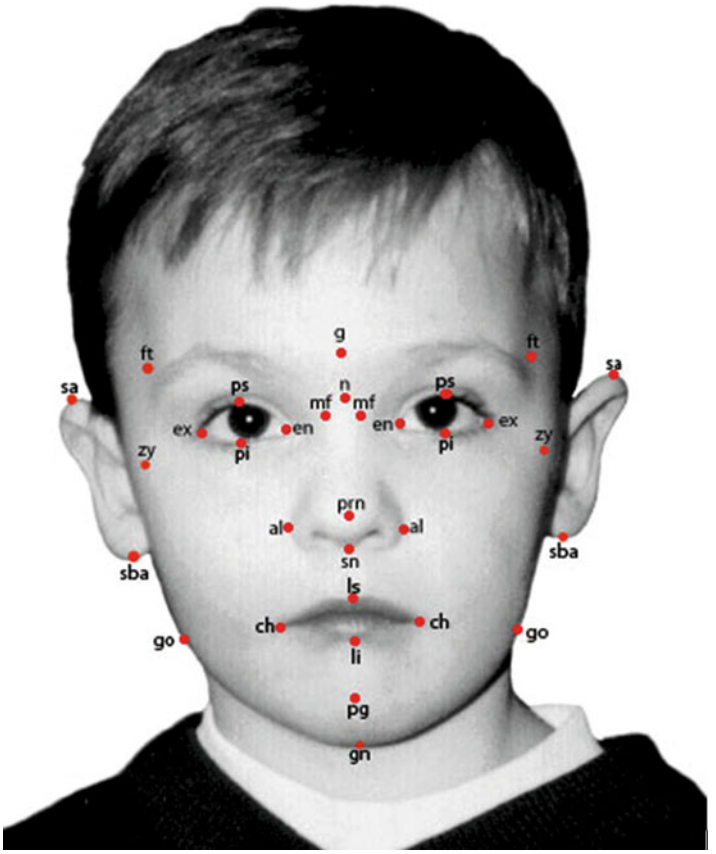

Fig. 29.1 Anthropometric landmarks (selected). See Table 29.1 for landmark abbreviation key

clinicians and researchers in other areas as well as others with a professional interest in dimensions of the head and face" (*Book News* Reference and Technical Reviews 1994).

The North American Caucasian norms include 132 craniofacial anthropometric measurements (70 single and 62 paired). Of these, 103 measurements are linear and 29 angular: 15 cranial (Table 29.2), 31 facial (Table 29.3), 21 orbital (Table 29.4), 28 nasal (Table 29.5), 18 labial (Table 29.6), and 19 auricular (Table 29.7).

In recent years, Farkas and his colleagues began collecting norms for additional ethnic groups, in conjunction with an international consortium of investigators. Their initial efforts are published in Farkas et al. (2005). Further efforts are underway to collect new normative databases outside of North America, for example in southern China (Jayaratne et al., in preparation).

29.3 Practical Methods and Techniques: Training and Reliability

These painstaking anthropometric measurement techniques require extensive training in order to be performed reliably (Farkas and Deutsch 1996). Autodidacts, who have learned merely from written methods, often find, after training, that many of their original measurements have substantial errors.

Table 29.1 Definitions of anthropometric landmarks (see Fig. 29.1)

Landmark	Name	Definition
g	*Glabella*	The most convex sagittal midline point between the eyebrows
ft	*Frontotemporale*	The point of concavity on each side of the forehead above the supraorbital rim, lateral to the elevation of the linea temporalis
zy	*Zygion*	The most lateral extents of the zygomatic arches
go	*Gonion*	The inferior aspect of the mandible at its most acute point (the mandibular angle)
sl	*Sublabiale*	The most inferior sagittal sagittal midline point of the lower cutaneous lower lip, at the labiomental sulcus
pg	*Pogonion*	The most protrusive anterior sagittal midline point of the chin
gn	G*nathion*	The lowest median landmark on the inferior aspect of the mandible
en	*Endocanthion*	The most medial point of the palpebral fissure, at the inner commissure of the eye
ex	*Exocanthion*	The most lateral point of the palpebral fissure, at the outer commissure of the eye
ps	*Palpebrale superius*	The most superior aspect of the palpebral fissure at the sagittal midline of the free margin of each upper eyelid
pi	*Palpebrale inferius*	The most inferior aspect of the palpebral fissure at the sagittal midline of the free margin of each lower eyelid
n	*Nasion*	The sagittal midline point of the nasal root at the nasofrontal suture
mf	*Maxillofrontale*	Lateral extents of the base of the nasal root at the junctures of the maxillofrontal and nasofrontal sutures
al	*Alare*	The most lateral extents of the alar contours
prn	*Pronasale*	The most protrusive point of the nasal tip (apex nasi), identified in lateral view
sn	*Subnasale*	The midpoint of the point of inflection of the columellar base at the juncture of its lower border with the surface of the philtrum
ls	*Labiale superius*	The sagittal midline point of the upper lip (at the upper vermilion line)
li	*Labiale inferius*	The sagittal midline point of the lower lip (at the lower vermilion line)
ch	*Cheilion*	The most lateral points at the labial commissure
sa	*Superaurale*	The most superior point of the helix of the auricle
sba	*Subaurale*	The most inferior point of the lobule of the auricle

The Standard deviations (SDs) for many population measurements are small, and minor measurement inaccuracies can translate into large errors in standardized scores. Take, for example, variability seen in measurements of the width of the head (the linear distance between the eurions, the most lateral extents of the cranium). For school-aged children of both genders, SDs for head width range between 4.2 and 6.3 mm. During our studies at the Craniofacial Centre of Children's Hospital Boston, we have trained many surgeons to perform Farkas-based measurement protocols. For those surgeons who already had some familiarity with the Farkas atlas (but not hands-on training), we conducted a pre-test to document their measurements before giving instruction, and then went on to provide formal training. After the surgeons had been trained, they repeated these measurements on the same subjects seen earlier. A comparison of the pre- and post-tests revealed that their measurements of head width in particular were frequently off by several millimeters; thus, it was not unusual for the

Table 29.2 Cranial anthropometric measurements

Width of the head
Width of the forehead
Skull-base width
Height of the calvarium
Height of the head from the vertex to the nasale
Height of the head from the vertex to the endocanthion
Height of the head from the vertex to the subnasale
Craniofacial height from the vertex to the gnathion
Height of the forehead
Height of the forehead
Length of the head from the glabella to the opisthocranion
Circumference of the head through the glabella and opisthocranion
Inclination of the anterior surface of the forehead
Auricular height of the head from the vertex to the porion
Distance between the vertex and the tragion

Table 29.3 Facial anthropometric measurements

Width of the face
Width of the mandible
Physiognomical height of the face (from the trichion to the gnathion)
Morphological height of the face (from the nasale to the gnathion)
Physiognomical height of the upper face (from the nasale to the stomium)
Height of the lower face (from the subnasale to the gnathion)
Height of the mandible
Height of the chin
Height of the upper profile (from the trichion to the pronasale)
Height of the lower profile (from the pronasale to the gnathion)
Lower half of the craniofacial height (from the endocanthion to the gnathion)
Distance between the glabella and the subnasale
Supraorbital arc
Maxillary arc
Mandibular arc
Inclination of the upper face profile
Inclination of the Leiber line
Inclination of the lower face profile
Inclination of the mandible
Inclination of the chin
Inclination of the general profile line
Mentocervical angle
Height of the mandibular ramus
Depth of the supraorbital rim
Depth of the upper third of the face (from the nasale to the tragion)
Depth of the maxillary region (from the subnasale to the tragion)
Depth of the mandibular region
Depth of the lower jaw
Lateral surface half-arcs (between the tragion and the glabella)
Maxillary half-arcs
Mandibular half-arcs

Table 29.4 Orbital anthropometric measurements

Intercanthal width
Biocular width
Length of the eye fissure
Endocanthion-facial midline distance
Pupil-facial midline distance
Orbito-aural distance
Orbitotragial distance
Orbitogonial distance
Orbitoglabellar distance
Height of the orbit
Combined height of the orbit and eyebrow
Height of the eye fissure
Height of the upper lid
Pupil-upper lid height
Height of the lower lid
Pupil-lower lid height
Difference between the sagittal levels of the upper and lower orbital rims
Difference between the sagittal levels of the endocanthion and exocanthion
Endocanthion-facial midline surface distance
Inclination of the eye fissure
Inclination of the line placed over the upper and the lower orbital rims

Table 29.5 Nasal anthropometric measurements

Width of the nasal root
Width of the nose (between the left and right alare)
Width between the facial insertion points of the alar base
Width between the cutaneous labial insertions of the alar base
Width of the columella
Height of the nose
Length of the nasal bridge
Nasal tip protrusion
Inclination of the nasal bridge
Inclination of the columella
Inclination of the nasal tip portion
Glabellonasal angle
Nasofrontal angle
Nasal root-slope angle
Nasal tip angle
Nasal alar-slope angle
Nasolabial angle
Deviation of the nasal bridge
Deviation of the columella
Width of the nostril floor
Thickness of the ala
Distance between the facial insertions of the alar base and subnasale
Length of the ala
Length of the columella
Depth of the nasal root
Surface length of the ala
Nostril axis inclination
Alar slope line inclination

Table 29.6 Labial anthropometric measurements

Width of the philtrum
Width of the mouth
Height of the upper lip (combined cutaneous and vermilion)
Height of the cutaneous upper lip
Vermilion height of the upper lip
Vermilion height of the lower lip
Height of the cutaneous lower lip
Lower lip height (combined cutaneous and vermilion)
Upper vermilion arc
Lower vermilion arc
Inclination of the labial fissure
Inclination of the upper lip (cutaneous)
Inclination of the lower lip (cutaneous)
Labiomental angle
Halves of the labial fissure length
Lateral upper-lip height (cutaneous)
Labio-aural distance
Labio-aural surface distance

Table 29.7 Auricular anthropometric measurements

Width of the auricle
Height of the tragus
Length of the auricle
Morphological width of the ear
Upper naso-aural distance
Lower naso-aural distance
Upper subnasale–aural distance
Lower subnasale–aural distance
Upper gnathion–aural distance
Lower gnathion–aural distance
Occipito-aural distance
Upper naso-aural surface distance
Lower naso-aural surface distance
Upper subnasale–aural surface distance
Lower subnasale–aural surface distance
Upper gnathion–aural surface distance
Lower gnathion–aural surface distance
Inclination of the medial longitudinal axis of the ear from the vertical
Protrusion of the ear from the head

standardized (z-) score to be in error for this measurement by a full SD or more. In contrast, after training, the surgeons and other extensively trained examiners typically have achieved test–retest and interrater reliability coefficients >0.90. More recently, these have been extended to include digital measurements using the Farkas system (see below; e.g., Aldridge et al. 2005; Baca et al. 1994; Weinberg et al. 2006; Wong et al. 2008).

Dr Farkas and his trainees have extended instruction to a network of investigators and clinicians. There is also a video introduction to the anthropometric landmarking system (Deutsch et al. 1995), with a discussion of direct measurements and 3D surface imaging. However, it provides only a brief initiation, and does not provide requisite training for the Farkas methods. Also, a complementary description of anthropometric procedures has been published by Kolar and Salter (1997).

A new edition of the Farkas methods and norms is under preparation (see later). It is worth noting that subsets of Farkas' normative data have been reproduced as nomographs in handbook form by Hall et al. (e.g., 2003), but these do not include the measurement means and SDs needed to compute *z*-scores, conditioned on age, gender, and ethnicity, that are found in the Farkas atlases.

29.4 Digital Imaging Techniques

As the means of 3D digital surface acquisition have become available (e.g., laser scanning and stereophotogrammetry), there has been increasing interest in the clinical and research community for image analytic techniques.

One clear advantage of using surface images is that they provide a resolute data set for storage, thus allowing subsequent morphometry. This provides an opportunity to the clinician and investigator for ad libidum post-acquisition measurement.

Another advantage of using digital surface scans is that they permit image acquisition of young children and developmentally disabled individuals, who sometimes cannot sit still for long for a direct anthropometric examination. Some of the 3D imaging devices that became commercially available in the 1990s could capture an image in a matter of seconds, but – rapid as this was – this period was long enough to introduce motion artifact. Fortunately, later advances in alternative imaging techniques (e.g., 3D stereophotogrammetry) permitted image capture in less than 2 ms. With this rapid acquisition, image distortion was no longer a problem (see discussion by Wong et al. 2008).

Morphometry can be performed directly on the 3D image. The point cloud generated by the imaging system is plotted in space, and *x*, *y*, *z* coordinates are computed for the scanned surface. 3D stereophotogrammetry measurements are resolute and reliable (Aldridge et al. 2005; Baca et al. 1994; Weinberg et al. 2006; Wong et al. 2008; Tan et al. in preparation). In order to utilize the Farkas direct anthropometric norms, it is important to provide validation of direct against digital measurement. Indeed, in a study of the metric qualities of the 3dMD sterophotogrammetry imaging device (Wong et al. 2008), the majority of measurements via direct anthropometry and image analysis by trained raters were highly correlated.

29.5 Digital Normative Database

Efforts are now underway to make available the Farkas norms in electronic format to the clinical and research community. These norms have recently been structured within a digital database, *FaceValue*, created with the support of the US National Institute of Dental and Craniofacial Research. This will provide the clinical and research community streamlined access to the norms, and the opportunity to readily compute standardized scores conditioned on demographics. The objective is to make the Farkas norms more user-friendly by creating a computer-based interactive craniofacial measurement database for them. The software is designed to (1) facilitate ready access to look-up tables conditioned on patient demographics, using a menu-driven, landmark-based interface; (2) permit computation of standardized measures for patients, including user-created functions; (3) generate reports for anthropometric protocols, conditioned on professional specialization; and (4) export derived scores to databases for documentation and statistical analysis.

29.6 Application to Plastic Surgery and Oral/Maxillofacial Surgery

In addition to being a medical anthropologist and dysmorphologist, Dr Farkas was a plastic surgeon. His anthropometric methods were designed to accommodate the craniofacial surgeon in pre-surgical planning and post-surgical evaluation. As Dr Paul Tessier wrote, it is first necessary to determine for the patient "what is 'ortho' and what is 'dys'" (foreword to Farkas and Munro 1986). The Farkas system permits the surgeon to establish concretely the degree and type of abnormality using his toolbox of measurements. We discuss further the quantitative assessment of dysmorphology in the context of medical and clinical genetics (see below).

Anthropometric work-ups have proven helpful in planning surgical procedures and evaluating outcomes for a number of conditions, including cleft lip–cleft palate and craniosynostoses (Farkas et al. 1993; Farkas and Forrest 2006; Mulliken et al. 2001; Oh et al. 2008). For example, in unilateral coronal synostosis (UCS), Burvin et al. (1999) employed anthropometric analysis to compare the outcome of two contrasting surgical techniques (homeotopic vs. heterotopic positioning of frontal elements) in the correction of dysmorphology. Further, Oh et al. (2008) used the Farkas procedures to study the long-term outcome of UCS patients who had fronto-orbital advancement in infancy. They determined that, even with surgical intervention, these patients displayed residual, consistent middle and lower facial asymmetry.

The Farkas quantitative measures provides the metrics for designing the type and degree of planned surgical alterations, and it can be useful to combine these measures with complementary imaging techniques. For example, instantiation of craniofacial surface images and their landmarks to radiographic, CT-, and MRI-based images will delineate the relationship between the facial surface and the underlying tissue. This multimodal approach can be useful in designing surgical interventions, as seen in an example drawn from a clinical work-up by Altobelli and his collaborators at the Surgical Planning Laboratory at Brigham & Women's Hospital (Boston, MA, USA). They merged a craniofacial surface image (acquired by a Cyberware laser scanner) with both 3D CT and MRI data for a case study of a patient with Crouzon syndrome. This autosomal dominant genetic condition, a form of craniofacial dysostosis, is characterized in part by orbital hypertelorism (an abnormally large distance between the eyes). A 3D digital template was then constructed and used to estimate the optimal parameters for repositioning the patient's orbits more medially (Altobelli 1994).

The response of soft tissues to the changes in the underlying bony architecture is still not well understood. As Altobelli points out, surgical design is best conceived from the "outside in," that is, first determine the ideal position of the craniofacial surface, then move the bones to accomplish the desired result. This approach is superior to the "inside out" model of repositioning and augmenting the bones, in the hopes that the surface response will be acceptable.

29.7 Application to Developmental Biology

Quantitative measures of dysmorphology can also be used to examine early developmental factors. It is possible to study anomaly combinations chosen to indicate specific developmental classes of dysmorphogenesis (Farkas and Deutsch 1996). These include the chronological origin of dysmorphogenesis, the mechanism of alteration, and embryonic primordia (Anlagen) from which dysmorphic features arise. By the 19th day of embryonic development, the germ layers and their subdivisions have formed into recognizable, discrete masses, and craniofacial differentiation first appears within these Anlagen. The brain and face derive in part from the same primordia, and embryologic "fate-mapping" studies describe how Anlagen correspond to specific derivatives in both craniofacial

and brain regions (Couly and LeDouarin 1987). Therefore, a gene or untoward environmental effect that produces brain maldevelopment can also affect the features of the head and face. Indeed, distinctive patterns of dysmorphology are often seen in genetic conditions and teratogenic syndromes. Quantitative tests of these brain–face relationships are made possible by anthropometric methods; one example is the correlation of craniofacial asymmetry, defined by Farkas' measurements, and brain midline maldevelopment predicted by fate maps (Deutsch et al. 2000).

29.8 Application to Medical and Clinical Genetics

The Farkas methods have also been used by geneticists in the diagnosis of craniofacial dysmorphology. With the aid of the Farkas atlases and normative databases, it has been possible to create a protocol permitting objective, reliable assessment of dysmorphic features (Deutsch and Farkas 1994; Farkas and Deutsch 1996). Here, craniofacial anomalies can be measured as standardized (e.g., *z*-) scores, conditioned on demographics. Importantly, they are quantified on a graded continuum that spans from normalcy to minor anomalies to major dysmorphic features.

A common challenge to the geneticist is the problem of heterogeneity with respect to both etiology and phenotype, and this holds true for many complex disease states (Thornton-Wells et al. 2004). This problem is particularly challenging in the field of neuropsychiatric disorders, for example, autistic disorders, which have a statistical overrepresentation of craniofacial anomalies. In addition to the large number of identified medical conditions found to be associated with one of these disorders, there may be numerous currently unidentified syndromes. Here, two approaches utilizing quantitative dysmorphology phenotypes can be used to come to grips with heterogeneity. Collections of anomalies across patients can be cluster-analyzed to determine whether they cohere. Alternatively, patients can be cluster-analyzed by anomalies to determine whether subgroups of individuals emerge as a function of anomaly combinations. The provision of continuously distributed measurements, for example, *z*-scores derived from the Farkas norms, rather than simple dichotomous variables, is likely to boost statistical power to detect existing associations.

Another anthropometric approach used in clinical genetics research is to describe dysmorphology associated with specific conditions. Farkas system measurements have been used to study several craniofacial disorders, including Apert (Farkas et al. 1985), Crouzon (Kolar et al. 1988), Down (Deutsch and Mulliken 2001), and Treacher-Collins (Farkas et al. 1989) syndromes. It is noteworthy that application of these methods to the study of these syndromes not only validated prevailing clinical opinion on the occurrence of specific anomalies, but also identified dysmorphic features that had gone hitherto unidentified. More recently, quantitative dysmorphology methods have been used to characterize specific genetic microdeletions and microduplications, including the recurrent copy number variant 16p11.2 (McCarthy et al. 2009). The Farkas methods revealed that the microdeletion and microduplication of this chromosomal region had contrasting effects on patients' head size, with the former associated with markedly larger head circumference than the latter.

29.9 Applications to Other Areas of Health

There is also potential for broad use in biometrics and bioinformatics. This has not yet been fully realized, perhaps because an electronic version of the Farkas databases has not been widely available. The distribution of the normative data in a digital format will hopefully make the databases more tractable to IT-based analysis.

Anthropometric methods have also been applied to a variety of other fields, including industrial fabrication. They have been used in the molding of helmets and goggles on a "tailor-made" basis that conform to the individual.

Further, the Farkas methods have also been used as a tool in forensics. One example is the application of facial morphology measures on a developmental continuum to "age" photographs. That is, a photograph of a child can be measured and morphed using existing norms to estimate facial appearance with advancing age. Farkas was an early adopter of aging algorithms that have aided search efforts for missing children (Farkas 1994).

Summary Points

- The Farkas anthropometric methodology permits objective, reliable quantification of craniofacial morphology.
- The anthropometric examination is painstaking and requires training.
- The Farkas normative databases allow computation of standardized (*z*-) scores, based on age, gender-, and ethnicity-specific characteristics.
- These methods permit quantitative assessment of dysmorphology on a continuum, and are commonly used for individual case studies, delineation of patterns of anomalies in heterogeneous patient groups, and in the description of distinctive facial appearance in identified craniofacial syndromes.
- The Farkas methodology is also a useful adjunct in craniofacial surgical planning and assessment.
- These procedures also are useful in population-based physical anthropology research, forensics, and biometrics.
- Advances in 3D craniofacial surface imaging are permitting rapid image capture, which can then be analyzed using Farkas system-based computer-aided morphometry.

Key Facts

Table 29.8 Key facts

• The Farkas craniofacial anthropometrics system delineates methods for landmark-based craniofacial anthropometry. These techniques provide objective, reliable quantification of craniofacial morphometry. Extensive normative databases allow computation of standardized (*z*-) scores, based on age-, gender-, and ethnicity-specific characteristics
• These methods permit quantitative assessment of dysmorphology on a continuum, for individual patients and groups, that are of utility in medical and clinical genetics. Further, they are helpful in plastic and oral/maxillofacial surgical planning and assessment. The methods and norms also find application population-based physical anthropology research, forensics, and biometrics
• 3D craniofacial surface images are increasingly used in computer-aided morphometry. Further, plans are underway for a release of the normative database in digital format, permitting flexible computation of mathematical functions

Acknowledgments It is with sadness that we report that Leslie G Farkas MD CSc Dsc FRCS passed away on 16 October 2008. He lived to the age of 93 years, and had continued working well into 2007. We owe a debt of gratitude to Dr Farkas for having the vision, energy, and dedication to create his measurement system and to apply it to numerous areas of clinical practice and research. He was truly the father of modern craniofacial anthropometry (Naini 2009), who served as a generous mentor to generations of students and colleagues.

Additionally, we would like to thank Marko Katic and Tanya Hreczko for their consultation.

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Chapter 30
Anthropometry of Soft Facial Tissues

John S. Bamforth

Abstract The head is the most visible part of the human anatomy and is the way that people recognize each other visually. It is the site of food intake; all the major sensory organs associated with food detection and procurement are located in the head (vision, smell and hearing), together with all the structures to protect these vital organs. The muscles associated with food capture and chewing are also those associated with defense and are powerful. They have prominent insertions into the jaw and broad areas of origin on the cranium.

Less powerful striated muscle take origin at the cranium or jaw and are inserted into the fascia of the skin. These muscles originally served as muscles protecting vital organs and orifices but have, with time, come to function more as muscles of facial expression and phonation, with very precise movements that convey the state of mind of the individual quickly.

The various components of the soft tissue of the face are usually considered separately (muscle, connective tissue and adipose tissue), although they function as one coordinated system. For example, the connective tissue network, which contains elastic fibers, permits rapid deformation and relaxation of the face by the muscles of facial expression and phonation.

This chapter will reflect upon the embryological and fetal development of the components of the soft tissues of the face; commonly used methods of assessing the soft tissues together with their advantages and disadvantages and variation of the soft tissues with sex, age, ponderosity and race. Finally, some practical uses of this information will be examined.

Abbreviations

CT	Computerized tomography
MRI	Magnetic resonance imaging
TEM	Technical error of measurement

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_30,

30.1 Introduction

The skull is the scaffold forming the foundation of the face, and determines to a large extent, the size and shape of a face and the individual components. The soft tissues cloak the skull and give the face recognizable form. Genetic influences determine the basic shape and structure of the face; this must include both the bony architecture and the distribution of the soft tissue, although this particular aspect has never been studied. The state of nutrition, sex, and racial group are other potential modifiers of facial soft tissue. External influences (trauma and disease) will also modify the appearance, together with surgical and dental manipulation.

Estimating the mass and distribution of the soft tissues of the face is not an easy task. Some areas of the face are very mobile and elastic; others are relatively fixed and vary little with facial movement.

Each method of measurement has its own strength and weakness; these must be considered when interpreting facial tissue depth measurements. Different investigators also have different levels of expertise and, therefore, different error rates.

30.2 Derivation of the Soft Tissues of the Face

The soft tissues of the face, in common with all other facial connective tissues including bone, are derived embryologically from the cephalic neural crest and the core mesoderm. This is distinct from other parts of the body, where all connective tissue is derived from the lateral plate mesoderm.

The initial embryological event requires setting up an axis in the cranial region, defining anterior and posterior, right and left, and rostral and caudal. This occurs under the influence of the homeobox genes, particularly the Hox series, which pattern the rhombomeres. With the development of the neural tube and the formation of the neural crest tissues, there is a coordinated migration of tissues to the branchial arches, where they will differentiate and further migrate to the facial primordia, and thence into the definitive fetal face. The process involves cell migration and programmed cell death, most of which is locally determined and coordinated after the cells have migrated into the branchial arches. Cell death occurs around the developing orifices and the points of fusion of facial primordia (particularly in the formation of the midface, the nose, and the upper lip and the palate). This whole process is under genetic control, and events take place over precise time periods (usually hours, but sometimes minutes) following gestation. The fate of cells migrating into branchial arches is not decided until after the migration, and is controlled to a large extent by local endoderm, ectoderm, neural crest and paraxial mesoderm interactions. The major genes involved in this process are the bone morphogenetic proteins, fibroblast growth factor supergene family, and hedgehog (see Chai and Maxson 2006 for a review).

As these events are sequential, development of both the brain and the face is interconnected. Basic malformations of the brain are therefore frequently accompanied by particular facial abnormalities.

30.3 Components of the Facial Soft Tissues

The soft tissues of the face are bounded on the outermost surfaces by the skin. The inner surface is the skull or cartilage. The skin comprises epidermis and dermis. These structures are thin and relatively constant in thickness in the face. Beneath the skin are muscle, adipose tissue, and connective tissue. The striated muscle in the face is grouped into discrete groups of fibers around the natural orifices in the head, and provides a sphincter-like action around these orifices. Adipose tissue is

universally dispersed within the subcutaneous layer in small quantities and between the muscle fibers. It is also aggregated in discrete subcutaneous fat pads over the front and side of the face. The deep fat pads (parapharyngeal and buccal fat pads) are pads that are placed between the masticatory muscles and within the pharynx, and facilitate muscle movement in swallowing.

These components will be considered individually. Although nerves, blood vessels, and lymphatics have a very important functional role in facial movement and nutrition, they are a minor component of the overall soft tissue, and will not be considered further here.

30.3.1 Facial Muscle

The face has a large number of muscles. Those that influence the appearance of the face may be divided into those that are concerned with mastication, those concerned with sphincter function (around the eyes and mouth), and muscles whose function has been modified through evolution to become more connected with facial expression and phonation.

Muscles of mastication have their origin at the skull, particularly the temporal region, and are inserted into the jaw. These are relatively large and powerful muscles; hence, both origin and insertion of the muscle are a bony structure. Humans do not typically use biting as a method of defense, and our food tends to be cooked, and is softer; therefore, human muscles of mastication are not as big as those in our closest primate relatives, and the points of attachments to the skull and jaw are not so marked.

Sphincteric muscles have their origin on the skull, and are inserted into aponeuroses that blend with the skin. These are concentrated around the natural orifices and perform sphincter functions, for example, aiding in closure of the eyes, retaining food in the mouth, aiding in suckling and feeding, and dilating or contracting the nostrils. Many of these muscles have become primary muscles of facial expression and speech, and control of these muscles is very precise.

Normal facial muscle function depends intimately on the normal function of other components of the soft tissue. For example, the muscles of mastication and of the pharynx will not function normally without the buccal and parapharyngeal fat pads that provide a virtual gel pad buffer. Similarly, the muscles of facial expression and those assisting in speech will not function normally without the reticular facial ligament system, which permits the face to quickly relax to a neutral position once a facial expression or spoken word has been communicated.

In standard anatomy textbooks, the facial muscles are shown as single discrete muscles implying a discrete but coordinated function. More recent work has suggested that the muscles are functionally connected to each other and to their points of insertion, so that they act in a more coordinate fashion than previously thought (Breitsprecher et al. 1999). In particular, all the muscles of facial expression situated around the upper lip, philtrum, and the nose essentially connect the chondral growth center of the nose (the septal cartilage) with the frontal and zygomaticomaxillary suture systems of the face. This coordinate action results in symmetrical forces being applied to these facial sutures, which in turn are intimately connected with development of the bony midface. The skull sutures in a fetus and young child are relatively parallel to each other and filled with osteoid, not the rigid interdigitating structures they become in later life. Therefore, relatively little force applied to the facial bones at this age can have a large influence on growth and symmetry of the skull. Where the muscle action is asymmetrical in utero (as in cleft palate), marked facial asymmetry of both soft and hard facial tissues will result. When muscle action is weaker than normal, or the connective tissue attachments are more lax, this often results in a characteristic, recognizable change in facial morphology.

Total muscle mass varies between individuals, but sexual dimorphism is not marked. The muscles are also in constant use and change with age appear not to be marked.

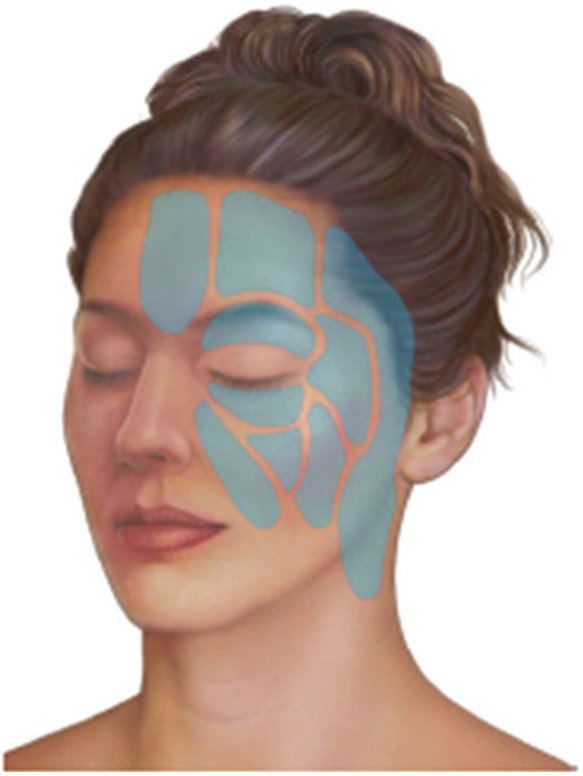

Fig. 30.1 Location of the subcutaneous fat pads of the face. An artist's rendition of the subcutaneous compartments of the face

30.3.2 Facial Ligaments

The face has a rich network of skin ligaments. The ligaments run from the periosteal surface to the fascia of the dermal layer. They are reticular in formation, often branching with adipose tissue interspaced between the lattices (for a review, see Nash et al. 2004). Ligaments are subject to changes with age and with exposure to sun, giving rise to a wrinkled appearance (Braverman 1986). The facial ligament system not only performs natural tissue boundaries (which are important in limiting diseases, such as infection and tumor), but also provides an elasticity to the face that permits muscles of facial expression and phonation to act quickly and sequentially.

30.3.3 Adipose Tissue

There are three main places where fat cells accumulate: diffusely in the dermis, in discrete symmetrical pads below the dermis at the front and side of the face, and deeply between muscles of mastication and the pharyngeal muscles.

Immediately below the surface of the skin in most parts of the face, there is a layer of adipose tissue that mingles with the subcutaneous capillary network, dermal papillae, and eccrine ducts.

The discrete accumulations of adipose tissue at the front and sides of the face are situated in multiple independent anatomical compartments (Rohrich et al., 2007). These fat compartments may broadly be divided into a nasolabial compartment, three cheek fat compartments, three orbital compartments, a forehead compartment, a temporal compartment, and a jowl compartment (Fig. 30.1).

The boundaries appear to form natural planes through which blood vessels and nerves run to serve both the fat compartment and the skin overlying it. The compartmentalization of the superficial fat layers has important implications for the face in terms of changes with aging and disease (Donofrio 2000), as no one compartment responds exactly the same way to a stimulus as another compartment. For example, the upper malar compartment in older people increases in size relative to the middle and inferior compartments in older people (Gosain et al. 2005), whereas the temporal compartment decreases in size with age (Stephan and Devine 2009). These changes alter the shape of face from the round, cherubic face associated with childhood to the more angular face associated with older age.

In addition to these superficial layers, there are deeper layers of facial fat, notably the buccal and parapharyngeal fat pads and the sub- and retro-orbicularis layers of fat.

The deeper fat pads (buccal and parapharyngeal) are metabolically inert fat pads that assist the function of masticatory and pharyngeal muscles by providing a gel-pad buffering separation between the muscles (Kahn et al. 2000). They have few mitochondria and show little change in size with state of nutrition (although they do atrophy in some disease states, notably facial hemiatrophy and AIDS).

30.4 Practical Methods and Techniques of Measuring Facial Soft-Tissue Depth

The next section will discuss: the soft-tissue landmarks; the most common methods that have been used to assess soft-tissue depths; and the accuracy of commonly used methods.

30.4.1 Soft-Tissue Landmarks

Facial soft tissue is surveyed by measuring the depth of the soft tissue, which overlies the conventional facial landmarks. Both landmarks and soft-tissue measurements can be reliably reproduced, both within and between observers (Farkas 1994). Facial landmarks are conventionally located and marked with the head in the Frankfort horizontal position. Measurement of tissue depths is also ideally measured with the head in this position in order to standardize the effect of gravity on the soft tissues. Tissue depth is the smallest measured distance between the epidermis of the skin and the nearest hard tissue element (usually the bone of the skull), generally measured at right angles to the hard surface.

The tissue depth at specific landmarks is denoted by a superscript dash placed above the accepted notation describing a landmark. Thus, tissue depth at the pogonion landmark is referred to as pg-pg′, sometimes abbreviated to pg′. No commonly used method of measuring tissue depth is routinely able to distinguish between the soft-tissue components (muscle, connective tissue, and adipose tissue), although special techniques may do so (Gosain et al. 2005).

Many of the facial landmarks are defined by palpation; thus, many of the bony landmarks used to locate the discrete facial points are close to the surface of the skin and, therefore, are likely to have less soft tissue between the skin surface and the bone than in non-landmark areas of the face. Therefore, fixed errors (e.g., instrument error) will tend to be relatively larger when the measurement is small. Measurements over non-bony landmarks rely on midpoint or chord constructions, and may be more difficult to reproduce. Tissue depths give little information about shape or architecture (e.g., of the superficial facial fat pads).

Table 30.1 Key features of anthropometry of soft facial tissues

1. Facial tissue depth is conventionally measured as the shortest distance between uncompressed skin and underlying cranial bone, measured in the Frankfort horizontal position
2. Methods used to measure tissue depth routinely include needle puncture, plain film radiography, computerized tomography, magnetic resonance imaging, and ultrasound. The technical error of measurement of any method is approximately 10%
3. The ponderosity of adult subjects has a greater influence on facial tissue depths than sex or race
4. Soft tissue comprises muscle, connective tissue, and adipose tissue, together with blood vessels, lymphatic vessels, and nerves. The tissues function as a coordinate system and their movement influences the growth of the bony cranium
5. Changes in shape and architecture of facial soft tissues are poorly represented by the traditional facial tissue depth measurements

This table lists the key features of facial soft tissue and measurement of these tissues

Despite this, measuring tissue depths over landmarks is useful, and nearly all the work published on soft-tissue depths of the face is based on such assessments. These studies have formed the basis for comparison of faces in medical, surgical, anthropological, and forensic literature.

30.5 Commonly Used Methods to Assess Tissue Depth

The commonly used methods of assessing tissue depth are needle puncture, plain radiography, computerized tomography (CT), magnetic resonance imaging (MRI), and ultrasound. All these methods have advantages and disadvantages (Table 30.2). All methods have a systematic bias; some methods give higher tissue depth values at some landmarks than given by other methods (Table 30.3; Stephan and Simpson 2008). Note that for methods that involve CT and MRI, different protocols have been used for scanning. For CT, this markedly affects tissue depth estimates even when the operator and the machine are constant (Kim et al. 2005). Although no similar data exists for MRI, it is likely that the same will apply. There is a need to standardize protocols when using these methods.

30.6 Precision and Accuracy of Commonly Used Methods

Little attention has been given to precision and accuracy of soft-tissue measurement of the face, until recently. Studies on accuracy (the relationship between the surface landmark placed on the skin and the bony landmark underneath it) are not easy to do, and there is limited data. Some of the newer techniques that permit a three dimensional reconstruction (e.g., CT and MRI), are able to examine this relationship to some extent, and the relationship appears accurate (Tilotta et al. 2009), but data are scare. There is more information concerning precision (relationship of two or more measurements of the same parameter taken at different times). Anthropologists routinely use the technical error of measurement (TEM) and its derivative, the coefficient of reliability (R), to estimate the precision of measurement. TEM is expressed in the unit of measurement; for most landmarks, it is estimated at 5–10% of the measured value. For a scientific measurement, this is just acceptable, but relatively imprecise. This lack of precision is remarkably similar, no matter what technique is being used to estimate soft-tissue depth (Domaracki and Stephan 2006; Smith and Throckmorton 2004; Van derPluym et al. 2007). Lack of precision of measurement complicates the comparisons between

Table 30.2 Comparison of advantages and disadvantages of the commonly used methods of measuring soft-tissue depth

Method of measurement	Advantage	Disadvantage
Needle puncture	Low cost	Invasive
	Operating characteristics well defined	Most information from cadavers, soft tissue may not accurately reflect living tissue
	Measurements can be made in Frankfort plane	Compression of soft tissues inevitable during measurement
Plain film radiography	Standard cephalograms widely used in dentistry and medicine	Exposure to ionizing radiation, patient selection may bias results
	Films generally taken in Frankfort plane	Only of use where surface landmark and bony landmark are parallel to the film plate
	Relatively inexpensive	Metallic implants (braces and fillings) may interfere with measurements
	No compression of tissue whilst taking measurement	
Computerized tomography	Widely used in medicine and dentistry	Expensive
	Images are digital and easy to manipulate (e.g., absorption characteristics of soft and hard tissue relatively easy to distinguish)	Requires exposure to ionizing radiation, patient selection may introduce bias
	Accuracy of surface landmark placement relative to bony landmark can be verified	Patient motion artifact (voluntary or involuntary) may interfere with measurements
	Paired landmarks easily measured	Radio opaque objects (e.g., fillings, braces) may distort images and measurements
		Images are not in Frankfort plane, gravity effects on soft tissue are possible
Magnetic resonance imaging	No exposure to ionizing radiation, ethically acceptable to image subjects for tissue depth estimation	Very expensive
	Can be repeated on same subjects to obtain longitudinal data	Images generally not acquired in Frankfort plane
	No soft-tissue compression during measurement	Requires exposure to high-intensity magnetic field, subjects with metallic exposure not eligible
	Images are digital and easy to manipulate (e.g., absorption characteristics of soft and hard tissue relatively easy to distinguish)	Subject motion artifact distorts images
	Accuracy of surface landmark placement relative to bony landmark can be verified	
	Paired landmarks easily measured	
Ultrasound	No exposure to ionizing radiation can be used repeatedly in the same subject	Probe must touch skin surface, tissue compression possible with inexperience operator
	Portable, can be used in the field	Operating characteristics of portable equipment differs according to manufacturer and must be defined before use
	Measurements made in Frankfort plane	

Table 30.3 Systematic bias of soft-tissue measurement according to method of measurement

Measurement technique	Landmarks at which tissue depths are consistently higher than with other techniques	Landmarks at which tissue depths are consistently lower than with other techniques	Measurement technique that most closely correlates
Needle puncture	–	–	–
Plain radiology	All midline landmarks	Lateral landmarks: gonion and zygion	–
CT scan	All midline landmarks	All midline points	MRI
MRI scan	–	All midline points	CT
Ultrasound	Supra M2, infra M2, gonion, mid infraorbital, anterior masseter border	–	Needle puncture (except for Supra M2)

individuals because relatively small differences will not be detectable. Significant differences between comparison groups reported in literature should be interpreted in light of some measurement of precision, preferably the TEM.

30.7 Normal Values for Tissue Depths

Tables 30.4 and 30.5 give two sets of recently published values for tissue depths. Tables 30.4 and 30.5 have been derived from the data of De Greef et al. (2006). These were measurements derived from a cohort of 967 normal North European Caucasian individuals, using ultrasound. This is the largest sample published by one group to date; the other commonly used databases (Rhine and Moore 1984; Helmer 1984) were based on much smaller sample sizes (73 and 123, respectively). In addition, the data of De Greef et al. are more modern (2006), which is important when considering the steady rise in obesity during the time interval.

Table 30.6 has been adapted from Stephan and Simpson (2008), and is a compilation of data derived from previous publications, weighted in favor of the larger studies. It has not been fractionated by age, sex, or race. When lumping data from diverse sources derived from using different techniques and over a timescale in excess of 100 years, it is very possible that the aggregate measurement error will overshadow small (but real) changes.

Note that the facial landmarks employed by the two studies are somewhat different. Only four landmarks are the same in both tables (nasion, mid-philtrum, zygion, and gonion) and four others are similar, but not identical (mid-mandibular, supra M2, sub (infra) M2, and glabella). For the four landmarks that are comparable, there is good agreement between the tables.

30.8 Soft-Tissue Variation with Sex

Sexual dimorphism in tissue depth has been reported (Manhein et al. 2000; Rhine et al. 1984; De Greef et al. 2006); these differences are small and variable between studies, and remain under investigation. When all data from all sources are pooled, there is very little difference between men and women (Stephan et al. 2005). This is largely corroborated by a single large study between men and women; in general, the variation in tissue depth in men is more than in women, as evidenced by the standard deviation.

Table 30.4 Soft-tissue depth for facial landmarks for women, fractionated for age and basal metabolic index

	Basal metabolic index																											
	<20										20–25										>25							
	Age range										Age range										Age range							
	18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60	
	Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation							
	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD
Supraglabella	3.9	0.6	3.7	0.5	3.9	0.7	3.7[a]	0.2	3.7[a]	0.5	4.1	0.6	4.1	0.5	4.3	0.6	4.3	0.5	4.4	0.7	4.5	0.7	4.5	0.5	5.1	1.2	4.9	0.7	4.6	0.8
Glabella	4.9	0.7	4.2	0.6	4.3	0.6	4.4[a]	0.4	4.4[a]	0.6	5.1	0.8	4.9	0.7	4.8	0.8	4.8	0.7	5.3	0.9	5.5	0.8	5.4	0.7	5.7	0.8	5.8	0.9	5.6	1.0
Nasion	5.9	1.3	5.4	0.9	5.4	1.0	5.9[a]	2.0	6.7[a]	1.2	6.3	1.2	6.2	1.4	6.3	1.1	6.2	1.2	7.2	1.2	6.4	1.2	6.6	1.4	6.7	0.7	7.2	1.6	7.3	1.7
End of nasal	2.5	0.6	2.7	0.7	2.6	0.9	2.7[a]	0.6	2.4[a]	0.5	2.6	0.8	2.5	0.6	2.5	0.6	2.6	0.6	2.5	0.5	3.0	0.7	3.0	0.8	2.8	0.5	2.9	0.7	2.8	0.7
Mid-philtrum	10	1.6	8.7	1.0	8.2	1.7	7.3[a]	0.8	7.0[a]	0.9	9.8	1.6	9.2	1.6	8.5	1.9	8.1	1.5	8.0	1.2	9.8	2.0	8.8	1.3	9.3	1.3	9.1	1.5	8.7	1.4
Upper lip margin	9.8	2.1	9.2	1.4	7.4	1.6	8.3[a]	1.9	9.0[a]	3.4	10.0	1.7	9.4	1.7	9.2	1.8	9.1	1.3	9.9	2.1	9.8	2.0	9.5	1.3	8.6	1.3	8.8	1.5	9.0	1.6
Lower lip margin	10.9	1.9	10.1	1.3	9.4	1.2	9.7[a]	2.7	9.7[a]	2.0	11.0	2.0	10.7	1.9	10.3	2.1	10.3	1.5	10.7	1.8	10.8	2.2	11.1	2.1	10.5	2.0	10.9	2.1	10.9	1.5
Chin–lip fold	9.5	1.0	8.7	1.2	9.0	1.2	9.7[a]	1.3	11.1[a]	0.6	9.6	1.0	10.2	1.7	10.3	1.1	10.1	1.4	10.8	1.7	9.7	1.3	10.4	0.9	10.7	1.0	10.9	1.2	11.2	1.6
Mental eminence	9.1	1.5	8.9	1.4	8.7	1.0	9.4[a]	0.3	9.7[a]	2.0	9.6	1.7	9.7	1.7	9.9	1.9	10.0	1.6	10.5	2.0	11.0	1.9	11.5	1.7	12.0	1.7	11.6	1.7	11.6	1.7
Beneath chin	5.6	1.1	5.9	1.8	4.8	0.8	5.5[a]	2.3	6.5[a]	2.6	5.6	1.3	5.7	1.4	5.7	1.4	5.9	1.4	7.0	2.1	7.1	1.5	7.6	2.1	6.9	1.8	6.9	1.7	7.3	2.0
Frontal eminence	3.8	0.5	3.7	0.7	3.8	0.6	3.9[a]	0.4	3.7[a]	0.4	3.9	0.6	4.0	0.5	4.1	0.6	4.3	0.5	4.6	0.8	4.5	0.6	4.6	0.5	5.0	0.9	5.0	0.5	4.8	0.9
Suprarbital	5.1	0.8	4.7	0.7	5.0	1.6	5.0[a]	0.3	4.8[a]	0.4	5.4	1.0	5.2	0.6	5.3	0.6	5.3	0.7	5.5	0.7	6.1	0.7	6.3	0.8	6.3	0.8	6.5	0.9	6.5	1.0
Lateral glabella	5.7	1.0	4.9	0.9	4.9	1.3	4.6[a]	0.8	5.8[a]	1.5	5.7	1.1	5.5	1.4	5.6	0.8	5.5	1.1	6.1	1.2	5.7	1.4	6.6	1.0	5.9	0.9	6.4	1.5	6.4	1.5
Lateral nasal	3.9	0.6	3.7	0.7	3.3	0.6	ND	ND	ND[a]	ND	3.7	0.6	3.6	0.7	3.4	0.5	3.4	0.6	3.7	0.5	3.7	0.8	3.8	0.7	3.9	0.7	4.0	0.7	3.8	0.6
Suborbital	9.3	2.2	7.9	1.8	9.5	4.0	9.7[a]	1.0	9.6[a]	1.9	9.4	2.1	9.3	2.9	10.0	2.5	9.1	2.9	10.4	1.9	10.3	2.4	10.5	2.0	10.9	2.9	11.1	2.7	10.4	2.5
Inferior malar	16.2	2.9	15.0	2.1	16.5	2.9	13.8[a]	2.0	17.6[a]	2.6	17.9	2.7	17.4	3.4	18.1	3.1	19.2	3.0	19.8	3.4	20.3	2.0	21.0	3.6	20.2	3.3	21.0	3.1	21.3	3.6
lateral nostril	9.6	1.1	8.3	1.6	7.6	1.0	8.8[a]	2.2	9.2[a]	0.8	9.5	1.3	8.8	1.2	9.2	1.5	8.4	1.4	9.6	1.1	9.4	1.8	9.0	1.2	9.4	1.1	9.4	1.4	9.5	1.1
Naso-labial ridge	10.1	1.7	8.5	1.3	8.0	1.8	7.6[a]	0.8	8.0[a]	1.3	9.5	1.6	9.4	1.6	8.7	1.3	8.4	1.1	8.4	1.0	10.0	2.1	9.3	1.2	9.4	1.7	9.3	1.1	8.9	1.5
Supra canina	9.6	1.9	8.5	1.7	7.4	1.1	7.4[a]	1.5	7.6[a]	1.3	9.5	1.9	8.4	1.9	8.3	1.2	8.1	1.6	8.1	2.2	9.2	1.9	8.7	1.6	9.1	2.2	8.4	1.9	9.5	2.4
Sub canina	10.3	1.6	8.7	1.6	9.1	1.9	9.7[a]	1.1	10.8[a]	2.1	10.3	1.5	9.9	1.6	10.5	1.5	9.9	1.1	11.1	1.3	10.9	1.8	10.8	1.6	11.0	1.6	10.8	1.9	11.1	1.8
Mental tubercle ant.	9.3	1.4	9.1	1.4	8.7	1.0	8.9[a]	1.8	10.6[a]	2.0	9.6	1.6	9.9	1.3	10.1	1.5	10.4	1.3	10.9	1.7	10.7	1.7	11.0	1.6	11.8	1.5	11.5	1.4	11.4	1.6
Mid-lateral orbit	4.8	0.7	4.6	0.8	4.2	0.9	4.5[a]	0.8	4.6[a]	0.6	5.0	1.1	4.7	0.9	4.8	1.0	5.0	1.4	5.0	1.3	5.0	1.0	5.4	1.1	5.5	1.7	5.6	1.3	5.9	1.0

(continued)

Table 30.4 (continued)

	Basal metabolic index																											
	<20										20–25										>25							
	Age range										Age range										Age range							
	18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60	
	Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation							
	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD
Supraglenoid	9.3	2.1	7.7	2.6	7.4	1.9	9.0[a]	2.6	8.8[a]	2.1	9.6	2.2	8.8	2.1	9.2	2.3	8.6	2.7	9.6	2.4	10.3	1.9	9.9	2.9	10.2	2.3	10.4	2.6	10.9	3.0
Zygomatic arch	6.1	1.4	5.6	1.2	5.7	1.3	4.6[a]	0.6	5.4[a]	1.7	6.9	1.5	6.8	1.8	7.0	1.8	6.8	1.4	6.5	1.6	8.7	1.9	8.7	2.4	8.9	2.1	8.4	1.7	8.7	1.9
Lateral orbit	9.4	1.5	7.9	1.3	7.5	1.3	8.0[a]	1.0	8.8[a]	1.1	10.0	1.7	9.7	2.2	9.5	1.8	9.9	2.5	9.7	1.5	12.6	2.2	12.5	1.7	12.4	1.7	12.4	2.3	12.1	2.0
Supra M2	25.8	3.9	23.1	3.1	22.7[a]	1.7	25.1[a]	2.9	24.5[a]	0.8	26.6	3.8	25.6	3.5	26.0	2.7	27.2	3.0	27.1	3.4	29.2	3.6	28.7	2.8	29.7	3.0	29.2	3.2	29.0	3.3
Mid-masseter	16.5	3.0	14.1	2.8	13.3	3.4	14.3[a]	3.2	14.1[a]	1.8	17.2	3.5	16.8	2.5	16.4	2.5	16.4	2.8	15.7	2.6	17.7	3.9	19.8	3.1	19.7	3.3	19.0	3.7	17.2	3.6
Occlusal line	18.8	2.4	17.5	1.1	15.9	2.1	15.7[a]	1.4	18.2[a]	2.7	19.4	2.0	18.8	2.0	17.7	2.2	18.0	2.4	18.0	3.3	22.0	2.7	21.5	2.6	21.8	2.2	21.0	2.3	20.8	2.2
Sub-M2	18.5	2.7	15.7	1.7	16.7	3.1	17.6[a]	0.6	21.5[a]	4.1	19.0	3.1	18.1	3.0	18.7	3.2	17.9	2.3	21.2	2.6	21.5	3.3	20.2	2.7	21.5	2.5	22.3	3.6	22.4	4.0
Gonion	13.8	2.3	13.4	1.8	11.5	2.3	11.8[a]	1.9	12.9[a]	2.5	14.4	2.6	14.2	2.6	13.9	2.7	14.0	2.0	13.6	1.9	16.7	2.7	17.6	2.5	18.1	2.6	17.6	3.0	17.2	2.5
Mid-mandibular angle	10.7	2.2	10.0	1.9	10.1	2.3	9.7[a]	1.6	13.7[a]	3.0	11.4	2.4	11.0	2.1	11.3	2.3	11.4	1.9	14.0	2.4	14.2	2.0	14.8	2.7	14.9	2.2	15.5	2.2	17.2	3.4

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Measurements obtained by ultrasound
ND indicates insufficient data available
[a]Based on less than 10 observations

Table 30.5 Soft-tissue depth for facial landmarks for men, fractionated for age and basal metabolic index

	Basal metabolic index																											
	<20										20–25										>25							
	Age range										Age range										Age range							
	18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60	
	Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation									
	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD
Supraglabella	3.9	0.39	3.6[a]	0.24	ND	ND	2.9[a]	0.08	ND	ND	4.1	0.55	4.1	0.54	4.5	0.66	4.6	0.53	4.3	0.54	4.8	0.85	4.8	0.84	5.3	0.95	5.1	0.78	5.0	0.94
Glabella	4.6	0.54	4.7[a]	0.55	ND	ND	3.8[a]	0.48	ND	ND	5.0	0.69	4.7	0.44	5.1	0.60	5.5	1.05	5.2	0.68	5.8	1.3	5.4	0.88	5.9	1.06	5.9	0.91	5.9	1.12
Nasion	5.6	0.85	5.3[a]	0.34	ND	ND	4.3[a]	0.71	ND	ND	5.9	1.1	5.6	1.0	6.4	1.15	6.8	1.48	6.3	1.46	6.3	1.32	6.8	1.54	6.8	1.53	7.2	1.66	7.0	1.24
End of nasal	2.7	0.67	3.1[a]	0.94	ND	ND	2.3[a]	0.04	ND	ND	2.8	0.69	2.7	0.68	3.1	0.81	2.7	0.35	3.2	1.26	3.2	0.73	3.0	0.78	3.2	0.89	3.2	0.74	3.4	1.06
Mid-philtrum	11.6	1.71	9.5[a]	1.48	ND	ND	ND	ND	ND	ND	11.2	1.78	10.6	1.63	9.7	1.88	10.4	1.87	9.0[a]	1.07	10.8	1.66	10.7	1.72	10.6	1.58	10.4	2.01	9.9	1.42
upper lip margin	11.1	2.14	10.1[a]	1.84	ND	ND	6.6[a]	2.46	ND	ND	11.0	2.15	9.8	1.65	10.6	2.52	9.8	2.28	9.4[a]	1.53	10.4	1.71	10.8	1.78	10.6	2.47	10.1	1.88	9.6	1.67
Lower lip margin	12.1	1.70	9.3[a]	1.65	ND	ND	11.8[a]	2.63	ND	ND	12.5	2.05	11.8	2.04	11.7	2.23	12.8	2.41	10.1[a]	1.85	12.2	2.17	13.1	2.43	12.5	2.16	11.8	2.67	12.9	2.76
Chin–lip fold	10.1	1.41	10.3[a]	0.96	ND	ND	9.3[a]	0.83	ND	ND	10.1	1.31	9.6	1.21	10.9	1.59	10.5	1.22	10.1	1.29	10.1	0.97	10.7	0.93	11.5	1.37	11.3	1.37	11.5	1.95
Mental eminence	8.7	1.57	9.6[a]	0.50	ND	ND	8.9[a]	2.76	ND	ND	9.5	1.66	9.4	1.6	10.8	1.45	10.2	1.48	10.5	2.12	10.3	1.91	11.3	1.26	12.1	2.16	12.2	2.23	12.6	2.15
Beneath chin	5.5	1.02	5.3[a]	0.67	ND	ND	5.0[a]	1.15	ND	ND	6.1	1.2	6.2	1.43	6.4	1.27	6.2	0.84	6.8	1.63	7.2	1.73	7.1	1.46	7.5	1.98	7.8	1.82	7.8	1.77
Frontal eminence	3.8	0.47	3.7[a]	0.56	ND	ND	3.1[a]	0.31	ND	ND	4.1	0.64	4.1	0.65	4.7	0.7	4.6	0.62	4.5	0.72	5.0	0.96	4.8	0.77	5.3	1.15	5.2	0.87	5.2	1.14
Supraorbital	4.7	0.52	4.9[a]	0.64	ND	ND	4.1[a]	0.31	ND	ND	5.1	0.65	5.0	0.53	5.3	0.72	5.8	1.06	5.5	0.78	6.1	0.66	6.3	0.89	6.6	1.3	6.5	0.73	6.8	1.11
Lateral glabella	5.9	1.12	5.9[a]	0.7	ND	ND	4.3[a]	0.14	ND	ND	6.0	1.29	5.5	1.4	6.6	1.25	6.0	1.56	6.6	1.55	6.2	1.31	5.9	1.32	6.8	1.61	6.5	1.39	6.2	1.59
Lateral nasal	3.7	0.59	4.8[a]	0.2	ND	ND	3.9[a]	1.9	ND	ND	3.7	0.64	3.6	0.5	4.0	0.69	4.0[a]	0.59	4.7[a]	1.29	4.1	0.68	3.8	0.84	3.9	0.6	3.7	0.35	4.0[a]	0.78
Suborbital	7.7	1.35	6.1[a]	2.5	ND	ND	7.8[a]	1.53	ND	ND	8.3	2.07	8.4	2.31	9.7	2.01	9.0	3.36	10.5	2.93	9.8	2.18	10.0	2.25	10.4	2.6	11.6	3.24	10.6	3.51
Inferior malar	14.7	2.44	13.7[a]	2.29	ND	ND	15.0[a]	0.28	ND	ND	16.2	2.8	16.5	3.19	17.9	3.43	18.2	3.77	18.3	3.83	18.9	3.23	20.2	3.5	21.8	3.88	20.7	4.39	22.3	3.98
lateral nostril	10.4	1.37	9.7[a]	1.34	ND	ND	7.7[a]	2.06	ND	ND	10.1	1.48	9.2	1.13	9.6	1.69	9.7	1.91	10.2	1.86	10.3	1.27	10.0	1.29	10.2	1.74	10.2	1.76	9.6	1.52
Naso-labial ridge	11.4	1.67	10.8[a]	1.35	ND	ND	ND	ND	ND	ND	11.1	1.93	10.8	1.66	10.4	2.15	10.4	1.5	9.0[a]	1.18	11.0	1.57	11.0	1.57	10.9	1.55	10.3	1.6	9.9	1.58
Supra canina	10.0	1.74	10.2[a]	2.46	ND	ND	ND	ND	ND	ND	10.4	1.93	9.7	1.87	9.9	2.01	9.4	1.58	9.2[a]	1.22	10.5	1.96	10.0	2.02	10.2	2.07	10.4	1.85	9.6	1.86
Sub canina	9.5	1.19	9.3[a]	0.7	ND	ND	9.1[a]	1.32	ND	ND	10.5	1.65	9.7	1.42	10.9	1.35	10.5	1.82	10.5[a]	1.16	11.1	1.95	11.2	1.81	12.0	2.33	11.8	1.7	11.3	1.6
Mental tubercle ant.	9.2	1.21	9.2[a]	1.15	ND	ND	7.4[a]	0.42	ND	ND	9.6	1.42	9.5	1.34	10.8	1.45	10.9	1.26	10.8	1.09	10.8	1.57	11.4	1.70	11.8	1.99	12.3	1.78	12.3	1.9
Mid-lateral orbit	4.8	1.34	4.7[a]	0.44	ND	ND	4.0[a]	0.45	ND	ND	4.6	0.82	4.4	0.68	5.0	1.32	4.8	0.84	4.5	0.45	5.4	1.67	5.2	1.23	5.3	1.04	5.7	1.4	5.4	1.08

(continued)

Table 30.5 (continued)

	Basal metabolic index																											
	<20										20–25										>25							
	Age range										Age range										Age range							
	18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60		18–29		30–39		40–49		50–59		>60	
	Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation										Tissue depth, mean and standard deviation							
	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD	X	SD
Supraglenoid	9.1	3.11	8.1[a]	1.2	ND	ND	ND	ND	ND	ND	9.8	2.92	8.8	2.71	10.8	3.88	9.5	1.77	9.1	2.9	10.7	3.26	10.5	2.63	10.2	3.41	11.0	3.16	10.3	3.61
Zygomatic arch	4.8	1.05	4.9[a]	0.73	ND	ND	ND	ND	ND	ND	5.7	1.15	5.8	1.23	6.1	1.26	6.3	1.78	5.9	1.13	8.4	1.66	7.9	1.48	8.1	2.22	8.1	1.9	8.3	1.63
Lateral orbit	6.7	1.15	6.8[a]	0.87	ND	ND	ND	ND	ND	ND	7.4	1.37	7.3	1.55	8.1	1.46	8.0	1.46	7.8	1.13	10.3	1.68	10.6	1.17	10.8	2.18	10.7	2.15	10.4	1.57
Supra M2	23.6	4.29	22.9[a]	0.58	ND	ND	ND	ND	ND	ND	25.0	3.48	24.1	3.83	24.9	3.84	23.7	4.29	28.0[a]	4.3	29.4	3.48	28.7	3.86	30.8	3.96	29.2	3.8	29.6	5.04
Mid-masseter	16.2	3.29	16.7[a]	1.03	ND	ND	ND	ND	ND	ND	16.8	3.98	16.9	3.45	18.2	3.88	18.0	2.85	17.3	3.54	19.0	4.06	21.7	4.58	23.0	3.61	21.5	4.02	19.8	5.28
Occlusal line	17.8	1.83	16.4[a]	0.52	ND	ND	ND	ND	ND	ND	19.4	2.38	18.8	2.36	19.5	1.62	19.1	2.24	18.6	1.92	22.8	2.37	22.3	3.01	23.1	3.66	21.8	3.14	21.8	3.41
Sub-M2	16.1	3.5	17.0[a]	1.63	ND	ND	ND	ND	ND	ND	17.2	2.82	16.5	2.86	18.7	2.91	17.3	2.79	19.8[a]	2.07	21.0	4.35	21.3	3.35	22.4	4.20	21.4	3.24	22.0	3.66
Gonion	13.6	2.16	12.9[a]	0.57	ND	ND	ND	ND	ND	ND	14.4	2.42	14.2	2.21	15.6	2.39	13.1	2.65	14.0	3.11	17.8	3.64	19.1	2.91	19.1	3.71	18.7	3.39	19.3	3.65
Mid-mandibular angle	8.9	1.88	9.5[a]	1.08	ND	ND	ND	ND	ND	ND	9.8	2.3	9.9	2.13	11.9	2.52	11.4	1.84	13.0	2.72	13.7	2.49	15.1	3.32	15.0	3.15	15.1	3.08	16.7	3.58

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Measurements obtained by ultrasound
ND indicates insufficient data available
[a] Based on less than 10 observations

Table 30.6 Soft-tissue depths at facial landmarks from historical data.

Soft-tissue depth measurement	Total weighted mean	Number of subjects	Number of samples	Weighted mean for s studies	s	Number of subjects in s	Number of samples	Estimated minimum (mean – 3 *Z*-scores)	Estimated maximum (mean – 3 *Z*-scores)
Opisthocranion (op-op′)	6.5	1,152	52	6.5	2.5	990	36	–0.5	13.5
Vertex (v-v′)	5.0	1,055	43	5.0	1.0	785	29	1.5	8.5
Glabella (g-g′)	5.5	5,791	163	5.5	1.0	4,542	115	2.5	8.5
Nasion (n-n′)	6.5	6,159	154	6.0	1.5	4,417	103	1.0	11.0
Mid nasal (mn-mn′)	4.0	1,272	67	4.0	1.0	919	38	0.5	8.0
Rhinion (rhi-rhi′)	3.0	5,511	146	3.0	1.0	4,307	100	0.0	5.5
Subnasale (sn-sn′)	13.0	1,768	78	12.5	3.0	1,170	43	3.0	22.5
Mid-philtrum (mp-mp′)	11.5	5,508	116	11.0	2.5	3,955	74	3.0	18.5
Labrale superius (ls-ls′)	11.5	5,106	133	11.5	3.0	4,216	97	3.0	20.0
Labrale inferius (li-li′)	13.0	4,886	110	13.0	2.5	4,017	77	5.0	21.0
Mentolabial sulcus (mls-mls′)	11.0	5,792	158	11.0	2.0	4,497	106	5.5	16.5
Pogonion (pg-pg′)	11.5	6,786	168	11.0	2.5	4,891	105	3.5	18.5
Gnathion (gn′)	8.5	545	18	8.5	3.0	381	10	–1.0	18.0
Mention (m-m′)	7.0	4,475	143	7.0	2.5	3,795	104	0.0	14.0
Bilateral points									
Mid-supraorbital (mso-mso′)	6.0	2,225	78	6.0	1.5	1,838	49	1.5	10.5
Mid-infraorbital (mio-mio′)	7.0	2,298	91	7.0	3.5	1,910	61	–4.0	18.0
Alare curvature point (acp-acp′)	9.5	1,511	43	9.3	2.0	1,361	31	2.5	16.0
Goinion (gn-gn′)	10.0	4,168	113	10.0	6.0	3,320	77	–8.0	27.5
Zygion (zy-zy′)	6.0	4,390	103	6.0	1.0	3,545	68	3.0	9.0
Supra canine (sC-sC′)	9.5	3,138	50	9.5	2.0	3,113	48	3.5	15.5
Infra canine (iC-iC′)	10.5	1,184	27	10.5	2.0	1,157	25	4.5	16.5
Supra M^2 (sM^2-$sM^{2\prime}$)	25.5	1,405	41	26.0	5.5	1,212	33	10.0	42.0
Infra M_2 (iM_2-iM_2')	19.0	1,344	39	19.5	4.5	1,151	31	6.0	33.0
Mid-ramus (mr-mr′)	17.5	2,858	60	17.5	4.0	2,637	37	6.0	28.5
Mid-mandibular border (mmb-mmb′)	10.5	935	26	10.5	4.5	548	21	–2.5	24

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Soft-tissue depth from 62 published papers on facial soft-tissue depth. The weighted mean is derived from a subset of studies that reported standard deviations

S is the number of studies used to generate the weighted mean. Negative values for estimated minimum indicate that the distribution of all the values was not normal

There also remains the possibility that the lack of precision of present techniques of soft-tissue measurement will not permit detection of differences between the sexes. For example, differences in the shape of the soft-tissue fat pads of the face will be difficult to detect using conventional techniques.

Data with respect to children and juveniles is lacking at present, so this conclusion cannot be extended to subjects with remaining growth potential.

30.9 Age-Related Changes on Soft Tissues of the Face

Age-related changes may broadly be discussed below as those that occur with growth and those that occur with senescence.

30.9.1 Soft-Tissue Changes with Growth

With growth, there are subtle facial changes that will affect the soft tissues of the face, for example, the increase in size of the nasal cavity and the change in mandibular angle with age as well as the development of the secondary dentition.

There have been a limited number of studies examining changes in soft-tissue depth over designated landmarks with growth (see review by Stephan and Simpson 2008). Pooled data from these studies show steady linear growth in soft tissue at all landmarks. The known exceptions include the nasion (the soft-tissue depth decreases from infancy until the age of 6–8 years, after which it remains relatively constant) and the temporal fat pad (which is relatively larger in sub adults, giving rise to a slight temporal bulge above the zygoma, which becomes less pronounced with age: Stephan and Devine 2009).

30.9.2 Soft-Tissue Changes Due to Senescence

Changes with senescence affect all soft tissues. Changes in the body muscle mass with age do not usually affect the muscles of facial expression (Gosain et al. 2005). However, the temporalis muscle does undergo some atrophy with age (Stephan and Devine 2009), although this decrease in mass is overshadowed by a decrease in the temporal fat pad, which overlies the muscle. Changes in adipose distribution, especially in the facial fat pads, give rise to a general change in facial contours with age (Donofrio 2000). Restoring the volume of these fat pads to the volumes present at a younger age may give an older face a more youthful appearance. Although preliminary, there is evidence that changes in fat pad content with age may not simply be a matter of loss or gain of adipose tissue, but a more complex redistribution of fat, for example, selective hypertrophy of the upper-cheek fat pad (Gosain et al. 2005). These changes are difficult to capture using conventional techniques for measuring soft-tissue depth.

In addition, there is a more general change resulting in loss of elasticity of connective tissue (especially elastin). When acted upon by the facial muscles, the skin will no longer spring back to a resting position, but will tend to sag and develop creases. This effect is compounded by accumulated actinic damage to which the face is prone (Braverman 1986).

30.10 Variation Due to State of Nutrition

The state of nutrition affects the appearance of the face. Selective pathological loss of facial fat, such as noted in HIV-associated lipoatrophy, results in atrophy of the facial fat pads, particularly the temporal and buccal fat pads, giving the face a more aged appearance than normal (Coleman et al. 2009).

Subjectively, it is apparent that fat people have fat faces. Objectively, one recent large study has demonstrated a positive relationship between ponderosity and facial tissue depths (see Tables 30.4 and 30.5). This relationship is particularly pronounced in the cheek and jowl area of the face, which are the sites of the superficial fat pads. The correlation of tissue depths, at landmarks in these regions, with the BMI was greater than with either age or sex, indicating that nutritional status has a relatively large impact on facial soft tissue.

30.11 Racial Variation

Although several studies have reported small but statistically significant differences in soft-tissue depths of the face between races (Aulsebrook et al. 1996), it is difficult to determine whether these are in fact meaningful. First, the definition of race varies between the papers, but usually depends on self-reporting. Second, the differences reported are small compared to the normal within race variation and compared to the error of measurement. Third, deviations between different studies in the same population vary as much as the well-known differences between the group under study and other racial groups.

Also, as noted, such variation as might exist could reside in the superficial fat deposits, for which there is as yet no universally accepted method of assessment.

30.12 Conclusions

30.12.1 Application to Other Areas of Health and Disease

Assessment of the soft tissues of the face have applications in forensic science, cosmetic and orofacial surgery, medical genetics, and other branches of medicine.

In forensic science, study of the soft tissue of the face permits reconstruction of the face for the purpose of identification. This is particularly important for solving homicides, and identifying victims of accidents, terrorist activity, victims of genocide. Once a tentative identification has been made from a skull reconstruction, molecular techniques involving living relatives can be used to assess the likelihood of a positive identification being correct. Forensic techniques have also been used to reconstruct the face of important historical individuals for whom a skull is available.

Knowledge of the soft tissues of the face is important in the practice of cosmetic surgery. Cleft lip and palate is one of the most common birth defects. Good cosmetic correction of this defect depends on a good understanding of the action of the muscles of the face and palate. In particular, because the repairs are done within the first year of life, it is important to try and achieve symmetry of muscle action, so that the action of the muscle on the underlying facial bone results in proper development of the midface and the nasal passages. Reconstruction to a resemblance of the previous appearance after major facial injury requires knowledge of muscle attachments and facial fat distribution.

As the population ages, there has been an increasing demand for cosmetic surgical procedures that can restore a more youthful appearance. The face is a particular challenge, as it is the area most exposed to sun, and therefore accumulates actinic damage. This aspect compounds the natural aging effect of decreased elasticity (due to elastin and collagen degradation), resulting in facial muscles acting on the skin to produce wrinkles. Temporary paralysis of these muscles using botulinum toxin will ameliorate the wrinkles, but the treatment is symptomatic and not permanent. Part of the problem is restoring the youthful contours of the face and this requires knowledge of the superficial fat pads of the face and changes that occur to these fat pads with aging. A study of what happens to the facial muscles with age is still in progress; preliminary evidence suggests that the facial muscles do not, unlike other skeletal muscles, atrophy with age. This is possibly because they are in constant use.

In the field of medical genetics, there are many conditions in which unrelated patients resemble each other so closely that positive identification (of a condition) can be made. This field is called dysmorphology. At present, this is almost entirely a subjective discipline, which depends heavily on memory and experience of the physician. Increasingly, attempts have been made to match faces using quantitative methods. Although the results of these studies are very interesting, the work has not yet produced a clinically useful method of assisting with diagnosis, possibly because we do not yet have sufficient knowledge of what constitutes normal (Hammond et al. 2004).

Finally, there are emerging diseases that will tax our ability to restore faces to normal, notably in patients undergoing treatment for HIV. In this condition, there is a tendency for the face to loose facial fat and become prematurely aged in appearance.

Summary Points

- Facial soft tissues cloak the skull and give the face a recognizable form.
- Measurement of facial soft-tissue depths over facial landmarks assist in reconstruction of faces from skulls, measurements rather less used for cosmetic surgical purposes.
- Different methods of measuring soft-tissue depth give slightly different results, depending on the method itself, the position of the subject when measurements are taken, and whether measurements are made *in vivo* or on cadavers.
- Differences in soft-tissue depth between the sexes, interracially, and with age are relatively insignificant compared to the differences noted with increasing ponderosity.
- Routine soft-tissue depth estimations are not typically fractionated into component tissues, and, in aggregate, give limited information about the shape and architecture of structures, which influence facial appearance, such as, the superficial fat pads.

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Chapter 31
Anthropometry of Facial Beauty

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Abstract Esthetic criteria have been defined in almost all cultures, but the actual existence of codified facial characteristics in attractive people is still matter of debate. In our laboratory, we analyzed the three-dimensional facial characteristics of 415 children, adolescents and women considered "attractive," selected either by casting agencies (children and adolescents, 4–17 years of age) or by juries of National beauty competitions (adult men and women, 18–30 years of age). Their facial soft tissues were measured with a non-invasive computerized instrument, and several measurements obtained. Data were compared to those collected in 629 healthy persons of the same sex, age, and ethnicity, selected using criteria of dentofacial normality.

In Caucasian children, facial attractiveness was characterized by an increased development of the facial middle (maxilla) and upper thirds (forehead), with a wider and deeper face, but less vertically developed in the lower third. During adolescence, a female face was considered attractive when it was wider, shorter and less deep, with relatively larger forehead and maxilla, and a reduced mandible relative to the maxilla. Facial attractiveness in adult Caucasian women was characterized by a prominent facial middle third, with full lips; a relatively large face with a reduced mandible and increased forehead; reduced vertical dimensions. Overall, attractive women seemed to maintain several facial characteristics of babyness. In adult Caucasian men and boys in their late adolescence, attractiveness seemed to be positively influenced by facial markers of high testosterone levels, with a more prominent chin. Esthetic guidelines offer information about the preferences of the general public within a given context, and possibly about the desires and requests of the patients. They can be useful tools for those professionals who can improve the facial appearance of their patients, providing indications for the best kind, timing and goals of orthodontic, orthopedic, and surgical treatments. However, esthetic guidelines should always be used within a well-founded knowledge of craniofacial and dental physiology. No procedure should be imposed on each face, or followed blindly. Even the best and most updated esthetic guidelines must remain only a part of the treatment goals.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_31,

Abbreviations

3D Three-dimensional
SD Standard deviation

31.1 Introduction

Investigations into the esthetic implications of dental and orthodontic treatments are becoming increasingly available in the international literature. For instance, a search on PubMed database using the keyword "Esthetic*" returned 17,411 entries for the period 1950–2009; using "Esthetic* and face," a total of 2,896 entries was obtained, and the combination "Esthetics and orthodontics" resulted in 1,787 entries (www.pubmed.gov, accessed on June, 7, 2009). Of these 1,787 entries, 177 had been published in the last 18 months.

Esthetic criteria have been defined in almost all cultures (Ferrario et al. 1995; Peck and Peck 1995; Nguyen and Turley 1998; Auger and Turley 1999; Matoula and Pancherz 2006), but the actual existence of codified facial dimensions, angles, and ratios in attractive people is still a matter of debate. Scientific researches on the quantitative, measurable bases of facial attractiveness are therefore still in progress (Bisson and Grobbelaar 2004; Kiekens et al. 2006; Matoula and Pancherz 2006; Orsini et al. 2006; Sforza et al. 2007, 2008, 2009).

Current theories of evolutionary psychology show that the esthetic appraisal of adult faces depends on various combinations of averageness, symmetry, neoteny (babyness), and youthfulness, and sexual dimorphism: attractive female faces possess several characteristics of babyness, attractive male faces offer a mix of masculinity, health, developmental stability, and social dominance (Fink et al. 2005; Bashour 2006a, b; Naini et al. 2006). From an evolutionary perspective, human facial attractiveness seems to signal mate quality (Lie et al. 2008).

Attractiveness is becoming a matter of concern, even in the case of children and adolescents. Cinema and television, fashion industry, advertising, all use the attractiveness of growing persons. Children and adolescents with a non-attractive face are considered less intelligent, and may be isolated and undervalued than persons with an attractive face, even by their peers (Johnson and Sandy 2003). An attractive face is often considered the key to success, and parents and children seek medical transformation of non-attractive dentofacial characteristics (Griffin and Langlois 2006; Kiekens et al. 2006).

Medical and dental practitioners therefore face an increasing demand for treatments, mostly esthetic requests, and should approach the problem with the most advanced instruments and methods for diagnosis and treatment planning (Van der Geld et al. 2007). The assessment of facial soft tissues should be made by three-dimensional analyses; and several non-invasive techniques allow a detailed reconstruction of facial anatomy (Ferrario et al. 1995, 2003; Sforza et al. 2007, 2008, 2009). Additionally, the practitioners should know those quantifiable, objective facial characteristics that are currently considered by the public as "attractive" (Ferrario et al. 1995; Nguyen and Turley 1998; Auger and Turley 1999; Fink et al. 2005; Griffin and Langlois 2006; Matoula and Pancherz 2006; Orsini et al. 2006; Sforza et al. 2007, 2008, 2009).

Notwithstanding general biological and psychological criteria for facial attractiveness, several studies demonstrated that secular trends, and even cultural background, can influence the perception of beauty, at least for adult subjects (Nguyen and Turley 1998; Auger and Turley 1999; Bashour 2006a). In our society, the perception of attractiveness is deeply influenced by media. Television, cinema, advertisements, and fashion industry; all enter our life projecting facial characteristics that

are implied to portray perceptions of beauty, health, and fitness, mixed with feelings of social achievement, intelligence, richness, and happiness: a beautiful face becomes the key to success (Johnson and Sandy 2003; Griffin and Langlois 2006; Orsini et al. 2006).

31.2 Quantitative Analysis of Facial Attractiveness

In our laboratory, we analyzed the three-dimensional facial characteristics of children, adolescents, and women, considered "attractive." Their facial soft tissues were measured with a non-invasive computerized instrument, and several measurements were obtained. Data were compared to those collected in healthy persons of the same sex, age, and ethnicity, selected using criteria of dentofacial normality. The possible presence of measurable esthetic characteristics was assessed. If esthetically pleasing faces possess codified facial dimensions, angles, and ratios, these measurements could be used by orthodontists and maxillofacial surgeons as a reference for dentofacial modifications.

31.2.1 Selection of Attractive Persons

Attractive children and adolescents were independently selected by a commercial casting agency located in northern Italy. The agency was asked to provide data for white Caucasian children and adolescents of both sexes with an attractive face (Sforza et al. 2007, 2008). These children normally act in cinema and television, and are used for advertising and in the fashion industry; overall, their faces could be considered "positive," "acceptable," and "trendy" by the general public (Orsini et al. 2006).

Attractive adult women and men were measured during several national beauty competitions that took place between 2006 and 2008. They were those admitted to the semifinal and final stages of the competitions, and were measured just before the semifinal stage of the relevant competition (Sforza et al. 2009).

31.2.2 Analyzed Subjects

A total of 1,029 white Caucasian, Northern Italian persons aged 4–30 years were analyzed.

As many as 614 were reference subjects; all were healthy, and had normal dentofacial dimensions and proportions; no subjects with a previous history of craniofacial surgery, trauma, or with congenital anomalies were included.

A total of 415 were attractive subjects, selected either by casting agencies (children and adolescents, 4–17 years of age) or by juries of national beauty competitions (adult men and women, 18–30 years of age). Parts of the data collected in the attractive persons were previously published (Sforza et al. 2007, 2008, 2009).

All the analyzed persons, and the parents/legal guardians of those underage, gave their informed consent to the experiment. All procedures were non-invasive, did not cause damages, risks, or discomfort to the subjects, and were preventively approved by the local ethic committee (Table 31.1).

Table 31.1 Analyzed subjects

	Sex	Age (years)	Attractive	Reference
Children	Girls	4–5	14	11
	Boys	4–5	8	19
	Girls	6–7	18	45
	Boys	6–7	21	13
	Girls	8–9	14	43
	Boys	8–9	47	55
Adolescents	Girls	10–12	24	39
	Boys	12–14	22	87
	Girls	13–15	23	51
	Boys	15–17	24	54
Adults	Women	18–30	139	71
	Men	18–30	61	126

More than 1,000 subjects were quantitatively assessed in our laboratory.

31.2.3 Collection of Facial Landmarks

A detailed description of the data collection procedure can be found elsewhere (Ferrario et al. 2003; Sforza et al. 2007, 2008, 2009). In brief, the procedure takes place in two separate steps, and is followed by off-line calculations. At first, for each person, a set of 50 soft-tissue landmarks were located and marked on the cutaneous surface using a black eyeliner (Fig. 31.1). Three-dimensional (x, y, z) coordinates of the facial landmarks were then obtained with a three-dimensional electromagnetic computerized digitizer (3Draw, Polhemus Inc., Colchester, VT). During data collection, the subject sat in a natural head position in a chair with a backrest. Landmark digitization took approximately 1 min. Files of the three-dimensional coordinates were obtained, and original computer programs were used for all the subsequent off-line calculations.

31.2.4 Data Analysis

The x, y, and z coordinates of the landmarks were used to estimate several facial linear distances, angles, areas, and volumes (Ferrario et al. 1995; Sforza et al. 2007, 2008, 2009). Euclidean geometry was used for all calculations; the volumes of facial structures were computed as the sum of several tetrahedra, with the 50 landmarks serving as nodes (vertices of the tetrahedra). In particular, the following were computed:

- Distances (unit, mm): upper facial width (ex-ex); lower facial width (go-go); mouth width (ch-ch); anterior upper facial height (n-sn); anterior lower facial height (sn-pg); posterior facial height (t-go); middle facial depth (sn-t); mandibular corpus length (pg-go); upper lip to E-line distance, ls-(prn-pg); and lower lip to E-line distance, li-(prn-pg);
- Angles (unit, degrees): facial convexity excluding the nose (n-sn-pg); facial convexity including the nose (n-prn-pg); upper face convexity (t-n-t); lower face convexity (t-pg-t); mandibular convexity (go-pg-go); maxillary prominence, soft-tissue analog of skeletal ANB angle (sl-n-sn); facial divergence (t-n)^(go-pg); nasolabial (prn-sn-ls); mentolabial (li-sl-pg); and interlabial (sn-ls^sl-pg);

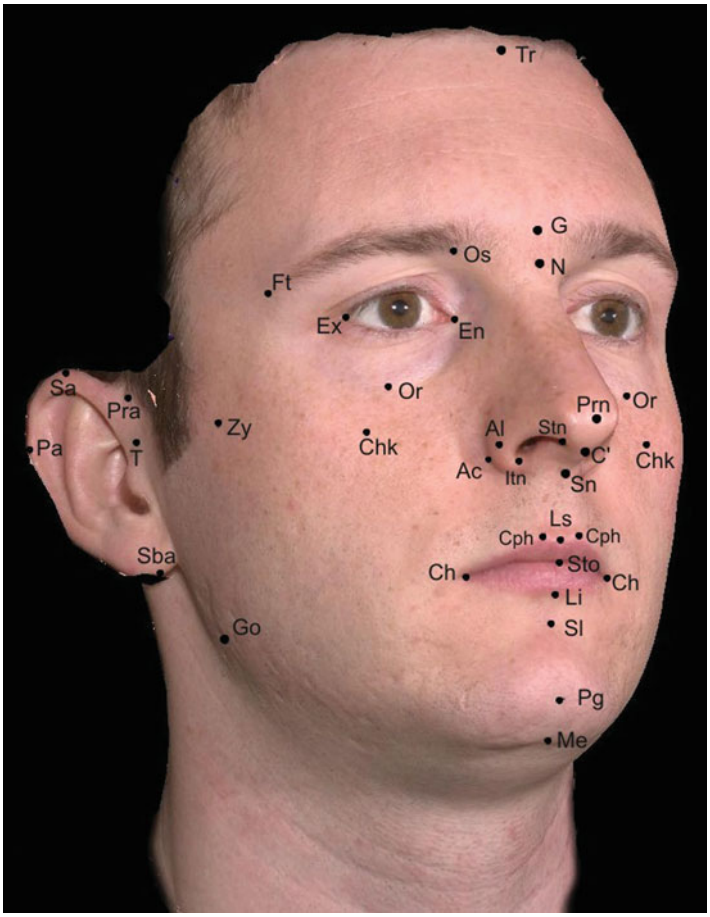

Fig. 31.1 Digitized facial landmarks: *Tr*, trichion; *G*, glabella; *N*, nasion; *Prn*, pronasale; *C'*, columella; *Sn*, subnasale; *Ls*, labiale superius; *Sto*, stomion; *Li*, labiale inferius; *Sl*, sublabiale; *Pg*, pogonion; *Me*, menton; *Ex*, exocanthion; *En*, endocanthion; *Os*, orbitale superius; *Or*, orbitale; *Ft*, frontotemporale; *Zy*, zygion; *Chk*, cheek; *T*, tragion; *Pra*, preaurale; *Sa*, superaurale; *Pa*, posturale; *Sba*, subaurale; *Al*, alare; *Ac*, nasal alar crest; *Itn*, inferior point of the nostril axis; *Stn*, superior point of the nostril axis; *Cph*, crista philtri; *Ch*, cheilion; *Go*, gonion. The 50 soft-tissue facial landmarks used in the analysis are shown

- Volumes (unit: mm^3): total facial volume (volumes of all facial structures from the external cutaneous surface up to a quasi-frontal plane passing through trichion, tragi, and gonia); facial upper-third volume (forehead), measured between the plane passing through the trichion, the frontotemporale landmarks, and the tragi, and a quasi-horizontal plane passing through the tragi and the exocanthia; facial middle-third volume (maxilla), comprised of the plane passing through the tragi and the exocanthia, and a plane connecting the cheilion landmarks and the tragi, approximately corresponding to the maxillary and cheek regions; facial lower-third volume (mandible), comprised of the cheilion–tragi plane and a plane drawn between pogonion and the gonia; and nasal volume;
- Ratios (unit, percentage): middle facial width to facial height (t-t/n-pg); posterior to anterior lower facial height (t-go/sn-pg); forehead to total facial volume; and mandibular to maxillary volume.

31.2.5 Statistical Calculations

"Reference" and "attractive" persons were divided into sex and age groups. For children, the same age groups were used for both sexes: 4–5 years, 6–7 years, and 8–9 years. For adolescents, different age groups were used for the two sexes because of the different timing of pubertal growth spurt (Ferrario et al. 2003). Girls and boys were divided into "young" and "old" adolescents: girls aged 10–12 years and 13–15 years, respectively; and boys aged 12–14 years and 15–17 years, respectively (Sforza et al. 2008).

Adult men and women measured in the different beauty competitions were analyzed together.

For each sex and age group, data were compared to those collected in the relevant reference subjects by computing z-scores. The z-score is a measure of the distance between a subject datum and the reference mean expressed in standard deviation units: z-score = (subject value − mean value of the reference group) divided by the standard deviation of the reference group. Positive z-scores indicate that the measurement is larger in the analyzed subject group than in the reference population; in contrast, negative z-scores indicate a smaller measurement in the subject group than in the reference population; by definition, the reference population has a mean z-score of 0, with a standard deviation of 1.

Descriptive statistics (mean and standard deviation) were computed for each group. Significance of the z-scores was assessed by Student's t tests (if the subject value is equal to the mean value of the reference group, the z-score is zero; the null hypothesis of the test is that the z-scores are null); the significance level was set at 5% ($p < 0.05$).

31.3 Results

On an average, attractive children had significantly larger upper (forehead), middle (maxilla), and total facial volumes than reference subjects (Fig. 31.2, Table 31.2). They also had a larger forehead-to-facial volume ratio, and a smaller mandible-to-maxilla volume ratio. Attractive adolescent girls

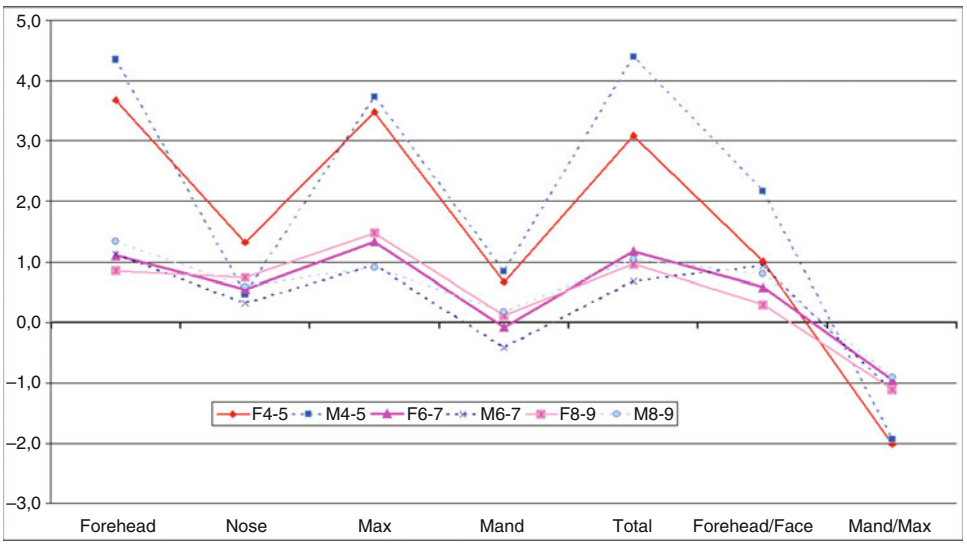

Fig. 31.2 Facial volumes and volume ratios in attractive children (F: girls; M: boys). All values are z-scores. Most soft-tissue facial volumes are larger in attractive children than in reference subjects

Table 31.2 Significance of the *z*-scores for the analyzed facial volumes and ratios

	Forehead	Nose	Maxilla	Mandible	Total	Forehead/Face	Mand/Max
Children							
F4–5	<0.001	0.019	<0.001	0.040	<0.001	0.001	<0.001
M4–5	<0.001	NS	<0.001	NS	<0.001	0.001	0.001
F6–7	<0.001	<0.001	<0.001	NS	<0.001	0.002	<0.001
M6–7	<0.001	0.017	<0.001	NS	0.003	0.002	<0.001
F8–9	0.004	<0.001	<0.001	NS	0.002	NS	<0.001
M8–9	<0.001	<0.001	0.001	NS	0.001	0.007	0.012
Adolescents							
F10–12	0.010	NS	<0.001	NS	0.001	NS	0.008
M12–14	<0.001	NS	<0.001	NS	0.001	<0.001	<0.001
F13–15	<0.001	0.001	0.115	0.045	NS	<0.001	<0.001
M15–17	<0.001	<0.001	<0.001	0.001	<0.001	NS	NS
Adults							
Miss	<0.001	NS	0.018	NS	<0.001	<0.001	NS
Mister	0.047	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

All comparisons were made by paired Student's *t* tests; NS: not significant ($p > 0.05$)
F girls; *M* boys; *miss* adult women; *mister* adult men
Several soft-tissue facial volumes allow one to discriminate between reference population and attractive subjects

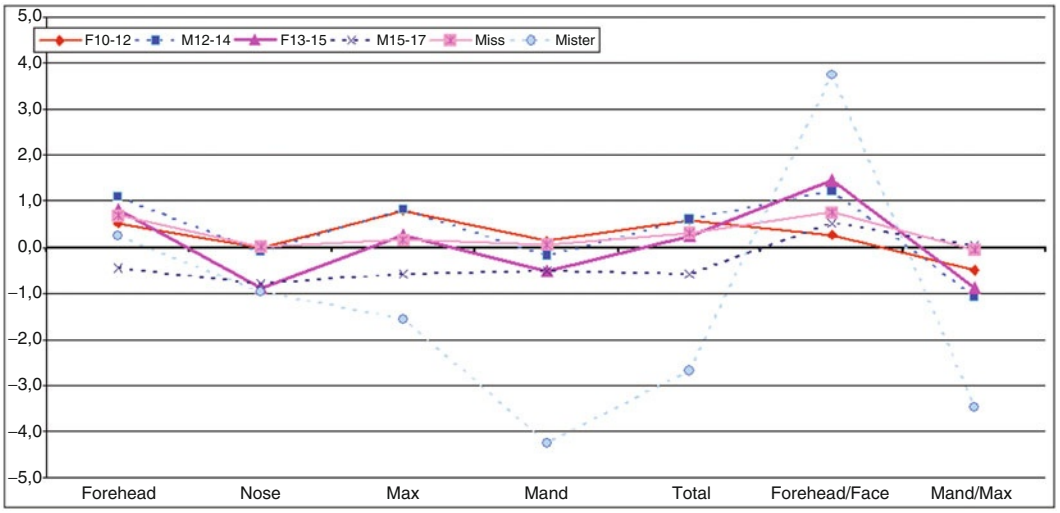

Fig. 31.3 Facial volumes and volume ratios in attractive adolescents and adults (*F* girls; *M* boys; *miss* adult women; *mister* adult men). All values are *z*-scores. In adolescents and young adults, the differences in soft-tissue facial volumes are less evident than in children

and women also had similar characteristics, with larger facial volumes (forehead, maxilla, and total) and forehead-to-facial volume ratios, and smaller mandible-to-maxilla volume ratios, than reference subjects (Fig. 31.3).

In contrast, attractive adolescent boys and men had different patterns: the youngest adolescents (12–14-year old) were similar to children and women, whereas the oldest adolescents (13–15-year old) and the men had smaller faces than reference subjects. In particular, attractive men had

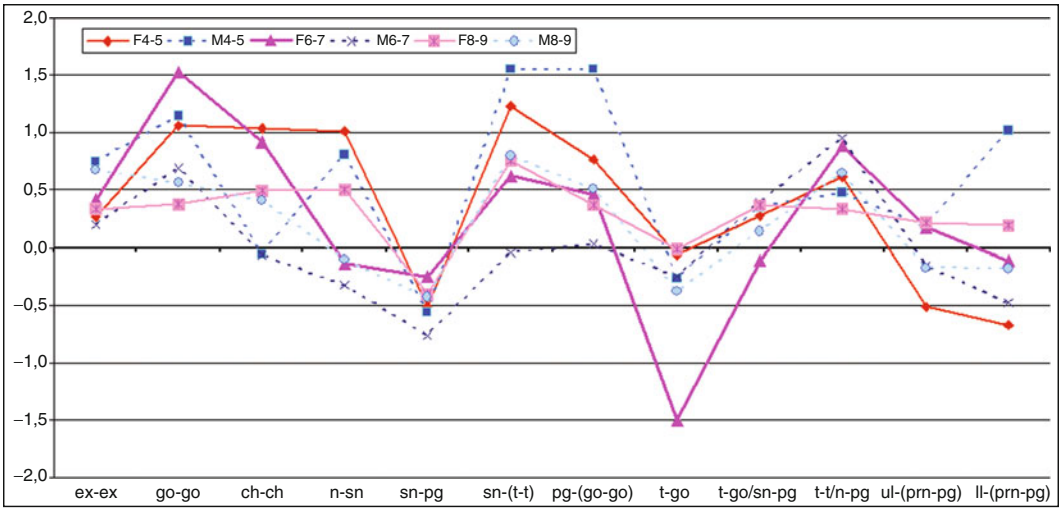

Fig. 31.4 Facial distances and ratios in attractive children (*F* girls; *M* boys). All values are *z*-scores. Several soft-tissue facial distances are different in attractive children as compared to reference subjects

significantly smaller total, maxillary, and mandibular volumes, with an increased forehead-to-facial volume ratio, and a reduced mandible-to-maxilla volume ratio.

In attractive children, horizontal and anteroposterior facial dimensions (upper and lower facial widths, mouth width, middle facial depth, and mandibular corpus length) were larger than in normal subjects (Fig. 31.4, Table 31.3). Vertical distances were either similar in attractive and reference children (lower posterior facial height), or somewhat larger (upper anterior facial height), or somewhat lower (lower anterior facial height). Overall, middle facial width to facial height ratio was larger in attractive children as compared to normal peers. The position of upper and lower lips relative to the esthetic prn-pg line varied in the various age groups.

Attractive adolescent girls, women, and younger adolescent boys had a significantly larger upper facial width than reference subjects (Fig. 31.5). Upper anterior facial height was significantly smaller in attractive adolescent boys, older adolescent girls, and adult persons than in the reference population. Middle facial width to facial height ratio was large in all attractive groups; the differences were significant in the 10–12-year-old girls, and in adult men and women.

When compared to reference women, the upper and lower lips of attractive women were significantly closer to the esthetic prn-pg line. Attractive women also had a significantly large posterior to anterior lower facial height than that of reference women.

In attractive men, mouth width, anteroposterior facial dimensions, posterior facial height, and posterior to anterior lower facial height were significantly larger, whereas lower facial width and upper anterior facial height were significantly smaller than in reference men.

Overall, the analyzed facial angles had a variable pattern in the attractive children (Fig. 31.6, Table 31.4). Among the most constant characteristics were reduced facial divergence and sagittal facial convexity (i.e., a more prominent face in the sagittal plane), a smaller mentolabial angle, and an increased maxillary prominence, than in reference children. Facial convexity in the horizontal plane was reduced in all attractive children except in the 4–5-year-old girls. Additionally, attractive girls had significantly increased nasolabial and interlabial angles than normal girls.

Table 31.3 Significance of the *z*-scores for the analyzed facial distances and ratios

	Ex-Ex	Go-Go	Ch-Ch	N-Sn	Sn-Pg	T-Go	Sn-(T-T)	Pg-(Go-Go)	Ls-(Prn-Pg)	Li-(Prn-Pg)	T-Go/Sn-Pg	T-T/N-Pg
Children												
F4–5	NS	0.001	0.001	0.022	0.027	NS	<0.001	0.001	0.001	0.000	NS	NS
M4–5	0.012	0.013	NS	NS	NS	NS	0.002	0.004	NS	NS	NS	NS
F6–7	NS	<0.001	NS	NS	NS	<0.001	0.008	0.002	NS	NS	NS	0.005
M6–7	NS	<0.001	NS	NS	0.007	NS	NS	NS	NS	0.008	NS	0.004
F8–9	NS	0.022	0.029	NS	NS	NS	0.004	NS	NS	NS	NS	NS
M8–9	0.038	0.005	NS	NS	NS	NS	0.008	0.042	NS	NS	NS	0.013
Adolescents												
F10–12	<0.001	0.035	NS	NS	0.015	NS	NS	NS	0.030	NS	NS	<0.001
M12–14	0.009	NS	NS	0.003	NS	NS	NS	NS	NS	NS	NS	NS
F13–15	0.006	0.023	NS	0.005	NS	NS	0.004	NS	NS	NS	NS	NS
M15–17	NS	<0.001	0.007	<0.001	NS	NS	0.015	NS	NS	NS	NS	NS
Adults												
Miss	<0.001	NS	NS	<0.001	0.046	NS	NS	NS	<0.001	<0.001	0.023	0.024
Mister	NS	<0.001	0.036	<0.001	NS	<0.001	0.001	<0.001	NS	NS	0.001	0.009

All comparisons were made by paired Student's *t* tests; NS: not significant ($p > 0.05$)

F girls; *M* boys; *miss* adult women; *mister* adult men

Several soft-tissue facial distances and ratios allow to discriminate between the reference population and attractive subjects

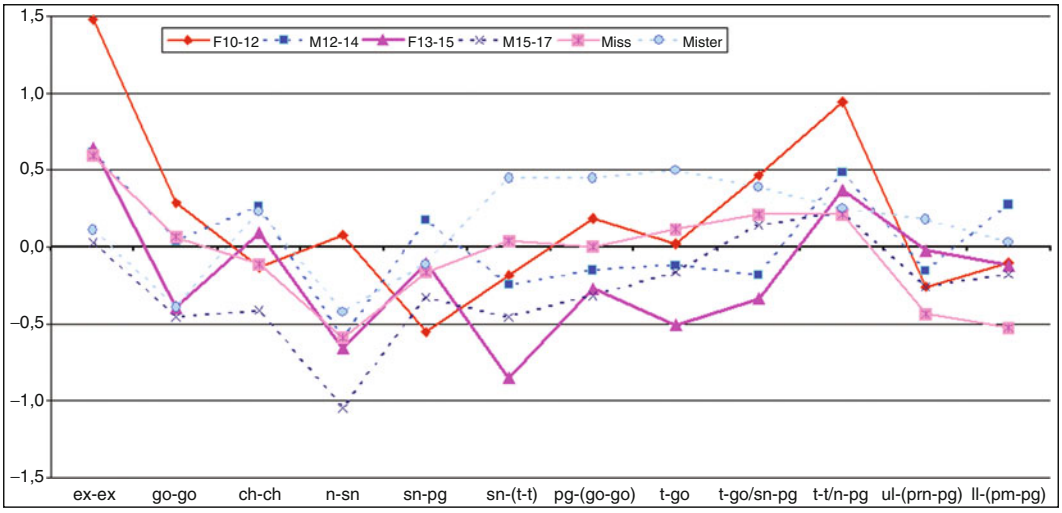

Fig. 31.5 Facial distances and ratios in attractive adolescents and adults (*F* girls; *M* boys; *miss* adult women; *mister* adult men). All values are z-scores. Several soft-tissue facial distances are different in attractive adolescents and young adults as compared to reference subjects

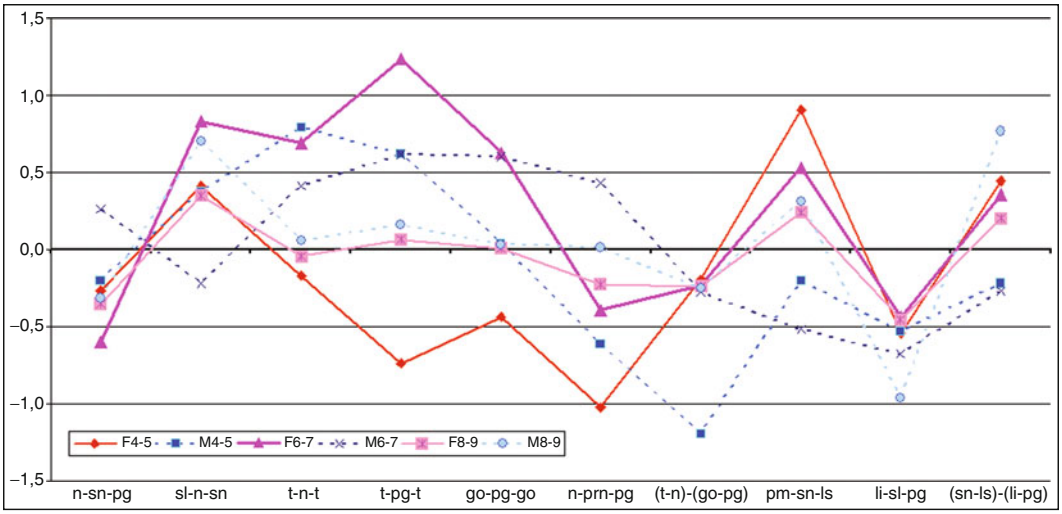

Fig. 31.6 Facial angles in attractive children (*F* girls; *M* boys). All values are *z*-scores. Several soft-tissue facial angles are different in attractive children as compared to reference subjects

The nasolabial angle was somewhat smaller in attractive adolescents and adults when compared to reference persons (Fig. 31.7). Attractive adolescent girls and the youngest adolescent boys had a larger facial convexity in the horizontal plane than their reference peers.

Attractive men had significantly smaller maxillary prominence and facial divergence than reference men. Overall, their faces were more prominent in the horizontal plane, with a larger mandibular prominence (more prominent chin), but were less prominent in the sagittal plane (increased facial convexity angle n-sn-pg).

Table 31.4 Significance of the *z*-scores for the analyzed facial angles

	N-Sn-Pg	Sl-N-Sn	T-N-T	T-Pg-T	Go-Pg-Go	N-Prn-Pg	(T-N)-(Go-Pg)	Prn-Sn-Ls	Li-Sl-Pg	(Sn-Ls)-(Li-Pg)
Children										
F4–5	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
M4–5	NS	NS	0.012	NS	NS	NS	0.018	NS	NS	NS
F6–7	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
M6–7	NS	NS	0.040	0.001	<0.001	NS	NS	0.043	0.004	NS
F8–9	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
M8–9	NS	0.039	NS	NS	NS	NS	NS	NS	0.048	0.047
Adolescents										
F10–12	NS	NS	<0.001	<0.001	NS	0.012	NS	NS	0.032	NS
M12–14	NS	NS	NS	NS	NS	0.034	NS	NS	NS	NS
F13–15	NS	0.010	0.040	NS	NS	NS	NS	NS	0.048	NS
M15–17	NS	NS	NS	NS	NS	NS	0.012	NS	NS	NS
Adults										
Miss	NS	NS	0.017	NS	0.039	0.042	NS	NS	NS	0.003
Mister	0.017	0.009	<0.001	<0.001	<0.001	NS	<0.001	0.040	NS	NS

All comparisons were made by paired Student's *t* tests; NS: not significant ($p > 0.05$)
F girls; *M* boys; *miss* adult women; *mister* adult men
Several soft-tissue facial angles allow to discriminate between the reference population and attractive subjects

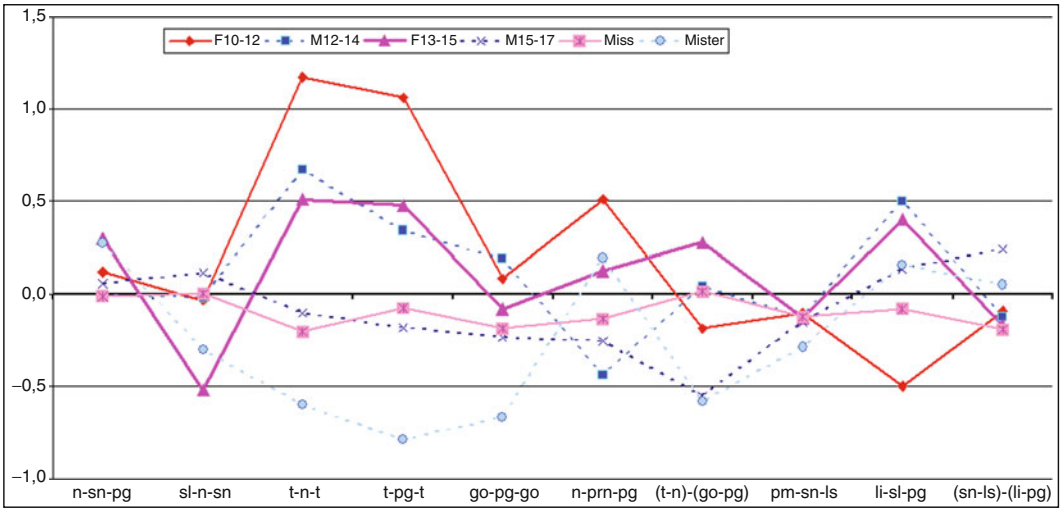

Fig. 31.7 Facial angles in attractive adolescents and adults (*F* girls; *M* boys; *miss* adult women; *mister* adult men). All values are *z*-scores. Several soft-tissue facial angles are different in attractive adolescents and young adults as compared to reference subjects

31.4 Discussion

In our society, the perception of attractiveness is highly influenced by media: every day television, cinema, advertisements, and the fashion industry give us facial "standards" that should describe persons on the basis of characteristics such as beauty, health, fitness, social achievement, intelligence, richness, and happiness (Sforza et al. 2009). In synthesis, a beautiful face becomes the key to success (Griffin and Langlois 2006).

Therefore, there is an increased esthetic demand for facial cosmetic surgery: patients not only ask to correct major disfigurements, but also to provide modifications of dentofacial physiognomies considered non-attractive. However, orthodontists and maxillofacial and plastic surgeons do not always know which facial characteristics are currently considered "attractive" by the general public (Bashour 2006b; Naini et al. 2006). Indeed, objective, quantitative data on the three-dimensional facial morphology of persons considered "attractive" are still scanty.

In the current investigation, the facial characteristics of a group of attractive children, adolescents, and young adults were examined in three-dimensional space to find some constant pattern of variation from reference persons of the same age, sex, and ethnicity. Considering the components believed to enter into the perception of attractiveness (Bashour 2006a, b; Edler et al. 2006; Naini et al. 2006), the faces of attractive children showed several general characteristics of babyness: a larger forehead, and a smaller mandible with a proportionately larger and more prominent maxilla than reference children. Attractive child faces had larger horizontal and anteroposterior facial dimensions, with a reduced facial convexity in the horizontal plane (flatter faces).

Facial characteristics of babyness were also found in attractive adolescent girls and women, whereas attractive adolescent boys had different patterns: the youngest adolescents (12–14-year old) resembled children and women, whereas the oldest adolescents (13–15-year old) were more similar to adult men. The faces of attractive adult men were characterized by smaller maxillary prominence, facial divergence, and facial convexity in the horizontal plane than those of reference men, with a

more prominent chin, a facial marker of increasing testosterone levels (Fink et al. 2005, 2007; Schaefer et al. 2005; Bashour 2006a, b; Orsini et al. 2006).

In synthesis, attractive younger persons and women shared several facial features resembling neoteny (babyness) and youthfulness, whereas attractive older adolescents and men had faces expressing a clear sexual dimorphism, with more masculine characteristics.

These findings are in good agreement with previous reports performed on either two-dimensional (photographs and radiographs) or three-dimensional (classic and digital anthropometry) records (Farkas 1994; Ferrario et al. 1995; Fink et al. 2005, 2007; Bashour 2006a, b; Isiksal et al. 2006; Naini et al. 2006; Sforza et al. 2007, 2008, 2009).

For instance, previous cephalometric studies found an increased facial convexity in adolescents, considered attractive (Kiekens et al. 2006; Matoula and Pancherz 2006), whereas a relatively more prominent chin was associated with high prenatal testosterone levels, and high circulating testosterone (Fink et al. 2005, 2007; Schaefer et al. 2005). Currently, facial markers of high testosterone levels are believed to signal a good immunocompetence, with a (possible) better genetic background: mating with men with these characteristics may result in a healthier offspring (Fink et al. 2005; Lie et al. 2008).

Previous studies in attractive women found that more prominent lips were associated with an increased esthetic appraisal (Auger and Turley 1999; Farkas 1994; Ferrario et al. 1995; Bisson and Grobbelaar 2004; Matoula and Pancherz 2006; Sforza et al. 2007, 2008, 2009; Van der Geld et al. 2007). Indeed, lips are very rich in estrogen receptors (Caisey et al. 2008), and richer and fuller lips are often associated with a larger female fertility (larger estrogen levels): mating with these women may offer larger probabilities of reproduction (Lie et al. 2008).

In the current investigation, this finding was well replicated for adult women, whereas no constant labial patterns were observed for children and adolescents. Indeed, physiological variations in dental formula (incisor and canine exfoliation and eruption) may explain this finding, at least between 6 and 14 years of age. Nevertheless, the position of maxillary incisors is one of the key factors for a balanced smile, and it should be attentively assessed by the orthodontist (Isiksal et al. 2006).

Children and adolescents were analyzed in a period of rapid somatic growth, when several facial and dental characteristics undergo large modifications, with individually determined growth velocities and growth spurs. This could explain the lack of statistical significance in some of the analyzed facial measurements. Nonetheless, all the measurements were sufficiently homogeneous, and allowed to determine some patterns typical of an attractive face.

According to previous reports, the cultural background of the judge seems to influence esthetic choices in the dentofacial region (Johnson and Sandy 2003; Isiksal et al. 2006; Matoula and Pancherz 2006): dental and surgical professionals are usually more critical in their assessment of facial esthetics than non-professionals (Johnson and Sandy 2003; Isiksal et al. 2006; Orsini et al. 2006). Moreover, esthetics should be evaluated by laymen, those people who actual seek orthodontic or maxillofacial treatment (Kiekens et al. 2006).

Esthetic guidelines could be obtained by measuring persons considered attractive by the general public (cinema and television actors and actresses, and fashion and advertising models) (Peck et al. 1991). Therefore, in the current investigation, attractive people were chosen by professionals from a casting agency, and by judges in beauty competitions, thus avoiding medical and dental practitioners. All judges were unaware that the persons were to be measured in a scientific investigation.

This method of selection has been widely used before for adult subjects: winners in beauty competitions, professional models, and performing actors (Peck et al. 1991; Sforza et al. 2009); television actresses (Ferrario et al. 1995); and photographs of professional models published in fashion

magazines (Nguyen and Turley 1998; Auger and Turley 1999; Bisson and Grobbelaar 2004). Apparently, no previous studies selected children and adolescents with similar procedures, apart from those made in our laboratory (Sforza et al. 2007, 2008).

In conclusion, professionals in the dental and medical fields should be provided with esthetic guidelines referring to subjects of the same age, sex, and ethnic group as their patients; the guidelines should also be updated, considering the evolution of the esthetic canons within a given society (Nguyen and Turley 1998; Auger and Turley 1999; Bashour 2006a, b). These guidelines may offer useful indications for the best kind, timing, and goals of orthodontic treatment, with the best cost/benefit ratio.

Among the limitation of the current study is the analysis of only some of the factors that are currently considered to enter into the appraisal of facial attractiveness (Bashour 2006a, b), and no assessments about symmetry and averageness were made. Theories of perceptual psychology underline the importance of a reduced fluctuating asymmetry for esthetic appraisal: a reduced level of fluctuating asymmetry is usually considered to reflect higher developmental stability, with better body characteristics that may be transmitted to the offspring (Brown et al. 2008). At the same time, literature reports contrasting results on facial symmetry: actual measurements made in attractive men and women do not support a direct link between attractiveness and perfect symmetry (Peck et al. 1991; Ing et al. 2006). A further study may assess symmetry in the current groups of attractive persons, together with a wider set of angles and distances including other facial structures, comprised of eyes and ears.

As to the averageness hypothesis (Bashour 2006a, b), the topic was not assessed in detail in the present study.

A further limitation of the present investigation is the assessment of only attractive persons from Italy. Possibly, a different ethnic/social context may prefer different kinds of attractive faces, even if the good accord between the current findings and previous literature reports makes the selected facial patterns sufficiently reliable for Caucasian persons.

31.5 Conclusions

In conclusion, when compared to the reference, healthy population, attractive persons from Italy had (Table 31.5):

- During childhood: a larger face, with an increased development of the facial middle (maxilla) and upper third (forehead); overall, the face was wider and deeper (dimensions and horizontal convexity), but less vertically developed in the lower third; a more convex profile, with a more prominent maxilla relative to the mandible.
- During adolescence: wider, shorter, and less deep faces with relatively larger upper and middle facial third, and a reduced mandible relative to the maxilla; a reduced nasolabial angle; and in older boys, a more prominent chin.
- During young female adulthood: wider faces with relatively larger upper facial third (forehead); larger facial width relative to facial height; more prominent lips, with a reduced interlabial angle;
- During young male adulthood: smaller faces with a relatively larger forehead; reduced mandibular to maxillary volume ratio; reduced horizontal and vertical dimensions in the facial lower third; increased anteroposterior facial dimensions; reduced facial divergence and maxillary protrusion; increased facial convexity angle in the sagittal plane (flatter face); and reduced facial convexity in the horizontal plane, with a more prominent chin.

Table 31.5 Features of attractive Caucasian persons in the twenty-first century

	Children	Adolescent girls	Young adolescent boys	Old adolescent boys	Women	Men
Facial volume	↑	↑	↑	↓	↑	↓
Upper facial third	Relatively larger	Relatively larger	Relatively larger	↔	Relatively larger	Relatively larger
Middle facial third	Relatively larger and more prominent	Relatively larger	Relatively larger	↓	Relatively larger	↓
Lower facial third	↔	↔	↔	↑Ant-post dimensions	↔	↑Ant-post dimensions
Facial convexity sagittal plane	↓	↓	↔	↔	↔	↑
Facial convexity horizontal plane	↓	↓	↔	↔	↓	↓
Horizontal facial dimensions	↑	↑	↑	↓	↑	↓
Upper facial height	↔	↔	↓	↓	↓	↓
Lower anterior facial height	↓	↓	↔	↓	↓	↓
Lower posterior facial height	↓	↓	↓	↓	↔	↑
Anteroposterior facial dimensions	↑	↑	↔	↓	↔	↑
Lips	More prominent	More prominent	↔	↔	More prominent	↔
Chin prominence	↔	↔	↔	↔	↔	↑

The principal quantitative soft-tissue facial differences between reference population and attractive subjects are listed

31.6 Applications to Other Areas of Health and Disease

Facial esthetics is one of the principal concerns of orthodontists and maxillofacial surgeons (Auger and Turley 1999). The creation of a harmonic occlusion, within a well-functioning stomatognathic apparatus, must always consider the effect of teeth position on facial soft tissues. Orthodontists and surgeons should therefore be provided with updated esthetic guidelines (Nguyen and Turley 1998; Auger and Turley 1999; Bashour 2006a, b).

These guidelines should therefore become useful tools for those professionals who can modify (possibly, improve) the facial appearance of their patients (Bashour 2006a, b; Kiekens et al. 2006; Naini et al. 2006), providing indications for the best kind, timing, and goals of orthodontic, orthopedic, and surgical treatments. Additionally, guidelines offer information about the esthetic preferences of the general public within a given context (Bashour 2006b; Naini et al. 2006), and possibly about the desires and requests of the patients. However, esthetic guidelines are tools that should only be used within a well-founded knowledge of craniofacial and dental physiology. No procedure should be imposed on each face, or followed blindly. Even the best and most updated esthetic guidelines must remain only a part of the treatment goals.

At the same time, when restoring harmony and function in the dental arches, the effect of teeth position on facial soft tissues should always be considered within the global framework of facial esthetics (Bashour 2006a, b; Isiksal et al. 2006; Naini et al. 2006).

Summary Points

- Esthetic guidelines offer information about the preferences of the general public within a given context, and possibly about the desires and requests of the patients.
- Esthetic guidelines can be useful tools for those professionals who can improve the facial appearance of their patients, providing indications for the best kind, timing, and goals of orthodontic, orthopedic, and surgical treatments.
- However, esthetic guidelines should always be used within a well-founded knowledge of craniofacial and dental physiology. No procedure should be imposed on each face, or followed blindly. Even the best and most updated esthetic guidelines must remain only a part of the treatment goals.
- In Caucasian children, facial attractiveness is characterized by an increased development of the facial middle (maxilla) and upper thirds (forehead), with a wider and deeper face, but less vertically developed in the lower third.
- During adolescence, a female face is considered attractive when is wider, shorter, and less deep, with relatively larger forehead and maxilla, and a reduced mandible relative to the maxilla.
- Facial attractiveness in adult Caucasian women is characterized by a prominent facial middle third, with full lips; a relatively large face with a reduced mandible and increased forehead; and reduced vertical dimensions. Overall, attractive women seem to maintain several facial characteristics of babyness.
- In adult Caucasian men and boys in their late adolescence, attractiveness seems to be positively influenced by facial markers of high testosterone levels, with a more prominent chin.

Acknowledgments We are deeply indebted to all the staff and students of our laboratory, who helped in data collection and analysis. Dr. Patrizia Frangella organized the data collection in attractive persons. The financial support of the Consiglio Direttivo of the Società Italiana Di Ortodonzia (SIDO) is also gratefully acknowledged.

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Chapter 32
Three-Dimensional Facial Morphometry: From Anthropometry to Digital Morphology

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Abstract Several basic and clinical disciplines are interested in the quantitative assessment of the dimensions of human facial soft-tissue structures (eyes, nose, mouth and lips, chin, ears), and of their reciprocal spatial positions and relative proportions. Anatomical and anthropometric descriptions, medical evaluations (genetics; maxillo-facial, plastic and esthetic surgery; dentistry), forensic medicine, they all need reference three-dimensional data collected on healthy, normal individuals selected for sex, age, ethnic group, to be compared to those obtained on the single patient. Data collection should be made non-invasively, rapidly, simply, directly on the subjects using low-cost instruments. All data should be digital, thus entering computerized data bases that can be used to visualize and simulate treatment. Currently, in clinical investigations and research classic direct anthropometry is being replaced with various three-dimensional image analyzers. Optical, non-contact digitizers (mainly, laser scanners and stereophotogrammetric devices) perform a fast digitization of the face, providing a detailed analysis of the soft-tissue surface. Contact instruments (electromagnetic and electromechanic digitizers) digitize discrete soft-tissue facial landmarks. Subsequently, landmark coordinates are used into mathematical and geometric models of the face, and angles, distances and ratios similar to those measured in conventional anthropometry can be obtained. Additionally, multivariate methods of analysis, obtained either from geometric morphometry or from other analytical methods, could be used. Overall, computerized instruments seem sufficiently reliable, simple and fast to be used also within clinical contexts, thus providing useful quantitative information to allow a better patient care, without submitting the subjects to potentially harmful procedures.

Abbreviations

3D	Three-dimensional
SD	Standard deviation
CAD	Computer aided design
CAM	Computer aided machinery

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_32,

32.1 Introduction

In man, the head is the most complex structure of the body. It accommodates the central nervous system, the eyes and ear structures, and the first parts of the digestive and respiratory apparatuses. It is characterized by the face. Communication and interaction with the environment, as well as personal identification, all depend on the face (Sforza and Ferrario 2006; DeAngelis et al. 2009).

Anthroposcopy (observation) and anthropometry (measurement) are currently used to analyze facial morphology in several basic and applied fields that cover a wide range of life and medical sciences (Sforza and Ferrario 2006). Both play an important role in the diagnosis of several dysmorphic syndromes, especially for the assessment of borderline patients (Douglas et al. 2003; Hammond et al. 2004; Dellavia et al. 2008; Maal et al. 2008; Fang et al. 2008; Schwenzer-Zimmerer et al. 2008).

Apart from expert observation of facial characteristics, quantitative assessments of the dimensions of facial soft-tissue structures (such as eyes, nose, mouth and lips, chin, and ears), their reciprocal spatial positions and relative proportions are important components in the clinical analysis of patients with facial alterations and deformities, as well as in treatment planning, and in the final evaluation of results (Yamada et al. 2002; Hajeer et al. 2004; Hammond et al. 2004; White et al. 2004; Dellavia et al. 2008; Maal et al. 2008).

Indeed, a global, three-dimensional, quantitative assessment of craniofacial characteristics may help in clinical diagnosis. This analysis should consider both the hard- and the soft-tissue structures. Clinical assessments for surgical (maxillo-facial, plastic, and esthetic) or dental (orthodontics and prostheses) treatments should combine the conventional radiographic analyses of the skeleton with evaluations of the soft-tissue structures, thus providing a complete evaluation of any patient. At all occasions, patient data should be compared to those of healthy subjects of the same age, sex, race, and ethnic group.

Classic direct anthropometry has greatly helped clinicians in the past (Farkas, 1994), but, presently, the advent of digital techniques for the imaging of the facial skeleton should be combined by some new methods for soft-tissue facial imaging and measurement (Table 32.1).

Currently, in clinical investigations and research, classic direct anthropometry is being coupled and even replaced with various three-dimensional image analyzers. These instruments can be divided into two main categories: optical, non-contact digitizers, and contact instruments. In the current chapter, classic anthropometry will be reviewed, and advantages and limitations of the modern facial digitizers will be presented and discussed.

Table 32.1 Key points: conventional anthropometry versus digital instruments

		Digital instruments	
	Conventional anthropometry	Optical	Contact
Cost	Negligible	Expensive (8–10 times higher than contact instruments)	Limited
Patient time	Long	Negligible	Limited
Off-line operator time	Negligible	Long	Negligible
Setting	Everywhere	Often laboratory or clinic only	Easy transport
Information content	Low	High	Medium to low
Adding new measurements, correcting errors	Impossible	Easy	Difficult
Assessment of anatomical landmarks	Direct (inspection/palpation)	Digital (inspection only)	Direct (inspection/palpation)

The main differences between conventional anthropometry and digital instruments are listed

32.2 Direct Facial Anthropometry

Direct anthropometry has been the first method for the in vivo, quantitative, three-dimensional assessment of the human face, and it still continues to be used in several basic and applied fields that cover a wide range of life and medical sciences (Farkas 1994). Conventional, direct anthropometry is currently considered the gold standard for in vivo assessments: it is simple and low cost; it is non-invasive; and it does not require complex instrumentation (Farkas 1994; Zankl et al. 2002).

A further advantage of conventional anthropometry is the existence of normal databases for almost all craniofacial measurements, at least for white Caucasians (Farkas 1994; Zankl et al. 2002), whereas norms for other ethnicities are more scanty (Farkas 1994; Farkas et al. 2005).

At the same time, direct anthropometry is time consuming, it necessitates very well trained and experienced examiners, and it is very demanding for both the clinician and the patient (Douglas et al. 2003; White et al. 2004). Each facial measurement (linear distance or angle) is taken individually, a long procedure prone to error (Aldridge et al. 2005), and no permanent record of the facial arrangement is maintained. Therefore, missing values, miscalculations, or reading errors cannot be corrected once the subject has been released.

Furthermore, direct anthropometry does not provide digital coordinate data that could be used to measure new features, or to extract more complex calculations (surface and volume estimations, analyses of symmetry, and form and shape quantification) (Shaner et al. 2000; Douglas et al. 2003; Ferrario et al. 2003; Hammond et al. 2004; White et al. 2004; Mori et al. 2005; Fang et al. 2008; Schwenzer-Zimmerer et al. 2008).

An ideal method for the quantitative evaluation of the patients should combine:

- Non-invasive, low-cost instruments that could directly be carried off-site to meet the patients
- A fast, simple, data-collection technique that provides three-dimensional digital data and a permanent record of the facial morphology
- Computerized reference databases collected from healthy, normal individuals of same sex, age, and ethnic group as the patients
- The use of computerized techniques for visualization, simulation, and quantitative assessment of the treatment

Most of these requirements are currently met by digital, computerized anthropometry. At the same time, several investigations performed both in vivo and on inanimate models also compare conventional and computerized anthropometric data to assess if they could be, at least in part, exchanged, thus opening new possibilities to basic researchers and clinicians (Sforza and Ferrario 2006). Good results have been obtained for both global facial analyses, and for the assessment of selected parts of the face (e.g., soft-tissue orbital features, facial profile measurements, and mouth and nasal dimensions) (Sforza and Ferrario 2006; Weinberg et al. 2006; Ghoddousi et al. 2007; Wong et al. 2008; Ozsoy et al. 2009; Plooij et al. 2009). Overall, the conventional anthropometric and digital data seem sufficiently interchangeable, at least from a practical, clinical point of view.

32.3 Instruments for Three-Dimensional Digital Morphometry

Two main groups of instruments can currently be used for computerized, soft-tissue three-dimensional facial anthropometry: optical, non-contact instruments (laser scanners, three-dimensional range cameras, optoelectronic instruments, stereophotogrammetry, and Moiré topography) and contact instruments (electromagnetic and electromechanical digitizers and ultrasound probes).

All these instruments are non-invasive, not potentially harmful (apart from some limitations for laser light, but that seem to have been overcome in the last generation of laser scanners), and do not provoke pain or discomfort to the subjects.

Both kinds of instruments have advantages and limitations that should be considered according to the investigated problem and the human resources (Table 32.2).

32.3.1 Optical Instruments

The most used instruments of this category are laser scanners and stereophotogrammetric systems. Laser scanners illuminate the face with a laser light source, and digital cameras capture the reflected light; the depth information is obtained by triangulation geometry (Majid et al. 2005; Hennessy et al. 2006; Schwenzer-Zimmerer et al. 2008). During data acquisition, either the face (with a rotating stool) or the laser light moves to scan the entire surface. In the first scanners, the laser light was not safe for the eyes, but current instruments are stated to be not dangerous. Accuracy and resolution are reported between 0.5 and 1 mm, and approximately 10 s are necessary for a complete scan. Critical parts of the face are the ears, the nostrils, and the chin. Shadows, local facial characteristics (hairs and nevi), and a dark complexion may hamper the digitization (Majid et al. 2005).

Stereophotogrammetry uses a light source (either patterned or conventional) to illuminate the face, and two or more coordinated cameras record images from different points of view (Fig. 32.1) (Majid et al. 2005; Ghoddousi et al. 2007; Sawyer et al. 2009; Wong et al. 2008; Plooij et al. 2009). A previous calibration, made with objects with known geometric characteristics, supplies the mathematical information to obtain a stereoscopic reconstruction of the face (Fig. 32.2). The system can also record facial texture, and combines the three-dimensional information with an accurate reproduction of all facial characteristics (Fig. 32.3). Accuracy and resolution are around 0.5 mm, and 2 ms can be sufficient for a facial scan. Surface artifacts, limited lateral coverage, and shadows effects are limitations that stereophotogrammetry shares with laser scanning, but they seem of relatively less importance.

Figure 32.4 shows an example of facial reconstruction by stereophotogrammetry. The finer the mesh is the better is the reconstruction. Some artifacts (low-resolution scan) can be found under the chin and the ear, and inside the nostrils.

Both these methods supply a wealth of data for each face (typically, laser scanning can describe the face with approximately 80,000 points, Hennessy et al. 2006, whereas stereophotogrammetry can obtain 300,000–450,000 surface points, Weinberg et al. 2004), thus allowing a complete assessment of both qualitative and quantitative features that are permanently recorded into the computer. Also, the time necessary to obtain a complete facial scan is negligible, thus reducing or abolishing motion artifacts, a feature particularly important for the assessment of children and disabled persons. In this aspect, stereophotogrammetry performs better than laser scanning, with appreciably faster scan times.

Both instruments have relatively lengthy post-processing times because the different facial pictures must be mathematically combined to obtain the three-dimensional surface. This time strictly depends on the host computer. Another limitation of these optical methods is the cost of the instrumentation, and, in some instances, the dimensions and need for special settings that cannot be taken away to meet the patients at other locations. Portable stereophotogrammetric instruments and handheld laser scanners have been developed, and used for facial analysis outside laboratory or clinical facilities (Douglas et al. 2003; Schwenzer-Zimmerer et al. 2008). Resolution and accuracy are around 1 mm, and are considered adequate for basic and clinical studies (Hennessy et al. 2006), even if motion artifacts may often limit their use.

Table 32.2 Principal characteristics of currently used computerized, three-dimensional, soft-tissue facial digitizers

	Motion artifacts	Post processing	Landmarks	Information	Critical parts of face	Dimensions	Cost
Optical scanners							
Laser scan	Limited (approx. scan time 2 s)	Lengthy (it depends on the host computer)	Identified only on the digital image; no physical compression	All surface	Imaging hairs impossible; difficult imaging of nostrils, ears, and neck	Transportable	Expensive
Stereo-photogrammetry	Negligible (approx. scan time 10 ms)	Lengthy (it depends on the host computer)	Identified on both the digital image and directly on the skin; no physical compression	All surface and texture	Potential problems with hairs; difficult imaging of ears	Often bulky but transportable	Expensive
Contact instruments							
Electromagnetic digitizer	Present (approx. scan time for 50 landmarks 60 s)	Fast	Directly identified on the skin; possible physical compression	Only selected landmarks	Potential problems with metal and electromagnetic fields (orthodontic brackets)	Movable with ease	Limited
Electromechanic digitizer	Present (approx. scan time for 50 landmarks 60 s)	Fast	Directly identified on the skin; possible physical compression	Only selected landmarks		Movable with ease	Limited

The main differences between the most used digital instruments for facial anthropometry are listed

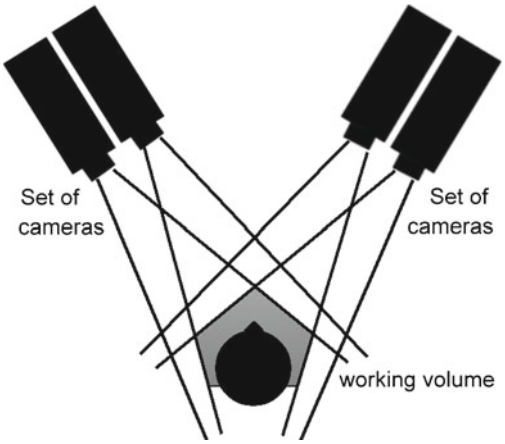

Fig. 32.1 Schematic diagram of a stereophotogrammetric set. The main components of a stereophotogrammetric instrument are shown

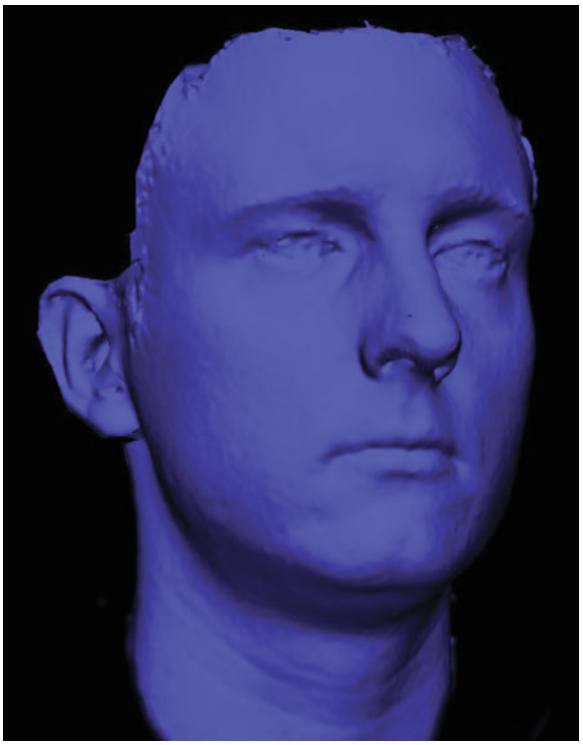

Fig. 32.2 Example of facial reconstruction made by stereophotogrammetry. Surface rendering of a three-dimensional facial reconstruction made by stereophotogrammetry

Although the optical instruments supply a detailed recording of the soft-tissue facial characteristics based on a large quantity of soft-tissue points, they do not individualize single anatomical landmarks. Landmarks are recognized on the digital reconstructions of the face, using all computer tools of zoom, rotation, and translation (of the image) (Hammond et al. 2004; White et al. 2004). This procedure can result in some discrepancies between the actual anatomical landmarks and their digital counterparts because some landmarks cannot be obtained by simple inspection, and only facial palpation allows their identification (for instance, gonion). Therefore, a number of standard landmarks (and subsequent measurements) should be excluded from the analysis (Weinberg et al. 2004; White et al. 2004).

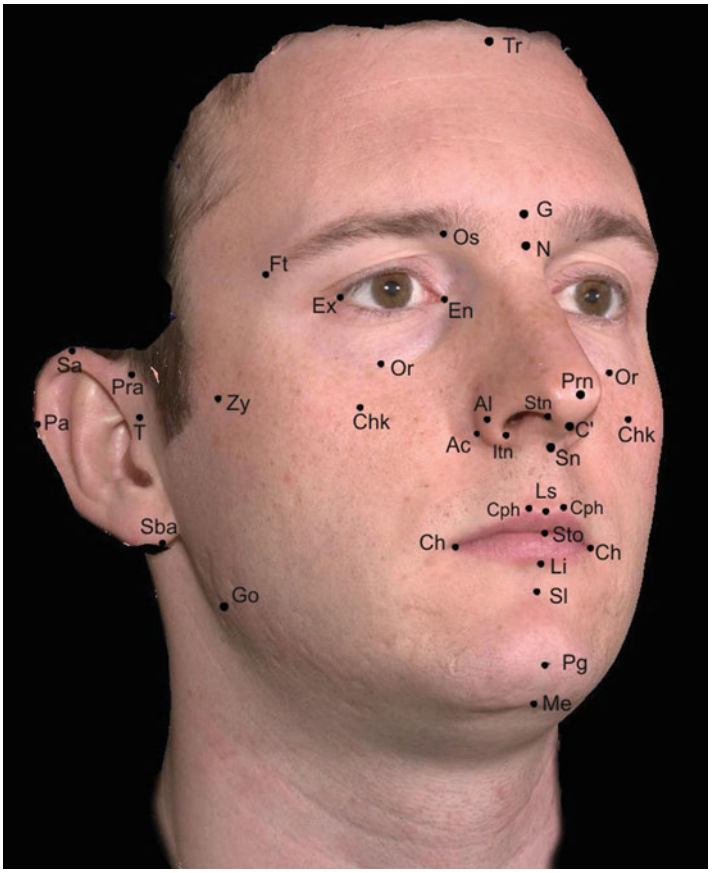

Fig. 32.3 Facial reconstruction made by stereophotogrammetry with the relevant facial texture. A set of soft-tissue facial landmarks is also identified. The final image produced by stereophotogrammetry is shown

Considering that stereophotogrammetry also collects the soft-tissue texture, for this technique some landmarks can be directly labeled on the face before data acquisition (Fig. 32.3) (Weinberg et al. 2004). Unfortunately, the procedure cannot be undertaken with most laser scanning systems because the ink used for the mark is not digitized by the scanner. Previous labeling also improves accuracy in landmark recognition (Weinberg et al. 2004).

The optical instruments need no physical contact with the skin, thus eliminating the risk of cutaneous compression, and of potential injuries during measurements (Douglas et al. 2003; Majid et al. 2005; Sawyer et al. 2009).

32.3.2 Contact Instruments

Ultrasound probes, and electromagnetic and electromechanic digitizers are among the most used contact instruments. They digitize single, selected, facial landmarks, thus reducing the information obtained from each face, but providing the coordinates of facial features that directly correspond to anatomical and anthropometric structures (Ferrario et al. 1998, 2003; Sforza et al. 2007, 2009; Dellavia et al. 2008; Ozsoy et al. 2009).

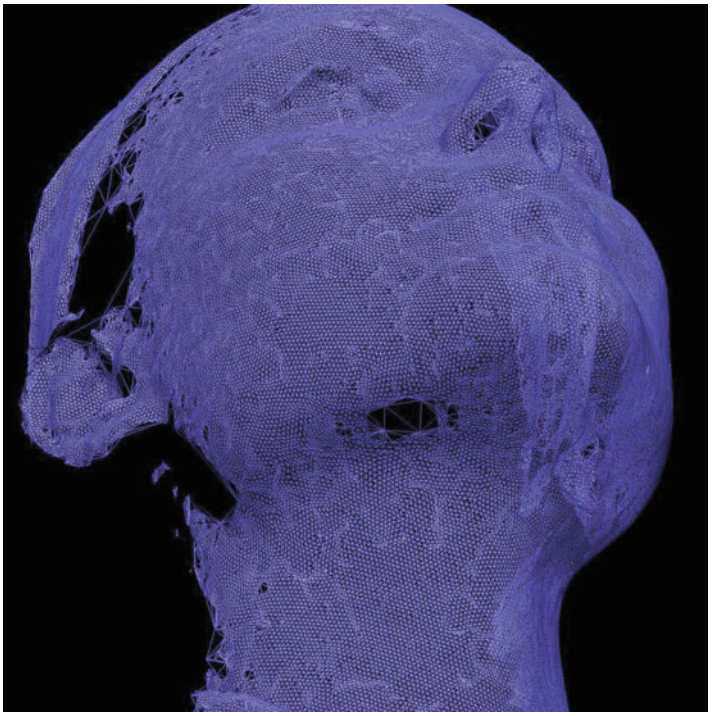

Fig. 32.4 Facial reconstruction made by stereophotogrammetry with mesh rendering. Under the chin, a small-size defect in the mesh reconstruction can be seen

Ultrasound probes use acoustic waves in the megahertz frequency domain, whereas electromagnetic and electromechanic digitizers are based on electromagnetic waves. The instruments have no invasiveness and pose no biological hazard.

For the face, ultrasound images the skeletal surface and its soft-tissue cover (Sforza and Ferrario 2006). While the method is widely used for prenatal, intrauterine imaging and diagnosis, and three-dimensional reconstructions of the fetal face are a current clinical practice, its application for postnatal facial morphometrics is limited. Currently, it is used only for the in vivo measurement of the thickness of facial soft-tissue cover.

Electromagnetic and electromechanic digitizers provide the three-dimensional coordinates of landmarks that are actually touched one by one by the instrument's stylus (Ferrario et al. 1998, 2003; Sforza et al. 2007, 2009; Dellavia et al. 2008; Ozsoy et al. 2009). The field of the electromagnetic digitizer used in our laboratory (3Draw, Polhemus Inc., Colchester, VT) provides a three-dimensional working volume (three spatial coordinates) of approximately $30 \times 30 \times 76$ cm; it has a resolution of 0.005 mm/mm range, and an accuracy of 0.08 mm. The electromechanical digitizer (Microscribe G2, Immersion Corporation, San Jose, CA) is a multi-joint-arm digitizer, with an accuracy of 0.38 mm in a 127-cm workspace. Within each joint, an optical encoder works with a microchip to send the joint angle to a host computer; the three-dimensional coordinates of the stylus are therefore provided.

A set of facial landmarks is previously marked on the face of the subject; landmarks are identified by inspection or palpation (as in conventional anthropometry), and are marked with a small black dot. Subsequently, the subject is positioned within the working volume of the instrument, and asked to stay motionless, while the operator gently touches the facial landmarks one by one using a stylus

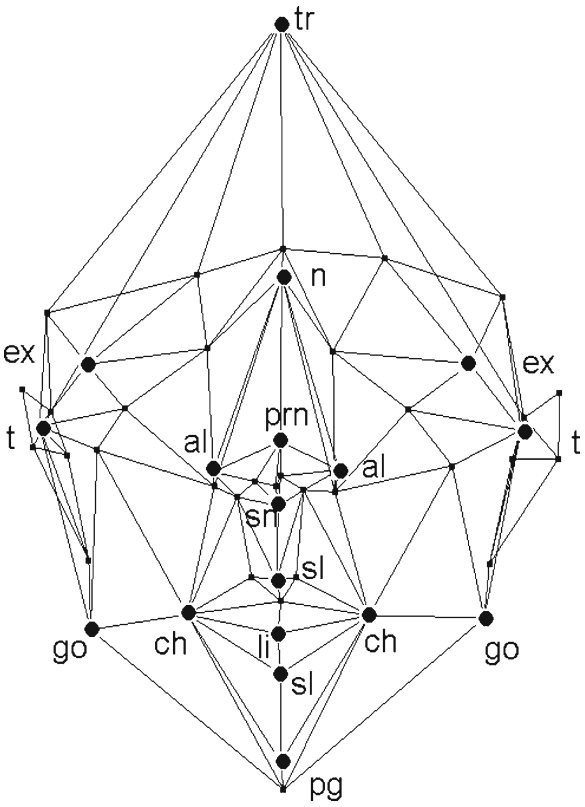

Fig. 32.5 Example of facial reconstruction made by contact instruments. All nodes of the image correspond to facial landmarks and some of them are labeled for clarity (tr, trichion; ex, exocanthion; n, nasion; prn, pronasale; ala, ala nasi; sn, subnasale; ch, cheilion; sl, sublabiale; go, gonion; pg, pogonion). A schematic facial diagram obtained from a 50-landmark digitization

connected to the digitizer. With both instruments, data collection for a set of 50 landmarks needs 50–60 s for each subject (Ferrario et al. 1998), and motion artifacts could occur.

The principal limitations of the instruments are the reduction of information, and the time necessary for data acquisition. The acquisition of only single, selected landmarks impedes the production of lifelike facial models (Fig. 32.5) (Ferrario et al. 1998), and the application of the method as a communication tool is difficult, in particular with the patients (Hajeer et al. 2004). Also, no permanent records of the facial appearance are obtained, and it is not possible to correct the position of a landmark off-line, or to introduce new landmarks.

Data acquisition time is extremely long when compared to that necessary for an optical facial scan (even if it is remarkably short when compared to conventional anthropometry, Farkas 1994; Douglas et al. 2003), and movements of facial muscles (especially around mouth and eyes), as well as global head movements, may occur during digitization.

The calibration of the electromagnetic instrument can be altered by electromagnetic interferences and metal objects. To avoid interferences with the electromagnetic field, data collection should be performed in a controlled environment, with all electromagnetic devices (e.g., computers, video recorder, power supply of the digitizer, and mobile telephones) and metal objects positioned at a minimum of 2 m from the digitizer (Ferrario et al. 1998). Also, the subject should not wear a metallic object on the head (for instance, voluminous earrings), and the operator should not wear a metallic object or a watch on the arm that uses the stylus.

In contrast, the electromechanic instrument does not need any special environment for acquisitions.

Both instruments provide the files of the three-dimensional (x, y, z) coordinates of the facial landmarks, and computer programs devised in the laboratory are used for all the subsequent off-line calculations. Using both digitizers, Ferrario and co-workers (Ferrario et al. 1998, 2003; Sforza et al. 2007, 2009; Dellavia et al. 2008) have analyzed more than 1,000 faces of healthy, normal persons from childhood to old age, together with a 100 faces of disabled or diseased persons; overall, the method seemed sufficiently reliable for anatomical and clinical investigations of selected facial characteristics. Some applications of their method are shown in other chapters of the current book. In their investigations, Ferrario and co-workers (Ferrario et al., 2003; Sforza et al. 2007, 2009; Dellavia et al. 2008) focused on the analysis of facial measurements similar to those obtained by conventional anthropometry (linear distances and angles), as well as on estimates of the volumes and surface areas of selected parts of the face (mouth and lips, nose, eyes, and ears). Additionally, they provided quantitative evaluations of facial symmetry and shape, independently from size (Sforza and Ferrario 2006).

In general, contact instruments are less expensive than optical ones (approximately 8–10 times less), and they can be moved with ease from the laboratory to meet the subjects at alternative locations; additionally, they directly provide the three-dimensional coordinates of the anatomical landmarks of interest, without any additional off-line calculations (Ozsoy et al. 2009).

32.4 From Anatomical Landmarks to Digital Morphology

Landmarks represent the link between conventional and digital anthropometry (Sforza and Ferrario 2006): conventional anthropometry identifies soft-tissue landmarks, and places some instrument (calipers or protractors) over them. Distances are obtained between a pair of landmarks; angles are comprised among three landmarks (Farkas 1994). The entire surface comprised between the landmarks is neglected, apart from observation of specific features (anthroposcopy). Fundamentally, digital anthropometry collects a set of digital landmarks from the soft-tissue surface, and uses their spatial x, y, z coordinates as endpoints for calculations based on Euclidean geometry: linear distances and angles similar to those provided by conventional anthropometry are computed.

Together with these classic measurements, mathematics and geometry allow the assessment of more complex characteristics from the same set of landmarks used by conventional anthropometry: estimations of volumes and surfaces, analyses of symmetry, and detailed assessments of shape independently from size (Ferrario et al. 1998, 2003; Shaner et al. 2000; Douglas et al. 2003; Hajeer et al. 2004; Aldridge et al. 2005; Mori et al. 2005; Sforza et al. 2007, 2009; Dellavia et al. 2008; Fang et al. 2008; Sawyer et al. 2009; Schwenzer-Zimmerer et al. 2008).

Additionally, the enormous amount of data collected by some of the digitizers allows detailed assessments of all inter-landmark surfaces, for instance, with the development of pattern recognition algorithms (Hammond et al. 2004; Hennessy et al. 2006).

In our laboratory, we currently identify 50 soft-tissue landmarks on each face (Ferrario et al. 1998). The landmarks are located on the forehead, eyes, nose, lips and mouth, chin, ears, and lateral facial surface (Table 32.3, Fig. 32.3). Twelve of them are on the midline, whereas 19 are identified on each hemi-half of the face. This set of landmarks was chosen to be used with the contact instruments, and it is a good compromise between a sufficiently detailed individuation of the anatomical characteristics of the face and digitization time. Currently, the use of an optical, stereophotogrammetric instrument allows the selection of an even wider set of landmarks, according to the problem being investigated. Nevertheless, the use of a standard set of landmarks allows the consistent assessment of subjects in both longitudinal and cross-sectional studies.

Table 32.3 Set of 50 facial landmarks currently digitized with contact instruments. The landmarks are shown in Fig. 32.3

			Midline	Paired
Forehead	tr	Trichion	✓	
	g	Glabella	✓	
Eyes	ex	Exocanthion		✓
	en	Endocanthion		✓
	os	Orbitale superius		✓
	or	Orbitale		✓
Nose	n	Nasion	✓	
	prn	Pronasale	✓	
	c′	Columella	✓	
	sn	Subnasale	✓	
	al	Alare		✓
	ac	Nasal alar crest		✓
	itn	Inferior point of the nostril axis		✓
	stn	Superior point of the nostril axis		✓
Mouth and lips	ls	Labiale superius	✓	
	sto	Stomion	✓	
	li	Labiale inferius	✓	
	sl	Sublabiale	✓	
	chp	Crista philtri		✓
	ch	Cheilion		✓
Chin	pg	Pogonion	✓	
	me	Menton	✓	
Lateral part of the face	ft	Frontotemporale		✓
	chk	Cheek		✓
	zy	Zygion		✓
	go	Gonion		✓
Ears	t	Tragion		✓
	pra	Preaurale		✓
	sa	Superaurale		✓
	pa	Postaurale		✓
	sba	Subaurale		✓

The set of 50 landmarks currently used in our laboratory is listed

32.5 Applications to Other Areas of Health and Disease

Basic human research has obtained valuable results using three-dimensional anthropometry, and several anatomical studies have quantitatively described normal facial growth, development, and aging, allowing the creation of databases that could be used for the quantitative assessment of patients (Zankl et al. 2002; Douglas et al. 2003; White et al. 2004; Mori et al. 2005; Dellavia et al. 2008; Maal et al. 2008; Sawyer et al. 2009; Sforza et al. 2009).

Clinicians working with the head and face (maxillo-facial, plastic, and esthetic surgeons; and orthodontists and prosthodontists) are those mostly interested in this three-dimensional information (Zankl et al. 2002; Ferrario et al. 2003; Hajeer et al. 2004; Sforza et al. 2007; Dellavia et al. 2008; Maal et al. 2008; Sawyer et al. 2009; Schwenzer-Zimmerer et al. 2008; Ozsoy et al. 2009; Plooij et al. 2009). Indeed, current non-invasive diagnostic methods could reduce the biological burden of repeated examinations for patient assessment, treatment planning, and evaluation of results. This is particularly important for those children whose malformations cannot be corrected in a single episode, but require several surgical, orthopedic, and orthodontic interventions between birth and

adult life (White et al. 2004; Dellavia et al. 2008; Schwenzer-Zimmerer et al. 2008; Plooij et al. 2009). Also, the use of a piece of three-dimensional information that considers both the underlying skeletal structure and the overlying soft-tissue cover is valuable in the global assessment of the patient (Maal et al. 2008; Plooij et al. 2009).

The three-dimensional digitization of craniofacial characteristics is also widely used for the manufacturing of individualized ortheses, prostheses, and safety headgears: the imaged part of the body is used as a CAD (computer-aided design) source, and via CAM (computer aided machinery) technology, the artificial manufact is produced, with a reduction in time, costs, and patient discomfort.

Along with these classical fields, internal medicine that deals with general diseases is currently investigating possible associations between variations in facial morphology and body disorders: the search for low cost, fast, and non-invasive markers of more complex diseases has been particularly important in the metabolic field. Rapid screening, standardization of functional examinations, progression of disease, and quantification of side effects can all benefit from specific markers that can be longitudinally repeated with minimal discomfort to the patient, and a reduced monetary cost. In particular, applications in uremic patients on chronic dialysis, in patients with undiagnosed celiac disease, in obese adolescents, and in HIV-infected patients, have been proposed (Sforza and Ferrario 2006).

Hypotheses about the relationships between facial shape and asymmetry, and aspects of cognition that involve the anterior brain, are currently tested with investigations on three-dimensional facial morphology. Indeed, during early fetal life, there is a strict relationship between face and anterior brain: the localization of facial alterations, together with the known timing of their embryological development, may offer more insights into brain development and its alterations (Shaner et al. 2000; Hennessy et al. 2006; Sforza and Ferrario 2006).

Three-dimensional assessments of facial morphology are also used for low-cost screening of neurodevelopmental alterations such as the fetal alcohol syndrome that involve characteristics facial alterations. Borderline patients or gene carriers could also be screened using quantitative tools assessing selected facial features (Douglas et al. 2003; Fang et al. 2008). The development of cost-effective methods for field screening seems particularly important in low-income countries and areas, where the patients cannot be offered all the opportunities which are available in more developed parts of the world (Douglas et al. 2003).

Together with the direct assessment of the living, digital facial morphology is currently successfully applied into several forensic fields (DeAngelis et al. 2009): for instance, all techniques for facial reconstruction from skeletal remnants need three-dimensional sex-, age-, and ethnic-based normal databases that should be renewed considering the secular trends in body dimensions. Three-dimensional data are also necessary to artificially “age” facial images of kidnapped children, as well as to give an age to victims of pornography and pedopornography.

Forensic, commercial, and security identification of persons is increasingly using virtual images, and three-dimensional digital images should be used instead of conventional anthropometry (DeAngelis et al. 2009) to determine the identity of probands.

Virtual applications are also usefully employed in computerized simulations for the entertainment arena: television, cinema, virtual reality, and computer games all use digital three-dimensional sources obtained non-invasively from both humans and animals.

32.6 Conclusions

In conclusion, digital, computerized, non-invasive instruments for three-dimensional facial anthropometry appear to offer new possibilities for both basic investigators and clinicians. Detailed quantitative (and often also qualitative) information about the facial soft tissues of a given patient may

allow a better and faster diagnosis, especially when the relevant reference values (selected for age, sex, and ethnic origin) are available.

Maxillo-facial, plastic, and esthetic surgery, as well as orthodontics and dental prostheses, may usefully apply this information.

Computerized tools may also permit to simulate treatment, and to provide an approximate idea of the final outcome, thus facilitating the process of informed consent. Longitudinal assessments can offer a quantitative evaluation of the post-treatment results, with concomitant evaluations of the possible relapse.

At the same time, the same clinical reasoning used for conventional anthropometry can be used, via the maintenance of landmark-based measurements.

Summary Points and Practical Methods

- A global, three-dimensional, quantitative assessment of the craniofacial characteristics may help in clinical diagnosis.
- Together with conventional radiographic analyses of the skeleton, the soft-tissue structures should also be analyzed to provide a complete evaluation of any patient, and should be compared to those of healthy subjects of the same age, sex, race, and ethnic group.
- Both contact and optical computerized instruments can be used for the three-dimensional analysis of facial soft tissues.
- Contact instruments allow the assessment of selected facial landmarks with a reduced monetary price.
- Optical instruments allow a detailed record of all facial surfaces, but they are more expensive.
- Three-dimensional virtual facial reconstructions are currently used in several medical, forensic, and industrial fields.

Acknowledgments We are deeply indebted to all the subjects who served as volunteers in our laboratory. The precious work of staff and students, who helped in data collection and analysis, is also gratefully acknowledged.

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Chapter 33
The Concept of Anthropometric Facial Asymmetry

Senem Turan Ozdemir

Abstract Facial asymmetry is a common finding in healthy subjects and in esthetically pleasing faces. It is believed that normal craniofacial skeletons have some degree of asymmetry which is compatible with normal dental occlusion, and mild facial asymmetry is often disregarded by clinicians. In parallel with increasing demand for facial aesthetics and recent advances in facial aesthetic surgery, patients have become more sensitive to facial asymmetry which may occur after the operation. In this context, objective evaluation of facial asymmetry by extended facial analysis before and after the operation has gained importance.

Facial asymmetry analysis can be performed as objective and/or subjective. Soft tissues of the face can be evaluated by subjective analysis; however, skeletal asymmetries compensated by the overlying soft tissue may not be recognized most of the time. Objective assessment of the asymmetry degree of both soft and hard tissues of the face before facial operations, aesthetic and orthodontic procedures in particular, will allow a more accurate analysis of the treatment results.

Anthropometric measurement is one of the methods used for the quantitative analysis of facial asymmetry. Although anthropological studies on face have been extensively addressed in the literature, anthropologists have rarely examined facial asymmetry. The concept of facial asymmetry and anthropometric measurement of facial asymmetry will be reviewed in this chapter.

Abbreviations

2D	Two dimensional
3D	Three dimensional
EDMA	Euclidean Distance Matrix Analysis
NHP	Natural head position
PA	Posteroanterior

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_33,

33.1 Introduction

The human face is an organ which is unique to an individual with its dental, skeletal, and soft-tissue structures, and has harmony and balance within itself. Symmetry is one of the fundamental features of these structures. Although symmetry is often considered to be an essential part of beauty and attractiveness, a feature lacking symmetry may also be regarded as beautiful, based on its inherent harmony and balance. Stedman's Medical Dictionary (2006) defines symmetry as the "equality or correspondence in form of parts distributed around a center or axis, at the two extremes or poles, or on two opposite sides of the body." When applied to facial morphology, symmetry and balance refer to the state of facial equilibrium, the correspondence in size, shape, and arrangement of facial features on opposite sides of the median sagittal plane.

It should be kept in mind that the body is not perfectly symmetrical. Interestingly, the human form is, in general, externally symmetrical and internally asymmetrical. The face is asymmetric to the extent that it is acceptable and regarded to be within normal limits. It is this degree of asymmetry that gives the face its natural appearance (Fig. 33.1). This is because a fully symmetric face with perfect mathematical ratios will present as a mechanical image rather than a natural one.

Facial asymmetry can be simply defined as one side being larger than the other (Smith 2000). It can further be classified into normal (minor or mild, i.e., non-pathologic) and abnormal (pathologic). In normal individuals, there are subtle differences between the dimensions of the left and right halves of the face, which alone do not normally result in an esthetically unpleasing appearance (Ferrario et al. 1995, 2001). Asymmetry becomes clinically important when it affects function, esthetics, or social acceptance of an individual. Numerous disorders, such as hemifacial microsomia, unilateral craniosynostoses, temporomandibular joint disorders, cleft lip/palate, and hemifacial athrophy (Parry–Romberg syndrome), have been reported to be associated with facial asymmetry. These conditions often result in pathologic asymmetry (Bishara et al. 1994).

Although many investigators consider asymmetry as a normal facial feature, with the increasing concern about facial appearance, patients now complain of even slight asymmetry. Some patients believe that asymmetry develops or progresses during, or after, plastic or orthodontic treatment. Preoperative and postoperative evaluations of facial asymmetries in plastic and maxillofacial surgeries make it possible to plan the scope and method of surgical operations, and a comparison with the limits of normal facial asymmetry allows evaluating the therapeutic results. In this regard, it is important to know the limits of normal facial asymmetry. Furthermore, Skvalirova (1993) emphasized that calculation of the range of normal asymmetry may have practical implications – for example, accurate definitions of congenital defects such as hemifacial microsomia – although the range of suggested normal asymmetry is arbitrary, and it is open to question how many standard deviations should be used for its determination. Several facial asymmetry studies have been conducted in healthy individuals to quantify the amount of normal variability. Shaner et al. (2000) have pointed out that normal limits of soft-tissue asymmetry in the measurements taken from the upper and middle regions of the face did not exceed 5 mm in males and 6 mm in females, as a general rule. In the same study, it has been suggested that measurements involving the lower regions of the face had a much higher normal variability, with the differences between the two parts being 6 mm or greater. Ferrario et al. (2001) indicated that differences between the most symmetric and asymmetric groups were less than 2.5 mm.

The focus of the majority of facial asymmetry research has been the identification of the facial side of greatest magnitude and the localization of asymmetry. In the literature, there is no consensus regarding the dominant side of face and the localization of asymmetry. Whereas the left side has been found to be more dominant in some studies (Vig and Hewitt 1975; McIntyre and Mossey, 2002; Ercan et al. 2008a), the right side has been found to be more dominant in others (Farkas and Cheung 1981; Ferrario et al. 1994, 1995, 2001; Shaner et al. 2000;). While Farkas and Cheung (1981) have reported that the most asymmetric part of the face (69.2%) was the upper-third portion,

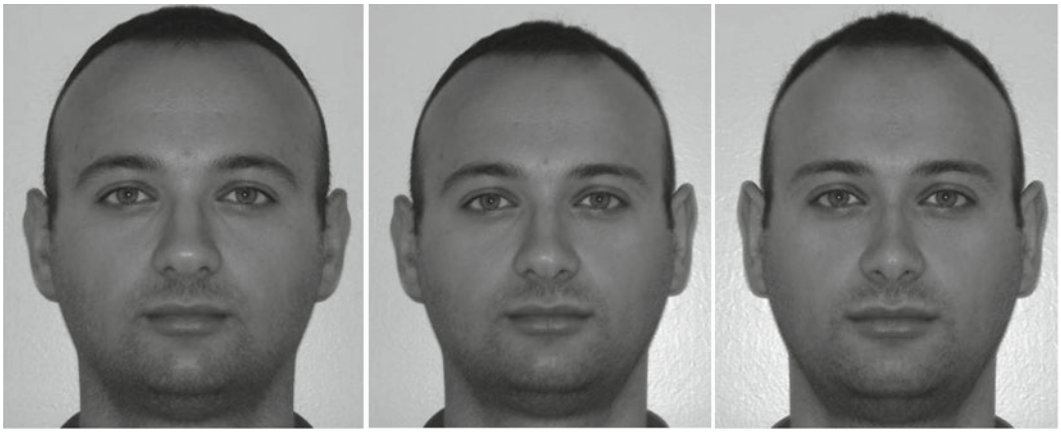


Fig. 33.1 Normal and perfectly symmetrical faces. *Left*: original face. *Middle*: a perfectly symmetrical face made of the left half of the original face. *Right*: a perfectly symmetrical face made of the right half of the original face

Ferrario et al. (1994) have reported that it was the middle and lower thirds. Shaner et al. (2000) have stated that measurements obtained from tragion and gonion had a much greater normal variability. The functional adaptation response to asymmetrical masticatory activity has been suggested as the main cause of asymmetries in the lower part of the face (Vig and Hewitt 1975). Asymmetric position of the right and left tragions as a cause of side differences has previously been mentioned by several authors (Farkas and Cheung 1981; Ferrario et al. 1994, 1995). Features of the central face including the orbits, nose, and orolabial region present much less asymmetry (Farkas 1981).

33.2 Analysis of Facial Asymmetry

Facial asymmetry analysis can be objective and/or subjective. Soft tissues of the face can be evaluated by subjective analysis; however, skeletal asymmetries compensated by the overlying soft tissue may not be recognized most of the time.

Quantitative analysis of facial asymmetry has increasingly become a subject of investigation in recent years. It has been conducted by measurements made to a midfacial symmetry plane, or by comparing paired measurements of bilateral facial features and, thus, local changes in the right and left halves of the face have been obtained. For such examinations, traditional morphometric measurements, such as metric distances, areas, angles, and ratios, have been calculated for the left and right sides (Burke and Healy 1993; Shaner et al. 2000; Ferrario et al. 2001; Baudouin and Tiberghien 2004). However, Ferrario et al. (1995) mentioned that such methods provide information, which only refers to local imbalances, and does not allow full facial analysis, and does not reflect shape differences between the two sides. In recent years, new methods, such as geometric morphometry, have emerged in terms of the quantitative evaluation of facial asymmetry (Ferrario et al. 1995; Ercan et al. 2008a). Different methods used for facial asymmetry analysis and their results have been summarized in Table 33.1.

The following issues are crucial in quantitative facial asymmetry analysis:

- Standardization of the method in use
- Accurate identification of landmarks to be used in the measurements
- Accurate determination of facial midline

Table 33.1 Facial asymmetry

Author	Year	Method	Subjects	Landmarks used	Result
		Direct anthropometry			
Farkas et al.	1981	Direct anthropometry, spreading caliper	308 healthy Canadian Caucasians (154 boys and 154 girls)	Tragion, nasion, exocanthion, gonion, subnasale, cheilion, gnathion	Asymmetry was found to be very common but average differences between right and left measurements were mild (3 mm or 3%) with the *right side* usually the largest. The most common and largest asymmetries were found in the upper third of the face.
Skvarilova et al.	1993	Direct anthropometry, sliding caliper	720 normal (360 boys and 360 girls) subjects aged 6–18 years	Tragion, otobasion superius, nasion, otobasion inferius, subnasale, cheilion, gonion, gnathion, exocanthion	Extend of facial asymmetry is the same in the both sexes and does not change with age. Facial asymmetries have mostly a fluctuating character, usually with slight predominance of the *right side*. The range of normal asymmetry for lateral facial dimensions was determined as 4–5mm.
		Indirect anthropometry			
		Two Dimensional			
Smith et al.	2000	Frontal photographs	90 subjects (45 male and 45 female)		Left hemiface of the males were reliable larger than the right hemiface. In contrast right hemiface of the females were reliable larger than the left hemiface.
Song et al.	2007	Fontal photographs	1,282 volunteers (761 males 521 females) 18–29 years of age	Exocanthion, cheilion, cross point between median line and bilateral exocanthion, cross point between median line and bilateral mouth corners	Right dominant type was observed more frequently than the left dominant type in both genders. Measurement of horizontal angulations of frontal photographs of faces can be used to assess facial asymmetry.
Chatrath et al.	2007	Frontal photographs	300 patients requesting rhinoplasty surgery	Tragus, lateral cantus, medial cantus, lateral alar margin, oral comissure	Objectively 97% of patients had significant degrees of facial asymmetry, with the midline to ala distances showing the most variations and the midline to oral comissures showing the least variations. Subjectively, 38% of results were perceived as asymmetrical.

Haraguchi et al.	2008	Frontal photographs	1,800 Japan subjects (651 males and 1149 females) mean age 15 years 3 months		Of subjects with facial asymmetry, 79.7% had a wider right hemiface, and 79.3% of those with chin deviation had left sided laterality. Laterality in the normal asymmetry of the face, which is consistently found in humans, is likely to be hereditary rather than an acquired trait.
		Others			
		Three Dimensional			
Ferrario et al.	1994	3D Distance From Symmetry (DFS)	80 young healthy white adults (40 female 40 male)	Midline landmarks: nasion, subnasale, pogonion, trichion, pronasale, B' point bilateral landmarks: eye lateral cantus, tragus, gonion, nasale ala, labial comissura	Soft tissue facial asymmetry was evident especially in the middle (tragus) and lower (gonion) thirds of the face. The right side of the face larger than the left side.
Ferrario et al.	2001	3D, Distance From Symmetry (DFS)	314 healthy white subjects (40 male 33 female adolescents), aged 12–15 years; 73 female and 89 male young adults, aged 18–30 years; 41 male and 38 female adults ages 31–56 years	Midline landmarks: nasion, pronasale, subnasale, pogonion, menton paired landmarks: exocanthion, endocanthion, orbitale superius, frontotemporale, zygion, tragion, nasal alar crest, cheilion, gonion	A slight soft tissue asymmetry found in normal subjects, maximum normal asymmetry slightly greater in females. Tragion, gonion and zygion were the most asymmetric landmarks
Ferrario et al.	2003	3D, Distance From Symmetry (DFS)	18 cleft lip and palate white patients (11 male and 7 females aged 19–27 years) and 161 healthy controls (73 female and 89 male)	Midline landmarks: nasion, pronasale, subnasale, pogonion, menton paired landmarks: exocantion, endocanthion, orbitale superius, frontotemporale, zygion, tragion, nasal alar crest, cheilion, gonion	Most patients had a larger left side of the face, female patients had a somewhat larger lateral asymmetry than the male patients, and UCLP patients were more asymmetrical 8CLP
		Stereophotogrammetry			
Shaner et al.	2000	3D Stereophotogrammetry	medically normal (32 normal males age 1.6 years to adulthood and 38 normal females age 1.7 years to adulthood) and syndrome affected individuals	Lateral landmarks: tragion, zygion, gonion, exocanthion, centre of the iris, endocanthion, alare, subalare, cheilion, christa philtri midline landmarks: glabella, sellion, pronasale, subnasale, labiale superius, labiale inferius, sublabiale, pogonion	In the statistically significantly different measurements, those from the right side were dominant, with one exception in each group, except normal males.

(continued)

Table 33.1 (continued)

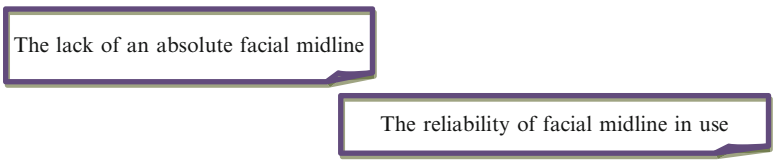
Author	Year	Method	Subjects	Landmarks used	Result
Hajeer et al.	2004	3D Stereophotogrammetry,	44 Patients; 20 ClassIII cases treated by bimaxillary osteotomy; 12 classIII cases treated by maxillary advancement alone, 12 class II cases treated by bimaxilary operations	Endocanthion, exocanthion, nasion, pronasale, alar curvature, subnasale, cheilion, superior label sulcus, stomion superius, stomion inferius, labiale superius, labiale inferius, inferior labial sulcus, pogonion, menton	
		EDMA, Shape analysis			
Ferrario et al.	1995	3D Photogrammetry, EDMA	80 Young Healthy White Caucasian Adults (40 Males, 40 Females 19–32 years old)	Trichion, nasion, pronasale, subnasale, B Point, pogonion, eye lateral canthi, nasal alae, labial comissures, tragic, gonia	Right side dominant
Ercan et al.	2008	2D Photogrammetry, EDMA	321 young adult (171 females and 150 males) 17–23 years of age	Midsagittal landmarks:trichion (tr), supraglabella (sg) nasion (n), pronasale (pr), subnasale(sn), labiale superior (ls), stomion (sto), labiale inferior (li), sublabiale (sl), and gnathion (gn). Bilateral landmarks: trichion; supraglabella; frontotemporale, frontozygomaticus, exocanthion; endocanthion; palpebrale superior; palpebrale inferior, zygion; gonion, nasion; pronasale; columella; subnasale; alare; labiale superior; stomion; labiale inferior; sublabiale; crista philtri;cheilion, pogonion; menton, and superaurale; subaurale.	Asymmetric linear distances between the two sides of face were found more commonly at the middle third of the face (maxillary bone, zygomatic corner and lower orbital border) in both sexes. The left side of the face was most commonly dominant in both sexes

Different methods used for facial asymmetry analysis and their results

Standardized method and subject position allow accurate facial asymmetry analysis. It is important to note that a standard head position is essential for measurement. Natural head position (NHP) is the most appropriate, as it is the most reproducible and provides a natural face orientation for treatment planning (Lane and Harrell 2008).

The accurate identification and reliability of the landmarks are the most important indicators of the accuracy of the facial asymmetry analysis. One way to increase accuracy is to mark the landmarks before measuring them (Kolar and Salter 1997). Many soft-tissue landmarks reflect the underlying bony structure. The bony points must be palpated with a finger to find the soft-tissue equivalent (Kolar and Salter 1997). Some soft-tissue landmarks, such as endocanthion, exocanthion, cheilion, and crista philtre can be clearly identified without palpation or marking. Meticulous identification of soft-tissue landmarks and marking of the landmarks determined by inspection and palpation before the acquisition of photographs will certainly improve the reliability of measurements (Ferrario et al. 1995, 1998). It is important to understand the various sources of error that can affect anthropometric measurements during location of landmarks. Lack of precision results in variability among repeated measurements of the same specimen, and has two components: (1) observer error in locating landmarks and (2) instrument error in identifying landmark coordinates (Kohn and Cheverud 1992; Lele and Richtsmeier 2000). It is crucial to analyze the reliability of the landmarks. To achieve reliability, all landmarks should be marked by the same investigator on all subjects (Ercan et al. 2008b). The reliability of the landmarks is also important while determining the midline. Inaccuracies while determining the landmarks will lead to substantial inaccuracies in measurement, thus reducing the method's reliability.

By definition, symmetry is the "correspondence in size, shape, and relative position of parts on opposite sides of a dividing line or median plane or about a center or axis"(Stedman 2006). This dividing line, which is used to attain symmetry, is known as the midline. It is the fundamental reference for all deviations causing asymmetric facial features. The key to evaluating facial asymmetry is defining the criteria that determine the facial midline (Haraguchi et al. 2008). However, the literature is not clear regarding verifiable guidelines for the determination of midline of the face (Bidra et al. 2009). Based upon convention and dogma, most clinicians choose one specific anatomic landmark and an imaginary line passing through it. Thus, the clinician is left with no predictable guidelines, and must determine the midline based on unverified landmarks (Bidra et al. 2009). Consequently, there are two basic caveats in terms of facial midline.



Facial midline (facial symmetry axis or vertical reference line) has been constructed in several ways. It can be constructed using two main landmarks (Naini et al. 2008). The mid-philtrum of the upper lip (Cupid's bow) will be in the midline of the face. A line joining this point to the mid-glabellar region (glabella), midway between the eyebrows, forms the facial midline (Fig. 33.2). In the symmetrical face, this line will extend to the midpoint of the chin (Naini et al. 2008). In routine medical practice, the facial midline can also be constructed beginning at the central hairline point and crossing the central point of the nasal bridge, the central point of Cupid's bow in the upper lip, and the bottom of the chin (Chatrath et al. 2007). In studies evaluating soft-tissue asymmetry with frontal facial photographs, the facial midline was defined as the perpendicular bisector of the line between the centers of the right and the left pupils (Fig. 33.3) (Haraguchi et al. 2008). First, the distance between the

Fig. 33.2 Facial midline. Facial midline determined using glabella and the mid-philtrum of the upper lip (Cupbid's bow)

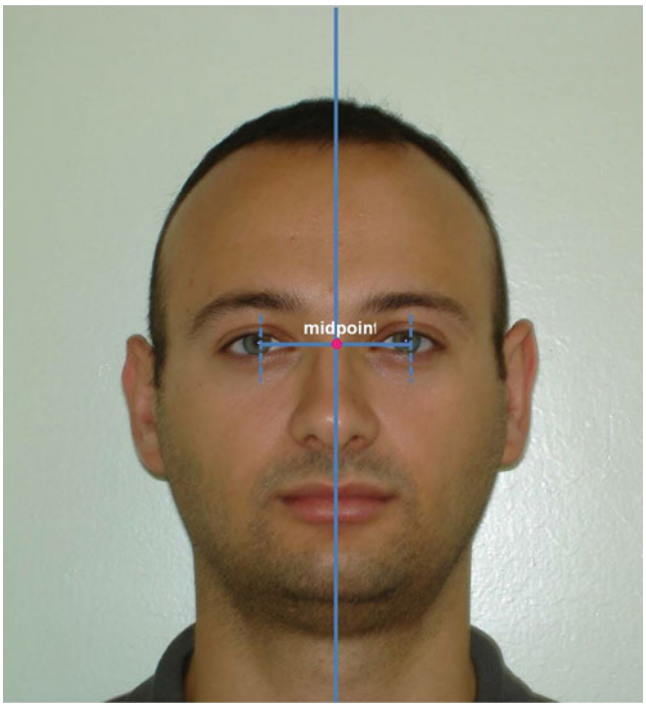


Fig.33. 3 Facial midline. The perpendicular line intersecting the middle point of the horizontal line which connects each pupil centers

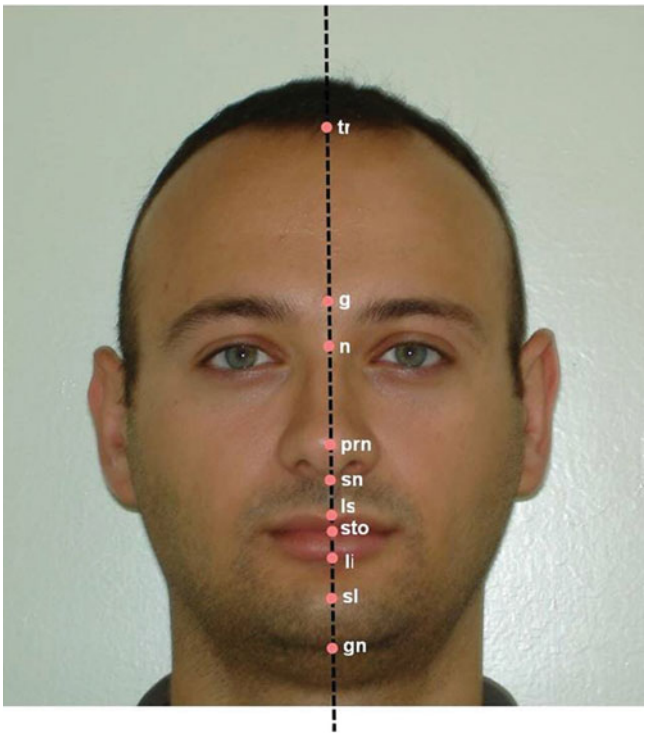


Fig. 33.4 Facial midline. The landmarks located on the midline frequently used to determine the facial midline. Dashed line represents facial midline (facial soft-tissue landmarks: *tr*: trcihion, *g*: glabella, *n*: nasion, *prn*: pronasale, *sn*: subnasale, *ls*: labiale superius, *sto*: stomion, *li*: labiale inferius, *sl*: sublabiale, and *gn*: gnathion)

centers of the two pupils is determined. Then, at the midpoint of this distance, a line perpendicular to the interpupillary line is drawn in order to divide the face into two halves.

In literature, landmarks situated on the midline are also used in order to specify the facial midline (Ferrario et al. 1994, 1995, 2001, 2003; Shaner et al. 2000; Ercan et al. 2008a). The most frequently used midline landmarks for determining the facial midline are trichion, glabella, nasion, pronasale, subnasale, labiale superius, stomion, labiale inferius, sublabiale, and gnathion (Fig. 33.4). However, the midline landmarks do not always refer to facial midline (Ferrario et al. 1994; Bidra et al. 2009). Ferrario et al. (1994) used a 3D coordinate system and found that the axis of symmetry was not located in the midline points. Moreover, the landmarks are frequently located in areas affected by asymmetry, and are thus unsuitable for correctly determining the symmetry axis.

The lack of a method to determine an accurate facial midline, and the question of reliability concerning the determined midline, are two important factors effecting the accuracy of the measurement distances obtained from each hemiface. Hence, further studies are required.

33.3 Anthropometric Facial Asymmetry Analysis

Anthropometric measurement is one of the methods used for the quantitative analysis of facial asymmetry. From the anthropometric point of view, facial asymmetry has been investigated in limited number of studies. Initial studies have been published by Farkas (1981). Anthropometric analysis of facial asymmetry is based on the comparison of homolog measurements that are obtained separately from the right and left hemifaces. These measurements can be performed both by direct and indirect

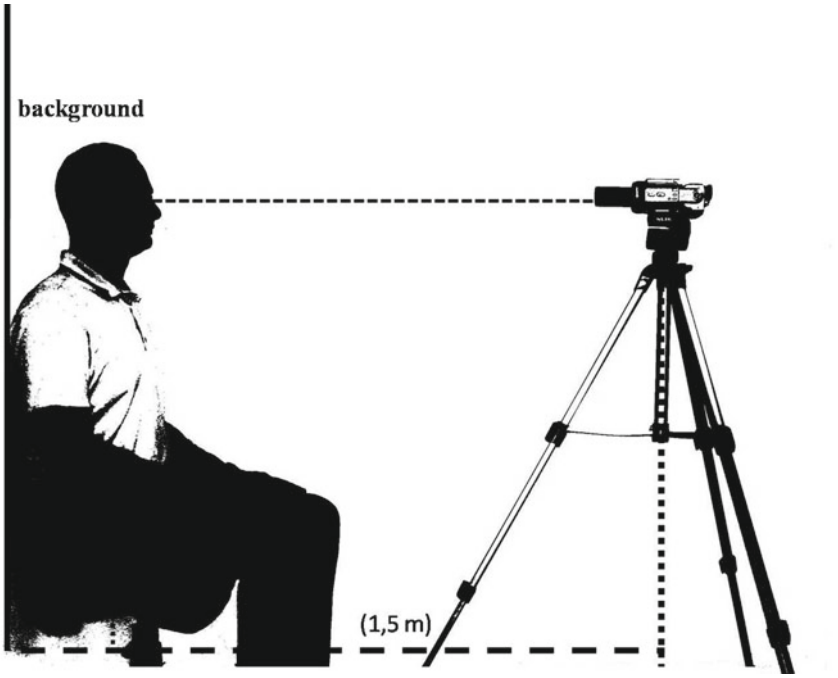


Fig. 33.5 Standardized photographic technique. The figure showing the photographic technique taken in a natural head position, while sitting in a chair within a standard distance (1.5 m is frequently recommended) in a comfortable position with eyes focusing on the lens

methods. Direct measurement is the oldest method used. This method is time-consuming and has several other disadvantages, such as difficulty of patient adaptation (especially in children and infants), problems concerning repeatability of measurements, and archiving of data. Therefore, indirect measurement instruments including photograph, cephalogram, stereophotograph, laser scanning, and computerized tomography have increasingly become popular in recent years. Photogrammetry is a fast and inexpensive method with superior patient compliance. The most important disadvantage of two-dimensional (2D) photogrammetry is its inability to assess facial depth. Three-dimensional (3D) photogrammetry appears to be a more appropriate technique in this respect.

Photogrammetric analysis: In photogrammetry, measurements are taken from standard photographs. The camera position, the distance between the camera and the subjects, and the head position of the subjects should be standardized (Fig. 33.5). The photographs should be obtained in the natural head position, while sitting in a chair within a standard distance (1.5 m is frequently recommended) in a comfortable position, with eyes focusing on the lens. Prior to imaging, careful attention should be paid to ensure that the subjects do not rotate their heads, especially along the vertical axis. In order to take optimal frontal and lateral images, the subjects should not be wearing glasses, their face should not be covered with hair, and their mouth should be closed as in a normal occlusion.

After acquiring the standardized digital images, these images are transferred to the computer and saved in JPEG format. In anthropometric measurements from digital images, tpsDig developed by F. James Rohlf is one of the most frequently used software, both for the marking of the landmarks and for the determination of the distance in pixels. Standard anthropometric landmark labeling on digital facial photograph through tpsDig is shown in Fig. 33.6. The reliability of the landmarks should be analyzed. Intra-observer reliability obtained from two consecutive monthly markings will significantly

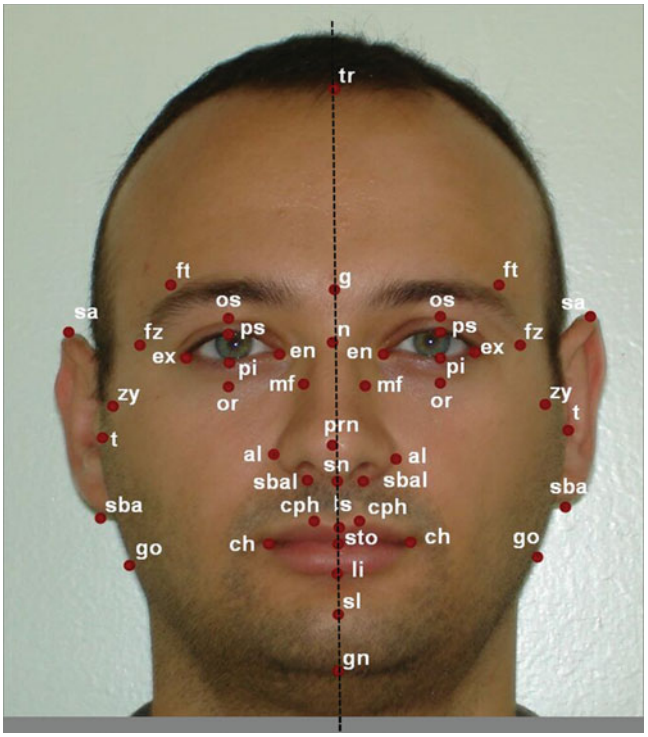


Fig. 33.6 Standardized anthropometric landmarks. *Midline landmarks*: trichion (*tr*), glabella (*g*), nasion (*n*), pronasale (*prn*), subnasale (*sn*), labiale superius (*ls*), stomion (*sto*), labiale inferius (*li*), sublabiale (*sl*), and gnathion(*gn*); *paired landmarks*: frontotemporale (*ft*), frontozygomaticus (*fz*), maxillofrontale (*mf*), endocanthion (*en*), exocanthion (*ex*), palpebrale superius (*ps*), palpebrale inferius (*pi*), orbitale superius (*os*), orbitale inferius (*or*), zygion (*zy*), alare (*al*), subalare (*sbal*), crista philtre (*cph*), cheilion (*ch*), gonion (*go*), supraaurale (*sa*), subaurale (*sba*), and tragion (*t*)

affect the reliability of the results. A ruler is used for the measurement of the distances between the landmarks in digital images, and, later on, the unit distance (1 cm) is calibrated with its equivalent in pixels in order to obtain measurement values separately from the right and left hemifaces.

33.4 Anthropometric Measurements

Several anthropometric measurements have been used by various authors to determine facial asymmetry. The majority of these measurements are from horizontal–linear measurements obtained from the left and right hemiface, and these are mainly defined by Farkas (1981). In the analysis of facial asymmetry, tragion-glabella (supraorbital depth), tragion-nasion (upper face depth), tragion-exocanthion (orbital depth), otobasion superius-nasion, and otobasion superius-exocanthion (temple depth) are located in the upper third; tragion-subnasale (maxillary depth), tragion-cheilion (mid-cheek depth), and otobasion inferius-subnasale (midface depth) are located in the middle third, and otobasion inferius-gnathion (lower face depth) and gnathion-gonion (mandibular body length) are located in the lower third of the face (Fig. 33.7). All paired linear measurements are given with their synonyms in Table 33.2. Of these distances, exocanthion-gonion, exocanthion cheilion, condylion laterale-gonion, and tragion-gonion are relatively perpendicular, the rest are horizontal–oblique. Besides the anthropometric measurements mentioned above, other different anthropometric measurements are noteworthy in the literature (Chatrath et al. 2007). One of the other anthropometric measurements used in facial asymmetry is the distance between the facial midline and homogeneous landmarks located on the left and right hemifaces, according to

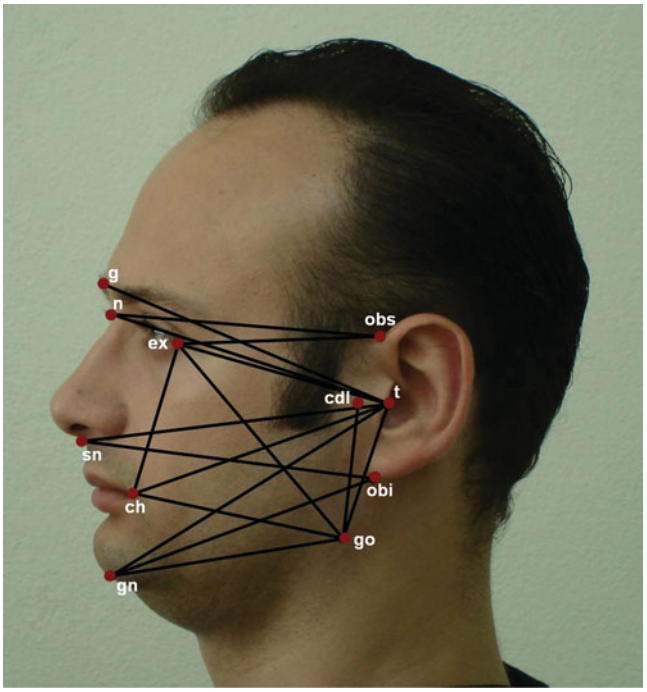


Fig. 33.7 Paired anthropometric measurements for facial asymmetry. Figure showing the left side of the paired measurements (facial soft-tissue landmarks: *g*: glabella, *n*: nasion, *obs*: otobasion superius, *ex*: exocanthion, *cdl*: condylon laterale, *t*: tragion, *sn*: subnasale, *obi*: otobasion inferius, *ch*: cheilion, *go*: gonion, and *gn*: gnathion) anthropometric measurements: t-g, t-n, t-ex, t-sn, t-ch, t-gn, t-go, cdl-go, gn-go, ex-go, ex-ch, obs-n, obs-ex, obs-gn, obi-sn, obi-gn

Table 33.2 Anthropometric measurements

Landmarks	Linear measurements	Synonyms
t-g (r&l)	Supraorbital depth (glabella-tragion)	Supraorbital–aural depth, tragio-glabellar depth
t-n (r&l)	Upper face depth (nasion-tragion)	Tragio-nasal distance, upper-third face depth
t-ex (r&l)	Orbital depth (exocanthion-tragion)	Orbito-tragial depth, upper cheek depth
t-sn (r&l)	Maxillary depth (subnasale-tragion)	Middle- third face depth, tragio-subnasal depth
t-ch (r&l)	Mid-cheek depth (tragion-cheilion)	Labio-aural depth
t-gn (r&l)	Mandibular depth (tragion-gnathion)	Lower-third face depth, gnathion-tragial depth
t-go (r&l)	Tragion-gonion	None
cdl-go (r&l)	Mandibular ramus height (gonion-condylion laterale)	None
gn-go (r&l)	Mandibular body length (gnathion-gonion)	Lower jaw/mandible depth/length
ex-go (r&l)	Lateral facial height (exocanthion-gonion)	Cheek height/orbito-gonial distance/orbito-mandibular
ex-ch (r&l)	Exocanthion-cheilion	None
obs-n (r&l)	Otobasion superius-nasion	None
obs-ex (r&l)	Temple depth (otobasion superius-exocanthion)	None
obs-gn (r&l)	Upper gnathion–aural depth	None
obi-sn (r&l)	Mid-face depth (otobasion inferius-subnasale)	Lower subnasale-aural depth
obi-gn (r&l)	Lower face depth (otobasion inferius-gnathion)	Lower gnathion-aural depth

The table lists and explains the most used facial asymmetry measurements. Paired anthropometric linear measurements obtained from the profile and their synonyms in different sources are given

the midline (Fig. 33.8). Anthropometric measurements obtained from frontal facial images for asymmetry analysis are given in Table 33.3. In addition, surface measurements obtained from each hemiface are also used in the analysis of asymmetry (Farkas 1981). These measurements are given in Table 33.4. Special measurements used in facial asymmetry analysis are summarized in Table 33.5 (Kolar and Salter 1997).

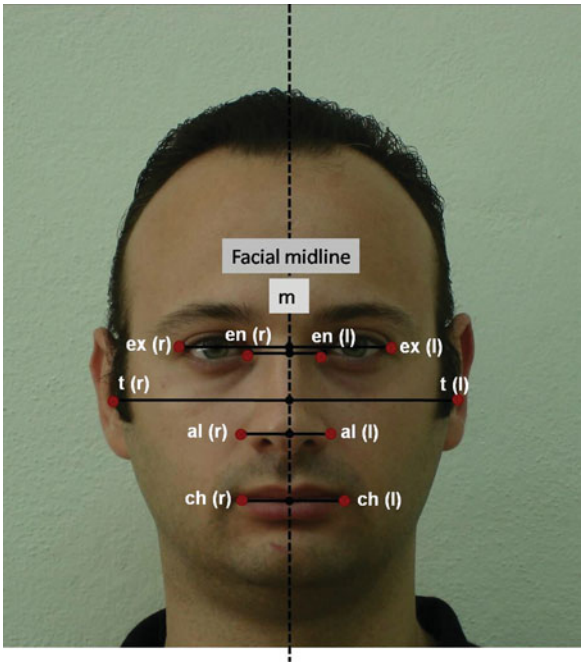


Fig. 33.8 Anthropometric measurements of facial asymmetry. Frontal facial photograph: m: facial midline (illustrated by dashed line) anthropometric facial soft-tissue landmarks for facial measurements: *ex*: exocanthion, *en*: endocanthion, *t*: tragion, *al*: alare, and *ch*: cheilion) Anthropometric measurements: en-m (r&l), ex-m (r&l), t-m (r&l), al-m (r&l), and ch-m (r&l)

Table 33.3 Anthropometric measurements obtained from frontal facial images

Landmarks	Linear measurements
en-m(r&l)	Endocanthion to facial midline
ex-m (r&l)	Exocanthion to facial midline
t-m(r&l)	Tragion to facial midline
al-m(r&l)	Alare to facial midline
ch-m(r&l)	Cheilion to facial midline

Measurements obtained from right and left hemifaces according to a certain facial midline

Table 33.4 Surface measurements

Landmarks	Linear measurements-surface
t-gn surf (r&l)	Lower-third face half arc/mandibular half arc
obi-gn surf (r&l)	Lower face half arc/lower gnathion-aural surface
obi-sn surf (r&l)	Mid-face half arc/lower subnasale-aural surface
t-ch surf (r&l)	Mid-cheek half arc/labio-aural surface
t-g surf (r&l)	Supraorbital half arc
t-sn surf (r&l)	Middle-third face half arc/maxillary half arc

Surface measurements from both hemifaces for facial asymmetry

Table 33.5 Special measurements used in facial asymmetry analysis

Landmarks	Special measurements
n-prn (nasion-pronasale)	Nasal bridge deviation
sn-prn (subnasale-pronasale)	Collumella deviation
ch-ch (cheilion-cheilion)	Labial fissure inclination
en-en (endocanthion), ex-ex (exocanthion), sbal-sbal (subalare), and ch-ch (cheilion)	Vertical landmark dislocation
prn (pronasale), sn (subnasale), and gn (gnathion)	Facial midline deviation

Other special measurements used in the analysis of the facial asymmetry

33.5 Applications to Other Areas of Health and Disease

The symmetric appearance of the face is an indication of health and attractiveness. Even a mild asymmetry can easily be noticed. An esthetic symmetric appearance is one of the main goals of plastic surgeons and orthodontists, within the treatment. Therefore, the evaluation of facial asymmetry is important for esthetic and orthodontic surgery. Another field in which facial asymmetry is taken into consideration is facial growth. Some authors indicated that asymmetric appearance of the face changes with age (Melnick 1992). Melnick showed that the side of mandibular dominance was a function of age: at 6 years, the left side was the largest, whereas, at 16 years, the right side was dominant in boys; the right side was dominant at 12 years in girls (Melnick 1992). It will be important to study asymmetry levels during certain age periods in terms of both acquiring information on the etiology of asymmetry and the planning of the treatment. Yet, there is an asymmetry in craniofacial anomalies accompanied by dysmorphology. Symmetry analysis of the face is helpful in the anthropological evaluation of dysmorphology. Regarding Shaner et al. (2000), considering that the facial asymmetry degree is higher in syndrome-effected individuals than in normal individuals, the obtained results may be helpful to detect the syndrome in some uncertain patients, if such a difference is accurate. Except for the congenital syndromes, other congenital anomalies, such as hemifacial microsomia, plagiocephaly, and cleft lip/palate; developmental anomalies, such as facial hemiathrophy (Parry–Romberg syndrome); and some acquired pathologies, such as condylar trauma and degenerative joint diseases (especially temporomandibular joint), are accompanied by facial asymmetry. The Parry–Romberg syndrome is a good example of a group of diseases accompanied by facial asymmetry. It is an acquired progressive hemifacial atrophy characterized by atrophy of subcutaneous fat and bone structure of unknown pathogenesis. Usually, the left side is affected rather than the right side. It is generally hard to determine a facial midline, according to the deviation in the facial midline structures, due to the loss of soft and bone tissues on one hemiface. It is important to make an objective determination of the facial asymmetry in terms of the accurate evaluation of the response given to the treatment applied in order to correct the asymmetry in this pathology and other similar pathologies.

Summary Points

- Facial asymmetry is a common finding in healthy subjects and in esthetically pleasing faces.
- No consensus exists in the literature regarding the degree, side, and spatial localization of facial asymmetry.
- Standardization of method, accurate identification of landmarks to be used in the measurements, and accurate determination of facial midline are crucial in facial asymmetry analysis.
- Anthropometric analysis of facial asymmetry is based on the comparison of homolog measurements that are obtained separately from the right and left hemifaces.
- Different anthropometric measurements have been used by various authors to determine facial asymmetry.

Key Features

Key features of facial asymmetry.

1. Anthropometric methods as well as other methods are used in the analysis of facial asymmetry.
2. Anthropometric measurements can be obtained by using both 2D and 3D images.
3. The measurements of healthy individuals are important for the normal asymmetry value assessed within the normal limits.
4. Different facial midline and paired landmarks used in the analysis of facial asymmetry and different results have been reported.
5. Studies of asymmetry in healthy individuals are emphasized regarding the issue of which side has dominancy, and it was reported that right side is more dominant.
6. In recent years, analysis of facial asymmetry was carried out by using a new method called EDMA shape analysis method.

Different methods used for facial asymmetry analysis and their results

Acknowledgment We would like to thank Dr. Ilker Ercan for statistical support.

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Chapter 34
Periorbital Anthropometric Measurements

Ümit Beden and Matej Beltram

Abstract Periorbital anthropometric measurements are important in defining cosmetic, pathologic and ethnic variations. In this term, assessment of periorbital landmarks is categorized into three subclasses: periorbital soft tissue, bony orbit, and ocular projection. Measurements of periorbital soft tissue include position of eyelids, height of eyelid skin crease and eyebrows, palpebral slant angle, position of the canthal commissura, epicanthal folds, and horizontal and vertical palpebral apertures. Additionally, margin reflex distances, which reflect eyelid position relative to the eye globe, are included in most cases. Function of the levator palpebralis and its indirect indicator, margin-limbal distance, are other parameters involved in evaluation of periorbital soft tissue. The bony orbit is the socket that encompasses the extra ocular muscles, and the eye with its appendages. Its shape and dimensions are noteworthy in many congenital and traumatic craniofacial malformations. In this respect, interorbital distance, interorbital angles, inter-canthal distances (between both medial and lateral canthi), and interpupillary distance are included during evaluation of the subjects. Ideally, assessment of bony orbit requires imaging techniques. The last parameter of the periorbital anthropometry, the ocular projection, is one of the most widely used parameters in diagnosis of orbital disorders. It reflects the intraorbital volume to content relationship. It is especially significant in orbital tumors and Graves' orbithopathy.

Abbreviations

HPA	Horizontal palpebral aperture
LCT	Lateral canthal tendon
VPA	Vertical palpebral aperture
MLD	Margin – limbal distance
MRD	Margin – reflex distance
MRD-1	Margin – reflex distance of the upper eyelid
MRD-2	Margin – reflex distance of the lower eyelid
IICD	Inner intercanthal distance
OICD	Outer intercanthal distance
IPD	Interpupillary distance

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_34,

34.1 Introduction

Having both cosmetic and functional relevance, the periorbital area is one of the most important regions in ophthalmic, reconstructive, plastic surgery and anthropometric evaluation. The structures that form the periorbital area, such as bony orbit, eyelids, canthal tendons, and eyebrows, are usually accepted to be the major landmarks in recognition of the sense of beauty and racial decent because interracial variation is usually most prominent in the periorbital area (Kunjur et al. 2006). In terms of periorbital anthropometric measurements, various dimensions are proposed hitherto (Figs. 34.1–34.4, Table 34.1), and, in clinical practice, it is usually not practical to address all these dimensions at once which mostly requires distinct software or photography (Gonzales et al. 2005). Nevertheless, any specialist interested in periorbital anthropometry in health and disease should have a sense of these dimensions and be competent in evaluating periorbital relations.

The structures that form the periorbital region can be subdivided into three groups: periorbital soft tissue, the bony orbit, and the ocular projection. In this chapter, we will give detailed information for evaluation and assessment of these dimensions individually.

34.2 Periorbital Soft Tissue

Eyelids, canthal tendons, and canthal commissura

Eyelids are composed of an anterior and posterior lamella. The anterior lamella is composed of skin and orbicularis oculi muscle. The posterior lamella is composed of a tarsal plate and a smooth muscle of Mullers, lined posteriorly by the mucosal membrane of conjunctiva. The firmness of the eyelids is supplied mainly by the tarsal plates that are anchored to the medial and lateral bony orbit by corresponding canthal tendons (palpebral ligaments). Thus, both tarsal plates and canthal tendons are necessary to maintain the horizontal stability of the eyelids.

Tarsal plates measure 10–12 mm vertically in the upper eyelid, and 3–4 mm in the lower eyelid. At the medial and lateral junctions of upper and lower eyelids, the superior and inferior limbs of canthal tendons join to form a canthal commissura. Thus, each eye has a medial and lateral canthal commissura. The medial and lateral commissura of one eye are aligned vertically with those of the

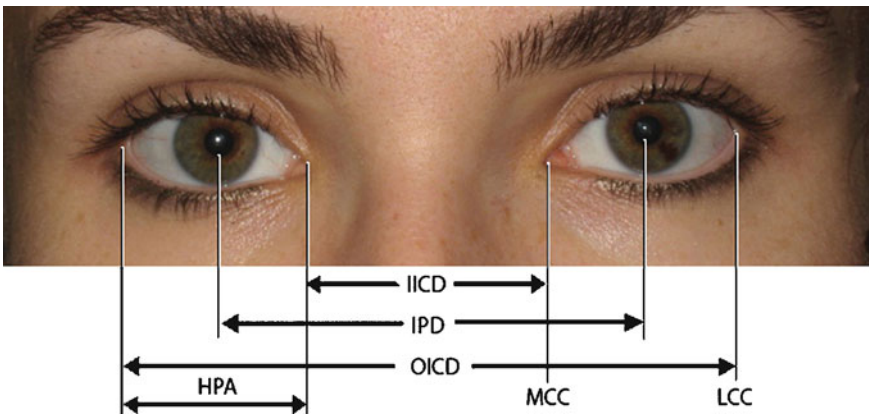

Fig. 34.1 Inner Intercanthal distance *(IICD)*, interpupillary distance *(IPD)*, outer intercanthal distance *(OICD)*, horizontal palpebral aperture *(HPA)*, medial canthal commissura *(MCC)*, and lateral canthal commissura *(LCC)*

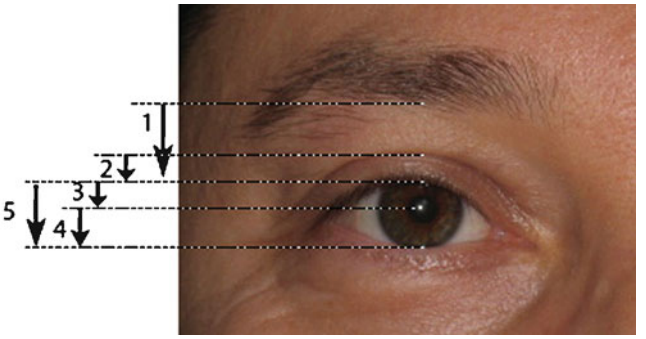

Fig. 34.2 Eyebrow height *(1)*, pretarsal skin height *(2)*, margin-reflex distance-1 *(3)*, margin-reflex distance-2 *(4)*, vertical palpebral aperture *(5)*

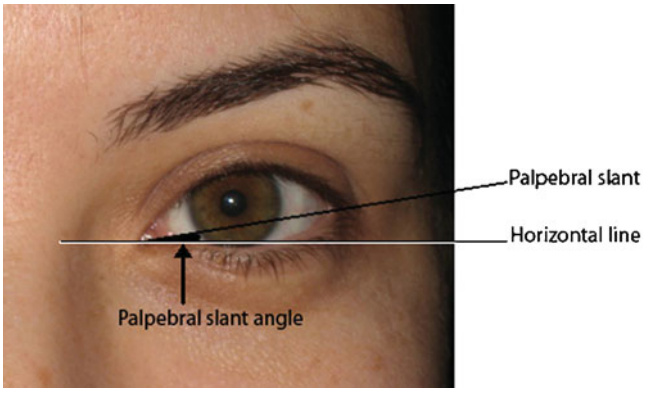

Fig. 34.3 Palpebral slant and palpebral slant angle

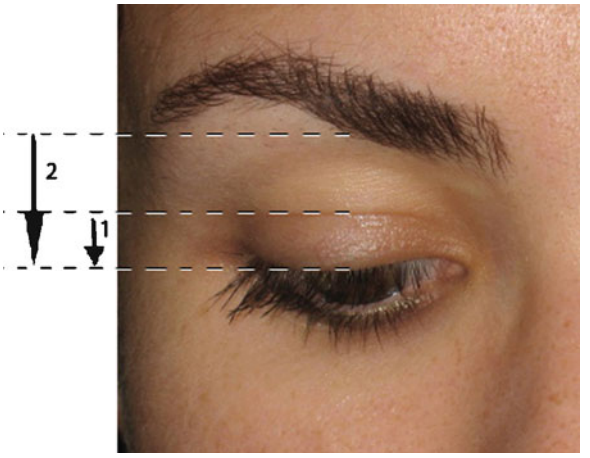

Fig. 34.4 Upper eyelid crease height *(1)*, upper lid skin distance *(2)*

Table 34.1 Description of parameters involved in periorbital anthropometric evaluation

Palpebral slant	An imaginary line connecting medial and lateral commissura of the same eye
Palpebral slant angle	The angle between palpebral slant and an imaginary horizontal line
Horizontal palpebral aperture	Distance between medial and lateral canthi
Vertical palpebral aperture	Distance between upper and lower eyelid in gaze of primary position of gaze
Levator function	Upper eyelid margin excursion from upgaze to downgaze
Margin–limbal distance	Distance from lower limbus (6 o'clock position) to the lower margin of the upper eyelid in upgaze
Margin reflex distance	Distance between eyelid margin and central pupillary light reflex
Margin reflex distance – 1	Margin reflex distance of the upper eyelid
Margin reflex distance – 2	Margin reflex distance of the lower eyelid
Upper eyelid crease	Line that is formed by levator aponeurosis insertion to the pretarsal skin, separating the lower pretarsal skin from the higher preseptal skin
Upper eyelid crease height	Distance between lower margin of the upper eyelid and eyelid crease line when it first appears as the patient starts to look up from downgaze
Epicanthus	Presence of a skin fold covering the medial canthus
Epicanthus tarsalis	Epicanthus involving the upper eyelid
Epicanthus palpebralis	Epicanthus involving both eyelids
Epicanthus inversus	Epicanthus involving the lower eyelid
Epicanthus superciliaris	Epicanthus involving the eyebrow
Inner intercanthal distance	Distance between the inner canthi of both eyes
Outer intercanthal distance	Distance between the outer canthi of both eyes
Interpupillary distance	Distance between pupils of the right and left eye
Eyebrow height	Distance between lower borders of the eyebrow and the upper eyelid when the eyes are open
Upper lid skin distance	Distance between lower borders of the eyebrow and the upper eyelid in downgaze
Interorbital distance	Distance between both medial walls of both orbits
Ocular projection	Distance between the corneal apex and the lateral orbital rim on side view

other eye. However, medial and lateral commissura of the same eye are not aligned vertically, as the lateral commissura is located superiorly to the medial commissura. Thus, an imaginary line connecting the medial and lateral commissura of the same eye is usually not horizontal, and is called palpebral slant (Fig. 34.3). The angle between this imaginary line and a horizontal line determines the palpebral slant angle (Fig. 34.3). The palpebral slant is usually directed upward laterally, as the lateral canthi are located about 1.5–2 mm superior to the medial canthi (van den Bosch et al. 1999; Gonzales et al. 2005; Beden et al. 2007). It is slightly higher in females (van den Bosch et al. 1999). This slant is increased in the Mongolian race, and it is called *mongolian slant* when the lateral canthi are located more superiorly. Otherwise (when the lateral canthi are located lower than the medial canthi), the palpebral slant is directed downward, and this configuration is called *antimongolian slant*. The palpebral slant is among the most important and useful entities in the detection of many traumatic and congenital anomalies, such as Down syndrome. It is also one of the most readily perceived characteristics of facial identity as well as racial descent. It is increased in Orientals, and tends to decrease with age. The palpebral slant angles reported in the literature are given in Table 34.2.

The lateral canthal tendon (LCT) has both static and dynamic functions. Among its static functions are: converting the circular contraction of the orbicularis to the horizontal-eyelid-converting vector, and being the insertion point of the Lockwood ligament, the lateral horn of the levator palpebralis muscle, the lateral check ligament of the lateral rectus muscle, and preseptal orbicularis muscles (Bedrossian 2002; McCord et al. 2003; Beden et al. 2007). A dynamic feature of the lateral canthal

Table 34.2 Palpebral slant angles reported in the literature

Population	Palpebral slant angle	References
African Americans younger than 45 years	3.00°	Odunze et al. (2008)
African Americans older than 45 years	1.15°	
White adults younger than 45 years	2.30°	
White adults older than 45 years	1.30°	
Asian males	7.9° ± 2.4°	Park et al. (2008a)
	8.5° ± 2.0°	Park (2007)
Asian females	8.8° ± 2.3°	Park et al. (2008a)
	8.8° ± 2.5°	Park (2007)

Table 34.3 Horizontal palpebral aperture measurements reported in the literature

Population	HPA (mm)	References
Black adult male	32.34	Barretto and Mathog (1999)
White adult male	29.51	
Black adult female	31.46	
White adult female	29.40	
White adults	28.98	Beden et al. (2007)
White adults	30.00	Ozturk et al. (2006)
Korean adult male	26.8 ± 1.9	Park et al. (2008a)
Korean adult female	26.1 ± 1.9	
North American white adults	31.0	Farkas et al. (1985)
Young adult white males	32.6	Bozkir et al. (2003)
Young adult white females	31.0	
White adult females	26.7	van den Bosch et al. (1999)
White adult males	27.2	
White newborns	18.5	Jones et al. (1978)
White newborns	17 – 20.7 (17.02)	Ozkagnici et al. (2001)
Neonates (all races)	16 – 30	Fuchs et al. (1980)
Hispanics neonates	19.5	
Black neonates	20	
White neonates	18.5	

tendon is provided by horizontal movement of the lateral canthus, and supposedly contributes to globe protection, non-verbal communication and preservation of the lateral visual field (Beden et al. 2007). The reported vertical width of the lateral canthal tendon is about 6.6 mm, with a horizontal length of 7.5–10.6 mm (Gioia et al. 1987; Beden et al. 2007). It inserts 1.5 mm posterior to the inner margin of the lateral orbital rim (Gioia et al. 1987; Beden et al. 2007). Involutional descent of the lateral commissura is a well-known feature, which results in palpebral slants directed downward with advancing age (Beden et al. 2007; Odunze et al. 2008).

Horizontal palpebral aperture (HPA) is the distance between the medial and lateral canthal commissura (Fig. 34.1). It tends to increase in the first two decades of life (Fox 1966; Ozturk et al. 2006). It increases by 10% between ages 12 and 25 years, and decreases after 45 years of age (van den Bosch et al. 1999). There are controversial reports about involutional decrease in HPA. Bosch reported that it decreases with age, and this decrease is due to the laxity of the LCT (van den Bosch et al. 1999). In another study, however, involutional decrease in HPA could not be confirmed (Beden et al. 2007). HPA was rather reported to stay constant in spite of increasing LCT/HPA ratio with advancing age (Beden et al. 2007). HPA is 28–30 mm long and the dimensions reported in the literature are given in Table 34.3.

Vertical palpebral aperture (VPA) is the distance between the upper and the lower eyelid in primary position of gaze (Fig. 34.2). The upper eyelid covers 1.5–2 mm of the limbus at 12 o'clock, and the lower lid barely touches the limbus at 6 o'clock. The higher point of the upper eyelid is usually slightly medial to the center of the pupil, and the lower point of the lower eyelid is usually slightly lateral to the center of the pupil. Normal VPA measures 9–11 mm, and is larger in women than in men. Peak values of approximately 8–13 mm were reported for blacks and whites in the Western population (Fox 1966; Ozturk et al. 2006; Beden et al. 2007; Park et al. 2008a). It increases until the second decade, and then remains constant until the fifth decade.

The average VPA distance is 9.6 mm for white adults (9.7 mm in males, 9.9 mm in females) (Ozturk et al. 2006; Beden et al. 2007). Values of 10.3 and 10.4 mm in young adult white males and females were also reported (Bozkir et al. 2003). It is reported to be 7.8–8.2 mm in Korean adult male subjects, and 8.2–8.5 mm in female subjects (Park et al. 2008a). It is 4.87 mm in white newborns (Ozkagnici et al. 2001).

Function of the levator palpebrae muscle is directly reflected to the upper eyelid, and measured as the excursion of the lower margin of the upper eyelid, from downgaze to upgaze. Levator function is essential in determination of surgery type for blepharoptosis repair. While measuring levator function, the physician applies gentle pressure on the eyebrow to prevent transfer of frontalis muscle action to the upper eyelid. Normally, levator function is between 12–18 mm in white adults and 8–13 mm in Asians (Bedrossian 2002; Park et al. 2008a).

Margin–limbal distance (MLD) is another way to predict the levator palpebralis muscle function. It is the distance from lower limbus (6 o'clock position) to the lower margin of the upper eyelid in upgaze. This measurement is not frequently used in routine practice, and normative data have not been established so far. However, when levator resection is planned for treatment of blepharoptosis, MLD of the ptotic eye is subtracted from that of the other (healthy) eye, and this difference is used to determine the amount of levator muscle resection in blepharoptosis surgery.

Margin reflex distance (MRD) is the distance between eyelid margin and central pupillary light reflex in primary position of gaze. MRD-1 is the measurement of the upper eyelid-reflex distance, and MRD-2 is the lower eyelid-reflex distance (Fig. 34.2). Thus, MRD-1 plus MRD-2 is equal to the vertical palpebral aperture size (Fig. 34.2).

MRD-1 is the distance between lower margin of the upper lid and light reflex on the cornea in primary gaze (Fig. 34.2). It is directly related to the resting position of the upper eyelid and palpebral aperture. Normally, the upper eyelid is set 1–2 mm inferior to the superior limbus and the MRD-1 is usually 3.5–4.5 mm (Beden et al. 2007).

MRD-2 is the distance between the upper margin of the lower lid and the light reflex on the cornea in primary gaze (Fig. 34.2). Put another way, it is the difference between vertical palpebral aperture and MRD-1 (Fig. 34.2). Beden reported MRD-2 to be 5.63 mm on average for white adults (Beden et al. 2007).

Upper eyelid crease is the line that is formed by levator aponeurosis insertion to the pretarsal skin (Fig. 34.4). It is the landmark separating lower pretarsal skin from higher preseptal skin. It is also an important landmark because of being the incision site in most upper eyelid or orbital surgeries. It is observed in most Western population, and in 30% and 41% in Asian males and females, respectively (Park et al. 2008a, b).

The distance between lower margin of the upper eyelid and eyelid crease line is the eyelid crease height (Fig. 34.4). It is measured in downgaze so that both the eyelid margin and the eyelid crease are clearly visible. In primary gaze, however, the skin above the eyelid crease

tends to sag downward, rendering visible eyelid crease height smaller. In that case, the distance measured is called pretarsal skin height (Fig. 34.2). Pretarsal skin height is 3.0 mm in females and 2.1 mm in males (van den Bosch et al. 1999). It is 1.7 mm in the fist decade of life in whites, and it increases to 2.3 mm in the third to fourth decade, and gradually decreases thereafter (Cartwright et al. 1994).

Measurement of eyelid crease is usually not consistent because the crease position is subject to change with gaze position, levator tonus, downward sagging of preseptal skin, and by the pressure applied to preseptal skin to observe the eyelid crease line during measurement. It should preferably be measured when it first appears as the patient starts to look up from downgaze (Fig. 34.4). It is 2–4.9 mm in the first decade of life, and it increases to 7.1 mm in adult life (Cartwright et al. 1994; Ozkagnici et al. 2001). Values reported in the literature vary between 5.9 and 11 mm in different studies (Cartwright et al. 1994; Ozturk et al. 2006; Park et al. 2008a). Although mean values of 7–8 mm for Western males, and 7–12 mm for Western females are usually accepted, recent studies have reported the effect of gender to be insignificant on eyelid crease position (Cartwright et al. 1994; Ozturk et al. 2006). When present, it is usually located lower in Asian subjects. Reported values are 6.6 and 6.5 mm in male and female Asian subjects, respectively (Park et al. 2008a).

Epicanthus (epicanthal fold) is the presence of a skin fold covering the medial canthus. It usually appears between the third and the sixth month of gestation in every race, and disappears before birth. It is called epicanthus tarsalis when this extra skin fold is in the upper eyelid, epicanthus superciliaris when it is located higher through the eyebrow, epicanthus inversus when it is in the lower eyelid, and epicanthus palpebralis when it involves both eyelids (Johnson's classification). Although it is said that only the Mongolians retain it after birth, it was detected in 42.2–50% in Koreans (Park et al. 2008a). It is present in more than 90% of both male and female subjects younger than 10 years, and it disappears gradually with age, presenting in only 10% of those in their fifties or older (Park et al. 2008a). Regarding the type of epicanthus, it is epicanthus tarsalis in 50.5%, epicanthus palpebralis in 25.7%, epicanthus superciliaris in 21.4%, and epicanthus inversus in 2.4% (Park et al. 2008a).

Intercanthal and interpupillary distances are distances between inner canthi (inner intercanthal distance – IICD), outer canthi (outer intercanthal distance – OICD), and pupils (interpupillary distance – IPD) (Fig. 34.1). They are important in detection of congenital and traumatic craniofacial anomalies. Although there are controversial reports in the literature about the effect of age and sex on these parameters, IICD and OICD usually stabilize after the first and second decades, respectively (Freihofer 1980; Singh and Banerjee 1983; Fledelius and Stubgaard 1986; Osuobeni and al-Gharni 1994; Ozturk et al. 2006).

Distance between both the medial canthi is called inner canthal distance (IICD) (Fig. 34.1). It should be noted that it is not the distance between both bony orbits, as soft tissue is taken as reference point. This distance is affected by the length of medial canthal ligament, which anchors tarsal plates to medial orbital wall. It is called telecanthus when this distance is increased. Telecanthus is primary when IPD and interorbital distances are normal, and secondary when IPD and interorbital distances are increased (i.e., hypertelorism) (Murphy and Laskin 1990).

Interpupillary distance is the distance between both pupils (IPD) (Fig. 34.1). Practically, it is measured as the distance between light reflexes of both eyes in primary position of gaze. As the light reflex is not a stationary point, this may lead to inaccurate measurements, and one can also measure the same distance as the distance between either the nasal or the temporal limbus of both eyes.

Table 34.4 IICD and IPD reported in the literature

Population	IICD (mm)	IPD (mm)	References
Black males	35.7	66.3	Murphy and Laskin (1990)
Black females	33.1	62.6	
White adults	32.1	60.83	Beden et al. (2007)
White adult males	30.7	60.6	Ozturk et al. (2006)
White adult females	30.2	60.1	
Black males	35.8	68.97	Barretto and Mathog (1999)
Black females	34.18	65.93	
White males	35.53	65.15	
White females	32.95	61.47	
Asian males	35.3–38.8	59.9–69.4	Park et al. (2008a)
Asian females	33.4–38.3	63.2–66.6	
Young adult white males	30.7	63.9	Bozkir et al. (2003)
Young adult white females	30.0	60.8	

According to accumulated data, IICD is 32±3 mm and IPD is 63±3mm (Murphy and Laskin 1990). IICD and IPD values reported in the literature are given in Table 34.4.

The distance between both outer canthi is outer intercanthal distance (OICD) (Fig. 34.1). Practically, it is the sum of HPA on both site and inner intercanthal distance, and it is not as popular as inner intercanthal distance and interpupillary distance in clinical practice. It is reported to be 91.3–95.9 mm in white males, and 90.1–92.0 mm in white females (Bozkir et al. 2003; Ozturk et al. 2006).

Eyebrows (the foundation of human expression) should be included in any periocular assessment because of their effect on eyelid position. While strongly affected by age and sex, eyebrows are usually located on the superior orbital rim in males, and slightly higher in females. The lateral end of the eyebrow is at the same line, with or slightly superior to its medial end, and 10 mm above lateral orbital rim. The brows' higher location and steeper temporal arching in females is proposed to be one of the most important landmarks that lend to esthetics. Although this is a widely accepted aim for upper face rejuvenation surgery, quantitative assessment of eyebrow height and position is not well established in the literature. Reports of eyebrow position are controversial because of racial differences and measurement technique discrepancies. They are usually inaccurate, especially if the patient plucks her eyebrow, has ptosis, and had botulinum toxin injection. Eyebrow position easily changes with gaze position and frontalis muscle contraction. Brow height is measured as the distance between lower borders of eyebrow and upper eyelid when the eyes are open (Fig. 34.2). When this distance is measured as the eyes are closed, or in downgaze, it is called upper lid skin distance (Fig. 34.4).

Cartwright reported eyebrow height to be 5.8–7.1 mm in white adults (Cartwright et al. 1994). Ozturk, however, reported an eyebrow height of 9.7–9.9 mm (Ozturk et al. 2006). According to Park, it is 12.4±2.4 mm in male subjects, and 12.0±1.9 mm in female subjects, in Koreans Park et al. 2008a). It is 7.18 mm in white newborns, and 11.8 and 9.4 mm in white females and males, respectively (van den Bosch et al. 1999; Ozkagnici et al. 2001).

Brow descent is a well-known entity, which is the main reason for most facial rejuvenation surgeries. It is due to progressive laxity of scalp and forehead tissue. Brow descent (ptosis) is defined as presence of brow level below the superior orbital rim. It is usually more pronounced laterally because the medial part of the brow has strong attachments to the orbital rim. Odunze reported that this descent of brow is noticeable in the third decade in whites, which is much earlier than in African Americans (Odunze et al. 2008).

34.3 Bony Orbit

The bony orbit has a pyramidal shape. The orbital rim is rounded and thicker than the orbital walls. It has an incomplete circular shape forming a spiral medially. The ends of the spiral represent the anterior and posterior lacrimal crest, which are the boundaries of the lacrimal fossa.

The distance between both medial orbital walls is the interorbital distance. Hypertelorism is an increase in distance between both bony orbits, and hypotelorism is the opposite. True hyper- and hypotelorism are usually congenital, and they are usually associated with other cranial or midfacial anomalies (Murphy and Laskin 1990). Clinically, measurement of hyper- or hypotelorism is controversial because of soft tissue overlying the bony orbit. IPD is usually used instead of interorbital distance, and is a useful value in evaluation of distance between both orbits. Other techniques that can be used for hyper- or hypotelorism are plain radiography and CT. Radio-opaque markers can also be used to facilitate measurement on X-ray film (Murphy and Laskin 1990).

The medial orbital rim is located 20 mm anterior to the lateral orbital rim. Medial walls of the orbits are 25 mm apart, and parallel to each other. The lateral wall of one orbit is at 45 degrees to the medial wall of the same side, and at right angles to the lateral wall of the opposite side. The volume of the orbit is approximately 30 cm^3, with vertical and horizontal lengths of 30 and 40 mm, respectively. It has a depth of 40–45 mm, and largest coronal dimension of 1 cm posterior to the orbital rim.

34.4 Ocular Projection

Ocular projection is the distance between corneal apex and lateral orbital rim. This distance reflects the relationship between intraorbital volume and content. It is an important clinical entity in orbital diseases, craniofacial anomalies, Graves' ophthalmopathy, and periocular rejuvenation surgeries. It is called exophthalmos when this distance is increased, and enophthalmos when decreased. An exophthalmometer is any device that measures the ocular projection. Although it is possible to measure this distance with a ruler from lateral view, there are other techniques that are used for clinical purposes, such as Hertel's, Krahn, Luedde's, Carl Zeiss, Keeler, and Naugle exophthalmometer, as well as radiographic techniques and computerized tomography (Kim and Choi 2001; Kumari Sodhi et al. 2001; Segni et al. 2002; Vardizer et al. 2005). In spite of being criticized as inaccurate, Hertel's exophthalmometry is still the most frequently used method in proptosis evaluation. Values measured by imaging techniques (such as computerized tomography) are reportedly greater or lesser than those measured by Hertel's exophthalmometer (Kim and Choi 2001; Segni et al. 2002).

It is called comparative exophthalmos when ocular projection is detected to increase over a period of time, relative exophthalmos when more than 2 mm of asymmetry is detected between left and right eyes, and absolute exophthalmos when ocular projection is beyond the established normative upper limit, which is around 21 mm in most studies (Barretto and Mathog 1999). A gradual increase in the first decade of life is reported with values of 9.11 mm in the 3-year-old group, to 11.67 mm in the 10-year-old group (Nucci et al. 1989).

It is relatively easy to establish comparative and relative exophthalmos in clinical practice. Racial anthropometric differences, however, render establishment of absolute exophthalmos much more difficult, as a widely accepted upper limit is impractical. Hence, there are many studies in the literature trying to establish normative data of ocular projection for different populations. Ocular projection values reported in the literature are given in Table 34.5.

Table 34.5 Ocular projection values (Hertel readings) reported in the literature

Population	Hertel (mm)	Lower limit (mm)	Upper limit	Standard deviation	Sample size	References
Adult white male	17.00	11.7	22.3	2.65	65	Barretto and Mathog (1999)
Adult white female	15.98	11.5	20.4	2.22		
Adult black male	18.23	13.7	22.8	2.26	61	
Adult black female	17.27	14.4	20.2	1.44		
Adult white male	16.55	11.31	21.71	2.58	127	Migliori and Gladstone (1984)
Adult white female	15.46	10.74	20.80	2.33	200	
Adult black male	18.56	12.30	24.65	3.08	113	
Adult black female	17.90	12.60	23.04	2.57	241	
Adult white male	16.0	11.4	20.6	2.30	325	de Juan et al. (1980)
Adult white female	14.7	10.9	18.5	1.92		
Adult black male	17.9	13.2	22.6	2.86	402	
Adult black female	17.1	11.7	22.5	2.71		
Adult black males	18.20	12.3	24.14	2.97	309	Dunsky (1992)
Adult black females	17.46	12.2	22.74	2.64		
Adult white males	13.49	5	20	2.49	970	Beden et al. (2008)
Adult white females	13.27	5	21	2.40	1,507	
Adult white males	13.49	8	20	2.60	240	Bilen et al. (2007)
Adult white females	13.39	8	19	2.60	240	
White children	14.2	10	19.5	1.8	289	Kashkouli et al. (2003)
White teenagers	15.2	10	21.5	1.9	319	
White adults	14.7	9	21	2.3	455	
Adult Korean	15.03	10.90	18.50	1.65	135	Kim and Choi (2001)
Indian males	12.43	7	19	–	821	Kumari Sodhi et al. (2001)
Indian females	13.30	7	21	–	1679	
Adult white Dutch males	13.85	9	18	2.06	80	Mourits et al. (2004)
Adult white Dutch females	12.55	10	16	1.75	80	

Summary Points

- Periorbital anthropometric measurements are mandatory for cosmetic, pathologic, or ethnic evaluation.
- Periorbital evaluation involves measuring soft tissue, bony orbit, and ocular projection.
- Main landmarks in periocular soft tissue are eyelids with anchoring canthal tendons, eyebrows, and upper eyelid crease.
- Parameters of periorbital soft tissue involves position of eyelids, height of eyelid skin crease and eyebrows, palpebral slant angle, position of the canthal commissura, epicanthal folds, and horizontal and vertical palpebral apertures.
- Bony orbit is the socket that encompasses the extra ocular muscles, and the eye with its appendages.
- Measurements of the bony orbit are important in many congenital and traumatic malformations.
- Measurements of orbital parameters include: interorbital distance, interorbital angles, intercanthal distances (between both medial and lateral canthi), and interpupillary distance.
- Ocular projection reflects intraorbital volume to content relationship.
- It is one of the most significant parameters for orbital tumors and Graves' ophthalmopathy.

Table of key facts of periorbital anthropometry
Periorbital anthropometric measurements are mandatory for cosmetic, pathologic, or ethnic evaluation.
Periorbital evaluation involves measuring bony orbit, soft tissue, and ocular projection.
Main landmarks in periocular soft tissue are eyelids with anchoring canthal tendons, eyebrows, and eyelid crease.
Measurements of the bony orbit are important in many congenital and traumatic malformations.
Ocular projection reflects the relationship between the intraorbital volume and content. It is one of the most significant parameters for orbital tumors and Graves' ophthalmopathy.

Practical Methods and Technique

Palpebral slant angle

Take a picture of the patient's face. Have a hard copy and draw a line passing through medial and lateral canthi of one eye (palpebral slant). Draw another line passing through both medial canthi of both eyes (horizontal line). Measure the angle between two lines at the intersection point in the medial canthus. You can also use a flat computer screen instead of a hard copy of the picture.

Horizontal palpebral aperture

Let the patient look straight ahead. Hold a ruler horizontally in front of his/her eye. Measure the distance between medial and lateral canthi..

Vertical palpebral aperture

Let the patient look straight ahead. Hold a ruler vertically in front of his/her eye. Measure the distance between upper and lower eyelid.

Levator function

Sit at the same level as the examinee. Let the patient look down. Put your thumb on his/her eyebrow to prevent frontalis muscle effect on the eyelid. Ask him/her to look upward. Measure upper eyelid

margin excursion from downgaze to upgaze. Repeat this maneuver a few times and take the average of two to three measurements.

Margin–limbal distance
Sit at the same level with the examinee, and let him/her look upward. Measure the distance from lower limbus (6 o'clock position) to the lower margin of the upper eyelid in upgaze.

Margin reflex distance
Sit at the same level as the examinee, and let him/her look straight toward a penlight. Measure the distance between the upper eyelid margin and the central pupillary light reflex and note it as MRD-1. Then, measure the distance between the lower eyelid margin and the central pupillary light reflex and note it as MRD-2.

Upper eyelid crease
Sit at the same level as the examinee, and let him/her look down. Ask him/her to look up slowly and note the skin crease on the upper eyelid when it first appears as the patient starts to look up from downgaze. Measure the distance between the lower margin of the upper eyelid and eyelid crease line.

Epicanthus
Epicanthus is noted if an extra skin fold covers the medial canthus. It is recorded as epicanthus tarsalis if the skin fold involves the upper eyelid, epicanthus palpebralis if the skin fold involves both eyelids, epicanthus inversus if the skin fold involves the lower eyelid, and epicanthus superciliaris if the skin fold involves the eyebrow.

Inner intercanthal distance
Let the patient look straight ahead. Hold a ruler horizontally in front of his/her eye. Measure the distance between inner canthi of both eyes.

Outer intercanthal distance
Let the patient look straight ahead. Hold a ruler horizontally in front of his/her eye. Measure the distance between outer canthi of both eyes.

Interpupillary distance
Hold a penlight to the patient's face and let him/her look straight ahead. Measure the distance between the pupillary light reflex of the right and left eye or the distance between the temporal limbus of the right eye and the nasal limbus of the left eye.

Eyebrow height
Let the patient look straight ahead. Hold a ruler vertically in front of his/her eye. Measure the distance between the lower borders of the eyebrow and the upper eyelid.

Upper lid skin distance
Let the patient look down. Hold a ruler vertically in front of his/her eye. Measure the distance between the lower borders of the eyebrow and the upper eyelid.

Ocular projection
Take a simple ruler, of transparent plastic preferably. Take your position laterally, at 90° to the examinee and palpate with a finger the lateral part of the orbital rim. Position the ruler horizontally and press it against the examinee's lateral orbital rim, at the height of the center of the eyeball. Read the distance on the ruler from the corneal apex to the lateral orbital rim.

*Measurement of ocular projection with an exophthalmometer is in the domain of a trained ophthalmologist.

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Chapter 35
Anthropometry of Eyelids

Dae Hwan Park and Chang Hyun Oh

Abstract The normal morphological and functional values of eyelids and orbits are varied according to race, sex, and age. Unfortunately, there is a paucity of information related to these values. The authors quantified and statistically analyzed nine morphologic and functional values in 234 male and 264 female. Among adults, the mean value for the palpebral fissure was 27.0 ± 1.8 mm in males and 26.8 ± 1.7 mm in females in the horizontal dimension and 8.0 ± 1.0 mm in males and 8.2 ± 1.1 mm in females in the vertical dimension. The average slant of the palpebral fissure was 7.9° ± 2.4° in males and 8.8° ± 2.3° in females and the average height of the opened upper eyelid was 12.4 ± 2.4 mm in males and 12.0 ± 1.9 mm in females. The average height of double fold in the closed eye was 6.6 mm in males and 6.5 mm in females, and the average intercanthal distance was 38.4 ± 3.0 mm in males and 38.2 ± 2.8 mm in females. The average interpupillary distance was 64.6 ± 2.9 mm in males and 63.6 ± 2.9 mm in females. The peak level of growth in the vertical dimension of the palpebral fissure was reached between ages 10 and 13 years, that of the intercanthal distance was between ages 14 and 16 years, and that of horizontal dimension of the palpebral fissure was between ages 17 and 19 years.

35.1 Introduction

Eyelids show significant differences in morphology and structure with age and race. In case of unilateral ptosis surgery, the size and shape of the normal eyelid might be used as a guide for operation. However, for bilateral operation, normal anthropometric values become important. Therefore, it can be said that normal values of eyelids by age and sex are most important in blepharoplasty and reconstruction. In this context, the authors were required to measure eight items including the horizontal dimension of the palpebral fissure (HDPfi) the vertical dimension of the palpebral fissure (VDPfi) and the slant of the palpebral fissure, applied to 498 male and female subjects between the age of 6 and 80 years, and to statistically analyze them according to age and sex.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_35,

35.2 Methodological Consideration

For measurements, we had the subject sit opposite an examiner at the same eye level and gaze at the center of the examiner's nasal muscle. With the McCoy facial Trisquare and a millimeter-gauged ruler, we measured the horizontal and vertical dimensions of the palpebral fissure, the height of open upper eyelid, the fold type and height, the incidence and type of epicanthus, the intercanthal distance, and the interpupillary distances. For accuracy, we took two measurements at an interval of 5 min, and recorded the mean values. To measure the slant of the palpebral fissure, a 105-mm camera was used at 1-m distance, to photograph both eyes clearly. We developed the photograph and measured it using a graduator.

We statistically analyzed measured results by age and sex. Considering that physical growth peaks during the teen years, we subcategorized it into three groups for statistical analysis, and categorized other age groups by 10-year intervals. For the statistical processing, all measured values are represented by mean ± SD, and the *t*-test was performed for the significance test with a less than 5% of significance level. No correction was made for multiple testing.

We subdivided the upper eyelid into eight items, and analyzed each item according to age and sex. In particular, we performed the *t*-test for two neighboring age groups by item-wise, verified significance, and compared mean values from the point of the completion of growth ($p < 0.05$).

35.3 Horizontal Dimension of the Palpebral Fissure

For the horizontal dimension of the palpebral fissure, Adler reported a mean value of 25 mm (Alder 1975), and Farkas et al. reported a mean value of 31.0 mm, in adults (Farkas et al. 1985). In Asians, Baek et al. reported a mean value of 29.1 mm in adults (Baek et al. 1995). Park et al. reported mean values of 29.7 mm in adult male subjects and 28.4 mm in adult female subjects (Park et al. 1990). Cho et al. reported mean values of 34.2 mm in male subjects and 33.4 mm in female subjects (Cho et al. 1993). This article showed slightly lower values than others, with a mean of 27.0 mm in adult male subjects and a mean of 26.8 mm in adult female subjects; and male subjects showed greater values than female subjects ($p < 0.05$) without significant difference from the other subjects with 27 and 30 mm values (Fig. 35.1). Values reached the peak level of growth at 10–13 years of age, and remained stationary and gradually decreased as subjects approached their fifties ($p < 0.05$).

35.4 Vertical Dimension of the Palpebral Fissure

For the vertical dimension of the palpebral fissure, Moses reported peak values of approximately 8–10 mm (Moses 1987) without a significant difference between blacks and whites. Duke-Elder reported a mean value, in the Western population, of approximately 9–13 mm (Duke-Elder 1916). Jung and Hong reported mean values of 8.2 mm in Korean adult male subjects and 8.5 mm in female subjects (Jung and Hong 1974), and Cho et al. reported values, in Asian male and female subjects, of 8.2 and 8.5 mm, respectively, at 18 years of age (Cho et al. 1993). This article also reported values of 8.0 mm in male subjects and 8.2 mm in female subjects, with no significant difference according to sex (Fig. 35.2). These values are similar to the figures reported by Cho et al. and Moses (Cho et al. 1993; Moses 1987). Noh and Choi reported that the vertical dimension of the

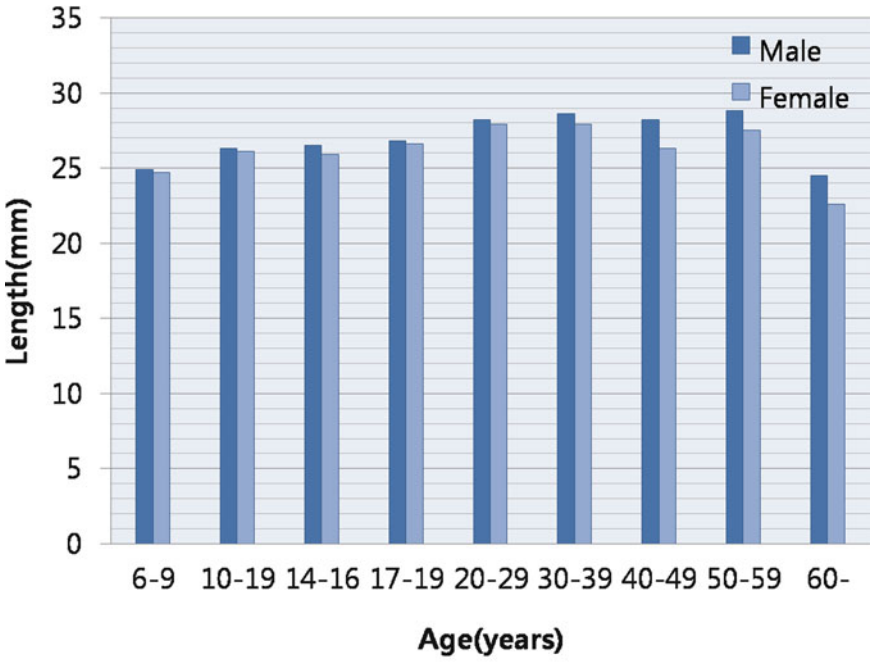

Fig. 35.1 Horizontal dimension of the palpebral fissure. The horizontal dimension of the palpebral fissure was 27.0 ± 1.8 mm in male subjects and 26.8 ± 1.7 mm in female subjects

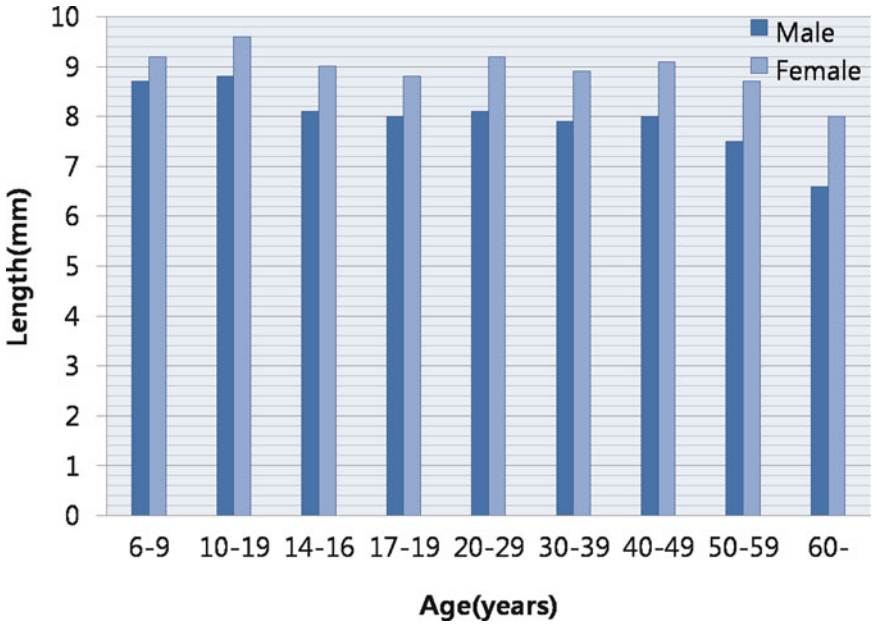

Fig. 35.2 Vertical dimension of the palpebral fissure. The vertical dimension of the palpebral fissure was 8.0 ± 1.0 mm in male subjects and 8.2 ± 1.1 mm in female subjects

palpebral fissure reached the peak value at 10 years, and showed no significant difference according to age subsequently (Noh and Choi 1981). However, this review showed that the vertical dimension of the palpebral fissure reached a specific level between 10 and 13 years of age and decreased gradually as subjects approached their fifties ($p < 0.05$).

35.5 Slant of the Palpebral Fissure

For the slant of palpebral fissure, Park et al. reported a mean value, in male and adult female subjects, of 9.5° and 10.6°, respectively, which appeared greater in male subjects than in female subjects (Park et al. 1990). This article also reported values of 8.4° in male subjects and 8.9° in female subjects, which appeared greater in female subjects than in male subjects ($p < 0.05$). Regarding the esthetic criteria, Adler suggested the same level of medial and lateral canthus at front gaze (Adler 1975). In terms of Western esthetic criteria, the lateral canthus lies slightly higher than the medial canthus, which is slightly low in the upper portion of the palpebral fissure. Park et al. reported that the slant of the palpebral fissure was a value of 8.8° (Park et al. 1990). In this review, which used a 105-mm lens to minimize distortion of photographs and maintained a 1-m distance between the camera and the examinee to prevent distortion; values of 8.4° in male subjects and 8.9° in female subjects were observed, in which female subjects showed a greater decline than male subjects. The slant of the palpebral fissure showed a peak level at 10–13 years of age. As the age increased, it showed a gradual decrease ($p < 0.05$) (Fig. 35.3).

35.6 Double Fold

A double fold is a crease which is generated when the levator palpebrae superioris is attached to pretarsal orbicularis and skin. It is observed in most Western female subjects and approximately 40% of Asian female subjects (Park and Na 1975). This article observed a double fold in 36.1%, slightly less than others. Regarding fold type, a single fold appeared in 68.9% of male subjects and 58.0% of female subjects. A double fold appeared in 30.5% of male subjects and 41.4% of female subjects, and a triple fold appeared in 0.6% of male subjects and 0.6% of female subjects. A single fold appeared more frequently in male subjects than in female subjects and vice versa with the double fold (Fig. 35.4). The size of double fold was 6.6 mm in male subjects and 6.5 mm in female subjects, with no significant difference according to sex.

35.7 Epicanthus

The epicanthus seemed to give an impression of upward slant of the palpebral fissure. It mostly appears between 3 and 6 months' gestation in the fetus in every race, and disappears before birth. However, it is said that only the Mongolians retain it after birth (Gifford 1928). Park et al. reported that the epicanthus was observed in about 45% of Asian male subjects and in approximately 62% of Asian female subjects. The younger the subjects, the higher the incidence with which it showed. The authors observed it in 51.0% of male subjects, in 49.0% of female subjects, and in 42% in total. Classified by

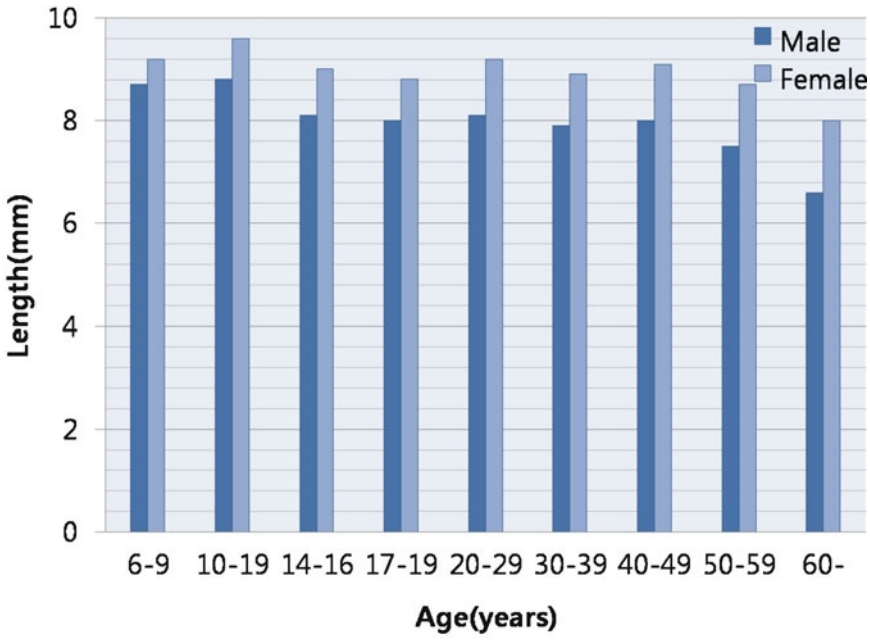

Fig. 35.3 Slant of the palpebral fissure. The slant of the palpebral fissure was 7.9° ± 2.4° in male subjects and 8.8° ± 2.3° in female subjects

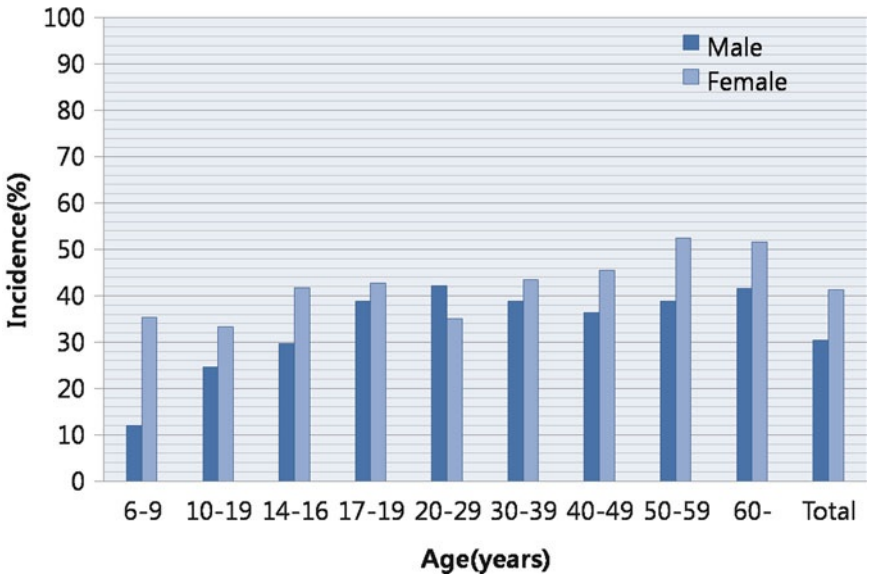

Fig. 35.4 Incidence of double fold. A double fold was found in 36.1%, in total, with a higher incidence in females (41.3%)

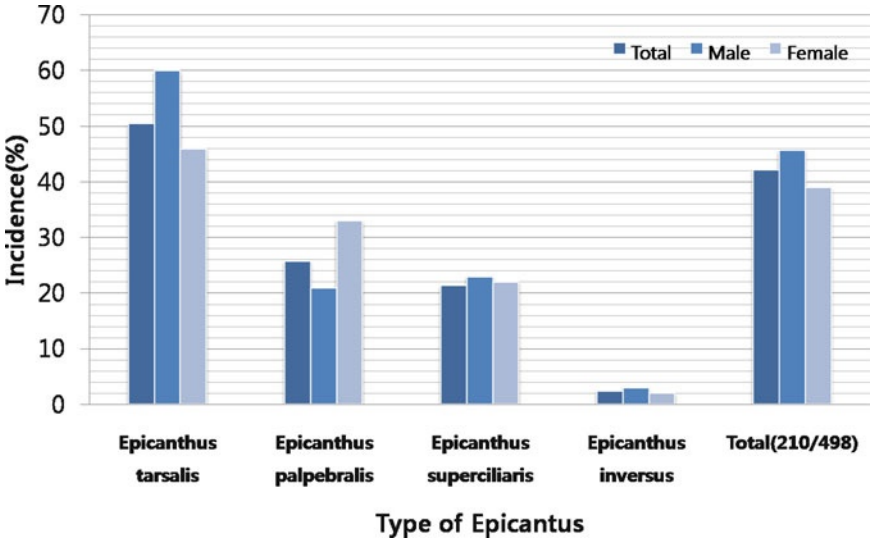

Fig. 35.5 Incidence and type of epicanthus. Epicanthus appeared 42.2% in total, and the most common type was epicanthus tarsalis. The growth pattern can be classified as continuously increasing, decreasing, and stationary after reaching the peak level

age, more than 90% of both male and female subjects younger than 10 years demonstrated it, and as the age increased, it disappeared gradually, and 90% was lost in those in their fifties or older. For the type of epicanthus, epicanthus tarsalis was found most frequently, with 31.3% in male subjects and 46.7% in female subjects, followed by epicanthus palpebralis, epicanthus superciliaris, and epicanthus inversus in descending order of frequency (Fig. 35.5).

35.8 Intercanthal Distance

For intercanthal distance, Kim et al. reported a mean value of 3.6 mm for female subjects between 12 and 26 years of age (Kim et al. 1985). The authors reported a mean value of 37.4 mm in male subjects and 35.9 mm in female subjects aged 21–22 years (Kim et al. 1988). Park et al. reported a mean value of 36.3 mm in male subjects and 33.4 mm in female subjects in their twenties (Park et al. 1989). Hwang et al. reported 34.0 mm for beautiful women in their twenties and 36.7 mm for average looking women (Hwang et al. 1996). Cho et al. reported mean values of 35.3 mm in male subjects and 35.5 mm in female subjects aged 18 years (Cho et al. 1993). Cho et al. reported mean values of 37.2 mm in male subjects and 35.0 mm for female subjects aged 18–27 years (Cho et al. 1989). Further, Park and Na reported that the distance increased rapidly between 1 and 4 years of age, then increased gradually, and reached its almost full-grown value at 10–14 years of age (Park and Na 1975). Park et al. reported that both male and female subjects attained the peak values of, respectively, 36.5 and 37.1 mm, at 15–19 years of age. This review also showed that both male and female subjects reached a specific level at 14–16 years of age and that their level slightly increased after their sixties ($p < 0.05$) (Fig. 35.6). It also displayed mean values of 38.4 mm in adult male subjects and 38.2 mm in adult female subjects without demonstrating statistically significant difference according to sex.

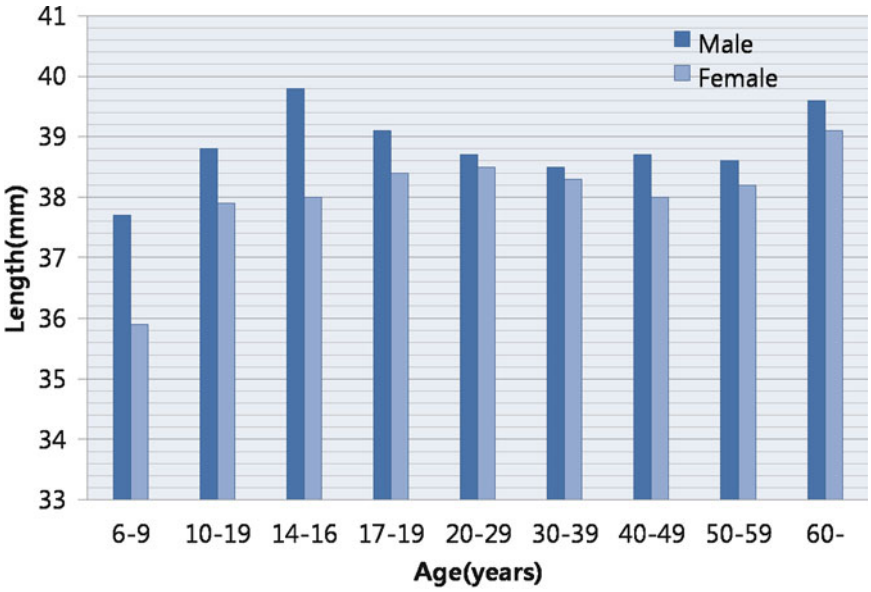

Fig. 35.6 Intercanthal distance. The intercanthal distance was 38.4 ± 3.0 mm in male subjects and 38.2 ± 2.8 mm in female subjects

35.9 Interpupillary Distance

Kim et al. reported the mean values of the interpupillary distance to be 59.9 mm in male subjects and 63.5 mm in female subjects (Kim et al. 1988). Park et al. reported mean values of 65.0 mm in male subjects and 63.2 mm in female subjects (Park et al. 1989). Hwang et al. reported a mean of 63.5 mm for beautiful women and 63.6 mm for average looking women (Hwang et al. 1996). Park et al. reported mean values of 65.8 mm in male subjects and 65.1 mm in female subjects between 20 and 24 years of age (Park et al. 1990). Cho et al. reported mean values of 69.4 mm in male subjects and 66.6 mm in female subjects, which proved greater in male subjects than in female subjects ($p < 0.05$). This review also showed that the interpupillary distance increased until 17 and 19 years of age, without change shown by age after that time (64.6 ± 2.9 mm in male subjects and 63.6 ± 2.9 mm in female subjects) (Fig. 35.7).

35.10 Vertical Dimension of Open Upper Eyelid

For the vertical dimension of upper eyelid, Kim et al. reported a mean value of approximately 18 mm in Asian male and female subjects between 12 and 26 years of age (Kim et al. 1985). For the vertical dimension of the open upper eyelid, Park et al. reported 10.3 mm in male subjects and 10.0 mm in female subjects (Park et al. 1990). This article reported mean values of 12.3 mm in male subjects and 12.5 mm in female subjects for open eyelid with no statistically significant difference according to sex. After reaching the peak at 17–19 years of age, it increased slightly after subjects reached their sixties ($p < 0.05$) (Fig. 35.8).

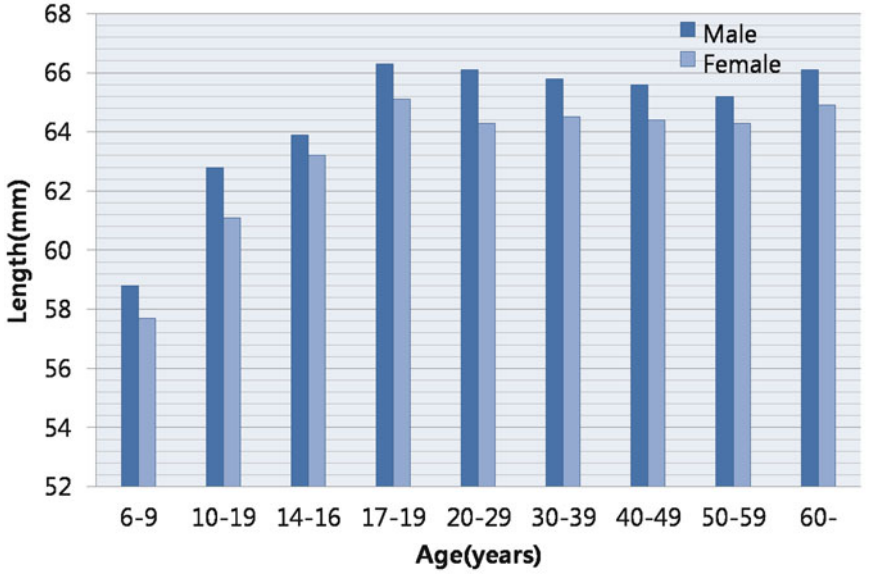

Fig. 35.7 Interpupillary distance. The interpupillary distance was 64.6 ± 2.9 mm in male subjects and 63.6 ± 2.9 in female subjects

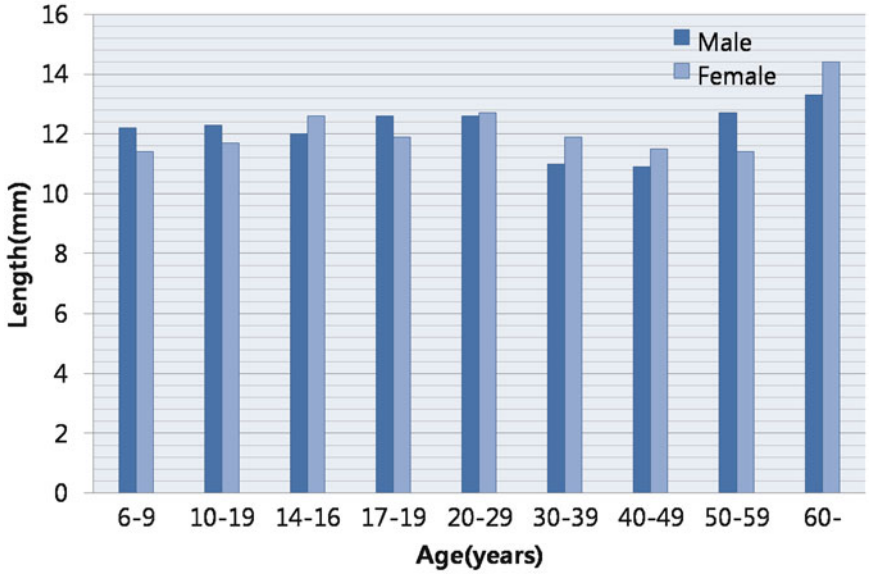

Fig. 35.8 Height of the opened upper eyelid. The height of the open upper eyelid was 12.4 ± 2.4 mm in male subjects and 12.0 ± 1.9 mm in female subjects

35.11 Applications to Other Areas of Health and Disease

In particular, for unilateral ptosis surgery, the size and shape of the normal eyelid might be used as a guide during surgery. However, for double-eyelid blepharoplasty (which is a ptosis correction surgery frequently performed, in cases of bilateral operation), the normal anthropometric value of eyelids becomes important to guide surgery.

Summary Points

- The horizontal dimension of the palpebral fissure was 27.0 ± 1.8 mm in male subjects and 26.8 ± 1.7 mm in female subjects.
- The vertical dimension of the palpebral fissure was 8.0 ± 1.0 mm in male subjects and 8.2 ± 1.1 mm in female subjects.
- The slant of the palpebral fissure was 7.9° ± 2.4° in male subjects and 8.8° ± 2.3° in female subjects.
- The height of the open upper eyelid was 12.4 ± 2.4 mm in male subjects and 12.0 ± 1.9 mm in female subjects.
- The height of the double fold in the closed eye was 6.6 mm in male subjects and 6.5 mm in female subjects.
- The intercanthal distance was 38.4 ± 3.0 mm in male subjects and 38.2 ± 2.8 mm in female subjects.
- The interpupillary distance was 64.6 ± 2.9 mm in male subjects and 63.6 ± 2.9 in female subjects.
- A double fold was found in 36.1%, in total, with higher incidence in females (41.3%).
- The epicanthus appeared in 42.2% in total, and the most common type was epicanthus tarsalis. The growth pattern can be classified as continuously increasing, decreasing, and stationary after reaching the peak level.
- The peak level of growth was attained at 10–13 years of age for the vertical dimension and the slant of palpebral fissure; at 14–16 years of age for the intercanthal distance; and at 17–19 years of age for the horizontal dimension of palpebral fissure, the height of upper eyelid, and the interpupillary distance ($p < 0.05$).

Table 35.1 Key points of anthropometry of the eyelid

The eight measured items are as follows:

1. Horizontal dimension of the palpebral fissure (HDPfi): the distance between the medial canthus and the lateral canthus.
2. Vertical dimension of the palpebral fissure (VDPfi): the distance between the open upper eyelid margin and the open lower eyelid margin.
3. Slant of the palpebral fissure: based on the line connecting the right and left medial canthus, and the angle of the line between the medial and lateral canthus of an eye.
4. Type and height of the double fold.
5. Type and height of the epicanthus.
6. Intercanthal distance (ICD): the distance between the right and left canthus.
7. Interpupillary distance (IPD): the distance between the right and left pupils.
8. Height of open upper eyelid: the perpendicular distance between the highest point of open upper eyelid margin and the lower margin of the eyebrow.

This table lists eight measured items and their definitions.

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Chapter 36
Neck Circumference: Its Usage in Medicine and Biology

Bernhard Fink

Abstract Neck circumference, measured as the distance around the neck, is a simple and timesaving screening measure to identify obesity in both men and women. It is positively correlated with the components of the metabolic syndrome and obstructive sleep apnea. Furthermore, neck circumference is positively associated with traditional anthropometric measures of body circumferences and indices, such as the body mass index and the waist-to-hip ratio, and other physiological and biochemical measures of cardiovascular risk. It is positively correlated with systolic and diastolic blood pressure, triglycerides and glucose levels and has been used as a clinical predictor of menstrual irregularity, hirsutism, infertility, and insulin resistance. This has led to and increased interest in this measure with regard to its usefulness in clinical and epidemiological studies, but also from biological studies, interested in the possibility of an early predisposition for cardiovascular risk through early sex-steroid exposure. This chapter briefly reviews the reported associations with neck circumference and suggests possible applications also in non-clinical studies.

Abbreviations

AHI	Apnea/hypopnea index
BMI	Body-mass index
CHD	Coronary heart disease
FAI	Free androgen index
MS	Metabolic syndrome
MI	Myocardial infarction
NC	Neck circumference
NHR	Neck-to-height ratio
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
PCOS	Polycystic ovary syndrome
PIH	Pregnancy-induced hypertension
T	Testosterone
WC	Waist circumference
WHR	Waist-to-hip ratio

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_36,

36.1 Introduction

Among the several anthropometric measures, such as body mass index (BMI, kg/m²) and waist-to-hip ratio (WHR, waist circumference divided by hip circumference), most of which have been shown to be increased in people suffering from metabolic syndrome (MS) and obstructive sleep apnea (OSA), neck circumference (NC) appears to be another simple screening measure. The usefulness of this measure has been demonstrated in recent reports using relatively large samples of obese and overweight patients (Ben-Noun et al. 2001; Ben-Noun and Laor 2003, 2006), and some reports found NC even superior in predicting MS, than, for example, measures of waist circumference (WC) (Onat et al. 2009). In addition to the reported relationship between NC and cardiovascular risk factors (e.g., Ben-Noun and Laor 2003, 2006), increased NC has also been observed in patients who suffer from obstructive sleep apnea (Davies et al. 1992; Pływaczewski et al. 2008; but see Dancey et al. 2003).

Further examination of potential risk factors for the development of MS and OSA revealed that NC was also a good clinical predictor of menstrual irregularity, hirsutism, infertility, insulin resistance, and polycystic ovary syndrome (PCOS) in obese pre-menopausal women (Dixson and O'Brien 2002). These results have also motivated non-clinical studies to study associations between NC and other anthropometric traits, such as the digit ratio 2D:4D, that is, the ratio of the lengths of the second and fourth digits, a supposed proxy of prenatal and adult concentrations of testosterone (T) (Manning et al. 1998) and implications for the risk of coronary heart disease (CHD) (Fink et al. 2006). While the number of clinical studies that have used NC in examining predictors of obesity and sleep apnea is still low compared to those that report the use of traditional anthropometric measures, such as BMI and WHR, they support the usefulness of this measure without other more complex techniques, particularly when examining larger groups of patients.

36.2 The Measurement of Neck Circumference

Neck circumference is defined as the measure of the distance around the neck. It is usually measured with a tape measure (see Fig. 36.1a). A simple (household) tape measure may suffice to measure NC accurately, but some companies (e.g., Seca® and Prestige Medical®) provide quite useful retractable

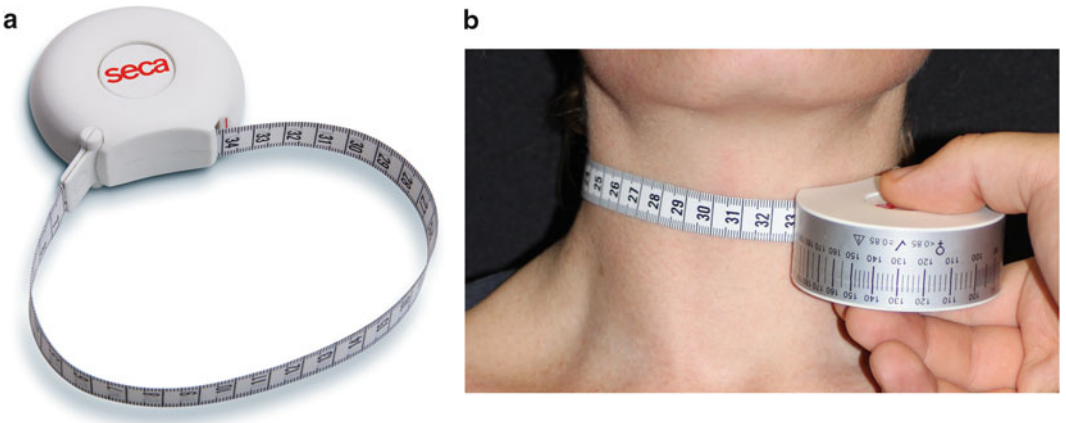

Fig. 36.1 (**a**) Retractable non-stretching tape measure for determining body circumference. Image courtesy of Seca® GmbH & Co. KG, Germany. (**b**) Image of neck circumference measurement. (Image courtesy of B. Fink, University of Goettingen)

Table 36.1 Measuring neck circumference

- Use a non-stretching tape measure.
- The head should be held erect with the eye facing the measurer.
- Measure at the most prominent portion of the thyroid cartilage (Adam's apple).
- Carefully follow the surface of the skin.

tape measures, usually made of non-stretching Teflon, with increments down to 0.1 cm or 1/16 inch, for measuring circumference. For careful and proper assessment, the participant (or patient) should be instructed to hold the neck erect (in the resting position) with the eyes facing forward to the measurer (see Fig. 36.1b). While NC is basically an easy-to-measure trait, some caveats remain. The neck can be very broad because of excessive prominence of the trapezius, skin folds or webs. In the presence of such anatomy, the tape measure should carefully follow the surface of the skin to reflect the circumference accurately. The horizontal plane at which measurement occurs should be carefully selected at the most prominent portion of the thyroid cartilage (Adam's apple) (Hall et al. 1989) (Table 36.1).

36.3 Neck Circumference as a Measure of Central Obesity

Body obesity and MS, defined by a cluster of clinical conditions associated with an enhanced propensity toward the development of type 2 diabetes and hypertension, are considered as a major risk factor for CHD, which itself is associated with an increased risk for stroke and early mortality (Cruz and Goran 2004; Jiamsripong et al. 2008a, b) (Table 36.2).

There are numerous methods of assessing obesity. In terms of anthropometrics, some of the most frequently used and reported measures associated with obesity are BMI and WC. For example, Balkau et al. (2007) reported measures of BMI and WC in a total of 168,000 primary care patients from 63 countries, aged 18–80 years, and found a significant increase of both measures in patients with CHD. However, there is considerable concern in the literature with regard to the optimum cut-off points of these anthropometric indices in predicting cardiovascular risk factors, also because of variation in definitions for different ethnic groups (e.g., Bouguerra et al. 2007; Al-Lawati and Jousilahti 2008).

While by tradition, BMI has been the most widely used index to determine the prevalence of overweight in, and across, populations as well as associated risk factors, most studies nowadays use more than one anthropometric measure to evaluate central obesity. In addition to BMI and WC, WHR, and to a lesser extent, the waist-to-height ratio (sometimes also referred to as waist-to-stature ratio, WSR), are the most prominent among the indices mentioned earlier. It is generally concluded that these measures perform the same way as indicators of body fatness, but is has also been reported that they are more closely related to each other than with percentage body fat (as measured by measured by dual-energy X-ray absorptiometry) (Flegal et al. 2009). In the attempt to determine whether BMI, WC, or percent body fat best predicts MS, Shen et al. (2006) evaluated these measures in 1,010 healthy white and African-American men and women. It was found that WC could significantly predict health risk indicators, followed by BMI, but no significant prediction could be made through the body fat percentage (Table 36.3).

There will probably be an ongoing controversy over the usefulness of the various anthropometric indices in predicting obesity and the associated health risks, including morbidity and mortality, which might not be resolved eventually in favor of only one measure. A more plausible scenario and

Table 36.2 Key features of the metabolic syndrome

- Central obesity (visceral adiposity with overweight and increased fat deposits mainly around the waist)
- High blood pressure
- Fasting hyperglycemia (diabetes mellitus type 2 or impaired fasting glucose, impaired glucose tolerance, or insulin resistance)
- Decreased HDL cholesterol
- Elevated triglycerides

Table 36.3 Anthropometric correlates of neck circumference

Trait	Direction of association	Authors	Year
Age	+	Ben-Noun et al.	2001
	+	Ben-Noun and Laor	2003
	n.s. (men) + (women)	Ben-Noun and Laor	2006
	n.s.	Onat et al.	2009
Weight	+	Ben-Noun et al.	2001
	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2006
Height	n.s. (men), – (women)	Ben-Noun et al.	2001
	n.s. (men), – (women)	Ben-Noun and Laor	2003
	- (men), n.s. (women)	Ben-Noun and Laor	2006
Waist circumference	+	Ben-Noun et al.	2001
	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Ben-Noun and Laor	2006
	+	Laakso et al.	2002
	+	Onat et al.	2009
Hip circumference	+	Ben-Noun et al.	2001
	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2006
WHR	+	Ben-Noun et al.	2001
	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Ben-Noun and Laor	2006
	+	Laakso et al.	2002
	+	Onat et al.	2009
BMI	+	Ben-Noun et al.	2001
	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Ben-Noun and Laor	2006
	+	Laakso et al.	2002
	+	Onat et al.	2009
	+	Pływaczewski et al.	2008

valuable advice is perhaps the consideration of one or another measure (or also the combination of some) with reference to the study question in focus. While some clinical setting may allow a more detailed assessment of subjects, physicians and scientists working in the field on demographic, epidemiological or anthropological questions may face time constraints, thus seeking a simple, quick to asses, but also accurate measure of obesity.

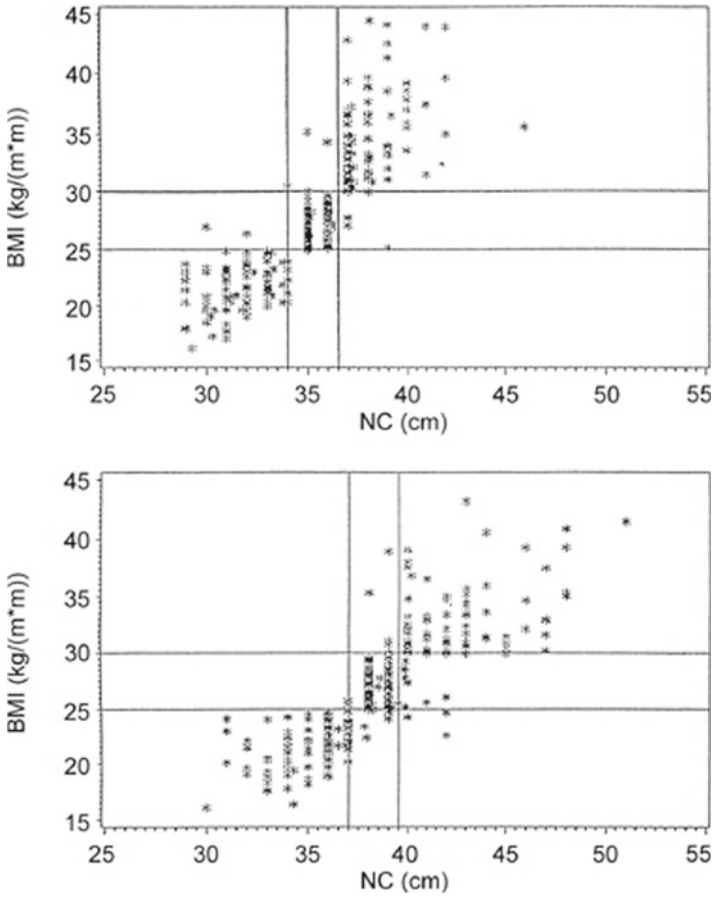

Fig. 36.2 Optimum cut-off points of NC as reported by Ben-Noun et al. (2001). NC of ≥37 cm for men and ≥34 cm for women identified most of the subjects with a BMI ≥25. NC of ≥39.5 cm for men and ≥36.5 cm for women identified most of the subjects with a BMI ≥30. (Adapted with permission from Macmillan Publishers Ltd)

Ben-Noun et al. (2001) and Ben Noun and Laor (2003, 2004, 2006) suggested that NC could be such a measure. In their first study (Ben-Noun et al. 2001), they aimed to identify overweight or obese patients solely by measuring the circumference of the neck. In a sample of 460 men and 519 women, NC was measured along with circumferences of the waist and hip, and age, height and weight were recorded to subsequently calculate BMI. In both, men and women, NC correlated positively and significantly with age, weight, and waist and hip circumferences, and also with indices of BMI and WHR in both men and women. Moreover, it was found that NC greater than or equal to 37 cm in men, and 34 cm in women, was the best cut-off level for determining the subjects with a BMI greater than or equal to 25, and an NC greater than or equal to 39.5 cm in men, and greater than or equal to 36.5 cm in women, performed best in identifying subjects with a BMI greater than or equal to 30 (Fig. 36.2). More recently, Onat et al. (2009) reported similar cut-off points of 39 cm in men and 35 cm and 35.5 cm, respectively, in women as corresponding to MS and OSA.

Ben-Noun and Laor (2003) studied NC in relation to potential risk factors for CHD, that is, anthropometric indices (BMI and WHR), systolic and diastolic blood pressure (SBP and DBP), and biochemical measures of lipoprotein, glucose, cholesterol, and uric acid levels. Higher NC was

Table 36.4 Physiological and biochemical correlates of neck circumference

Trait	Direction of association	Authors	Year
SBP, DBP	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Onat et al.	2009
Total cholesterol	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2006
	+ (men), n.s. (women)	Onat et al.	2009
LDL-cholesterol	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2006
	n.s.	Onat et al.	2009
HDL-cholesterol	n.s.	Ben-Noun and Laor	2003
	n.s.	Ben-Noun and Laor	2006
	–	Onat et al.	2009
Tryglicerides	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Ben-Noun and Laor	2006
	+	Onat et al.	2009
Uric acid	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Ben-Noun and Laor	2006
Glucose	+	Ben-Noun and Laor	2003
	+	Ben-Noun and Laor	2004
	+	Ben-Noun and Laor	2006
	n.s.	Dixon and O'Brian	2002
	n.s (men), + (women)	Onat et al.	2009
Insulin	+	Dixon and O'Brian	2002
	+	Onat et al.	2009
SHBG	–	Dixon and O'Brian	2002
	–	Onat et al.	2009

associated with higher values and levels of all measures, leading the authors to conclude that NC is correlated positively with components of MS, and thus likely to increase CHD. In a follow-up study, Ben-Noun and Laor (2004) further examined the associations of NC with SBP and DBP, in a sample of 155 men and 209 women with no known major medical conditions. NC was positively and significantly correlated with changes in SBP and DBP in both men and women. Furthermore, significant positive associations of NC were also found with other components of MS, such as triglycerides and glucose levels, which again leads to the conclusion that NC is a useful measure in predicting MS and cardiovascular risk (for a similar study, see Ben-Noun and Laor 2006). Severe obesity, however, is associated with physiological and biochemical changes, including androgen excess and insulin resistance, which are also features of, for example, the polycystic ovary syndrome (PCOS) in women (Table 36.4).

Dixson and O'Brien (2002) examined these relationships in combination with anthropometric measures by studying their changes in a sample of 107 severely obese pre-menopausal women after 1-year post-obesity surgery. NC and age were independent predictors of higher free androgen index (FAI) by explaining 36% of the variability, while WHR was not a significant predictor. NC was further a clinical predictor of menstrual irregularity, hirsutism, infertility, insulin resistance, and the PCOS, with NC lesser than 39 cm, 39–42 cm, and greater than 42 cm, reflecting, respectively, a low, intermediate, and high risk for developing PCOS and MS. Similar observations were made by Laakso

et al. (2002), who tested the association of NC with abdominal and general obesity, as well as with insulin resistance-related factors, showing that neck NC was associated with measures of metabolic disorders (e.g., blood lipids, insulin, and glucose concentrations) related to insulin resistance. Taken together, NC seems to be a good predictive measure of hyperinsulinemia and raised androgens in obese pre-menopausal women, thus making it additionally useful in clinical screening for persons at an enhanced risk for insulin resistance.

36.4 Neck Circumference and Obstructive Sleep Apnea

Obesity is also a risk factor for obstructive sleep apnea (OSA) and the obesity hypoventilation syndrome (OHS), leading to increased morbidity and mortality, with reduced quality of life (Table 36.5).

Katz et al. (1990) provided the first study of the association between NC and sleep apnea (as defined by the apnea/hypopnea index, AHI). They found that NC (together with BMI) accounted for 39% of the variability in AHI, and reasoned that the association of obesity and OSA is via fat deposition in the neck (see also Davies et al. on the combination of features and symptoms in the clinical diagnosis of OSA).

The current literature supports this early observation and the suggestion that NC shows the strongest association with OSA (but see Onat et al. (2009) on the superiority of NC over WC in Turkish men, but not women; and Pływaczewski et al. (2008) on comparison to BMI). Moreover, the frequency and severity of sleep apnea in the sleep clinic population seems to be greater in men than in women. With reference to the original suggestion by Katz et al. (1990), there is some support for the claim of a sex-dependent fat distribution in the neck from magnet resonance imaging. Whittle et al. (1999) reported that the neck soft-tissue volume was greater in men than women, although no significant difference was observed for the volume of fat (Fig. 36.3).

More recently, Dancey et al. (2003) investigated this observation in relation to the gender differences in NC. Sleep apnea was examined together with NC in a sample of 2,753 men and 1,189 women. Men had significantly higher AHI and NC, although the difference in NC was less pronounced when adjusted for height (neck-to-height ratio, NHR). However, NHR was found to be the best predictor of AHI, accounting for about 19% of the variability, and a higher slope in men than women.

Mortimore et al. (1998) compared anthropometric measures of BMI and NC in addition to resonance images of the neck in obese and non-obese age-matched subjects with sleep apnea, and found excess fat deposition in even relatively non-obese patients with sleep apnea, especially anterolateral to the upper airway (Fig. 36.4a, b).

The effect of neck circumference on symptoms of OSA may be even increased in physically demanding situations accompanied with hormonal changes, such as pregnancy. Ursavas et al. (2008) investigated self-reported snoring in pregnant women, and the relationship of snoring, obesity and

Table 36.5 Key features of obstructive sleep apnea

- Sleep-disordered breathing
- Loud snoring that stops when a person tries to breathe
- Hypersomnia (excessive amounts of sleepiness, also during the daytime)
- Often associated with obesity, large neck circumference, mood swings or depression, and concentration difficulties

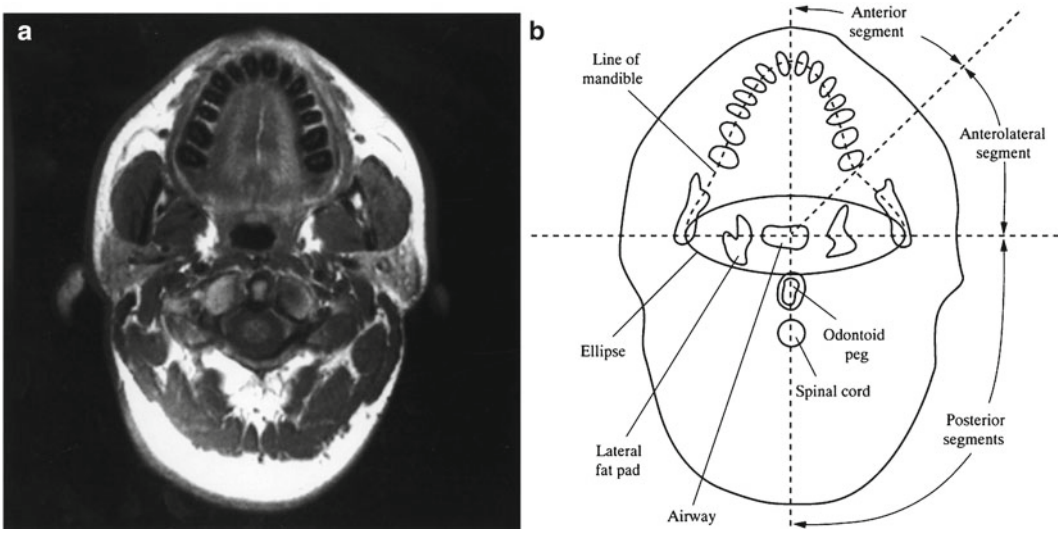

Fig. 36.3 (**a**) Representative transverse T1-weighted magnetic resonance image (MRI) of the neck of a normal man. (**b**) Schematic representation of the MRI illustrating the segmental divisions used for analysis of neck fat volumes, the subdivision of the anterior and anterolateral segments by the line of the mandible, and the position of the ellipse used for analysis of fat volumes close to the airway. (Reproduced from Whittle et al. (1999). With permission from BMJ Publishing Group Ltd)

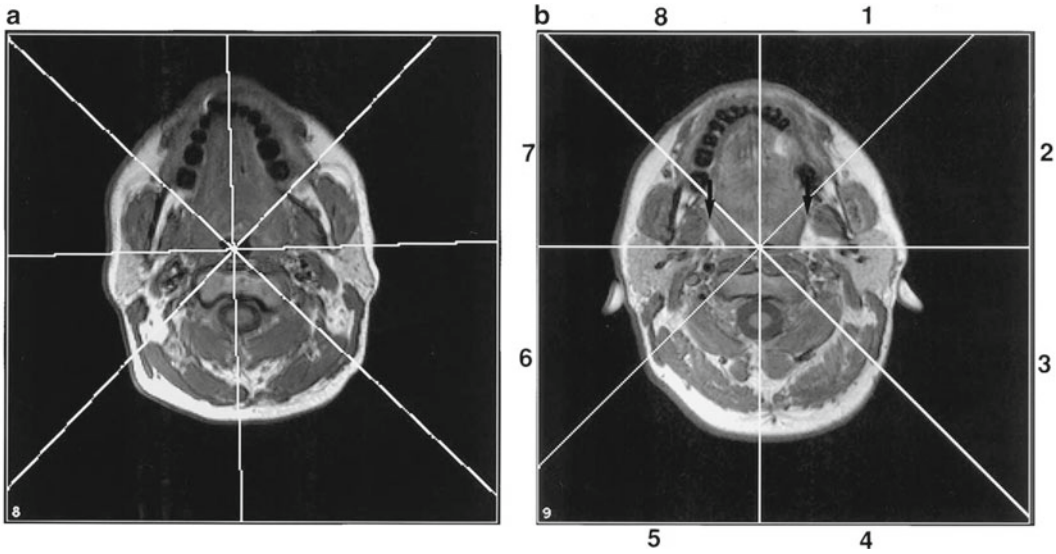

Fig. 36.4 Cross-sectional T1-weighted magnetic resonance scans of a control subject (**a**) and a non-obese patient with sleep apnea (**b**), showing distribution of neck fat. The anterolateral fat deposits (segments 2 and 7) are marked with *arrows*. (Reproduced from Mortimore et al. (1998). With permission from the American Thoracic Society)

NC to pregnancy-induced hypertension (PIH) and preeclampsia in a sample of 469 pregnant and 208 (age-matched) non-pregnant women. It was found that habitual snoring was increased in pregnant women, and that NC, age, smoking during pregnancy, and weight before delivery were independent risk factors for its prevalence.

36.5 Applications to Other Areas of Health and Disease

Most studies on the significance of NC have considered the predictive nature and usefulness of this trait (compared to or in combination with traditional anthropometric measures) in the clinical study of cardiovascular risk factors and sleep apnea. Given that NC has turned out to be a valuable measure, which not only shows strong associations with other body indices (such as WHR and BMI), but also correlations with physiological and biochemical measures, it may serve as additional measure for medical, epidemiological, and social anthropological studies. However, with the rise of the evolutionary biological and psychological study of human physical appearance (see for review Fink and Penton-Voak, Gangestad and Scheyd 2005), health, and its perception, NC researches in related disciplines may find it to be an additional (and perhaps less offensive) measure than some subjects consider BMI and WHR to evaluate physical condition.

The fact that NC shows considerable sexual dimorphism may be of particular interest in this context. Some 15 years ago, Antoszewska and Wolański (1992) examined 37 somatic traits and ratios in a sample of 1,034 newborns, and compared them with those of adults. Head and neck showed a moderate sexual dimorphism, like, for example, the length of the upper extremities or the breadth of the hips. Sexual differences in physical measures were basically more pronounced in adults than in newborns. While studies use MRI to capture possible differences in fat deposition, recent research also considered anthropometrical properties of the head and neck to explain this sexual dimorphism and accompanied sex specific syndromes. Vasavada et al. (2008) found that the geometric differences of men and women in neck anthropometry (an average of 9–16% smaller in females) were even greater than those in head anthropometry (an average of 3–6% smaller in females) and that there were also significant strength differences. Hence, it was concluded that male necks are not simply scaled versions of female necks, which should be considered when studying sex differences in neck-related disorders.

While there is corroborating evidence for the sexual dimorphism of the neck, which is present even in newborns, and this relates to the neck's geometry as well as to the differences in soft tissue and possibly fat depositions, the cause of this dimorphism remains to be investigated. Sex differences in body composition and the expression of physical traits are well known in humans, although their early development is rarely considered (however, see, for a recent study, Fields et al. 2009). One measure that has received considerable attention in recent years in medicine and biology is the ratio of the lengths of the second (index finger) and fourth (ring finger) digits, also referred to as 2D:4D or digit ratio, a supposed proxy of prenatal and adult concentrations of T (Manning et al. 1998). Digit ratio has been related to numerous physical and behavioral traits that show sex differences, including face and body shape, and anthropometric measures. It is beyond the scope of this chapter to outline the evidence in detail (however, see Manning, Chapter 48). However, digit ratio has also been studied in relation to NC, based on the possibility that T protects men against myocardial infarction (MI). Fink et al. (2006) investigated associations between 2D:4D ratios and NC in a sample of 127 men and 117 women and found positive and significant correlations in men, but not in women, after controlling for the effect of BMI, that is, men with higher 2D:4D (indicating less T) had thicker necks. Given that 2D:4D is supposed to be determined in utero, the link between digit ratio and NC suggests the possibility of a predisposition for men toward CHD via 2D:4D as proxy to early sex-steroid exposure. If this association can be confirmed also in clinical studies, it will be interesting to see how well other factors that characterize MS, such as obesity, insulin resistance, hyperlipidemia, and hypertension, all of which increase the risk of CHD, correlate with digit ratio. Such a link would argue for the significance of early sex-steroid exposure on the development of CHD and shed further light on sex differences in its prevalence.

Summary Points

- Neck circumference is the measure of the distance around the neck.
- Neck circumference correlates positively with age, weight, and waist and hip circumferences, and also with indices of body mass index and waist-to-hip ratio in both men and women.
- Men – on average – have larger neck circumference than women.
- Men with a neck circumference ≥37 cm and women with a neck circumference ≥34 cm are considered overweight and men with a neck circumference ≥39.5 cm and women with a neck circumference ≥36.5 cm are obese.
- Neck circumference correlates with some physiological and biochemical measures associated with the metabolic syndrome and risk factors in coronary heart disease.
- Neck circumference is positively associated with systolic and diastolic blood pressure, triglycerides and glucose levels.
- Neck circumference is a clinical predictor of menstrual irregularity, hirsutism, infertility, and insulin resistance.
- Neck circumference shows strong associations with obstructive sleep apnea.
- Obstructive sleep apnea patients have excess fat deposition, especially anterolateral to the upper airway.
- Neck circumference is a risk factor for pregnancy-induced hypertension.
- Neck circumference correlates with digit ratio (2D:4D), a proxy of prenatal and adult concentrations of testosterone.

Acknowledgments The preparation of this article was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft (DFG)) through the Institutional Strategy of the University of Goettingen. B.F. is currently funded by an Emmy-Noether Fellowship of the DFG (FI 1450/4-1).

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Part VI
Regions and Anatomical Areas of the Body: Limbs, Extremities and Bones

Chapter 37
Prediction of Upper and Lower Extremity Tissue Masses Using Surface Anthropometric Measures and DXA

David M. Andrews and Timothy A. Burkhart

Abstract This chapter reviews the few studies that have reported regression equations that enable the prediction of upper and lower extremity soft and rigid tissue masses of living people, including lean (muscle), fat, and bone mineral content, from surface anthropometric measures such as segment lengths, breadths, circumferences, and skinfolds. Predicted tissue masses from the upper extremity segments (arm, forearm, forearm and hand) and lower extremity segments (thigh, leg, leg and foot) were validated against those obtained from full body Dual Energy X-ray Absorptiometry (DXA) scans. Twenty-four tissue mass prediction equations for the upper and lower extremity segments have been compiled which are highly predictive of measured tissue masses from DXA, with adjusted R^2 values ranging from 0.67 to 0.97. The studies that have evaluated the reliability of the methods used to develop the prediction equations are also reviewed. Almost 90% of the between- and 100% of the within-measurer reliability coefficients for the segment anthropometric measurements needed as inputs to the tissue mass prediction equations were found to be greater than 0.75 in magnitude, signifying good to excellent reliability. The reliability of manually segmenting tissue masses of the upper and lower extremities from DXA scans using analyst-assigned regions of interest was also assessed, and values were very high, ranging in magnitude from 0.991 to 1.000 across all tissue types and segments. In general, the low errors in predicted tissue masses and high reliability coefficients for the measured anthropometric measurements reported herein indicate that the methods used to develop and validate the tissue mass prediction equations are robust and appropriate for a variety of applications involving living people.

Abbreviations

Ant.	Anterior
A-P	In the Anterior/Posterior direction
BMC	Bone Mineral Content (kg or grams)
DXA	Dual Energy X-Ray Absorptiometry

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_37,

FM Fat Mass (kg or grams)
ICC Intra-class Correlation Coefficient
Lat. Lateral
LM Lean Mass (kg or grams)
Med. Medial
M-L In the Medial/Lateral direction
Pos. Posterior
Prox. Proximal
ROI Region of Interest (from DXA scans)
WM Wobbling Mass (W = LM + FM) (kg or g)

37.1 Introduction

Impacts to the upper and lower extremities, which are common during sport and recreational activities such as in-line skating and running, have been associated with musculoskeletal injuries and disorders in humans, including fractures to the distal upper extremity (Jaffe et al. 1997), joint and back pain (Light et al. 1980; Voloshin and Wosk 1982), articular cartilage degeneration and osteoarthritis (Radin et al. 1973), and tibial stress fractures (Milner et al. 2006).

In order to better understand the mechanisms by which injuries occur to the body during such activities, numerous biomechanical models have been developed and proven useful. However, traditional rigid link-segment and mass/spring/damper biomechanical models do not incorporate both soft (e.g., fat, muscle, and skin) and rigid (bone) tissues of body segments, even though the effect that soft tissues have on impact dynamics has been described in the literature (Gruber et al. 1998; Pain and Challis, 2006).

Widespread incorporation of soft and rigid tissues into biomechanical models has been limited in part because of the lack of tissue-specific mass data in the literature for living subjects. These types of data have traditionally been obtained from cadaver segmentation studies (e.g., Clarys et al. 1999), but the application of these limited data to living subjects, particularly younger adults and women, is questionable. Imaging technologies, such as Dual Energy X-ray Absorptiometry (DXA) (Table 37.1), have been shown to be valid and reliable for body composition analysis (Haarbo et al. 1991; Durkin et al. 2002; Ball et al. 2004), but the cost of scanning, and the limited availability of DXA for research applications can be significant hurdles to overcome, for many researchers.

The limitations associated with obtaining person-specific tissue masses punctuate the importance of having an inexpensive, readily accessible, accurate, and reliable method of quantifying tissue masses in vivo, in order to improve our understanding of injury mechanisms and to facilitate biomechanical modeling of impact applications.

It is reasonable to assume that the magnitude of the different tissue masses within body segments is related to the dimensions of those segments. Consequently, if there was a strong relationship between surface anthropometric measurements and the internal tissue masses for each segment, then, obtaining person-specific tissue masses for integrating into biomechanical models would facilitate the evaluation of applied biomechanical problems in order to quantify the associated risk and to develop strategies for injury prevention.

To date, an extensive array of upper and lower extremity surface anthropometric measures, including segment lengths, breadths, circumferences, and skinfolds have been taken from 168 healthy, young men and women, and used to develop in vivo soft and rigid tissue mass prediction equations for the upper and lower extremities (Holmes et al. 2005; Arthurs and Andrews 2009)

Table 37.1 Key features of dual energy X-ray absorptiometry (DXA)

1. Dual energy X-ray absorptiometry is a diagnostic imaging technique used to measure bone density and body composition
2. Two X-ray beams of alternating high (140 keV) and low (70 keV) intensity are passed through the body
3. Tissue masses including lean tissue (muscle and skin), fat tissue, and bone mineral content are calculated by measuring the attenuation of the beams and incorporating the calibration coefficients for the different tissues
4. The patient dose from DXA (approximately 0.37 μSv) is relatively low compared to the annual dose from natural background radiation (2,400 μSv per annum) and from other imaging techniques, such as chest X-rays (50 μSv) and lateral spine X-rays (820 μSv)

This table lists the key features of DXA, including the system for attaining body composition masses
keV kiloelectron volt, measures the intensity of energy, where 1 keV = 1×10^{-16} J, μSv micro Siverts, a unit of radiation

Table 37.2 Key features of regression analysis and prediction equations

1. Regression analysis is a statistical technique that is used to show the relationship between variables
2. In multiple linear regressions, the independent relationship that each descriptor (input) variable has on the dependent (output) variable is investigated
3. The technique is based on finding the line that best fits the data in the form of $y = b + m_1x_1 + ...m_nx_n$
4. In general, variables are included or removed from the equation until the addition or subtraction of variables does not result in an improvement in the explained variance (R^2) of the output variable
5. Prediction equations are validated by calculating the error and relationship between a gold standard measurement of the output variable and the value of the variable calculated from the prediction equation
6. A limitation of prediction equations is that they can only be used on populations with similar characteristics to the population used to generate the equations

This table lists the key features of regression analysis and the steps involved in creating prediction equations
y the output variable, b the y intercept or constant, m_1 the slope (i.e., prediction equation coefficient) of the line that describes the relationship between the first input variable x_1 and the output variable y, m_n the slope (i.e., prediction equation coefficient) of the line that describes the relationship between the n^{th} input variable x_n and the output variable y

(Table 37.2). The following chapter summarizes the procedures used to develop and validate the tissue mass equations using DXA, and provides a compilation of the prediction equations that currently exist. The reliability of the measurement methods used to collect the surface anthropometric measurements needed as inputs into the prediction equations, and of the manual segmentation of body segments from the DXA scans using regions of interest (ROIs) by trained analysts, is also presented.

37.2 Practical Methods and Techniques

37.2.1 Tissue Mass Prediction Equations from Anthropometric Measurements

Numerous equations have been developed over the years for the purpose of determining body composition (Clarys and Marfell-Jones 1986b). However, only a few have used DXA as a reference method for generating and validating equations that predict in vivo soft and rigid tissue masses of the segments of the upper and lower extremities (Holmes et al. 2005; Arthurs and Andrews 2009). The basis for these equations is an array of surface anthropometric measurements of the upper and lower extremities, including segment lengths, breadths, circumferences, and skinfolds.

37.2.1.1 Participants

Tissue mass prediction equations were developed in two separate studies: one for the upper extremities (Arthurs and Andrews 2009) and one for the lower extremities (Holmes et al. 2005). A total of 168 healthy, young participants (upper extremities: 50 M, 50 F; 21.8 (6.2) years old, 70.4 (9.5) kg, 1.71 (1.94) m; lower extremities: 26 M, 42 F; 21.9 (2.6) years old, 65.4 (10.6) kg, 1.69 (0.09) m) were measured and scanned using DXA.

In order to facilitate the development and validation of the tissue mass prediction equations, participants were randomly assigned to two groups: a generation sample used to develop the prediction equations (Arthurs and Andrews (2009): $n = 76$: 38 M, 38 F; Holmes et al. (2005): $n = 52$: 20 M, 32 F), and an independent validation sample used to assess their accuracy (Arthurs and Andrews (2009): $n = 24$: 12 M, 12 F; Holmes et al. (2005): $n = 16$; 6 M, 10 F).

37.2.1.2 Surface Anthropometric Measurements

Comprehensive bilateral anthropometric measurements of the upper and lower extremities were taken from participants by trained measurers while they stood in anatomical position in a private room near where the DXA scans were performed within the hospital facilities. A total of six lengths, six circumferences, eight breadths, and four skinfolds were taken from each of the upper and lower extremities, using standard anthropometric measuring equipment, including flexible measuring tapes, anthropometers (Layfayette Instrument Company, Layfayette, IN), and skinfold calipers (Slimguide, Creative Health Products, Plymouth, MI). A full list of the measurements taken can be found in Holmes et al. (2005), Burkhart et al. (2008), and Arthurs and Andrews (2009), but the subsamples of measurements (and descriptions) that were ultimately used as inputs into the tissue mass prediction equations are included in Tables 37.3 and 37.4.

37.2.1.3 DXA Scanning and Scan Analysis

The magnitudes of the actual tissue masses in the upper and lower extremity segments were quantified by having each participant undergo a whole body scan for less than 5 min using DXA (Hologic QDR 4500/W (Holmes et al. 2005), and GE Lunar Prodigy Advance (Arthurs and Andrews 2009)). Participants were scanned in a supine position with upper extremities by their sides. DXA scan files were analyzed using the software that came with each scanner. Segments on each image were manually sectioned by trained analysts using custom regions of interest (ROIs) via segmentation guidelines similar to those used on cadavers by Clarys and Marfell-Jones (1986a) and Dempster (1955). For the upper extremities, arm, forearm, and forearm and hand segments were sectioned (see Table 37.5 for sample ROIs). Comparable sections were taken for the lower extremities, resulting in thigh, leg, and leg and foot segments (Table 37.6).

37.2.1.4 Statistical Analyses

Statistical differences and homogeneity of variance between the generation and validation samples were evaluated using one-way ANOVAs and Levene's test, respectively. Pearson correlation coefficients were computed between all of the anthropometric measurements to establish if any measurements could be eliminated prior to regression analysis. The inclusion of highly correlated variables (i.e., $r \geq 0.70$)

Table 37.3 Description of the upper extremity anthropometric measurements used as prediction equation inputs (see equations in Table 37.7), and the associated mean (SD) measurements

Anthropometric variables		Description	Mean (SD) (cm)	Mean difference (cm)	
				Between	Within
$x1$	Sex	0 for females; 1 for males			
$x2$	Height (m)				
$x3$	Body mass (kg)				
$x4$	Elbow circumference	Distance around the epicondyles of the humerus	26.3 (2.7)	0.15	0.04
$x5$	Med. arm length	Distance between the axilla and the joint space just distal to the medial epicondyle of the humerus	24.4 (0.4)	1.28	0.21
$x6$	Styloid circumference	Distance around the radial and ulnar styloids	16.7 (1.6)	0.09	0.06
$x7$	Lat. forearm length	Distance between the lateral aspect of the elbow joint space and the distal aspect of the radial styloid	25.8 (1.5)	1.07	0.10
$x8$	Pos. forearm skinfold	Vertical fold on the posterior aspect of the forearm	0.6 (0.1)	0.03	0.01
$x9$	Med. forearm length	Distance between the medial aspect of the elbow joint space and the distal aspect of the ulnar styloid	25.7 (1.2)	0.13	0.28
$x10$	Pos. arm skinfold	Vertical fold on the posterior aspect of the arm midway between the acromion and olecranon processes	1.5 (0.4)	0.03	0.01
$x11$	Ant. arm skinfold	Vertical fold on the anterior aspect of the arm midway between the acromion and olecranon processes	0.8 (0.3)	0.25	0.04
$x12$	Prox. arm breadth	Distance across the arm between the axilla and deltoid	10.4 (0.7)	1.99	0.18
$x13$	Med. forearm skinfold	Vertical fold on the medial aspect of the forearm	0.6 (0.2)	0.04	0.01
$x14$	Prox. arm circumference	Distance around the arm at the level of the axilla and deltoid	31.2 (4.8)	0.87	0.26
$x15$	Mid-forearm circumference	Distance around the forearm between the elbow joint and styloids	24.0 (2.9)	1.28	0.19
$x16$	Mid-forearm breadth (M-L)	Distance across the forearm at the level of maximum circumference in the frontal plane	8.0 (1.0)	0.17	0.03

(Modified from Holmes et al. 2005; Burkhart et al. 2008; Arthurs and Andrews 2009)

The mean absolute between- and within-measurer errors (cm) for the upper extremity anthropometric measurements were found to be small overall. The variables listed (e.g., $x1$) correspond to the input variables to the tissue mass prediction equations shown in Table 37.7

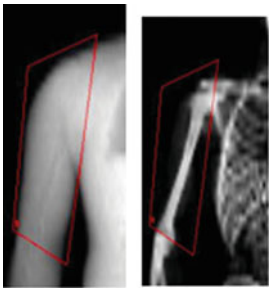
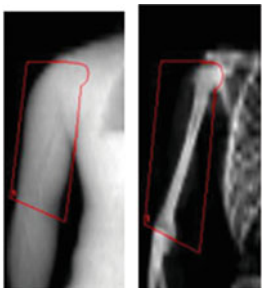
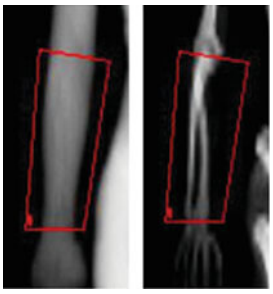
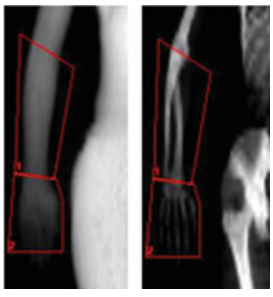
Table 37.4 Description of the lower extremity anthropometric measurements used as prediction equation inputs (see equations in Table 37.7), and the associated mean (SD) measurements

Anthropometric variables		Description	Mean (SD) (cm)	Mean difference (cm)	
				Between	Within
*x*17	Prox. mid-thigh length	Distance between the anterior level of the pubis symphysis and the medial aspect of the femur midway between the superior iliac crest and the tibial plateau	24.4 (3.8)	1.76	0.58
*x*18	Lat. thigh length	Distance between the superior iliac crest and the lateral aspect of the tibial plateau	57.3 (1.7)	0.73	0.17
*x*19	Ant. mid-thigh skinfold	Vertical fold on the anterior aspect of the thigh midway between the superior iliac crest and the tibial plateau	1.9 (0.8)	0.25	0.03
*x*20	Mid-thigh breadth (M-L)	Distance across the femur and overlying tissue midway between the superior iliac crest and the tibial plateau	15.5 (0.2)	0.08	0.11
*x*21	Prox. mid-calf length	Distance between the medial aspect of the tibial plateau and the medial malleoli	16.6 (0.6)	3.94	0.56
*x*22	Med. mid-calf skinfold	Vertical fold on the medial aspect of the unweighted calf at the level of maximum circumference	1.3 (0.5)	0.04	0.04
*x*23	Mid-calf breadth (M-L)	Distance across the tibia and fibula at the level of maximum calf circumference	10.5 (0.0)	0.03	0.07
*x*24	Prox. thigh circumference	Distance around the femur and overlying tissue just inferior to the gluteal fold	58.5 (0.6)	1.15	0.19
*x*25	Mid-thigh circumference	Distance around the femur and overlying tissues midway between the superior iliac crest and the tibial plateau	53.8 (1.3)	0.58	0.73
*x*26	Mid-thigh breadth (A-P)	Distance across the femur midway between the superior iliac crest and the tibial plateau in the sagital plane	16.8 (0.6)	0.14	0.22
*x*27	Knee circumference	Distance around the outmost projections of the tibia	33.9 (3.4)	0.43	0.10
*x*28	Mid-calf breadth (A-P)	Distance across the tibia and fibula at the level of maximum calf circumference	10.9 (0.3)	1.35	0.03
*x*29	Malleoli breadth	Distance between the most lateral and medial projections of the tibia and fibula	6.9 (0.7)	0.19	0.03
*x*30	Lateral leg length	Distance between the lateral aspect of the tibial plateau and the inferior base of the lateral malleoli	41.8 (2.1)	0.58	0.47
*x*31	Malleoli circumference	Distance around the most lateral and medial projections of the tibia and fibula	25.6 (2.1)	0.19	0.03
*x*32	Ankle circumference	Distance around the tibia and fibula, just superior to the malleoli	26.5 (1.6)	0.85	0.22

Modified from Holmes et al. (2005), Burkhart et al. (2008), Arthurs and Andrews (2009)

The mean absolute between- and within-measurer errors (cm) for the lower extremity anthropometric measurements were found to be small overall. The variables listed correspond to the input variables to the tissue mass prediction equations shown in Table 37.7

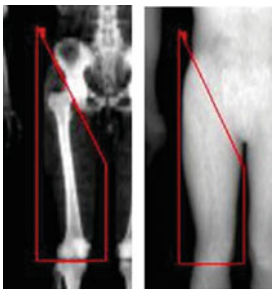
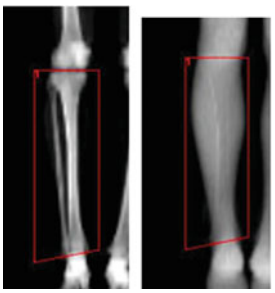
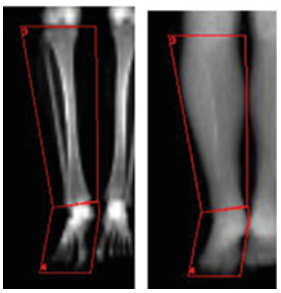
Table 37.5 Sample regions of interest (ROIs) used to manually segment the upper extremities from DXA scans and the corresponding mean (SD) upper extremity tissue masses

Regions of interest (ROIs)	Segment tissue masses		Mean ICC	
	*Arm with shoulder*	Mean (g)	Between	Within
	Wobbling mass	2,416 (728)	0.995	0.992
	Bone mineral content	99 (28)	0.992	0.987
	Fat mass	599 (251)	0.997	0.995
	Lean mass	1,816 (685)	0.996	0.994
	*Arm*			
	Wobbling mass	2,248 (672)	0.996	0.996
	Bone mineral content	92 (156)	0.993	0.994
	Fat mass	560 (229)	0.993	0.998
	Lean mass	1,695 (651)	0.999	0.996
	*Forearm*			
	Wobbling mass	978 (279)	0.992	0.996
	Bone mineral content	73 (20)	0.991	0.994
	Fat mass	90 (54)	0.998	0.996
	Lean mass	887 (281)	0.994	0.997
	*Forearm and hand*			
	Wobbling mass	1,211 (301)	0.997	0.998
	Bone mineral content	97 (27)	0.996	0.995
	Fat mass	94 (54)	0.991	0.994
	Lean mass	1,111 (356)	0.998	0.998

Modified from Burkhart et al. (2009)

The method of upper extremity manual segmentation was found to be highly reliable between and within measurers. Reliability was assessed using intra-class correlation coefficients (ICC) with high reliability occurring at an ICC of ≥0.75

Table 37.6 Sample regions of interest (ROIs) used to manually segment the lower extremities from DXA scans, and the corresponding mean (SD) lower extremity tissue masses

Regions of interest (ROIs)	Segment tissue masses		Mean ICC	
	*Thigh*	Mean (g)	Between	Within
	Wobbling mass	8,678 (1,735)	0.995	0.993
	Bone mineral content	262 (59)	0.999	0.998
	Fat mass	2,813 (1,135)	0.998	0.998
	Lean mass	5,415 (1,500)	0.996	0.995
	*Leg*			
	Wobbling mass	2,790 (463)	0.996	0.998
	Bone mineral content	214 (45)	0.991	0.998
	Fat mass	664 (273)	0.999	0.999
	Lean mass	2,142 (451)	0.998	0.999
	*Leg and foot*			
	Wobbling mass	3,564 (593)	0.999	0.999
	Bone mineral content	293 (63)	1.000	0.999
	Fat mass	736 (285)	0.999	0.997
	Lean mass	2,611 (585)	1.000	0.999

Modified from Burkhart et al. (2009)
The method of lower extremity manual segmentation was found to be highly reliable between and within measurers. Reliability was assessed using intra-class correlation coefficients (ICC) with high reliability occurring at an ICC of ≥0.75

was assessed in terms of how difficult and reliable (Burkhart et al. 2008) they were to collect. Prediction equations were then developed for wobbling mass (WM), bone mineral content (BMC), fat mass (FM), and lean mass (LM) for the individual upper and lower extremity segments using forward/backward multivariate linear regression analysis. Anthropometric measurements were added and eliminated via the regression analyses until the final models that explained the most variance were generated.

37.2.1.5 Prediction Equation Accuracy

Anthropometric data from the independent group of participants in the validation sample were input into the developed equations to assess equation accuracy. Accuracy of the predicted tissue masses was assessed via absolute errors (g) and percentage (%) errors with respect to the measured tissue masses from DXA. Simple linear regression was performed to quantify the amount of variance (R^2 values) in measured tissue masses explained by the predicted masses.

37.2.2 Reliability of Measurement Methods

Two studies are reported here that determined the between- and within-measurer reliability of the upper and lower extremity anthropometric measurements needed to develop the tissue mass prediction equations described herein. Between- and within-measurer reliability was also quantified for the process of manually segmenting the upper and lower extremities from DXA scans using the ROI option available in the scan software.

37.2.2.1 Surface Anthropometric Measurements

Fifty healthy, young adults (25 M, 25 F; 22.5 (2.79) years old, 72.3 (13.3) kg, 1.72 (0.09) m) were recruited from the University of Windsor student population. Anthropometric measurements, including six lengths, six circumferences, eight breadths, and four skinfold thicknesses, were taken from the right upper and lower extremities, by two trained measurers using the standard anthropometric measuring equipment described previously (flexible measuring tape, anthropometer, and skinfold calipers). A full list of the measurements taken can be found in Burkhart et al. (2008), but a sample of the measurements and the descriptions that incorporate the anatomical landmarks used to measure them, are included in Tables 37.3 and 37.4. Prior to measurement, anatomical landmarks were identified using 0.64 cm diameter colored stickers, as participants stood in anatomical position. After all anthropometric measurements were recorded, the stickers were removed, and the procedure was repeated by the same measurer without reference to the first set of measurements. Separately, and without feedback, the second measurer repeated the measurement protocol.

37.2.2.2 Manual Segmentation from DXA Scans

Using enCORE software (2006, GE Healthcare, v. 10.51.006), custom ROIs were traced manually over the DXA scan images by three trained measurers to segment the upper and lower extremities of the 100 participants described in Arthur and Andrews (2009). Sample ROIs for the upper and lower extremities are included in Tables 37.5 and 37.6, respectively. The criteria for determining the ROI borders were adapted from the segmentation methods presented by Clarys and Marfell-Jones (1986a) and Dempster (1955). The measurers segmented each segment twice independently using the original DXA scans (i.e., no ROIs or personal information were included on the scans to help the measurers). Segmentations for all participants were completed by each measurer before repeating the procedure, and the order in which the measurers segmented the upper and lower extremities was randomized. Segment tissue masses, including WM, BMC, FM, and LM, from within each ROI were recorded for analysis.

37.2.2.3 Statistical Analyses

Errors in tissue masses were expressed as percentage (%) errors (the difference in tissue masses between trials (within-measurer error) and between measurers (between-measurer error), divided by the mean tissue masses of each segment (Burkhart et al. 2008)). Intraclass correlation coefficients (ICCs) were used to quantify between- and within-measurer reliability. Good to excellent reliability was accepted for ICCs ≥ 0.75 (Portney and Watkins 2000).

37.3 Results

37.3.1 Tissue Mass Prediction Equations from Anthropometric Measurements

The generation and validation samples for the upper and lower extremities were compared and standard data preparation techniques were utilized in order to reduce the number of input variables prior to multiple regression analysis (see Statistical Analyses section above).

A total of 24 tissue mass prediction equations were generated for the upper and lower extremities (4 tissues × 6 segments) (Table 37.7) from a total of 32 anthropometric variables, including sex,

Table 37.7 Tissue mass prediction equations for the upper and lower extremities

Tissue type and body segment	Adj. R^2	SEE (g)
Wobbling mass		
Arm = −3349.7 + 64.8($x4$) + 14.1($x3$) − 20.2($x10$) + 71.6($x14$) + 36.3($x5$)	0.96	127.1
Forearm = −1492.8 + 22.1($x15$) + 100.0($x1$) + 4.9($x3$) + 32.2($x7$) + 90.3($x16$)	0.97	49.8
Forearm and hand = −2500.7 + 127.4($x16$) + 29.6($x7$) + 289.2($x2$) + 22.9($x15$) + 127.6($x1$) + 5.0($x3$) + 20.5($x9$)	0.96	69.4
Thigh = −7523.1 + 11.4($x1$) + 76.2($x3$) + 238.2($x26$) + 34.7($x19$) + 57.5($x18$) + 42.1($x24$)	0.89	419.0
Leg = −5263.5 − 4.0($x1$) + 37.2($x31$) + 9.3($x22$) + 11.0($x30$) + 38.1($x32$) + 230.6($x28$) + 915.1($x2$) + 42.2($x27$)	0.92	121.0
Leg and foot = −6612.428 + 14.7($x1$) + 1563.5($x2$) + 73.2($x27$) + 250.6($x28$) + 78.0($x31$)	0.92	139.0
Bone mineral content		
Arm = −310.1 + 5.5($x4$) + 102.1($x2$) + 3.4($x5$)	0.87	79.7
Forearm = −196.3 + 4.3($x6$) + 37.9($x2$) + 3.0($x4$) + 2.3($x7$) − 1.1($x8$)	0.86	7.7
Forearm and hand = −269.6 + 6.7($x6$) + 54.8($x2$) + 3.7($x4$) + 3.2($x9$) − 1.5($x8$)	0.84	10.7
Thigh = −444.4 + 18.3($x1$) + 275.3($x2$) − 1.7($x17$) + 3.5($x18$) − 1.8($x19$) + 7.5($x20$)	0.74	26.0
Leg = −85.5 + 0.1($x1$) + 3.1($x3$) + 4.2($x21$)	0.67	22.0
Leg and Foot = −173.7 − 1.6($x1$) + 3.2($x3$) + 4.4($x21$) − 1.4($x22$) + 12.2($x23$)	0.74	24.0
Fat mass		
Arm = −653.9 + 18.6($x10$) + 7.7($x3$) + 21.1($x11$) − 95.0($x1$) + 30.2($x12$)	0.87	79.7
Forearm = 148.9 + 10.5($x8$) + 2.0($x3$) + 11.0($x13$) − 180.8($x2$)	0.86	22.5
Forearm and hand = 135.6 + 10.3($x8$) + 2.1($x3$) + 10.9($x13$) − 173.1($x2$)	0.86	22.4
Thigh = −5796.8 − 622.7($x1$) + 83.6($x19$) + 120.0($x24$) − 110.3($x25$) + 191.2($x26$) + 1301.7($x2$)	0.89	431.0
Leg = −927.8 − 140.3($x1$) + 44.8($x22$) + 29.6($x27$)	0.81	193.0
Leg and foot = −1052.8 − 96.3($x1$) + 42.9(22) + 37.0(27)	0.78	200.0
Lean mass		
Arm = −3621.6 + 85.8($x4$) − 37.8($x10$) + 75.4($x14$) + 55.1($x5$) − 27.8($x11$)	0.94	154.8
Forearm = −2193.0 + 49.3($x6$) − 24.6($x13$) + 21.2($x15$) + 26.8($x7$) + 76.2($x16$) + 339.1($x2$) + 45.2($x1$)	0.97	50.5
Forearm and hand = −2837.1 + 66.2($x6$) − 31.7($x13$) + 19.8(15) + 34.5($x7$) + 15.1($x4$) + 57.3($x1$) + 71.7($x16$) + 400.3($x2$)	0.97	65.4
Thigh = −2826.8 + 718.1($x1$) + 61.9($x3$) − 49.7($x19$) + 79.2($x25$) − 54.9($x24$) + 39.8($x18$) + 123.4($x20$)	0.91	409.0
Leg = −3951.9 + 141.1($x1$) + 105.7($x28$) − 33.2($x22$) + 762.3($x2$) + 176.2($x23$) + 160.9($x29$) + 23.1($x30$)	0.86	187.0
Leg and foot = 4869.8 + 153.6($x1$) + 93.9($x31$) − 34.0($x22$) + 231.2($x23$) + 35.4($x30$) + 920.2($x2$)	0.87	209.0

Modified from Holmes et al. (2005), Burkhart et al. (2008), Arthurs and Andrews (2009)

Tissue mass equations were developed for the arm, forearm, and forearm and hand segments of the upper extremity (n = 100) and the thigh, leg, and leg and foot segments of the lower extremity (n = 68). The corresponding input variables can be found in Tables 37.3 and 37.4

Table 37.8 The mean absolute and percentage errors between the actual and predicted tissue masses for the upper and lower extremity segments

	Error		
Tissue mass and segment	Absolute (g)	Percentage (%)	Adj. R^2
Wobbling mass			
Arm	0.3	0.1	0.97
Forearm	−14.2	−0.1	0.95
Forearm and hand	−13.0	−0.4	0.92
Thigh	26.1	0.7	0.85
Leg	91.6	3.7	0.91
Leg and foot	93.7	3.0	0.95
Bone mineral content			
Arm	2.6	4.3	0.70
Forearm	0.6	1.7	0.81
Forearm and hand	0.9	1.9	0.80
Thigh	7.7	5.1	0.78
Leg	9.6	7.3	0.49
Leg and foot	7.4	5.6	0.51
Fat mass			
Arm	−17.3	1.2	0.91
Forearm	7.1	1.2	0.76
Forearm and hand	7.0	12.5	0.77
Thigh	−272.7	−11.3	0.67
Leg	3.0	5.9	0.61
Leg and foot	−36.8	−0.8	0.63
Lean mass			
Arm	30.6	3.2	0.95
Forearm	−21.0	0.0	0.68
Forearm and hand	−30.8	−2.2	0.94
Thigh	64.9	2.2	0.92
Leg	68.1	4.5	0.90
Leg and foot	96.2	4.7	0.92

Modified from Holmes et al. (2005) and Arthurs and Andrews (2009)
The small absolute (g) and percentage (%) errors combined with the high agreement (Adj. R^2) between the actual (measured from DXA) and predicted (from tissue mass equations) tissue masses validate the use of prediction equations for calculating segmental bone mineral content, fat mass, and lean mass of the upper and lower extremities

height, and body mass (Tables 37.3 and 37.4). Equations with the lowest number of predictor variables that explained the most variance in tissue mass outputs (highest adjusted R^2) comprised the final regression models. The final equations incorporated three to eight variables and exhibited high adjusted R^2 values, ranging from 0.84 to 0.97 and 0.67 to 0.92 for the upper and lower extremities, respectively.

The mean absolute errors between the predicted and the measured tissue masses were small in general, ranging from < 1.0 g for several tissues in the upper extremity, to just over 270 g for the FM of the thigh (Table 37.8). Mean percent errors ranged from 0.1% to 12.5% across both extremities, with only 2 of 24 error measures > 10.0% in magnitude. The predicted and measured tissue masses were highly correlated in general with strong linear relationships and high R^2 values ranging from 0.68 to 0.97 and 0.49 to 0.95, for the upper and lower extremity segments, respectively (Table 37.8).

37.3.2 Reliability of Measurement Methods

37.3.2.1 Surface Anthropometric Measurements

Over 70% of the between-measurer differences in the upper and lower extremity anthropometric measurements used for the tissue mass prediction equations were < 1.0 cm in magnitude, whereas all within-measurer measurement differences were less than this amount for the same variables (Tables 37.3 and 37.4). Averaged across measurement type, length measurements had the highest between- and within-measurement differences for both the upper and lower extremities at 1.35 and 0.34 cm, respectively. Skinfold measurement differences were the lowest on average, at 0.11 and 0.02 cm.

Almost 90% of the between-measurer ICCs for the upper and lower extremity anthropometric measurements used in the tissue mass prediction equations demonstrated good to excellent reliability, with more than half being greater than 0.90 (Table 37.9). Within-measurer ICCs were higher on average than between-measurer ICC, with all within-measurer coefficients demonstrating good to excellent reliability.

37.3.2.2 Manual Segmentation from DXA Scans

The overall percentage errors across all segments and tissue types were relatively small between measurers, ranging between 1.1% and 6.0%, with the maximum values being in the upper extremity for the forearm (4.79%) and BMC (6.0%) (Fig. 37.1). All of the within-measurer errors were less than 5.0% in magnitude. The largest mean within-measurer errors were found in the upper extremity for the arm with shoulder segment (4.5%) and for FM (4.1%).

In all cases, the mean between- and within-measurer ICCs for the upper and lower extremities (ranging from 0.991 to 1.000) far exceeded the 0.75 criterion set as good to excellent reliability (Tables 37.5 and 37.6). The ICC values across the different segments and tissue types were consistently very high, but were highest in the lower extremity for the leg and foot segment and for BMC.

37.4 Discussion

The methods by which regression equations for predicting upper and lower extremity soft and rigid tissue masses in living subjects were developed and validated by using surface anthropometric measures and DXA have been described. In general, the prediction equations were shown to result in tissue masses that compared very favorably to those measured using DXA. The reliability of the anthropometric measures used as inputs to the prediction equations, and of the tissue masses resulting from the manual segmentation of the DXA scan images, were also highlighted, and were very high in magnitude across all tissue types and segments.

In general, the predicted tissue masses from the developed equations were highly correlated with the masses measured from DXA and comparable to previous efforts in the literature (Jackson and Pollock 1977; Lean et al. 1996). Although the errors in anthropometric measurements and tissue mass predictions were small overall, it is important to acknowledge and evaluate those aspects of the procedures and techniques, which might have contributed negatively, even in a small way, to the outcomes. Therefore, the following discussion will be focused on specific issues related to the regression procedures used, and the sources of error associated with obtaining the anthropometric measures

Table 37.9 Between- and within-measurer reliability coefficients (ICCs) for the anthropometric measurements used as inputs to the tissue mass prediction equations

Anthropometric variables		ICCs	
		Between	Within
$x1$	Sex		
$x2$	Height (m)		
$x3$	Body mass (kg)		
Upper extremity			
$x4$	Elbow circumference	0.985	0.986
$x5$	Med. arm length	0.846	0.802
$x6$	Styloid circumference	0.985	0.975
$x7$	Lat. forearm length	0.881	0.865
$x8$	Pos. forearm skinfold	0.894	0.908
$x9$	Med. forearm length	0.887	0.817
$x10$	Pos. arm skinfold	0.957	0.962
$x11$	Ant. arm skinfold	0.867	0.878
$x12$	Prox. arm breadth	0.590	0.872
$x13$	Med. forearm skinfold	0.960	0.946
$x14$	Prox. arm circumference	0.942	0.899
$x15$	Mid-forearm circumference	0.929	0.960
$x16$	Mid-forearm breadth (M-L)	0.939	0.934
Lower extremity			
$x17$	Prox. mid-thigh length	0.814	0.911
$x18$	Lat. thigh length	0.939	0.943
$x19$	Ant. mid-thigh skinfold	0.967	0.968
$x20$	Mid-thigh breadth (M-L)	0.856	0.892
$x21$	Prox. mid-calf length	0.266	0.768
$x22$	Med. mid-calf skinfold	0.942	0.960
$x23$	Mid-calf breadth (M-L)	0.623	0.937
$x24$	Prox. thigh circumference	0.964	0.974
$x25$	Mid-thigh circumference	0.883	0.873
$x26$	Mid-thigh breadth (A-P)	0.920	0.896
$x27$	Knee circumference	0.966	0.994
$x28$	Mid-calf breadth (A-P)	0.850	0.938
$x29$	Malleoli breadth	0.983	0.981
$x30$	Lateral leg length	0.894	0.889
$x31$	Malleoli circumference	0.972	0.952
$x32$	Ankle circumference	0.991	0.994

Modified from Burkhart et al. (2008) and Arthurs and Andrews (2009)
Anthropometric measurements were found to be highly reliable between and within measurer. Results are presented as ICCs and high reliability was attained at a value ≥0.75

(used as regression inputs) and during the quantification of criterion tissue masses from DXA scan images (that have been used for validation purposes).

37.4.1 Regression Procedures

In determining the full range of anthropometric measurements that would be originally considered as inputs into the regression analyses, a mix of measurement types was targeted, as it was the intent

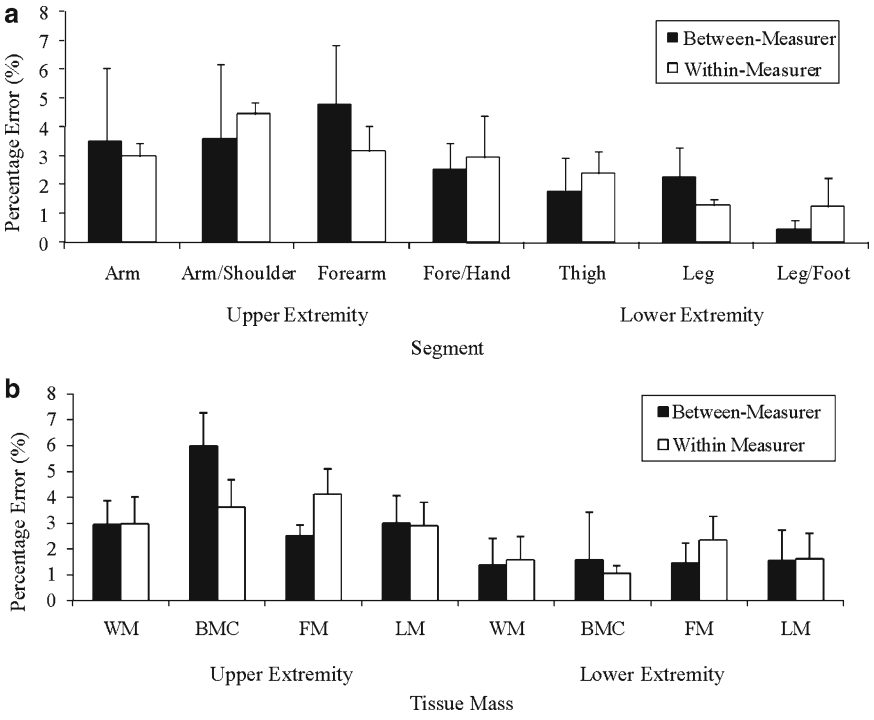


Fig. 37.1 Between- and within-measurer errors associated with specific segments (**a**) and tissue masses (**b**) from manually segmented DXA scans. Manual segmentation of DXA scan images resulted in small between- and within-measurer percentage errors. Results are shown as mean (SD) percentage errors (Modified from Burkhart et al. 2009)

to be able to predict both soft and rigid tissue masses equally well. Consequently, measurements such as circumferences and skinfolds, were selected because it was thought that these types of measurements would be more reflective of soft tissue mass than lengths and breadths. Lengths and breadths were also selected, as they have been conventionally associated with the prediction of BMC (e.g., Clarys and Marfell-Jones 1986b).

The decision of which variables to include in each regression analysis depended, in part, on how highly correlated the variables were. The most reliable (as per Burkhart et al. 2008) of two highly correlated variables would have been selected for inclusion in the regression analysis. In a few cases, input variables were eliminated based on the relative ease with which the type (e.g., breadths and lengths), and direction of the measurements (e.g., medio-lateral and antero-posterior) were taken. For example, if medial and lateral arm length had been equally predictive, the lateral arm length might have been selected because it is easier for the measurer to obtain and did not require the axilla to be landmarked, which was uncomfortable for some participants. If the reliability and ease of measurement of two highly correlated variables were similar, they were run separately to determine which resulted in the equation that explained the most variance. In these ways, the number of input variables was reduced while keeping the most reliable and easily measured variables available for equation generation.

37.4.2 Surface Anthropometric Measurements

The methods used to take the anthropometric measurements in this work are a potential source of systematic bias that may have resulted in the within-measurer differences that were reported. Measurement differences in circumferences, breadths, and skinfolds specifically can result when the soft tissues beneath and between the measuring tape and calipers are compressed. This effect is most evident when measurements around fleshy parts of segments (e.g., proximal arm or thigh circumference) are compared to those around bony processes with little underlying soft tissue (e.g., styloid or malleoli circumference).

The between-measurer differences in anthropometric measurements may be explained, in part, by the method used for anatomical landmark identification. For example, in the reliability study described herein, the sticker placed at the mid-leg location was used as a point of reference for four different anthropometric measurements for the leg (including mid-calf breadth and medial mid-calf skinfold: Table 37.4). Small variances in the placement of the mid-leg sticker between measurers would therefore have had a significant overall effect on multiple measurement outcomes, which would in turn have contributed to reduced equation prediction power (Burkhart et al. 2008).

37.4.3 Manual Segmentation from DXA Scans

The development and validation of the tissue mass prediction equations presented in this chapter were dependent on the use of DXA as the criterion method by which the living tissue masses of the participants were quantified. DXA has been shown previously to be a valid and reliable method for body composition measurement by a number of authors (e.g., Haarbo et al. 1991; Ball et al. 2004). Of particular importance to the current work is that DXA can also provide accurate estimates of both soft and rigid tissue masses for the whole body from a single scan. Despite the advantages of using DXA, all methods have limitations which can contribute to errors in tissue mass estimates.

Systematic bias in the DXA tissue masses could have resulted from reduced image quality caused by participants moving during scanning (Cawkwell 1998) and by the level of training of the measurers who carried out the segmentations (Atkinson and Nevill 1998). Discerning soft tissue edges and joint spaces may have been particularly affected by movement. However, this source of error was limited as much as possible by having very quick scans and vigilant technicians. Further, while no research on expertise using DXA has specifically studied manual segmentation, Lewiecki et al. (2006) comment on the importance of utilizing highly trained and qualified personnel to improve the quality of bone mineral density analysis. To this end, the three analysts in the current work received extensive training and demonstrated very high between- and within-measurer reliability on the tissue masses obtained from DXA, as a result.

Errors in the rigid tissue mass estimates (BMC) were likely caused, in part, by visualizing joint geometries, and determining where the proximal and distal borders of the ROIs were placed during segmentation. As the DXA images only provided a frontal view of the participants, any bony landmark on the posterior aspect of joints and segments would not be able to be accounted for by the analyst. The wider the joint space between segments, the easier was the segmentation. The lower mean percentage errors for the lower extremity segments may be attributed to the fact that the joint space between the femoral condyles and the tibial plateau is generally wider and more easily discernable on the scans than the elbow joint space in the upper extremities.

Soft tissue measurement errors are more attributable to the placement of the medial and lateral borders of the ROIs. A limitation of the imaging software used in this work was the inability to draw smooth curved lines. Consequently, if different body parts are pressed tightly together in an image, soft tissue from one segment might be incorrectly attributed to another segment when using ROIs. The closer the segments are to each other, the harder it is for the analyst to slice the segments cleanly. The upper extremities were most affected by this issue due to the arms being held along the sides during scanning, positioning that was done in order to keep the arms within the scan boundaries on the DXA machine bed. This may also help explain why the percentage errors in upper extremity tissue masses were greater on average compared to the lower extremity.

The validity of DXA under different physiologic conditions, including hydration, must also be considered as a contributing factor to soft tissue mass errors. DXA has been shown to overestimate fat content when the people being scanned are hydrated more than average, as DXA assumes that the hydration of fat-free tissue remains constant (Laskey and Phil 1996). Although hydration was not controlled in the experiments described herein, its overall effect was deemed to be minimal based on previous evaluations (e.g., Lohman and Going 1998).

37.4.4 Recommendations for Future Research

The work presented herein is limited in several important ways. The most important limitation is that the generalizability of the prediction equations developed to date (Holmes et al. 2005; Arthurs and Andrews 2009) is restricted to healthy, young adults (17–30 years of age). Body composition has been shown to fluctuate with age (Baumgartner 2000), sex (Daniels et al. 1997), and health status (Poehlman et al. 1995). To improve the generalizability of the equations, large numbers of working-age and older adults and children with body compositions characteristic of the general population, from underweight to overweight, need to be sampled. Current work has also been limited to the extremities due to the challenges of working with the trunk and head. How the masses are actually distributed within the segments is also not represented by the developed equations. Mass distribution will have a significant effect on the determination of body segment parameters, such as radius of gyration and moment of inertia, which play a major role in biomechanical analyses of dynamic human movements.

More work is also needed to determine the impact that the anthropometric measurement errors have on the predicted tissue masses quantified using the developed equations. Learning what measurements are most difficult to carry out will help during training. Knowing how much error in the predicted tissue masses can result as a function of how well the anthropometric measurements are taken is critical in terms of providing the user an idea of how much variability in tissue masses can be expected compared to other measurement techniques.

The impact of factors, such as body mass and overall body fat percentage, on soft tissue mass estimation using manual ROIs in DXA software, also needs to be investigated further. The range of body masses and body fat percentages in this work was fairly limited compared to the general population, and may contribute to greater errors when larger and heavier people are analyzed.

37.4.5 Applications to Other Areas of Health and Disease

The developed prediction equations provide a means by which the mass of the soft and rigid tissues of the upper and lower extremities of young people can be determined using simple surface anthropometric measurements, without the need for expensive imaging technologies. Although the exposure to radiation during a whole body DXA scan is very small compared to other X-ray based technologies (Haarbo et al. 1991), bypassing the need to scan living subjects in order to obtain regional tissue mass composition information has definite health benefits to the subject and technician. Having the ability to predict the mass of tissues other than fat, to which traditional skinfold measurement techniques are restricted, helps to extend their use to other health applications. For example, bone tissue degeneration, that is characteristic of osteoporosis, could be monitored over time without the need to scan individuals repeatedly. Being able to determine the ratio of bone mineral content to muscle or fat within a segment may also have implications for injury risk prediction, as the soft and rigid tissue properties may play an important role with respect to the development of stress fractures in some athletes (Milner et al. 2006).

Summary Points

- A total of 24 tissue mass prediction equations for the segments of the upper and lower extremity that use surface anthropometric measurements such as lengths, breadths, circumferences, and skinfolds as inputs were presented.
- Soft (e.g., wobbling mass, lean mass, and fat mass) and rigid (bone) tissue mass estimates from the predicted equations compared very well to measured tissue masses from DXA.
- Accurate and reliable person-specific tissue mass information can therefore be obtained without the need to scan participants with technologies such as DXA.
- The anthropometric measurements used as inputs into the equations were found to have excellent reliability between and within measurer.
- The process of manually segmenting DXA images using regions of interest for obtaining the upper and lower extremity soft and rigid tissue masses of living subjects was also found to have excellent between- and within-measurer reliability.
- More prediction equations need to be developed for other populations including older adults and children, for people of varying body compositions, and for other body segments such as the trunk and head.

Acknowledgments The authors wish to thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for funding this research. Thanks also to Diagnostic Imaging at Windsor Regional Hospital and Nuclear Medicine at McMaster University Medical Centre for the use of their facilities, equipment, and technical support, and to the people who agreed to participate in the studies described in this chapter.

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Chapter 38
Demographic Trends in Mid-Arm Circumference in Children and Adults over a 35-Year Period

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Abstract Upper mid-arm circumference, measured in a standard way, has been used as an indicator of nutrition, for tracking malnutrition and obesity in populations and as a guide to proper sized cuff selection in the indirect measure of blood pressure. There are few published national data from which to observe changes in arm circumference over time that are gender-specific, in a wide range of ages from infancy through old age. The present chapter presents such detailed tables for the United States for the first time. The span of time covered is 35 years, from 1971 to 2006. Arm circumference adjusted for age and gender increased steadily over the earlier parts of this period but shows some signs of leveling off in the most recent periods. The increase over time has been greater among children and young adults than among older age groups. The increase in mid-arm circumference is mirrored both by an increase in stature and an increase in obesity. Detailed age-sex-specific tables are presented

Abbreviations

BMI	Body mass index
MA	Mexican American
NHANES	National Health and Nutrition Examination Survey
NHB	Non-Hispanic black
NHW	Non-Hispanic white

38.1 Introduction

Mid-arm circumference reflects the stature and nutritional status of individuals. It is an anthropometric measurement that is of importance in establishing obesity patterns and blood pressure measurement standards in populations. This measurement, on the right arm, has been a standard anthropometric measure in all National Health and Nutrition Examination Surveys (NHANES) of the National Center for Health Statistics, Centers for Disease Control and Prevention in the USA.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_38,

We previously reported on trends in the USA for mid-arm circumference in adults from 1988 to 2002 (Ostchega et al. 2005) and in children from 1988 to 2004 (Prineas et al. 2007). Among adults, mid-arm circumference increased significantly for both males and females between the two adult surveys (NHANES III and NHANES 1999–2002) for all year age groups (those 20 years or older through 60 years and older). The greatest increase occurred in the 20–59-year age group. The overall increase was true for blacks and whites, but not for Mexican-American women.

Among children (ages 7–17 years), the periods examined were NHANES III and NHANES 1999–2004. Across these two surveys, girls 7–12 and 13–17 years of age, and boys 7–12 years of age showed significant increase in mid-arm circumference. We now extend these findings by examining earlier surveys (NHANES I and NHANES II) and later NHANES periods including 2003–2006, that is, for a 35-year time span. Further, we have extended the data to include infants and the end of childhood ages so that children of ages 1–19 years are tabulated and analyzed separately from adults 20 to 74 years of age.

38.2 Data Sources

38.2.1 Populations Surveyed

The National Health and Nutrition Examination Survey (NHANES) program of the National Center for Health Statistics, Centers for Disease Control and Prevention, includes a series of cross-sectional nationally representative health examination surveys beginning in 1960. In each survey, a nationally representative sample of the US civilian non-institutionalized population was selected using a complex, stratified, multistage probability cluster sampling design (US Department of Health and Human Services 2006). A home interview was followed by a physical examination in a mobile examination center. Beginning in1999, NHANES became a continuous survey. The procedures followed to select the sample and conduct the interview and examination were similar to those for previous surveys (Lewis et al. 2003).

Since 1960, there have been eight periodic surveys; this chapter will focus on the first, second, and third National Health and Nutrition Examination Surveys (NHANES I, 1971–1974; NHANES II, 1976–1980; and NHANES III, 1988–1994), and on two periods of the current continuous surveys (NHANES 1999–2002 and NHANES 2003–2006). The age range for NHANES I was 1–74 years; for NHANES II, 6 months to 74 years; and for NHANES III, 2 months and older; for NHANES 1999–2002 and NHANES 2003–2006, there were no age limits. Trends in mean arm circumference are based on comparisons of data on children and adults aged 1–74 years from five surveys: NHANES I (1971–1974) (n = 20,685); NHANES II (1976–1980) (n = 19,899); NHANES III (1988–1994) (n = 25,871); NHANES 1999–2002 (n = 17,014); and NHANES 2003–2006 (n = 16,773).

In NHANES III and in the current survey, the race/ethnic group based on self-report was categorized as non-Hispanic white (NHW), non-Hispanic black (NHB), Mexican American (MA), or other. In previous national surveys, the group was based on observation, and categorized as white, black, or other. In NHANES II, but not in previous surveys, information on Hispanic origin was also collected. Subjects in NHANES II were also categorized as non-Hispanic white, non-Hispanic black, or other. However, NHANES II did not have an adequate sample size to permit separate estimates for Mexican Americans. Therefore, arm circumference and its relationship with race ethnicity (NHW, NHB, and MA) was analyzed using NHANES III and current continuous NHANES data only.

38.2.2 Measurements and Indices Used in the Tables of This Chapter

Mid-arm circumference has been measured consistently in the same standard way since NHANES I (1971–1974), as detailed below under Sect. 38.4. Height in centimeters and weight in kilograms were measured in the mobile examination center following a standard protocol (for height: using a stadiometer with the examinee without shoes; for weight: using a platform balance Toledo scale, with the examinee without shoes and heavy outer clothing). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

38.3 Applications to Other Areas of Health and Disease

Mid-arm circumference is a necessary measurement for the selection of correct cuff size for measuring blood pressure. The cuff-bladder width to mid-arm circumference ratio (CW/AC) affects the determination of blood pressure level with the usual indirect clinical measurement methods (Rastam et al. 1990; Sprafka et al. 1991). As early as the 1950s, Smirk (1957) showed that the effect of this soft-tissue factor was independent of the underlying tissue whether it be fat or muscle, and this has recently been confirmed for muscular arms (Fonseca-Reyes et al. 2009).

38.4 Practical Methods and Technique

38.4.1 Measuring Mid-Arm Circumference

(a) Standard measurement of the mid-upper arm circumference involves the examinee standing erect with the right arm by the side and flexed 90° at the elbow. Then, the arm is measured from the outer edge of the acromial process to the olecranon process of the ulna. The instructions for the measuring technician are: mark the outer edge of the acromial process first, then place the tape (a steel or non-stretchable tape checked against a standard) on the mark, and locate the midpoint between the acromial and olecranon processes. Mark this midpoint carefully. This is the level at which the measurement is taken to the nearest 0.1 cm. The tape should fit snugly against the skin in the whole circumference of the arm without indenting the skin. The right arm is chosen as standard in national statistical studies.

(b) Comparison of mid-arm circumference between a reference population and study population, or for an individual and a reference population standard, can best be expressed as a *Z*-score (also known as a standard deviation score), rather than as a percentile comparison. *Z*-score = (observed value) - (median reference value)/standard deviation of reference population. A fixed *Z*-score interval indicates fixed mid-arm circumference difference for persons of a given age and gender (WHO 1995). From a group of *Z*-scores in population-based applications, the mean and standard deviation of the *Z*-scores can be calculated. The problem arises then as how to construct a standard population for reference of individuals and study populations. This can no longer rest on NHANES II data that were earlier used by WHO because the population is now no longer well nourished, in that, a great proportion of the population is now obese.

(c) Estimating mid-arm circumference from self-reported anthropometric parameters may be used for inter-population comparison of mid-arm circumferences when one population has

no direct measurements. Tables are available derived from earlier data from NHANES surveys that give separate equations for men and women based on *self-reported* mid-arm circumference (AC) (Ostchega et al. 2006) such that for men: AC cm = 32.52145 + 0.10975 × (weight) – 0.26057 × (height) – 0.03028 × (age); and for women: AC cm = 30.22126 + 0.13534 × (weight) – 0.34121 (height) + 0.09014 × (age) – 0.00082565 × (age^2). These equations differ from those using *measured* height and weight (Ostchega et al. 2004), where for men: AC cm = 31.76749 + 0.22626 × (weight) – 0.10109 × (height) + 0.05092 × (age) – 0.00081813 × (age^2); and for women: AC cm = 39.29946 + 0.26410 × (weight) – 0.18230 × (height) + 0.01972 × (age) – 0.00104 × (age^2) + 0.00045901 × (weight × age) + 0.00037509 × (height × age).

38.4.2 Estimating the Correct Blood Pressure Cuff-Bladder Width from the Mid-Arm Circumference

Cuff-bladder width should be equal to 120% of the diameter of the mid-upper arm in children and adults (Frohlich et al. 1988; Guntheroth and Nadas 1955; Park et al. 1976). This translates to 38% of the circumference of the upper mid-arm [$120\%D = (C \times 120\%)/\pi = 38\%C$, where C = circumference and D = diameter of arm] (Prineas and Elkwiry 1992).The American Heart Association (Frohlich et al. 1988) has used the approximation of 40% for the CW/AC in the past and have also has given useful directions for estimating the correct cuff-bladder width, given the mid-arm-circumference measurement:

(a) "If the manufacturer provides the width of the inflatable bladder … mark this measurement in indelible ink on the cuff. If not, measure the width of the *inflatable bladder* … (Do not measure the cuff width [i.e. the cuff containing the bladder] which is wider).
(b) Multiply the bladder width in centimeters by 2.5 [which gives the reciprocal of CW/AC of 0.4 or 40%]. This calculation is the correct arm circumference for the bladder. Measuring distally from the index line of the cuff, mark this with a line C [from the top to the bottom of the cuff] which indicates the ideal arm circumference."

Then, an acceptable range of mid-arm circumferences can be marked on the cuff with appropriately placed lines on either side of line C. The ranges that are acceptable will depend upon the range of cuff sizes available, but should be within ±4% of a CW/AC of 40% (the ideal ratio) (Prineas 1991). For CW/AC ratios that are too small, the diffusion of the cuff pressure during inflation requires a higher pressure to collapse the brachial artery, and, so, a falsely high blood pressure recording will result. Similarly, a CW/AC ratio that is too large will result in falsely low estimates of blood pressure level (see illustrations in Prineas 1991). The acceptable mid-arm circumference range marked on the cuff is also critical, and probably should be of the order of 38% ± 5%, that is, 33–43%. A larger range than this could lead to unacceptable systematic blood pressure differences between the smallest and largest arm circumference enclosed by the same cuff (Rastam 1990).

Earlier recommendations for appropriate cuff-bladder width, which are still erroneously quoted, required that the cuff size be determined in children both by mid-arm circumference and upper arm length (AL). Such a requirement would require the AC/AL be a constant ratio, which is not the case. In more than 10,000 children aged 6–10 years, the AC/AL ratio varied from 0.4 to 1.9 and was not linearly related to age or height (Prineas and Elkwiry 1992).

Rational standardization of cuff sizes needs to be agreed upon by the interested parties including institutions, manufacturers, and regulatory agencies working together. Despite repeated calls for such action, this has still not been achieved.

38.5 Distributions of Mid-Arm Circumference by Age, Race, and Sex for Children (1–19 Years of Age) and Adults (20–74 Years of Age) in the USA for Five Survey Periods from 1971 to 2006

In the tables below, the *p*-values are for trend of mid-arm circumference measures between surveys, where NHANES I is the reference. Because there is an interaction between age-group*survey, the trend is calculated separately for each age group and gender. Further, the *p*-values need to be adjusted using a Bonferroni adjustment; so, for youth, the significant alpha will be .05/19 = .00263 ~ .002 or .003, for adults .05/5 = .01.

38.5.1 Changes in the Distributions of Mid-Arm Circumference for the Men, Women, Children, and the Total Population by Age Group, Separately

Table 38.1 ((a) children, (b) adults) is a *key summary table* that shows the changes from NHANES I through NHANES 2003–2006. Table 38.1 a for children has a range of 7,620–11,805 sample sizes examined cross-sectionally at five separate time points. For all five survey periods, for all ages (increasing from a mean of 22.25–23.45 cm), and for boys and girls separately, there is a significant steady increase in mid-arm circumference across the survey periods (*p*-value for trend <0.001). However, for ages 1–2 years, the increase is not sustained from NHANES III to NHANES 2003–2006, and there is an actual decrease from NHANES 1999–2002 to NHANES 2003–2006. For ages 3–15 years, the increase is not sustained from NHANES 1999–2002 to the NHANES 2003–2006 survey.

Table 38.1b similarly summarizes the changes for adults from age 20 years through 74 years by three age groups. The sample sizes at each of the five surveys vary from 7,962 to 14,066. Again, the mid-arm circumference increases significantly overall (from 30.68 to 33.14 cm), for each of the three age groups and for men and women separately (*p*-value for trend <0.001). However, for women of ages 60–74 years, the increase is observed across all surveys until 2002; but later, there is a small decrease. Figures 38.1a and 38.1b show the relation of mid-arm circumference with age for males and females separately. It can be seen that there is a steady increase in arm circumference from childhood to adulthood, and a slight decline in old age, across all surveys.

38.5.2 Percentiles of Mid-Arm Circumference by Detailed 1-Year Age Groups for Infants and Children (1–19 Years) for All and for Males and Females Separately for NHANES I and for NHANES 2003–2006

Tables 38.2 and 38.3 show the mean and standard errors of the 1st, 5th, 10th, 25th, 75th, 90th, 95th, and 99th percentiles of age-specific mid-arm circumference for all children and for males and females separately, at two time periods: 1971–1974 and 2003–2006, a span of 32 years. The upper percentiles, 50th through 99th for the total 1–19-year olds are all greater in the later time period, so that the 50th, 75th, 90th, 95th, and 99th centimeter percentile values for 1971–1974/2003/2006 are, respectively: 21.6/22.7, 25.8/27.7, 29.3/32.1, 31.6/34.9, and 36.6/40.4. These differences are reflected generally in each gender and for each separate 1-year age groups, with a few minor exceptions. This indicates that the increase in mid-arm circumference from the early1970s to 2003–2006 is not

Table 38.1 Mid-arm circumference in centimeters by age and survey (key summary table)

	Survey															
	NHANES I			NHANES II			NHANES III			NHANES 1999–2002			NHANES 2003–2006			
	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	P value
(a) Youth																
Total	7,620	22.25	0.08	8,072	22.86	0.11	11,805	22.74	0.12	8,955	23.51	0.11	8,811	23.45	0.15	<.001
1–2 years	1,173	16.01	0.06	1,410	16.16	0.06	2,333	16.23	0.03	1,017	16.14	0.05	1,219	15.84	0.05	<.001
3–5 years	1,766	17.16	0.04	2,330	17.27	0.05	3,157	17.51	0.06	1,073	17.59	0.08	1,195	17.50	0.08	<.001
6–11 years	2,017	20.34	0.10	1,720	20.74	0.11	3,217	21.32	0.16	2,210	21.79	0.16	2,051	21.76	0.13	<.001
12–15 years	1,458	25.25	0.11	1,319	25.57	0.12	1,599	26.52	0.26	2,408	27.03	0.16	2,143	27.17	0.19	<.001
16–19 years	1,206	28.08	0.13	1,293	28.51	0.15	1,499	29.02	0.18	2,247	29.96	0.12	2,203	30.12	0.19	<.001
Male																
Total	3,818	22.54	0.13	4,182	23.16	0.14	5,794	23.00	0.14	4,528	23.81	0.15	4,393	23.70	0.19	<.001
1–2 years	611	16.17	0.08	740	16.30	0.06	1,179	16.32	0.05	543	16.20	0.08	605	15.88	0.05	<.001
3–5 years	886	17.25	0.06	1,210	17.31	0.06	1,526	17.40	0.06	538	17.64	0.11	598	17.54	0.13	0.03
6–11 years	1,000	20.29	0.13	884	20.67	0.13	1,631	21.18	0.17	1,121	21.79	0.17	989	21.57	0.16	<.001
12–15 years	727	25.27	0.12	687	25.85	0.16	751	26.86	0.35	1,156	27.13	0.23	1,090	27.39	0.24	<.001
16–19 years	594	29.54	0.19	661	29.71	0.14	707	30.37	0.25	1,170	31.23	0.16	1,111	31.38	0.25	<.001
Female																
Total	3,802	21.95	0.10	3,890	22.55	0.12	6,011	22.48	0.17	4,427	23.19	0.14	4,418	23.19	0.13	<.001
1–2 years	562	15.85	0.07	670	16.02	0.08	1,154	16.14	0.04	474	16.07	0.07	614	15.79	0.07	<.001
3–5 years	880	17.06	0.07	1,120	17.23	0.07	1,631	17.62	0.09	535	17.55	0.12	597	17.46	0.09	<.001
6–11 years	1,017	20.39	0.13	836	20.81	0.16	1,586	21.47	0.21	1,089	21.78	0.22	1,062	21.97	0.17	<.001
12–15 years	731	25.23	0.17	632	25.28	0.21	848	26.17	0.25	1,252	26.92	0.17	1,053	26.92	0.22	<.001
16–19 years	612	26.64	0.20	632	27.32	0.18	792	27.65	0.21	1,077	28.62	0.17	1,092	28.87	0.24	<.001

(b) Adults															
Total	13,065	30.68	0.06	11,827	31.39	0.07	14,066	32.02	0.09	8,059	33.05	0.09	7,962	33.14	0.11	<.001
20–39 years	5,599	30.14	0.08	4,473	30.65	0.09	6,615	31.37	0.11	3,301	32.60	0.12	3,377	32.63	0.14	<.001
40–59 years	3,434	31.34	0.10	2,941	32.16	0.10	4,245	32.74	0.12	2,744	33.54	0.15	2,684	33.72	0.14	<.001
60–74 years	4,032	30.48	0.09	4,413	31.44	0.12	3,206	31.92	0.12	2,014	33.02	0.11	1,901	33.06	0.11	<.001
Male																
Total	4,974	31.87	0.07	5,584	32.55	0.06	6,621	33.19	0.09	3,773	34.03	0.08	3,792	34.30	0.12	<.001
20–39 years	1,637	32.02	0.11	2,126	32.38	0.08	3,016	32.96	0.12	1,408	33.88	0.11	1,517	34.15	0.16	<.001
40–59 years	1,426	32.17	0.10	1,385	33.05	0.09	1,994	33.71	0.13	1,362	34.44	0.12	1,321	34.72	0.17	0.03
60–74 years	1,911	30.69	0.10	2,073	31.75	0.12	1,611	32.53	0.12	1,003	33.40	0.14	954	33.65	0.17	<.001
Female																
Total	8,091	29.60	0.09	6,243	30.32	0.10	7,445	30.89	0.13	4,286	32.11	0.13	4,170	32.03	0.16	<.001
20–39 years	3,962	28.42	0.09	2,347	29.02	0.13	3,599	29.83	0.18	1,893	31.35	0.18	1,860	31.14	0.22	<.001
40–59 years	2,008	30.56	0.16	1,556	31.36	0.16	2,251	31.82	0.16	1,382	32.69	0.22	1,363	32.77	0.19	<.001
60–74 years	2,121	30.32	0.13	2,340	31.18	0.15	1,595	31.41	0.16	1,011	32.71	0.14	947	32.57	0.18	<.001

Age-adjusted for the entire population, by the direct method, to the US census population projected estimates for the year 2000 using the age groups 20–39, 40–59, and 60–74 years

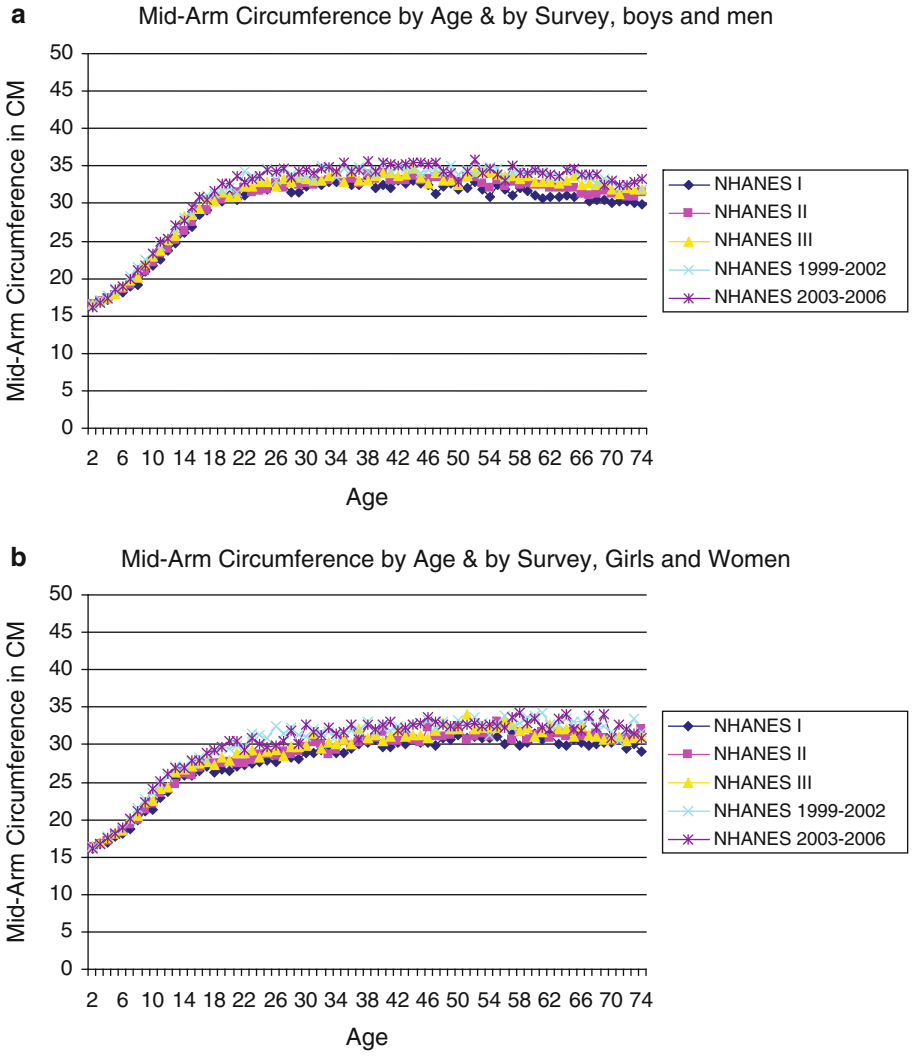

Fig. 38.1 (**a**) Males and (**b**) females, mid-arm circumference by age

just a rise in the mean levels, but is a shift to the right in the whole mid-arm circumference size distribution. There is a steady increase in the 95th percentile values for all children, and boys and girls separately from age 1 year through 19 years, at both time periods.

38.5.3 Changes in the Mid-Arm Circumference for All Children and for Boys and Girls at Each of Five Survey Periods from 1971–1974 to 2003–2006 by Separate Ages from 1 to 19 Years

Table 38.4 shows the mean and standard errors of the mean for each separate 1-year age group from 1 to 19 years, for the total, and for boys and girls separately for the survey periods 1971–1974 (NHANES I), 1976–1980 (NHANES II), 1988–1994 (NHANES III), 1999–2002, and 2003–2006.

Table 38.2 Selected percentiles of mid-arm circumference in centimeters for children aged 1–19 years: Gender all NHANES I, and males and females, separately

	Sample size	Mean	SE mean	1st Ptile	5th Ptile	10th Ptile	25th Ptile	50th Ptile	75th Ptile	90th Ptile	95th Ptile	99th Ptile
Total	7,620	22.3	0.08	14.2	15.3	16.1	17.8	21.6	25.8	29.3	31.6	36.6
1 years	595	15.8	0.08	12.9	13.8	14.2	14.9	15.7	16.5	17.4	18.0	19.2
2 years	578	16.2	0.08	13.4	14.2	14.5	15.3	16.1	16.8	17.7	18.5	20.2
3 years	586	16.8	0.06	13.9	14.6	15.1	15.9	16.7	17.4	18.3	18.9	20.4
4 years	591	17.0	0.06	13.4	14.7	15.2	16.0	17.0	17.9	18.5	19.1	20.4
5 years	589	17.8	0.10	14.2	15.3	15.8	16.5	17.4	18.5	19.6	21.0	25.9
6 years	325	18.0	0.12	14.7	15.6	16.0	16.8	17.7	18.7	20.2	21.1	25.8
7 years	338	18.9	0.15	14.8	15.7	16.6	17.5	18.4	19.8	21.7	22.8	26.0
8 years	301	19.6	0.16	15.4	16.5	17.1	17.9	19.1	20.6	22.7	25.0	27.3
9 years	350	21.0	0.19	16.4	17.5	17.9	18.9	20.5	22.3	24.9	25.7	29.6
10 years	371	21.4	0.18	16.5	17.8	18.4	19.5	21.0	22.7	25.2	26.7	30.8
11 years	332	22.6	0.20	16.9	18.5	19.1	20.4	22.0	24.2	26.6	28.7	34.7
12 years	381	23.7	0.19	18.3	19.3	20.0	21.4	23.1	25.2	27.9	29.3	34.0
13 years	373	25.0	0.24	18.8	20.1	21.3	22.6	24.4	26.7	29.8	31.4	35.4
14 years	365	26.0	0.27	20.4	21.5	22.3	23.5	25.0	27.6	30.7	32.2	37.8
15 years	339	26.4	0.20	19.6	21.7	22.2	24.0	25.8	28.3	30.9	32.3	37.3
16 years	345	27.5	0.20	21.3	22.4	23.4	24.8	26.8	29.2	32.1	34.1	38.7
17 years	325	28.1	0.27	21.5	22.6	23.5	25.3	27.4	30.4	33.6	34.9	38.6
18 years	258	28.1	0.29	20.4	22.6	23.3	25.0	27.5	30.3	33.4	35.7	40.9
19 years	278	28.7	0.30	21.6	22.8	23.8	25.7	28.3	31.0	33.5	35.9	38.4
(a) Gender male												
Total	3,818	22.5	0.13	14.3	15.4	16.1	17.8	21.7	26.5	30.2	32.3	36.9
1 years	311	16.0	0.11	13.3	14.0	14.5	15.0	15.8	16.9	17.6	18.5	19.3
2 years	300	16.4	0.14	13.4	14.1	14.7	15.3	16.2	17.0	17.9	18.6	20.3
3 years	301	16.9	0.11	14.3	14.9	15.3	15.9	16.7	17.5	18.3	18.9	21.5
4 years	305	17.1	0.07	13.4	14.7	15.3	16.1	17.1	18.0	18.6	19.2	20.7
5 years	280	17.9	0.14	14.1	15.5	16.0	16.7	17.6	18.7	19.5	20.6	27.7
6 years	165	18.1	0.17	14.7	15.6	16.0	16.7	17.9	18.5	20.2	21.7	25.0
7 years	164	19.0	0.19	14.5	16.0	16.5	17.6	18.6	19.9	22.2	23.0	24.5
8 years	148	19.2	0.22	15.3	16.3	16.9	17.6	18.9	20.1	21.9	23.1	26.3
9 years	177	20.9	0.31	16.4	17.2	17.8	18.8	20.2	22.2	25.0	25.7	na
10 years	177	21.6	0.23	16.6	18.1	18.4	19.6	21.0	23.0	25.8	27.3	30.9

(continued)

Table 38.2 (continued)

	Sample size	Mean	SE mean	1st Ptile	5th Ptile	10th Ptile	25th Ptile	50th Ptile	75th Ptile	90th Ptile	95th Ptile	99th Ptile
11 years	169	22.4	0.29	na	18.6	19.0	20.3	21.8	23.8	26.0	28.3	35.2
12 years	204	23.7	0.26	18.4	19.4	20.1	21.7	22.8	25.1	28.0	29.8	34.1
13 years	175	24.8	0.28	18.0	20.1	21.6	22.7	24.3	26.3	28.5	30.0	34.1
14 years	173	26.0	0.30	20.7	22.0	22.7	23.6	25.2	27.9	30.3	32.1	37.6
15 years	175	26.8	0.25	20.1	22.2	23.0	24.5	26.3	28.4	31.3	32.7	34.9
16 years	172	28.5	0.32	22.4	24.1	24.7	26.1	28.1	30.3	32.4	34.0	37.7
17 years	167	29.1	0.33	23.5	24.4	25.0	26.6	28.5	30.8	33.7	34.7	37.2
18 years	119	30.6	0.43	23.8	24.5	25.9	27.8	29.8	32.4	36.1	38.3	na
19 years	136	30.2	0.41	23.8	25.1	26.2	27.9	29.7	32.2	34.2	36.8	38.4
(b) Gender female												
Total	3,802	22.0	0.10	14.1	15.2	16.0	17.7	21.6	25.2	28.4	30.5	35.6
1 years	284	15.6	0.10	12.4	13.6	14.0	14.8	15.6	16.3	17.0	17.6	18.8
2 years	278	16.1	0.09	13.3	14.2	14.5	15.2	16.0	16.7	17.5	18.4	19.2
3 years	285	16.6	0.10	13.8	14.3	15.0	15.8	16.6	17.4	18.1	18.9	19.9
4 years	286	16.8	0.11	13.4	14.7	15.1	16.0	16.8	17.6	18.5	19.0	20.2
5 years	309	17.7	0.14	14.0	15.3	15.6	16.4	17.3	18.4	20.4	21.4	25.7
6 years	160	18.0	0.16	14.0	15.7	16.1	16.9	17.6	18.7	20.4	20.7	25.4
7 years	174	18.7	0.22	na	15.2	16.6	17.4	18.2	19.8	21.0	22.1	25.7
8 years	153	20.0	0.23	14.5	16.9	17.4	18.2	19.3	21.3	23.5	25.4	27.4
9 years	173	21.0	0.22	16.0	17.6	17.9	19.3	20.9	22.2	24.7	25.7	26.6
10 years	194	21.3	0.21	15.9	17.5	18.3	19.4	20.9	22.5	24.9	26.0	29.0
11 years	163	22.8	0.27	17.0	18.2	19.2	20.4	22.1	24.3	27.0	29.5	32.1
12 years	177	23.6	0.32	18.2	19.1	19.8	21.2	23.4	25.3	27.5	29.2	32.6
13 years	198	25.3	0.32	18.9	20.1	21.1	22.4	24.6	27.2	30.2	32.8	35.5
14 years	192	25.9	0.35	20.3	21.1	21.7	23.4	24.8	27.6	30.8	32.7	37.3
15 years	164	25.9	0.30	na	20.8	21.8	23.3	25.2	28.0	30.2	32.2	38.6
16 years	173	26.4	0.34	20.8	21.9	22.6	23.8	25.7	28.3	31.7	33.7	38.4
17 years	158	27.1	0.43	17.3	22.0	22.6	23.9	26.2	29.5	32.4	34.8	40.9
18 years	139	26.4	0.35	20.2	21.6	22.7	23.9	25.8	27.8	30.7	32.4	37.2
19 years	142	26.8	0.43	na	22.1	22.8	24.3	26.0	28.3	31.6	33.3	38.2

Table 38.3 Selected percentiles of mid-arm circumference in centimeters for children aged 1–19 years: gender all NHANES 2003–2006, and males and females, separately

	Sample size	Mean	SE mean	1st Ptile	5th Ptile	10th Ptile	25th Ptile	50th Ptile	75th Ptile	90th Ptile	95th Ptile	99th Ptile
Total	8,811	23.5	0.15	14.1	15.2	16.0	17.9	22.7	27.7	32.1	34.9	40.4
1 years	644	15.5	0.06	12.4	13.5	14.0	14.6	15.5	16.3	17.1	17.5	18.2
2 years	575	16.2	0.07	13.2	14.2	14.5	15.2	16.0	17.0	17.8	18.4	19.5
3 years	373	16.7	0.09	14.0	14.6	15.0	15.7	16.5	17.4	18.5	19.4	22.0
4 years	415	17.4	0.10	14.2	15.0	15.4	16.1	17.1	18.2	19.3	20.6	22.1
5 years	407	18.3	0.16	14.8	15.5	16.0	16.7	17.8	19.4	21.1	22.3	27.8
6 years	352	18.8	0.14	14.6	15.9	16.3	17.4	18.4	20.0	21.9	22.7	25.9
7 years	324	20.0	0.19	15.4	16.6	17.0	18.0	19.3	21.4	23.8	25.2	29.7
8 years	335	21.1	0.29	16.3	17.0	17.5	18.5	20.3	22.6	25.5	28.0	32.1
9 years	351	22.0	0.27	16.7	17.2	18.1	19.3	21.3	24.3	26.4	28.2	31.1
10 years	363	23.7	0.27	17.8	18.5	19.1	20.7	23.0	26.2	29.4	30.9	32.4
11 years	326	24.9	0.32	17.9	19.4	20.0	21.5	24.0	28.0	31.1	33.0	36.4
12 years	539	25.7	0.34	17.7	19.4	20.4	22.4	24.5	28.7	32.3	34.3	37.3
13 years	552	27.0	0.27	18.4	20.1	21.7	23.7	26.1	29.5	32.7	35.1	41.6
14 years	530	27.3	0.32	19.7	21.2	22.5	23.9	26.6	29.5	33.5	35.7	40.4
15 years	522	28.7	0.20	20.7	22.7	23.9	25.4	27.7	31.4	34.1	36.3	42.4
16 years	556	29.3	0.27	21.0	23.2	24.1	26.0	28.0	32.0	37.2	39.3	43.1
17 years	550	29.6	0.31	21.5	23.1	24.4	26.3	28.7	32.0	35.7	38.8	45.0
18 years	573	30.5	0.26	21.9	23.4	24.5	26.8	29.5	33.2	37.3	40.0	44.5
19 years	524	31.2	0.31	22.7	24.6	25.4	27.3	30.0	34.1	38.4	40.4	45.6
(a) Gender male												
Total	4,393	23.7	0.19	14.2	15.3	16.0	18.0	22.4	28.4	32.9	35.5	40.5
1 years	330	15.7	0.09	12.8	13.9	14.1	14.8	15.6	16.4	17.2	17.4	18.3
2 years	275	16.2	0.08	na	14.3	14.6	15.3	16.0	16.8	17.5	18.1	19.1
3 years	196	16.7	0.11	13.7	14.5	14.8	15.6	16.4	17.5	18.4	19.2	22.0
4 years	194	17.3	0.18	na	14.6	15.2	16.0	17.0	18.1	19.3	20.9	21.7
5 years	208	18.6	0.21	14.6	15.7	16.0	16.7	18.1	19.4	21.6	23.5	28.0
6 years	171	18.8	0.17	na	15.9	16.3	17.4	18.5	20.0	21.7	22.2	26.0
7 years	169	19.9	0.26	16.0	16.6	17.1	17.9	19.2	21.2	23.2	24.3	28.9
8 years	149	21.1	0.31	16.7	17.5	18.0	18.5	20.4	22.4	25.4	26.8	31.7
9 years	172	21.7	0.35	16.9	17.1	17.8	19.1	21.2	23.6	25.6	27.4	31.1
10 years	178	23.4	0.30	17.9	18.6	19.3	20.5	22.2	26.0	28.7	29.8	31.5

(continued)

Table 38.3 (continued)

	Sample size	Mean	SE mean	1st Ptile	5th Ptile	10th Ptile	25th Ptile	50th Ptile	75th Ptile	90th Ptile	95th Ptile	99th Ptile
11 years	150	24.8	0.55	18.1	19.3	19.8	21.4	23.4	27.7	31.3	33.3	35.0
12 years	289	25.4	0.39	17.7	19.5	20.3	22.0	24.1	28.3	32.4	34.2	36.8
13 years	270	27.1	0.38	18.4	20.8	22.2	23.8	26.2	29.5	32.6	34.9	44.3
14 years	258	27.7	0.39	20.1	21.3	22.8	24.5	27.3	29.8	33.7	36.0	39.4
15 years	273	29.5	0.34	22.0	24.1	24.7	26.1	28.4	32.4	34.8	37.4	44.3
16 years	301	30.9	0.41	23.3	24.4	25.8	26.9	30.0	33.7	38.4	39.8	43.2
17 years	279	30.5	0.24	22.8	24.8	25.9	27.4	29.5	33.0	36.3	38.0	42.6
18 years	268	31.6	0.44	22.4	24.9	26.2	28.3	31.1	34.4	37.9	39.9	44.2
19 years	263	32.6	0.39	25.1	25.7	27.1	29.1	32.0	35.5	38.9	40.6	45.4
(b) Gender female												
Total	4,418	23.2	0.13	13.9	15.2	16.0	17.9	22.7	27.0	31.2	33.7	40.3
1 years	314	15.4	0.09	12.1	13.1	13.8	14.6	15.4	16.2	17.0	17.5	18.2
2 years	300	16.2	0.10	13.0	14.0	14.4	15.2	16.1	17.1	18.1	18.4	19.5
3 years	177	16.8	0.14	14.0	14.9	15.2	15.8	16.5	17.3	18.7	19.5	21.8
4 years	221	17.4	0.12	14.6	15.2	15.6	16.3	17.2	18.3	19.2	20.3	22.2
5 years	199	18.0	0.19	14.8	15.4	15.8	16.8	17.4	19.2	20.6	21.7	na
6 years	181	18.9	0.20	15.1	15.9	16.3	17.4	18.4	19.8	22.0	22.8	25.2
7 years	155	20.2	0.26	na	16.6	17.0	18.1	19.4	21.7	24.1	25.6	30.0
8 years	186	21.1	0.42	16.2	16.9	17.1	18.5	20.1	22.6	25.8	28.5	32.1
9 years	179	22.4	0.34	na	17.9	18.7	19.8	22.1	25.1	26.8	28.4	31.0
10 years	185	24.1	0.39	17.5	18.5	19.0	20.9	23.4	26.5	30.3	31.5	33.1
11 years	176	25.0	0.39	17.8	19.4	20.0	21.6	24.4	28.1	30.9	31.8	36.5
12 years	250	26.0	0.45	na	19.3	21.1	23.1	24.9	29.0	32.2	34.5	39.2
13 years	282	26.8	0.35	18.7	20.0	21.5	23.6	25.7	29.4	32.7	35.4	40.3
14years	272	26.9	0.47	19.3	21.2	22.4	23.4	26.1	28.9	33.2	35.3	40.7
15years	249	27.8	0.31	na	22.4	23.0	24.8	27.1	30.5	33.1	35.8	38.7
16years	255	27.8	0.37	19.7	21.7	23.2	24.8	26.9	29.6	33.5	37.3	40.2
17 years	271	28.8	0.45	21.1	22.7	23.2	24.9	28.0	31.3	34.8	40.0	45.2
18 years	305	29.4	0.49	21.5	22.8	23.5	25.7	28.4	32.1	36.1	39.8	44.6
19 years	261	29.6	0.48	22.6	23.6	24.5	25.9	28.2	32.5	37.6	40.0	45.1

Table 38.4 Mean mid-arm circumference in centimeters by survey period for boys and girls aged 1–19 years

	NHANES I			NHANES II			NHANES III			NHANES 1999–2002			NHANES 2003–2006			
	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	*P* value
Total	7,620	22.25	0.08	8,072	22.86	0.11	11,805	22.74	0.12	8,955	23.51	0.11	8,811	23.45	0.15	<.001
1 year	595	15.80	0.08	705	15.97	0.07	1,218	16.05	0.05	515	15.93	0.08	644	15.54	0.06	<.001
2 years	578	16.22	0.08	705	16.37	0.06	1,115	16.43	0.05	502	16.34	0.08	575	16.18	0.07	.054
3 years	586	16.76	0.06	776	16.81	0.07	1,049	16.96	0.09	374	16.95	0.12	373	16.74	0.09	.230
4 years	591	16.96	0.06	796	17.25	0.06	1,072	17.48	0.10	366	17.65	0.12	415	17.35	0.10	<.001
5 years	589	17.79	0.10	758	17.74	0.08	1,036	18.06	0.08	333	18.25	0.19	407	18.31	0.16	.009
6 years	325	18.05	0.12	268	18.54	0.13	533	18.76	0.20	357	18.87	0.16	352	18.84	0.14	.001
7 years	338	18.85	0.15	304	19.17	0.15	534	19.87	0.18	383	20.12	0.17	324	20.00	0.19	<.001
8 years	301	19.60	0.16	269	19.94	0.17	504	20.33	0.20	388	21.49	0.31	335	21.07	0.29	<.001
9 years	350	20.95	0.19	293	21.13	0.20	550	22.10	0.32	359	22.58	0.23	351	22.02	0.27	<.001
10 years	371	21.45	0.18	292	22.15	0.21	542	22.71	0.29	340	23.39	0.27	363	23.73	0.27	<.001
11 years	332	22.62	0.20	294	23.34	0.20	554	23.83	0.33	383	24.53	0.28	326	24.93	0.32	<.001
12 years	381	23.65	0.19	292	24.04	0.18	419	24.78	0.24	625	25.57	0.29	539	25.65	0.34	<.001
13 years	373	25.02	0.24	335	24.96	0.29	412	26.05	0.30	619	26.77	0.39	552	26.96	0.27	<.001
14 years	365	25.95	0.27	363	26.24	0.20	401	27.43	0.58	599	27.61	0.22	530	27.31	0.32	.004
15 years	339	26.38	0.20	329	26.70	0.21	367	27.77	0.30	565	28.23	0.31	522	28.73	0.20	<.001
16 years	345	27.45	0.20	348	27.96	0.22	411	28.47	0.30	584	29.62	0.23	556	29.35	0.27	<.001
17 years	325	28.11	0.27	306	28.34	0.23	398	29.19	0.36	592	29.35	0.22	550	29.64	0.31	<.001
18 years	258	28.15	0.29	334	28.85	0.27	351	28.71	0.39	554	30.25	0.22	573	30.47	0.26	<.001
19 years	278	28.67	0.30	305	28.91	0.24	339	29.74	0.53	517	30.74	0.23	524	31.18	0.31	<.001
Boys																
Total	3,818	22.54	0.13	4,182	23.16	0.14	5,794	23.00	0.14	4,528	23.81	0.15	4,393	23.70	0.19	<.001
1 year	311	15.98	0.11	370	16.15	0.07	610	16.19	0.06	287	15.98	0.11	330	15.66	0.09	<.001
2 years	300	16.36	0.14	370	16.45	0.09	569	16.46	0.08	256	16.44	0.11	275	16.16	0.08	.188
3 years	301	16.87	0.11	412	16.92	0.09	487	16.94	0.13	209	17.05	0.14	196	16.70	0.11	.305
4 years	305	17.07	0.07	402	17.33	0.08	545	17.36	0.06	174	17.67	0.15	194	17.26	0.18	.026
5 years	280	17.89	0.14	396	17.65	0.08	494	17.89	0.11	155	18.40	0.22	208	18.55	0.21	<.001
6 years	165	18.06	0.17	133	18.62	0.21	259	18.90	0.29	181	18.96	0.20	171	18.84	0.17	.029
7 years	164	18.98	0.19	148	19.09	0.19	271	19.67	0.22	190	20.29	0.25	169	19.85	0.26	<.001
8 years	148	19.19	0.22	147	19.97	0.24	258	20.19	0.26	208	21.47	0.39	149	21.09	0.31	<.001
9 years	177	20.88	0.31	145	20.88	0.26	282	21.88	0.37	177	22.52	0.27	172	21.67	0.35	<.001

(continued)

Table 38.4 (continued)

	NHANES I			NHANES II			NHANES III			NHANES 1999–2002			NHANES 2003–2006			
	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	Sample size	Mean	SE mean	*P* value
10 years	177	21.63	0.23	156	22.18	0.30	288	22.83	0.35	183	23.24	0.36	178	23.40	0.30	<.001
11 years	169	22.42	0.29	155	23.27	0.32	273	23.61	0.36	182	24.34	0.38	150	24.81	0.55	<.001
12 years	204	23.67	0.26	145	23.94	0.34	203	25.17	0.25	304	25.39	0.42	289	25.39	0.39	<.001
13 years	175	24.77	0.28	173	25.13	0.36	188	25.78	0.32	299	26.40	0.60	270	27.11	0.38	<.001
14 years	173	26.03	0.30	185	26.31	0.30	181	28.19	1.06	272	28.07	0.38	258	27.73	0.39	.038
15 years	175	26.80	0.25	184	27.58	0.25	179	28.57	0.48	281	28.78	0.34	273	29.52	0.34	<.001
16 years	172	28.47	0.32	178	29.13	0.28	193	29.34	0.39	309	30.83	0.37	301	30.89	0.41	<.001
17 years	167	29.08	0.33	172	29.06	0.28	190	30.60	0.43	312	31.08	0.35	279	30.51	0.24	<.001
18 years	119	30.60	0.43	164	30.29	0.35	169	30.31	0.49	283	31.32	0.25	268	31.59	0.44	.051
19 years	136	30.24	0.41	147	30.45	0.28	155	31.42	0.62	266	31.73	0.27	263	32.63	0.39	<.001
Girls																
Total	3,802	21.95	0.10	3,890	22.55	0.12	6,011	22.48	0.17	4,427	23.19	0.14	4,418	23.19	0.13	<.001
1 year	284	15.61	0.10	335	15.77	0.09	608	15.89	0.06	228	15.87	0.11	314	15.42	0.09	<.001
2 years	278	16.08	0.09	335	16.28	0.07	546	16.40	0.06	246	16.24	0.10	300	16.20	0.10	.142
3 years	285	16.64	0.10	364	16.70	0.10	562	16.99	0.08	165	16.82	0.17	177	16.79	0.14	.300
4 years	286	16.84	0.11	394	17.16	0.09	527	17.62	0.21	192	17.63	0.21	221	17.44	0.12	.004
5 years	309	17.69	0.14	362	17.84	0.12	542	18.22	0.12	178	18.12	0.25	199	18.04	0.19	.212
6 years	160	18.04	0.16	135	18.47	0.21	274	18.59	0.25	176	18.78	0.22	181	18.85	0.20	.052
7 years	174	18.71	0.22	156	19.24	0.21	263	20.09	0.33	193	19.94	0.22	155	20.17	0.26	<.001
8 years	153	20.01	0.23	122	19.91	0.23	246	20.48	0.28	180	21.50	0.45	186	21.06	0.42	.007
9 years	173	21.03	0.22	148	21.37	0.28	268	22.28	0.50	182	22.64	0.30	179	22.40	0.34	.005
10 years	194	21.27	0.21	136	22.13	0.24	254	22.57	0.42	157	23.56	0.37	185	24.13	0.39	<.001
11 years	163	22.85	0.27	139	23.41	0.27	281	24.02	0.46	201	24.73	0.40	176	25.03	0.39	<.001
12 years	177	23.63	0.32	147	24.12	0.31	216	24.30	0.44	321	25.76	0.30	250	26.03	0.45	<.001
13 years	198	25.27	0.32	162	24.76	0.38	224	26.36	0.54	320	27.19	0.38	282	26.81	0.35	<.001
14 years	192	25.88	0.35	178	26.17	0.28	220	26.70	0.36	327	27.19	0.32	272	26.91	0.47	.072
15 years	164	25.95	0.30	145	25.82	0.28	188	27.05	0.38	284	27.60	0.45	249	27.83	0.31	<.001
16 years	173	26.45	0.34	170	26.85	0.27	218	27.48	0.34	275	28.26	0.36	255	27.80	0.37	<.001
17 years	158	27.06	0.43	134	27.51	0.37	208	27.61	0.34	280	27.82	0.29	271	28.82	0.45	.018
18 years	139	26.36	0.35	170	27.47	0.33	182	27.28	0.50	271	29.02	0.30	305	29.37	0.49	<.001
19 years	142	26.76	0.43	158	27.50	0.29	184	28.22	0.53	251	29.64	0.41	261	29.65	0.48	<.001

There is a significant trend, overall, for the five survey periods, with a steady increase in mid-arm circumference for ages 5, 10, 12, 13,15, 17, 18, and 19 years. For ages 2 and 3 years, there is no significant increase across the time span, and, for 1-year olds, the increase ceases after NHANES III (1988–1994). For ages 4, 6, 7, 8, 9, 11, 14, and 16 years, the increase ceases after the 1999–2002 survey. The changes are generally reflective for boys and girls. So, infants show no sustained increase in mid-arm circumference, whereas the older (17-, 18-, and 19-year old) children show a sustained increase across all five surveys.

38.5.4 Mid-Arm Circumference Trends by Race

Comparable race/ethnicity categorizations (only for adults) are only available for the last three surveys: 1988–1994, 1999–2002, and 2003–2006. During that time, age-sex-adjusted mid-arm circumference was greatest among African-Americans and increased by the greatest amount compared to non-Hispanic whites and Mexican Americans. The measurements in centimeters for African Americans at each successive survey were 33.22, 34.39, and 38.4, respectively, compared with equivalent values for non-Hispanic whites: 31.94, 32.96, and 33.06; and for Mexican Americans: 32.43, 32.8, and 32.9.

38.5.5 Mid-Arm Circumference Trends Adjusted for BMI, Age, Race, Sex, and Triceps Skinfold Thickness for Children Aged 2–19 Years and Adults Aged 20–74 Years

Tables 38.5 and 38.6 show the effect of adjustment for BMI and triceps skinfold thickness (measured on the same arm as the mid-arm circumference), considering the trend in mid-arm circumference across all survey periods. Table 38.5 has the results of weighted regression analysis for children aged 2–19 years across survey periods, with multivariable adjustment for age, gender, BMI, and triceps skinfold thickness. There are significant increases in mid-arm circumference from NHANES I through NHANES 1999–2002, but no further significant increase was observed for the last survey in 2003–2006, confirming the results displayed earlier. However, the change is most affected by BMI, followed by triceps skinfold thickness, which, although statistically significant, has only a minor role. Stated differently, together, BMI and triceps skinfold values alone explain. Eighty-three percent of the variation in mid-arm circumference values (R^2 = 0.834); removing triceps skinfold values from the model reduces the explained variability by.005% (R^2 = 0.829). This is an indication that total body size, including muscle and bone, has a greater effect on mid-arm circumference than does triceps skinfold thickness. Table 38.6 shows similar results for men and women aged 20–74 years of age, with the exception that the increase of the mid-arm circumference values continues across all survey periods, and that obesity has a greater effect in this population sample than in children. Similar to the findings in youth, BMI alone is associated with most of the explained variance in mid-arm circumference (R^2 = 0.78); adding triceps skinfold thickness to the adult model containing BMI actually reduces the amount of explained variation in mid-arm circumference values by 2% (R^2 = 0.76).Indeed, triceps skinfold thickness is more correlated with the independent variable BMI (r = 0.57) than with the outcome variable mid-arm circumference (r = 0.44), explaining the decrease in R^2 value when triceps skinfold thickness is added to the adult model."

Table 38.5 Weighted regression analysis for AC youth aged 2–19 years

Variables	Beta coefficient	SE beta	*p* value
Survey			
NHANES I	Reference		
NHANES II	0.24	0.06	<.001
NHANES III	0.19	0.05	<.001
NHANES 1999–2002	0.20	0.05	<.001
NHANES 2003–2006	0.02	0.05	0.718
Gender			
Boys	Reference		
Girls	–0.89	0.02	<.001
Age	0.44	0.003	<.001
Triceps skinfold	0.04	0.003	<.001
BMI	0.77	0.007	<.001

Table 38.6 Weighted regression analysis for AC adults aged 20–74 years

Variables	Beta coefficient	SE beta	*p* value
Survey			
NHANES I	Reference		
NHANES II	0.47	0.06	<.001
NHANES III	0.37	0.06	<.001
NHANES 1999–2002	0.40	0.06	<.001
NHANES 2003–2006	0.21	0.06	<.001
Gender			
Men	Reference		
Women	–3.40	0.03	<.001
Age	–0.01	0.0007	<.001
Triceps skinfold	0.11	0.002	<.001
BMI	0.61	0.004	<.001

BMI trends and mid-arm circumference trends (except for extreme levels) match each other almost exactly, as can be seen in Fig. 38.2a, b for males and females, respectively. Further demonstration of the importance of generally increased body size and not just obesity of the upper arm can be seen in Fig. 38.3a (males), b (females), where much of the overall observed increase of mid-arm circumference across the five surveys is mitigated by adjustment for triceps skinfold thickness, but not so markedly, as for BMI, when separate adjustment is made for each of these parameters. This suggests that effects of underlying tissues other than fat, such as bone and muscle increase, also add to the observed changes in mid-arm circumference. Regardless of the origins of the increase in arm size, there is a need to be aware of changing requirements of blood pressure cuff sizes to appropriately match mid-arm circumference and avoid overestimate of actual blood pressure levels. In population samples, this could result in false, secular trends of blood pressure level estimates. Also, rather than reflecting optimal nutrition, US current mid-arm circumference measurements reflect levels of obesity to be prevented in the future.

Summary Points

- Mid-arm circumferences for males and females, from childhood to age 74 years have increased successively from 1971–1974 to 2003–2006, over a 35-year period in five surveys in the USA.
- Mid-arm circumference increases from age 1 year to adulthood and decreases slightly but steadily from age 50 years to older ages.

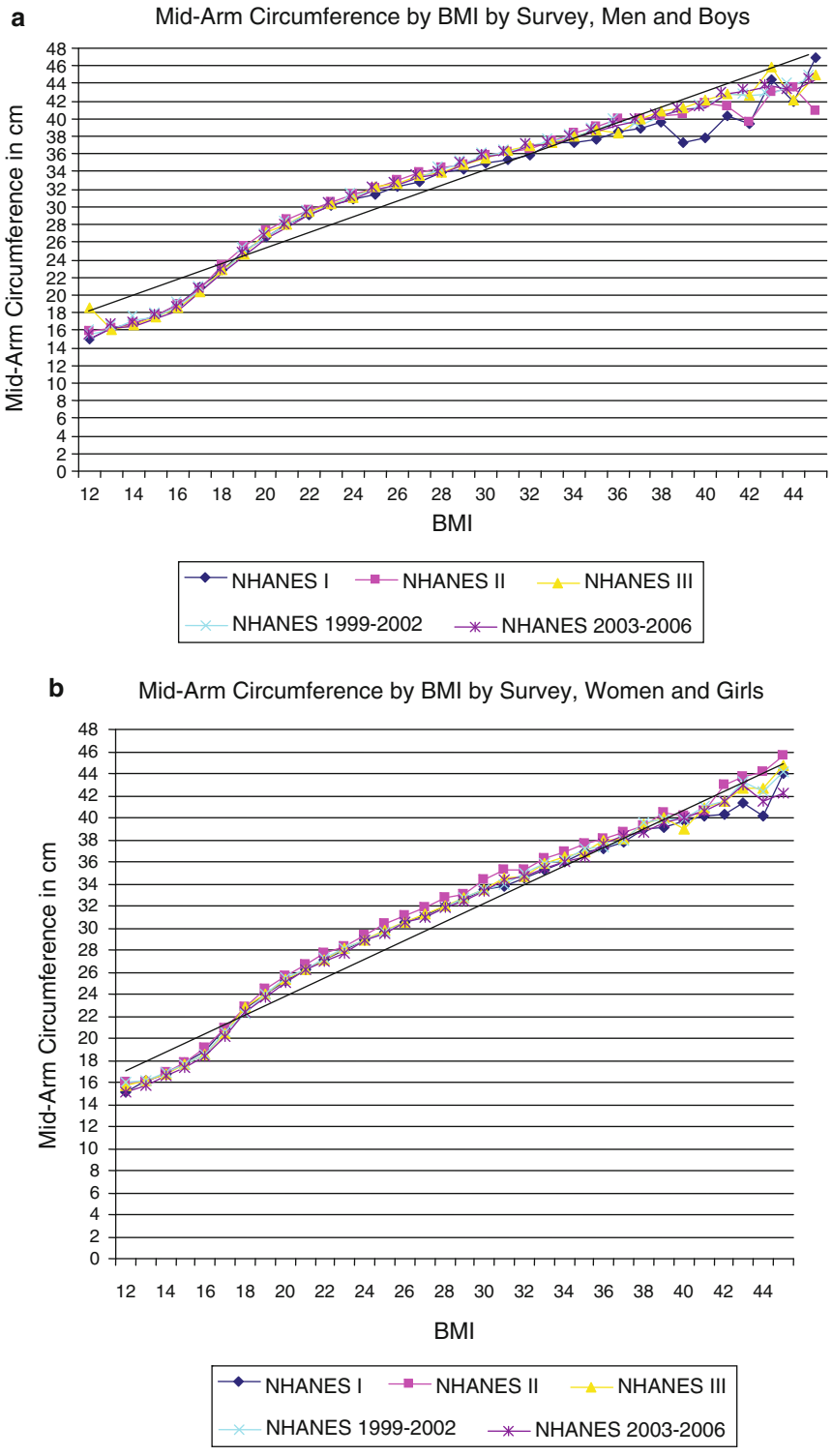

Fig. 38.2 (**a**) Males and (**b**) females mid-arm circumference by body mass index (BMI)

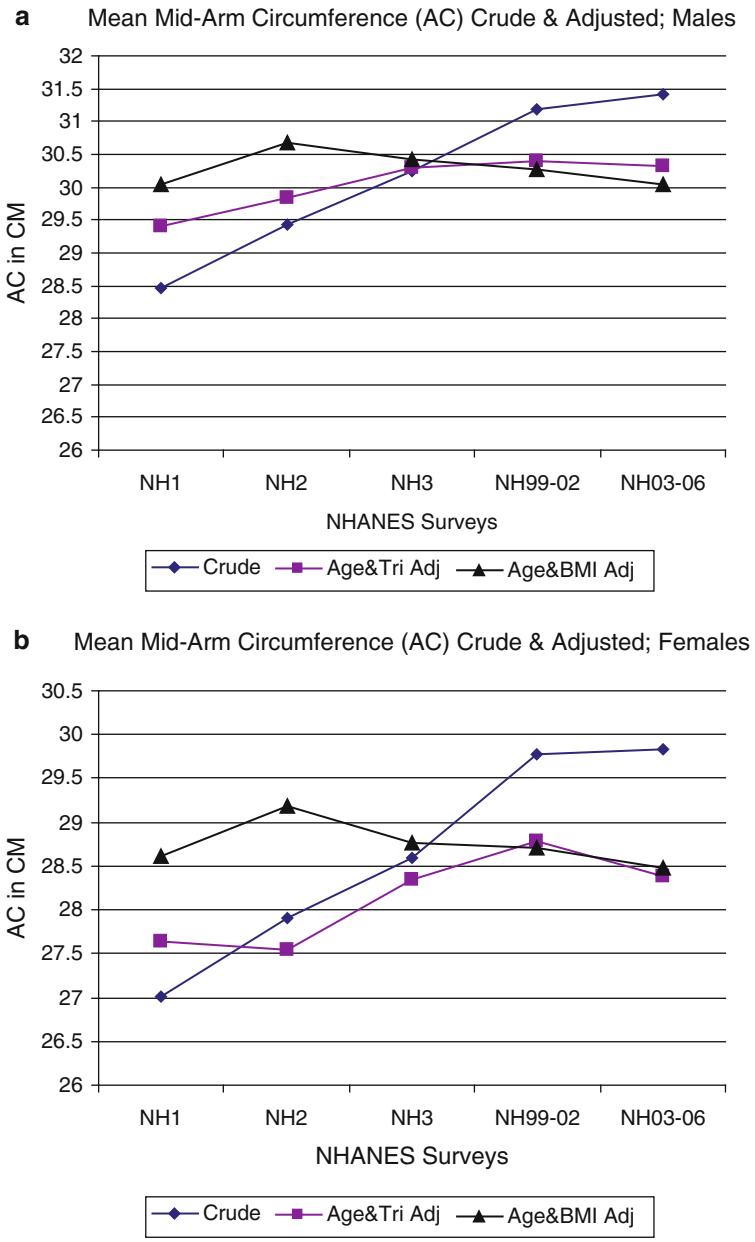

Fig. 38.3 (**a**, **b**) Mid-arm circumference by survey, adjusted separately for Age and Triceps Skinfold Thickness (Tri) and Age and Body Mass Index (BMI)

- The increase in mid-arm circumference is due to a shift to the right in the distribution of mid-arm circumference measurements.
- Infants show no sustained increase in mid-arm circumference, whereas the older children (17-, 18-, and19-year olds), like adults, show a sustained increase across a 35-year period.
- In more recent times, from 1988–1994 through 2003–2006,African Americans exhibit larger mid-arm circumferences and greater increase in size over the period than do non-Hispanic whites or Mexican Americans.

- The increase in mid-arm circumference over the past three and a half decades is modified by the increase in triceps skinfold thickness and BMI.
- The increase in mid-arm circumference size is almost entirely due to the parallel increase in BMI.

Acknowledgments We are grateful to the US Centers for Disease Control for access to public use documents regarding the NHANES surveys.

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Chapter 39
Anthropometric Wrist and Arm Circumference and Their Derivations: Application to Amyotrophic Lateral Sclerosis

Luciano Bruno de Carvalho-Silva

Abstract ALS is a degenerative disorder described as the loss of upper and lower motor neurons. ALS patients have an unfavourable prognosis that may influence alterations in the body mass. As a way of following up the clinical evolution of individuals with ALS, nutritional evaluation techniques are frequently used, however, they are not specific for ALS. In this review, we discuss the main anthropometric techniques emphasizing the circumferences, as well as their applications and limitations in ALS patients. All available articles were investigated, and anthropometry is suggested as a good tool, nevertheless, having some limitations and observations. Wrist and arm circumferences and their derivations are good indicators of these individuals' nutritional state and body composition. It should be noted that these patients typically have asymmetry, a low body mass index and an increase of fat mass. An equation is available for the calculation of fat-free mass in ALS patients. Among the complementary techniques, the bioelectrical impedance analysis at a frequency of 50 kHz is the most suitable. A strong correlation between this bioelectrical method and the measurement of circumferences and their derivations was observed. Therefore, the use of circumferences is suggested in the evaluation and follow-up of ALS patients.

Abbreviations

ALS	Amyotrophic lateral sclerosis
AMA	Arm muscle area
BIA	Bioelectrical impedance
BMI	Body mass index
BSF	Bicipital skinfold
DXA	Dual X-ray absorptiometry
FFM	Fat-free mass
MAC	Mid-arm circumference

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_39,

MAMC Mid-arm muscle circumference
SESF Subscapular skinfold
SISF Suprailiac skinfold
TSF Tricipital skinfold

39.1 Introduction

'Amyotrophy' refers to the atrophy of muscle fibres, which are denervated as their corresponding anterior horn cells degenerate, leading to weakness of affected muscles and visible fasciculations. 'Lateral sclerosis' refers to hardening of anterior and lateral corticospinal tracts, as motor neurons in these areas degenerate, and are replaced by gliosis (Rowland and Shneider 2001; Wijesekera and Leigh 2009). Amyotrophic lateral sclerosis (ALS) is characterised by progressive paralysis, secondary to the compromise of both the upper motor neurons and lower motor neurons. Individuals with ALS lose skeletal muscle mass secondary to denervation. This neurologically induced muscle mass loss is inevitable as the disease progresses; so, tracking muscle wasting is one way to monitor disease progression (Gubbay et al. 1985; Nau et al. 1997; Nelson et al. 2000).

In approximately 50% of patients, the disease first affects the arms (Fig. 39.1), in 25% the legs, and in 25% the onset is bulbar (Fig. 39.2). Manifestation forms progressive muscle atrophy is observed. This atrophy may mask the increase in metabolic demand, as metabolic energy is channelled to maintain pulmonary ventilation, thus causing the increase in basal energy expended by ALS patients (Nau et al. 1995; Silva et al. 2008a; Silva et al. 2008b).

Changes in body composition may be followed through anthropometry. The anthropometric assessment of muscle mass has been widely utilised in studies of malnourished populations and in the nutritional assessment of hospitalised patients (Blackburn et al. 1977; Heymsfield et al. 1994). For individuals with ALS, in addition to the body mass index (BMI) [weight (in kg)/height^2 (in m)], the determination is made on the upper extremities, although the methodology has been expanded to evaluate the lower extremities as well (Callaway et al. 1988). Typically, the circumference and skinfold thickness of the mid-upper arm are measured.

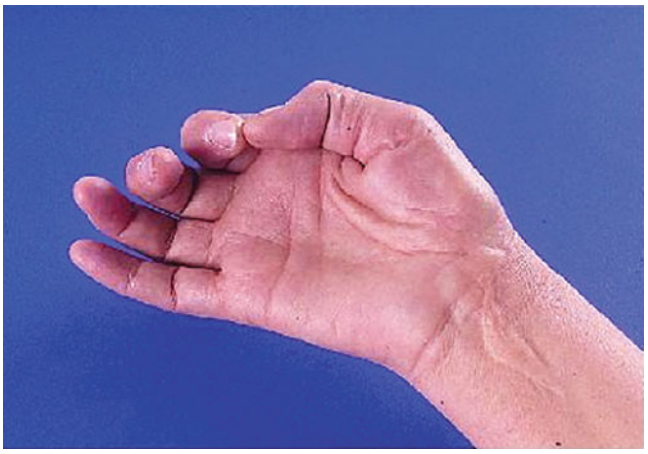

Fig. 39.1 Appendicular onset

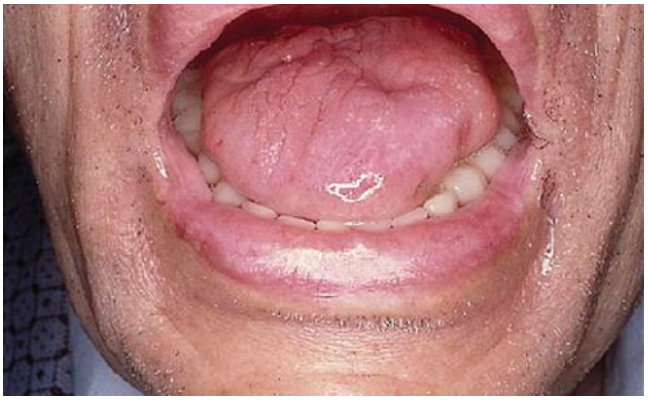

Fig. 39.2 Bulbar onset

In such context, in the present chapter, the main uses of anthropometric parameters will be discussed, particularly the wrist and mid-arm circumference (MAC), as well as their derivations, in individuals with ALS. It is important to highlight that there are few studies available that are related to nutritional evaluation in ALS patients. However, considering the available articles addressing this issue, some research groups are mentioned for their contribution: Desport et al.

39.2 Arm and Wrist Circumference and Application to Amyotrophic Lateral Sclerosis

As ALS evolves, a decrease of muscle mass may be observed, independently from its manifestation, in addition to an increase of fat mass. Nau et al. (1997) assessed the body composition and caloric intake of 12 ambulatory males with ALS over a 6-month period. The men lost 1.5 kg of body mass during this period. Body composition analysis revealed that the mass loss was composed of a 2.0 kg reduction in lean mass and a 0.55 kg increase in fat mass. In this case, the loss in body mass underrepresented the degree of muscle wasting they had experienced, and the muscle wasting masked fat accumulation.

Several anthropometric parameters may be used for the estimate and follow-up of a patient's nutritional status. Some relevant research data are presented in Table 39.1.

The MAC is assessed on the arm extended along the body, measured at the middle point between the tip of the acromion and olecranon process, using a flexible, non-elastic, metric plastic tape (Callaway et al. 1988). In anthropometry, the circumference is very important because other nutritional status indicators may be estimated from it. Desport et al. (2003) used MAC for calculating mid-arm muscle circumference (MAMC) and follow-up of the nutritional status of ALS patients. Researchers have used circumferences as parameters for assessing these body composition modifications.

The wrist circumference is measured using a tension-gated tape measure positioned over Lister's tubercle of the distal radius and over the distal ulna (Fig. 39.3). In ALS, both sides should be measured.

Body frame size is determined by a person's wrist circumference in relation to his or her height. The body frame size is determined by measuring the wrist with a tape measure to determine whether the person is small, medium or large boned (Table 39.2)

Table 39.1 Anthropometric parameters and objectives in ALS patients

	Anthropometric parameters	Objective
Slowie et al. (1983)	BMI, TSF, % weight loss	Management of patients with ALS.
Kasarskis et al. (1996)	BMI, TSF, MAC, MAMC and AMA.	Relation of nutritional status and proximity of death in ALS patients.
Nau et al. (1997)	BIA, DXA, skinfolds and circumference.	Validated BIA and anthropometric techniques in ALS patients.
Desport et al. (2000)	BMI, TSF, MAC, BIA and indirect calorimetry	Nutritional assessment in ALS patients.
Desport et al. (2001)	BMI, BIA and indirect calorimetry	Clarify the metabolic level of ALS patients.
Desport et al. (2003)	BMI, skinfold thickness, DXA, BIA, MAC, WC, MAMC and AMA.	Compare reference measures of FFM obtained by DXA with FFM obtained by BIA and skinfold thickness, MAC and WC.
Silva et al. (2008a)	BMI, skinfold thickness, % weight loss, MAC, WC, MAMC and AMA	Validation and application of anthropometric parameters on Brazilian patients with ALS.

BMI (kg/m^2) Body mass index, *DXA* dual X-ray absorptiometry, *BIA* bioelectrical impedance, *FFM* (kg) fat-free mass, *TSF* (mm) tricipital skinfold, *MAC* (cm) mid-arm circumference, *WC* (cm) wrist circumference, *MAMC* (mm) mid-arm muscle circumference and *AMA* (mm) arm muscle area

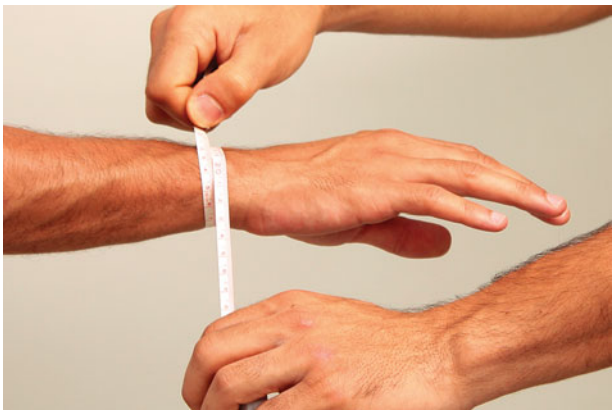

Fig. 39.3 Representation of wrist circumference measurement on the radial styloid process and ulna

Table 39.2 Determination of whether a person is small, medium, or large boned based on wrist circumference

Women
Height under 1.6 m
Small = wrist size less than 14 cm
Medium = wrist size 14–15 cm
Large = wrist size over 15 cm
Height 1.60–1.67 m
Small = wrist size less than 15 cm
Medium = wrist size 15–16 cm
Large = wrist size over 16 cm
Height over 1.67 m
Small = wrist size less than 16 cm
Medium = wrist size 16–17 cm
Large = wrist size over 17 cm
Men
Height over 1.67 m
Small = wrist size 14–16.5 cm
Medium = wrist size 16.5–19 cm
Large = wrist size over 19 cm

Table 39.3 Nutritional assessment technique used by dieticians (Adapted from Rio and Cawadias 2007)

Parameters	Total (n = 23)	Canada (n = 11)	Northern Ireland (n = 12)
Body weight	23	11	12
Body mass index	19	8	11
Percentage weight loss	22	11	11
Mid-arm anthropometry	2	0	2
Bioelectrical impedance analysis	0	0	0
DXA	0	0	0

DXA dual X-ray absorptiometry

Table 39.4 Equations for the estimate of mid-upper arm muscle circumference, arm muscle area in males and females, and fat-free mass, specifically validated for ALS patients

Parameters	Equations
MAMC	MAMC = MAC – (π × TSF)
AMA	AMA (males) = [MAC – (π × TSF)^2/4 π – 1]
AMA	AMA (females) = [MAC – (π × TSF)^2/4 π – 6.5]
	FFM Equation for ALS patients
FFM	FFMfin50 = (0.436 W) + (0.349 mean H^2/Z_{50}) – (0.695 mean TSF) + 9.245

TSF (mm) triceps skinfold, *MAC* (cm) mid-arm circumference, *MAMC* (mm) mid-arm muscle circumference, *AMA* (mm) arm muscle area, *FFM* (kg) fat-free mass, W (kg) weight, H (m) height, Z_{50}: 50 kHz.

Rio and Cawadias (2007) performed a study with 23 dieticians working in ALS/Motor Neuron Disease centres/clinics across England, Wales, Northern Ireland and Canada. By means of a standardised questionnaire, the researchers obtained information on nutritional assessment techniques, requirement equations, sources of nutritional information and perception of quality of information. The techniques used for anthropometrics evaluation are shown in Table 39.3.

Determination of upper extremity anthropometrics is simple, requires little equipment, is independent of patients' effort and is highly reproducible (Heymsfield et al. 1994; Callaway et al. 1988). In these cases, a MAC may be used. The MAC reflects the total body composition without separating the fat mass from the lean mass. This parameter is obtained from the middle point on the extended arm from the non-dominant side. Nevertheless, for individuals with ALS, due to the asymmetric characteristic, it is worth noting that measurements should be taken from both the right and left upper extremities, calculating the average between the two assessments for the correct estimate of body mass (Kasarskis et al. 1997).

Obtained from MAC, the MAMC is used to distinguish the muscle mass (Heymsfield et al. 1994), as it takes into consideration the tricipital skinfold (TSF). In ALS, as well as in other situations, the isolated TSF measurement provides an estimate of the subcutaneous fat mass.

Once the MAMC is estimated, it is possible to obtain the arm muscle area (AMA). In ALS, AMA and the percent body fat are lower among subjects closer to death (Heymsfield et al. 1982; Kasarskis et al. 1996). The equation used for the AMA estimate is the same as the one used in other clinical situations (Table 39.4).

There are no specific equations applicable for individuals with ALS. Therefore, as described before, it is advised to take the average measurements from the patient's right and left sides, especially in case of individuals with bulbar onset.

Table 39.5 Anthropometric methods for the estimate of fat mass and muscle mass

Compartments	Equations
Fat mass	Jackson and Pollock (1985)
	Durnin and Womersley (1974)
	Deurenberg et al. (1991)
	MacArdle et al. (1991)
	Siri (1961)
Muscle mass	Heymsfield et al. (1982)
	Martin et al. (1990)

In 2003, Desport et al. compared the fat-free mass (FFM) obtained by dual X-ray absorptiometry (DXA) with FFM obtained by BIA and by the skinfold-thickness technique. In this study, the FFM and fat mass of the patients were calculated from BIA, the measured resistance to a weak alternative current applied to wrist and ankles. A recent formula for FFM has been validated against a reference method in ALS, both transversally and longitudinally.

Serial body composition measurements are necessary to measure and track changes in the fat and muscle components of the body. It is common to use the loss of body mass as an estimate of both muscle atrophy and nutritional status (Nau et al. 1997). The equations frequently used to convert anthropometric values into estimates of lean and fat mass are the same as the ones utilised and validated in other clinical conditions (Table 39.5).

Research in the application of common anthropometric techniques in nutritional practice as well as in obtaining evidence for upper extremity anthropometrics in the clinical assessment of patients with ALS, Kasarskis et al. (1997) accomplished a study with 18 non-obese ALS patients with a body mass index (BMI) < 30. In this study, the use of standard, upper extremity anthropometrics was studied and these measurements were correlated with quantitative isokinetic muscle force output, computerised tomography scan muscle area, pulmonary functions and creatinine excretion. The MAC was determined using a standard tape measure. The MAMC and AMA were calculated according to Heymsfield et al. (1982). The researchers noticed that the upper extremity AMA correlated positively with quantitative measures of body weight, net muscle area and biceps and triceps muscle force generated using slow- and high-speed isokinetic dynamometry. AMA correlated well with important measures of pulmonary function including forced vital capacity, slow vital capacity, maximal voluntary ventilation, tidal volume and vital capacity. The authors concluded that the upper extremity bone-free muscle mass, as a method to quantify the progression of the muscle atrophy in ALS and the measurement of AMA, might have utility as an outcome measure for ALS progression.

Silva et al. (2008a) studied the nutritional, respiratory and functional profiles of a cohort of 20 ALS patients regularly followed up at the Neuromuscular Outpatient Clinic of Campinas State University Hospital (UNICAMP). The anthropometric parameters used were BMI, MAC, wrist circumference, MAMC, AMA and TSF and bicipital (BSF), suprailiac (SISF) and subscapular (SESF) skinfolds. The authors looked for correlations between these variables to identify determinant factors in the severity of the disease. In both appendicular and bulbar onset patients, correlations were noticed between the BMI and the following variables: mass (kg), fat, MAC, wrist circumference and TSF, SESF, SISF, the MAMC and AMA. Based on these correlations, the researchers suggested that the application of anthropometric measurements could be useful in routine monitoring of patients with ALS.

Table 39.6 Main limitations for the use of anthropometry in individuals with ALS

ALS versus Anthropometrics parameters
Abnormal fat distribution is possible in ALS.
The disease can have effects that are more marked on one side of the body than on the other.
Non-specific manner, TSF and MAC have an operator-based risk of variation.

TSF (mm) triceps skinfold, *MAC* (cm) mid-arm circumference

It is important to point out that, in ALS, there are some limitations for the use of MAC, and also the equations obtained from this parameter, as in AMA. First, in obese ALS patients (BMI>30), the accurate measurement of TSF may be difficult, which may introduce an error in the computed value of AMA. Another limitation of the use of this anthropometric parameter is related to the predominant muscle atrophy due to the 'lower motor neuron' component of the illness, thus causing the parameter to be less sensitive to 'upper motor neuron' weakness or spasticity (Kasarskis et al. 1997). As described in Table 39.6, Desport et al. (2003) correlated some of the limitations to the use of MAC in ALS patients.

Despite the presented limitations, anthropometric measurement of upper limbs may be acceptable in ALS patients, and several authors have used this technique (Kasarskis et al. 1997).

39.3 Other Estimate Methods for Body Mass Composition in ALS Patients

The most advised methods for persons with ALS include DXA, bioelectrical impedance (BIA) and anthropometry (Nau et al. 1997). DXA categorises the body into three components: bone mass, fat mass and non-fat soft tissue (lean mass minus the bone). The use of such techniques in these individuals presents some advantages and disadvantages, as shown in Table 39.7.

DXA is limited in ALS patients because it is relatively expensive and is available primarily as a research tool. Also, it may not be well tolerated by patients with respiratory muscle weakness, as it requires the person to lie flat in a supine position for about 20 min (Nau et al. 1997). BIA, which categorises the body into fat and lean mass, is based on the premise that conductance is directly related to the percentage of water, and lean mass is hydrous compared to fat (Nau et al. 1997). To perform this technique, it is expected that the individuals are normally hydrated, which may or may not apply to persons with more advanced stages of ALS. The limitation for the use of anthropometry is related to the equations for the estimate of body mass. Anthropometric equations are frequently applied on the general population so, the current equations may not apply to persons with ALS. Most equations assume the subject is in a standing or upright position, which is not always possible among persons with ALS (Desport et al. 2003).

Desport et al. (2003), accomplished a validation study on bioelectrical impedance analysis in patients with ALS. Using 32 ALS patients, the researchers compared reference measures of fat-free mass (FFM) obtained by DXA with FFM obtained by BIA, and by the circumference and skinfold techniques. BIA was performed by measuring the bioimpedances at 5, 50 and 100 kHz of each side of the body and from one side to the other. As a result of this study, an equation was developed using multivariate analysis, with impedance at 50 kHz. This equation was validated in a second population of 15 ALS patients, and with the use of two successive measurements performed on 18 patients. It was concluded that BIA is a simple method, which is valid for use in ALS patients, both for a single exam measure and for longitudinal monitoring using an equation and applying a frequency of 50 kHz.

Table 39.7 Advantages and disadvantages of the use of anthropometry, bioelectrical impedance and dual X-ray absorptiometry in individuals with ALS

Parameters	
Anthropometry	Advantages: Simple, low cost and with strong correlations between BMI, MAC, WC, TSF and BIA.
	Disadvantages: Demands professional training; may underestimate fat mass percentage; some techniques are not validated for ALS yet.
BIA	Advantages: Fast, simple and low-cost method and validated at 50 kHz frequency in ALS patients.
	Disadvantages: Varies according to the hydration degree.
DXA	Advantage: Differentiates FM from FFM.
	Disadvantage: High cost of equipment, requires the subject to be flatly supine for >10 min, which is difficult for ALS patients.

BMI (kg/m^2) Body mass index, *DXA* dual X-ray absorptiometry, *BIA* bioelectrical impedance, *FFM* (kg) fat-free mass, *TSF* (mm) tricipital skinfold, *MAC* (cm) mid-arm circumference, *WC* (cm) wrist circumference, *MAMC* (mm) mid-arm muscle circumference and *AMA* (mm) arm muscle area

39.4 Anthropometry, ALS and Its Relation to Gender and to the Presentation Form of the Illness

ALS affects mainly males, in the proportion 1.8:1, when compared to females, and among the races, whites more than the blacks. Onset usually occurs between 59 and 65 years of age. About 4–6% of cases occur in people younger than 40 years (Dietrich et al. 2000).

Individuals with ALS present progressive decreases in BMI, body fat and lean body mass. However, in cases nearing death, the proportion of fat mass is greater in females than in males (Kasarskis et al. 1996).

ALS is progressive, with death occurring on average from 2 to 5 years after onset (Li et al. 1990; Norris et al. 1993). About 8–22% survive for at least 10 years. The prognosis tends to be worse in individuals with bulbar onset, ageing and atrophy predominance (Walling 1999). In individuals with bulbar onset, respiratory insufficiency, with or without pneumonia, is usually the cause of death, generally associated with dysphagia and bronchoaspiration.

In individuals with appendicular onset, asymmetry is more commonly observed between the most and least compromised side. This difference was noted according to anthropometric evaluation data of individuals with bulbar and appendicular ALS, who were studied at the Neuromuscular Outpatient Clinic of UNICAMP. On the most compromised side, the wrist circumference was on average 0.9 cm smaller than on the other side (unpublished data). This highlights, once again, the necessity to use both sides to estimate the body composition in ALS patients.

39.5 Final Considerations

Anthropometric parameters, especially the circumferences, which allow us to estimate the body composition, are good markers of the nutritional state and alterations in the body composition of individuals with ALS. For these patients, such parameters should be used carefully, with attention to their asymmetry. It is added that MAC, wrist circumference and their derivations present strong correlations to BIA. However, it is necessary to perform longitudinal studies to identify the sensitivity and viability of different techniques during the stages of ALS.

Summary Points

- There are strong correlation between bioelectrical method and the measurement of circumference in ALS patients.
- MAC and wrist circumference are good markers of the nutritional status in ALS patients
- In individuals with ALS with appendicular onset it more common to observe asymmetry between the most and least compromised side. MAC and wrist circumference should be taken from both the right and left upper extremities, calculating the average between the two assessments.
- Abnormal fat and mass distribution may be one limitation for the use of anthropometry in individuals with ALS.
- It is necessary to perform longitudinal studies to identify the sensitivity and viability of different techniques during the stages of ALS.

Acknowledgements Federal University of Alfenas – MG (UNIFAL-MG), Center for Food Security Studies (NEPA), State University of Campinas (UNICAMP), Brazil, Neuromuscular Outpatient Clinic of UNICAMP and Dra Ana Lúcia de Magalhães Leal Chiappetta (for ALS photos).

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Chapter 40
Mid-Upper Arm Anthropometric Measurements as a Mortality Predictor for Community-Dwelling Dependent Elderly

Masafumi Kuzuya and Hiromi Enoki

Abstract It remains controversial whether mid-arm anthropometric measurements are reflected with physical impairment or useful predictors of mortality in the elderly. The inconsistency in terms of the relationship between mid-arm anthropometric measurements and physical function and mortality may be due to the difference in study population, i.e., a healthy younger population vs frail/dependent older people. In this article we overviewed the relationships between mid-arm anthropometric measurements and mortality of elderly based on our studies and previous reports targeting older people. Our cohort study, which was composed of cross-sectional and prospective cohort analyses of 957 community-dwelling dependent elderly, demonstrated that significant higher average triceps skinfold (TSF) levels were observed in participants, compared with age-matched (5-year intervals) those of the standard Japanese population. In contrast, the average arm muscle area (AMA) levels at 5-year intervals were significantly lower than the Japanese norm. The AMA levels of the study participants were correlated with activities of daily living (ADL) score after adjusting for gender and age. Whereas TSF levels were not correlated with ADL function after adjusting for gender, age among study participants. Survival analysis of 2-years mortality was conducted using multivariate Cox proportional hazards models. AMA, TSF, and mid-arm circumference (MAC) were independent risk factors for 2-years mortality in the participants. In conclusion among community-dwelling dependent elderly, mid-arm anthropometric measurements were independent predictors of 2-years mortality.

Abbreviations

ADL	Activities of daily living
AMA	Arm muscle area
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
JARD2001	In 2001, Japanese Anthropometric Reference Data
MAC	Mid-upper-arm circumference
NLS-FE	The Nagoya Longitudinal Study of Frail Elderly

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_40,

LTCI Long-term care insurance
TSF Triceps skinfold
SPSS Statistical Package for the Social Sciences

40.1 Introduction

Anthropometric indices of weight, height, body mass index (BMI), skinfold thickness, muscle area, and circumference are simple, easily obtainable, and inexpensive measures of assessing nutritional status. Among them, BMI, the most widely used anthropometric index, has been frequently used as an indicator of nutritional status, and is well known as an important predictor of mortality and activities of daily living (ADL) decline among older people (Liu et al. 2002; Flodin et al. 2000). However, it is not uncommon to find dependent older people who cannot be weighed or measured for height. When subjects living at home have severe functional disabilities, it is essential to have special equipment, such as beds or wheelchair scales, to measure their weight. Frequently, it is difficult to measure the height of older people with postural changes, including muscle and arterial contracture and kyphosis. In fact, we have previously shown in a cohort study of community dwelling dependent elderly that 35.9% and 30.7% had missing data for height and weight, respectively (Izawa et al. 2007).

In addition, measuring height reliably in older individuals is one of the most problematic areas of anthropometry. In old age, there is a decline in sitting and standing height due to vertebral compression, change in the height and shape of vertebral disks, loss of muscle tone, and postural changes. When these height measurements are used in the calculation of BMI, it will tend to be artificially inflated. In addition, it can be difficult to measure the standing height of older people with ADL impairment (Hickson and Frost 2003; Zang et al. 1998).

Anthropometric measurements of the mid-upper arm are often taken for measuring body composition, because they are a quick, inexpensive, and non-invasive method of measuring nutritional status. Triceps skinfold (TSF) thickness reflects subcutaneous fat, whereas mid-upper-arm circumference (MAC) takes into account the humeral diameter as well as the skeletal muscles, and fat covering the limb, therefore reflecting changes in lean body mass and fat. Mid-upper-arm muscular circumference and arm muscle area (AMA), which are derived from MAC and TSF, are also useful indicators of muscle mass.

Although these mid-arm anthropometric measurements may be useful indicators of undernutrition in older adults, it remains controversial whether these measurements are useful predictors of mortality in the elderly or whether physical impairment reflects these measurements in the older population. In this article, we overview the mid-arm anthropometric measurements as a predictor of mortality among older people and their relationships with physical functions.

40.2 Mid-Arm Anthropometric Measurements and Mortality of Elderly-Brief Review

In the general population, it has been believed that low muscle mass and high fat mass are associated with higher mortality (Janssen et al. 2002). In fact, Miller and colleagues demonstrated that among 1,396 community dwelling Australian participants aged 70 years and older, those with a low corrected AMA ($\leq$21.4 cm^2 for men and $\leq$21.6 cm^2 for women) had an increased risk of mortality at 8-year

follow-up. (Miller et al. 2002), whereas no increased risk in 8-year mortality was identified for those with a high or low BMI (Miller et al. 2002). Another study reported that, in a geriatric assessment unit, it was found that an abnormally low AMA (lower than the fifth percentage of age-matched reference data) is strongly associated with increased mortality at 4.5-year follow-up (Muhlethaler et al. 1995). In contrast, over 24 years of follow-up study of random samples of participants aged 65 years and over living in the community revealed that higher AMA was associated with a significantly reduced risk of mortality from all causes only in men, and not in women (Gale et al. 2007).

The relationship between TSF thickness and mortality in the elderly remains controversial. It has been reported that among 408 elderly long-term-care residents aged 60 years and older, TSF was a significant predictor of mortality during 19 months' follow-up in the univariate analysis, but not in the multivariate analysis (Allard et al. 2004). TSF thickness did not show a statistically significant association, with 4.5-year mortality among 219 geriatric patients in a geriatric assessment unit (Muhlethaler et al. 1995). It has been observed that TSF thickness below the 5th percentile was associated with a significant increase in the relative risk of death during 40–46 months' follow-up in a community sample of 758 older people (Campbell et al. 1990).

Another study showed that, during admission in an acute care geriatric ward, MAC had a more negative trend in patients who died than changes in weight, BMI, and subjective nutritional assessment (Antonelli Incalzi et al. 1996).

40.3 Japanese Cohort Study

40.3.1 Study Design and Aim

We examined whether anthropometric measurements of mid-upper arm may be a good predictor of mortality among disabled community-dwelling older people (Enoki et al. 2007). In the present study targeting dependent community dwelling elderly persons, using the baseline and 2-year follow-up data of the Nagoya Longitudinal Study of Frail Elderly (NLS-FE), the following hypotheses were tested: (1) in community-dwelling elderly persons, who are disabled or dependent and receiving some assistances using the long-term care insurance (LTCI) program, MAC, TSF, and AMA levels are lower than those of not-frail, independent elderly persons living in the community; (2) these lower levels of measurements are associated with physical function impairment and comorbidity status; and (3) lower levels of MAC, TSF, or AMA are independent predictors of relative short-term (2-year) mortality.

40.3.2 Study Participants

This analysis was conducted using a total of 957 subjects (men, 355; women, 602) extracted from the NLS-FE data set. The study population of NLS-FE consisted of 1,875 (men, 632; women, 1,243) community-dwelling elderly (aged 65 years or older) eligible for the LTCI, who lived in Nagoya city (Central Japan) and were provided various home care services from the Nagoya City Health Care Service Foundation for Older People, which is comprised of 17 visiting nursing stations accompanying care-managing centers (Kuzuya et al. 2006, 2008). The LTCI system provides care for the

elderly aged 65 years and older. Under the LTCI program, care levels (levels 0–5) are determined according to eligibility criteria (Izawa et al. 2006). The elderly in the community, who are eligible for LTCI, are disabled and chronically ill, have physical and mental problems, and easy to admit to the acute hospital or institute care setting. A total of 957 (men, 355; women, 602) using visiting nurse services under LTCI were enrolled for the anthropometric measurements.

40.3.3 Data Collection

Anthropometric measurements were conducted by trained nurses at the clients' home. Measurement of TSF (to the nearest 2 mm) was made using caliper and MAC (to the nearest 0.1 cm) using a flexible measuring tape, on the right side of the participant's body, unless affected by disability or disease. These measurements were taken at least twice, by one trained nurse, according to the instruction sheet, and reported values were the means of the repeated measurements. Arm muscle circumference (AMC = MAC (cm) – $\pi \times$ TSF (mm)/10) and AMA were calculated using a standard formula: AMA cm^2 = (AMC (cm))$^2/4\pi$. BMI was defined as weight in kilogram divided by height squared.

The mean scores of anthropometric measurements of patients grouped by age and gender were compared with the JARD 2001, anthropometric norms for healthy men and women without physical function impairment in each 5-year age bracket, including subjects over age 65 years (Japanese Anthropometric Reference Data 2002). In JARD 2001, a mean value, a central value, standard deviation, maximum value, minimum value, and percentile (5th, 10th, 25th, 75th, 90th, and 95th) were determined according to the age division. Therefore, it was possible to compare the obtained measurement values and these reference values.

40.3.4 Sample Description

Characteristics of subjects in the present study are given in Table 40.1. The mean (SD) age of 957 patients studied was 80.4 (7.9) years, with a range of 65–102 years. Among those, 318 patients (33.2% of total) were 85 years or older. Most were capable of oral food intake (91.5% of total). The physical function of the participants (basic ADL, score range: 0–20) was markedly impaired with a mean (SD) score of 10.3 (6.9). A history of cerebrovascular disease was the most frequent diagnosis observed in this cohort (334 patients, 34.9% of total).

40.3.5 Comparison of Anthropometry Between Study Participants and Japanese Norms

BMI is the anthropometric measurement most widely used for assessing nutrition status. However, it is often difficult for older people with impaired physical function to be measured for height and weight at their homes. In fact, in our cohort, BMI data were not available for 437 out of 957 participants, even though we asked visiting nurses and caregivers to measure weight and height as far as possible. It should be noted that there were no differences in BMI levels between the participants and Japanese norms for any age group in either gender (Enoki et al. 2007) (Tables 40.2 and 40.3).

Table 40.1 Demographic characteristics of patients (Reprinted from Enoki et al. (2007). With permission from Elsevier)

Variables	Categories (year)	Male $N = 355$ N (%), average ± SD	Female $N = 602$ N (%), average ± SD	p-Value
Age (year)		78.50 ± 7.49	81.57 ± 7.97	<0.001
	65–69	47 (13.2)	46 (7.6)	<0.001
	70–74	63 (17.7)	82 (13.6)	
	75–79	100 (28.2)	119 (19.8)	
	80–84	58 (16.3)	124 (20.6)	
	85+	87 (24.5)	231 (38.4)	
Nutrition	Peroral	322 (90.7)	554 (92.0)	0.622
	Enteral feeding	32 (9.0)	45 (7.5)	
	Parenteral nutrition	1 (0.3)	3 (0.5)	
Basic ADL (0–20)		11.0 ± 6.5	9.9 ± 7.1	0.013
Charlson comorbidity index (0–35)		2.5 ± 1.6	2.2 ± 1.6	0.019
Illness	Ischemic heart disease	31 (8.7)	64 (10.6)	0.496
	Congestive heart failure	32 (9.0)	60 (10.0)	0.818
	Liver disease	13 (3.7)	20 (3.3)	0.714
	Cerebrovascular disease	147 (41.4)	187 (31.1)	<0.001
	Diabetes	38 (10.7)	68 (11.3)	0.914
	Dementia	92 (25.9)	221 (36.7)	0.001
	Chronic pulmonary disease	38 (10.7)	42 (7.0)	0.037
	Neoplasia	37 (10.4)	51 (8.5)	0.242
	Hypertension	70 (19.7)	150 (24.9)	0.068
Anthropometric measurements				
Body mass index, kg/m^2		20.8 ± 3.4 ($n = 219$)	20.8 ± 4.4 ($n = 301$)	0.978
Mid-arm circumference, cm		24.3 ± 4.1	23.1 ± 4.5	<0.001
Triceps skinfold thickness, mm		14.3 ± 9.4	15.5 ± 9.5	0.200
Arm muscle area, cm^2		32.4 ± 11.6	28.0 ± 11.5	<0.001

Statistical analysis: unpaired t-test (age, basic ADL, Charlson comorbidity index, and anthrometric measurements) and χ^2 test (age group, nutrition route, and illness)

Table 40.2 Comparison of anthropometry between cohort and Japanese reference data (Male)

Male	Age (Year)	Cohort Average ± SD	JARD Average ± SD	p-value
Mid-arm circumference, cm	65–69	25.3 ± 3.6	27.3 ± 2.7	<0.001
	70–74	25.4 ± 5.5	26.7 ± 2.9	0.078
	75–79	24.0 ± 3.7	25.8 ± 3.0	<0.001
	80–84	24.0 ± 3.4	25.0 ± 3.0	0.046
	85+	23.6 ± 3.5	23.9 ± 3.1	0.351
Triceps skinfold thickness, mm	65–69	14.9 ± 8.6	10.6 ± 4.2	<0.001
	70–74	13.0 ± 10.1	10.8 ± 5.3	0.058
	75–79	14.8 ± 10.1	10.2 ± 4.2	<0.001
	80–84	16.5 ± 9.9	10.3 ± 4.3	<0.001
	85+	12.9 ± 8.1	9.4 ± 4.6	<0.001
Arm muscle area, cm^2	65–69	34.9 ± 13.5	46.1 ± 9.4	<0.001
	70–74	38.0 ± 19.3	43.9 ± 10.2	<0.001
	75–79	30.9 ± 10.9	41.4 ± 9.6	<0.001
	80–84	29.4 ± 10.9	38.2 ± 10.1	<0.001
	85+	31.6 ± 11.9	35.4 ± 8.9	0.004

JARD Japanese Anthropometric Reference Data

Table 40.3 Comparison of anthropometry between cohort and Japanese reference data (female)

Female	Age (Year)	Cohort Average ± SD	JARD Average ± SD	*p*-Value
Mid-arm circumference, cm	65–69	25.6 ± 4.2	26.4 ± 2.7	0.193
	70–74	25.2 ± 4.8	25.6 ± 3.2	0.436
	75–79	24.2 ± 4.8	24.6 ± 3.5	0.381
	80–84	22.5 ± 4.1	23.9 ± 3.3	<0.001
	85+	21.5 ± 3.9	22.9 ± 3.4	<0.001
Triceps skinfold thickness, mm	65–69	18.1 ± 10.4	19.7 ± 7.0	0.068
	70–74	17.9 ± 9.4	17.1± 6.8	0.051
	75–79	17.7 ± 10.0	14.4 ± 6.8	<0.001
	80–84	13.5 ± 9.0	13.0 ± 5.9	0.057
	85+	13.1 ± 8.6	11.7 ± 5.9	<0.001
Arm muscle area, cm^2	65–69	32.5 ± 11.9	32.7 ± 7.6	0.890
	70–74	31.5 ± 12.3	33.2 ± 8.6	0.218
	75–79	29.6 ± 12.6	32.7 ± 8.6	0.011
	80–84	27.4 ± 10.5	31.8 ± 8.1	<0.001
	85+	25.2 ± 10.2	29.4 ± 8.8	<0.001

JARD Japanese Anthropometric Reference Data

Anthropometric measurements of the mid-upper arm including TSF and MAC can be introduced easily in the community-dwelling elderly, as it is a quick, handy, inexpensive and non-invasive method. AMA, as an index for muscle mass, can easily be calculated from TSF and MAC. As shown in Table 40.2, the MAC levels of male participants of the 75–84 years age group were significantly lower than the Japanese norm. In female participants, MAC levels in the 80–84 years and 85 years and older age groups were lower than the Japanese norms (Table 40.3). There were significantly higher TSF levels in male participants of all age groups except for 70–74 years and higher TSF levels in female participants of the 75–79 years and 85 years and older age groups, compared with Japanese norms. The AMA of male participants was significantly lower than the Japanese norm in all age groups. In female participants, lower AMA levels were observed in the 75–79 years, 80–84 years, and 85 years and older age groups. We observed that AMA or TSF levels were lower and higher, respectively, in participants of NLS-FE than those of the standard Japanese population. The lack of differences in BMI levels for each 5-year-interval, gendered age group between our cohorts with some disabilities and the Japanese norm suggested that though there were clear differences in body composition between Japanese subjects with or without physical impairment, total body mass did not reflect those differences.

40.3.6 Anthropometry and ADL

The correlation between anthropometric measurements and ADL function was evaluated using the partial rank correlation coefficients, after adjusting for gender and age. ADL score was significantly correlated with BMI (correlation coefficient (r) = 0.191, $p < 0.01$), MAC ($r = 0.288$, $p < 0.01$), and AMA ($r = 0.298$, $p < 0.01$), but not with TSF ($r = 0.019$, $p = 0.749$). It has been reported in cross-sectional observations that physical disability is associated with increases in percentage body fat as well as a decrease of fat-free mass (Liou et al. 2005; Broadwin et al. 2001; Davison et al. 2002). In cross-sectional analyses from the Rancho Bernardo Cohort Study,

a significant positive association was shown between fat mass, which was estimated by bioelectric impedance analysis, and overall functional disability, and a significant negative association was shown between fat-free mass and overall functional disability in both men and women (Broadwin et al. 2001). In agreement with these previous findings, we demonstrated that AMA levels in the study participants were lower than Japanese norms and that AMA levels of the study participants were correlated with ADL score after adjusting for gender and age (i.e., lower AMA levels with lower ADL function). Although recent observation suggested that lower extremity muscle mass is a strong independent predictor of the level of functional impairment in community-dwelling older adults (Reid et al. 2008), our results may also suggest that not only leg muscle mass but also arm muscle mass is an important determinant of physical performance among functionally limited elders.

Our study results were also consistent with previous findings of higher TSF levels in the study participants than those in Japanese subjects without impairment of physical function. However, we observed that TSF levels were not correlated with ADL function after adjusting for gender and age among study participants. When analysis was conducted after adjustment for BMI, ADL score was still correlated with AMA ($r = 0.151$, $p = 0.001$), but not with TSF ($r = -0.081$, $p = 0.072$). These results indicated that TSF levels are influenced by other factors, such as nutritional status, besides only the level of physical function, at least among our participants with ADL disabilities.

40.3.7 Anthropometry of Mid-Arm and 2-Year Mortality

Among the 957 participants, 236 died during the 2-year follow-up period. Tables 40.4 and 40.5 show the univariate and multivariate Cox proportional hazards regression models to identify independent predictors of 2-year mortality. The following baseline data were used in a Cox proportional hazards model to identify independent predictors of 2-year mortality: age, gender, ADL status, comorbidity status, and levels of MAC, TSF, and AMA. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). For the analysis, age was categorized into three groups: 65–74 years, 75–84 years, and 85 years or older. The ADL score (range: 0–20) and the Charlson comorbidity index score, which represents the sum of a weighted index that takes into account the number and seriousness of preexisting comorbid conditions, were categorized into three groups with approximately equal numbers of participants in each group: ADL, high function, ≥18; mild function, 12–17, and low function, ≤11; the Charlson comorbidity index score, <2, 2–3, ≥4. AMA (cm^2) was categorized into three groups by tertile: high, ≥33.4; mild, 23.5–33.3; and low, <23.5. TSF (mm) was categorized into three groups by tertile: high, ≥17; mild, 10–16; and low, <10. MAC (cm) was also categorized into three groups by tertile: high, ≥25.2; mild, 24.5–25.1; and low, <24.5 (Tables 40.4 and 40.5).

Unadjusted univariate analysis suggested that the oldest age category (≥85 years), low ADL function, ≥4 Charlson comorbidity index score, <10 mm TSF thickness, <23.5 cm^2 AMA, and <24.5 cm MAC were associated with 2-year mortality (Tables 40.4 and 40.5). A multivariate Cox proportional hazards regression model based on the all the variables used in univariate analysis showed that low TSF(<10 mm) and low AMA (<23.5 cm^2) were associated with 2-year mortality (Table 40.4). In addition, when MAC was used instead of TSF and AMA, it (mild: 24.5–25.1 cm and low: <24.5 cm) was associated with mortality (Table 40.5) with higher hazard ratio than that of TSF or AMA.

In the general population, it has been demonstrated that fat-free mass and TSF, an indicator of fat mass, have clear negative and positive relationships, respectively, with mortality (lower fat-free mass and higher TSF with higher mortality) (Zhu et al. 2003; Allison et al. 2002). Consistent with those

Table 40.4 Cox proportional hazard models for 2-year mortality (Reprinted from Enoki et al. (2007). With permission from Elsevier)

	Univariate		Multivariate	
Variable	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Gender				
Female[a]	1.00		1.00	
Male	1.16 (0.90–1.51)	0.260	1.31 (0.96–1.80)	0.088
Age group				
65–74[a]	1.00		1.00	
75–84	1.31 (0.92–1.87)	0.135	1.01 (0.67–1.51)	0.966
85 year ≤	1.70 (1.19–2.42)	0.004	1.16 (0.76–1.76)	0.486
Basic ADL				
High function (≥18)[a]	1.00		1.00	
Mild function (12–17)	1.26 (0.78–2.03)	0.340	1.03 (0.62–1.69)	0.922
Low function (≤11)	2.36 (1.53–3.63)	<0.001	1.76 (1.09–2.83)	0.020
Charlson comorbidity index				
<2[a]	1.00		1.00	
2–3	1.36 (0.96–1.92)	0.083	1.33 (0.94–1.90)	0.112
≥4	1.70 (1.17–2.46)	0.005	1.35 (0.91–2.02)	0.141
Triceps skinfold thickness (mm)				
High (≥17)[a]	1.00		1.00	
Mild (10–16)	1.14 (0.81–1.59)	0.459	1.26 (0.85–1.88)	0.230
Low (<10)	1.75 (1.26–2.42)	0.001	1.89 (1.30–2.75)	0.001
Arm muscle area (cm^2)				
High (≥33.4)[a]	1.00		1.00	
Mild (23.5–33.3)	1.34 (0.93–1.92)	0.115	1.26 (0.85–1.88)	0.256
Low (<23.5)	2.04 (1.47–2.85)	<0.001	2.03 (1.36–3.02)	<0.001

CI confidence interval
[a]Reference category

Table 40.5 Cox proportional hazard models to examine the association between 2-year mortality and MAC

	Univariate		Multivariate	
Variable	Hazard Ratio (95% CI)	*p*-Value	Hazard Ratio (95% CI)	*p*-Value
Gender				
Female[a]	1.00		1.00	
Male	1.16 (0.90–1.51)	0.26	1.34 (0.98–1.83)	0.061
Age group				
65–74[a]	1.00		1.00	
75–84	1.31 (0.92–1.87)	0.135	0.99 (0.66–1.48)	0.954
85 year ≤	1.70 (1.19–2.42)	0.004	1.16 (0.77–1.76)	0.471
Basic ADL				
High function (≥18)[a]	1.00		1.00	
Mild function (12–17)	1.26 (0.78–2.03)	0.340	1.04 (0.62–1.72)	0.889
Low function (≤11)	2.36 (1.53–3.63)	<0.001	1.71 (1.06–2.76)	0.029
Charlson comorbidity index				
<2[a]	1.00		1.00	
2–3	1.36 (0.96–1.92)	0.083	1.38 (0.97–1.98)	0.075
≥4	1.70 (1.17–2.46)	0.005	1.52 (1.02–2.26)	0.040
Mid-upper-arm circumference (cm)				
High (≥25.2)[a]	1.00		1.00	
Mild (24.5–25.1)	1.81 (0.81–1.59)	0.002	1.63 (1.07–2.47)	<0.001
Low (<24.5)	2.98 (1.26–2.42)	<0.001	2.77 (1.83–4.18)	<0.001

CI confidence interval
[a]Reference category

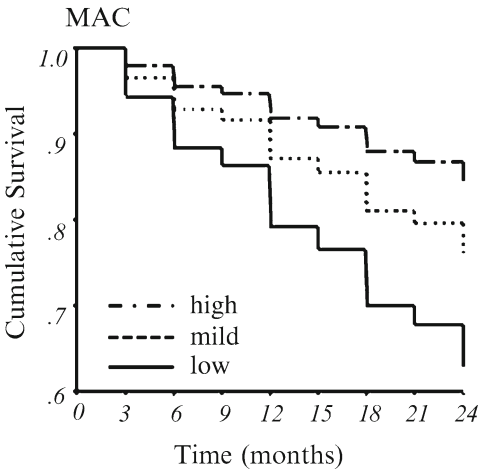

Fig. 40.1 Kaplan–Meier survival curves for elderly subjects with various levels of MAC (cm). MAC (cm) levels were classified as low (<24.5), mild (24.5–251), and high (25.2≤). Survival curves were plotted using the Kaplan–Meier method, adjusting for age, gender, ADL status, and Charlson comorbidity index

findings, a number of studies have demonstrated that AMA or AMC, another indicator of muscle mass, is a predictor of mortality in older people (Miller et al. 2002; Muhlethaler et al. 1995). As described above, controversial results have been reported in terms of the relationships between TSF and mortality in older people. Our prospective observation demonstrated that lower TSF was an independent predictor of 2-year mortality among community-dwelling dependent older people, even after adjusting for possible confounding factors. The inconsistency between our study and previous studies targeting the general population in terms of the relationship between TSF and mortality may be due to the difference in study population, that is, a healthy younger population versus frail older people with some disabilities. A higher TSF seems to reflect obesity and hyperalimentation in the general population, but in our frail elderly participants, a lower TSF seems to reflect undernutrition. However, it may be possible that cultural differences between Japan and other Western countries may affect this inconsistency. Recently, a study demonstrated that fat mass index, measured with a gold standard technique (X-ray absorptiometry) and bioelectrical impedance analysis, is a predictive marker of morbidity and mortality in hospitalized elderly patients (Bouillanne et al. 2009), suggesting that, at least among vulnerable older people, fat mass including TSF has protective role on adverse outcomes of the elderly.

We also observed that MAC was a better predictor of 2-year mortality among community dwelling dependent older people compared with AMA or TSF. This result is not surprising. Because MAC takes into account the humeral diameter as well as the skeletal muscles and fat covering the limb, therefore reflecting both TSF and AMA.

40.3.8 Kaplan–Meier Survival Curves

Figures 40.1 and 40.2 show the multivariate-adjusted Kaplan–Meier survival curves exploring the association between MAC, TSF, or AMA categories and time to death (3-month interval). The lowest category of MAC (<24.5 cm), TSF (<10 mm), and AMA (<23.5 cm^2) showed an increased risk of death during the 2-year follow-up compared with the middle and highest categories (Figs. 40.1 and 40.2a, b).

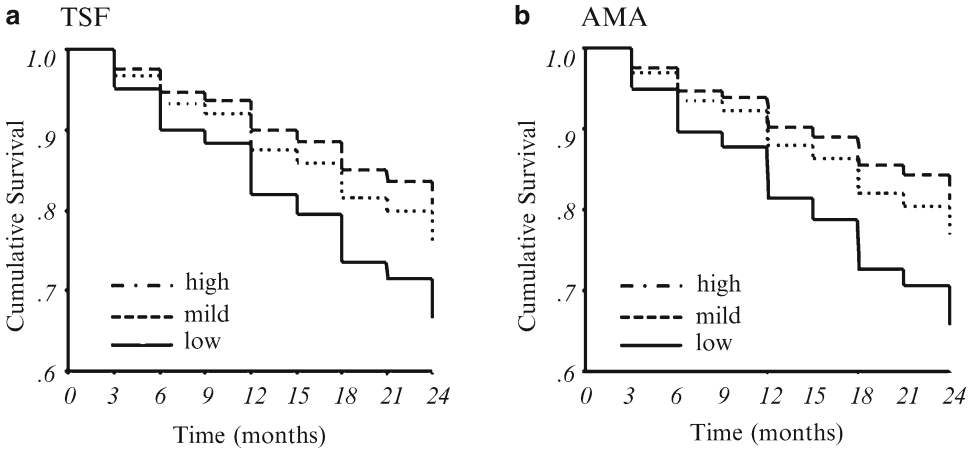

Fig. 40.2 Kaplan–Meier survival curves for elderly subjects with various levels of TSF (A) and AMA (cm^2) (**b**). (**a**) TSF (mm) levels were classified as low (<10), mild (10–16), and high (17≤). (**b**) AMA (cm^2) levels were classified as low (<23.5), mild (23.5–33.3), and high (33.4≤). Survival curves were plotted using the Kaplan–Meier method, adjusting for age, gender, ADL status, and Charlson comorbidity index (Reprinted from Enoki et al. (2007). With permission from Elsevier)

40.3.9 Combined Evaluation of AMA and TSF

We further characterized study participants using a nine-level measurement that combined AMA levels and TSF levels. Within each level of TSF, risk of mortality rose as levels of AMA decreased. Within each level of AMA, risk of mortality rose as TSF decreased. A striking increase in the risk of 2-year mortality, adjusted for age and gender, was observed in the low TSF with low AMA group (HR: 3.83, 95% CI: 1.97–7.47), versus the high TSF with high AMA (Fig. 40.3). These findings indicate that a combined evaluation of AMA and TSF strengthens the prediction of relative short-term mortality among community-dwelling dependent older people (Fig. 40.3).

40.3.10 Limitations

The current study had several limitations. NLS-FE is a large-scale observational study but does not include the complete spectrum of elderly patients in the Nagoya area, an urban area. In the analysis, baseline data of the anthropometric measurements were included, but changes in the measurements during the follow-up period were not considered. Although recent study suggested that muscle strength is more powerful predictor of mortality than muscle mass (Newman et al. 2006), data of muscle strength were not available in our study. Another limitation is that we enlisted each station to perform evaluation because of a shortage of hands and the large number of settings. This may have biased assessors' evaluations and limited the validity of the results. The results of the present study cannot transfer to the non-frail independent older population, as there should be many differences between the participants of NLS-FE and the standard non-frail older, including ADL levels and comorbidity. In addition, these findings may not be generalizable to other populations given that they may have been influenced by cultural differences, health practices, and a variety of social and economic factors.

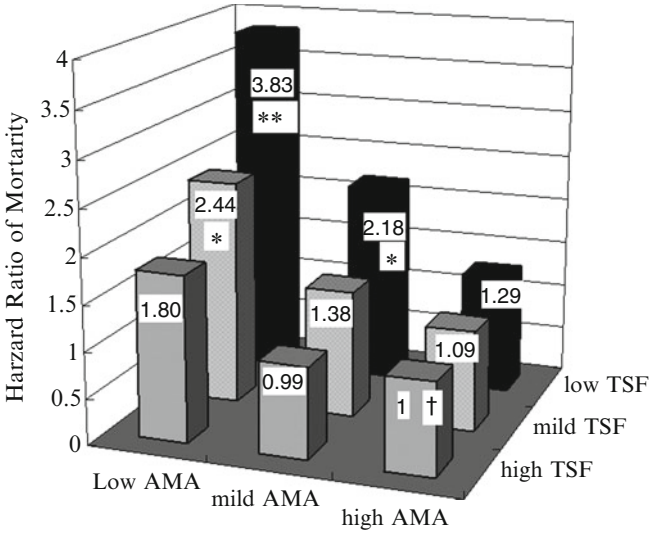

Fig. 40.3 Relative risks for all-cause mortality. Estimations were obtained from Cox regression models adjusting for age and gender. Eight independent variables, created for each level of AMA (low: <23.5 cm^2, mild: 23.5–33.3 cm^2, high: 33.4 cm^2≤) and TSF (low: <10 mm, mild 10–16 mm, high: 17 mm ≤) combined, were used as indicator variables and compared with the reference group (defined as those with high AMA and high TSF). Number on each bar indicates hazard ratio. *: $p < 0.05$, **: $p < 0.01$, †: reference group (Reprinted from Enoki et al. (2007). With permission from Elsevier)

40.4 Conclusion

Anthropometric measurements of the mid-upper arm are performed often in research, but rarely on a clinical basis, even although they are a quick, inexpensive, and non-invasive way of measuring nutritional status. In the present study, we demonstrated a striking picture of increased mortality risk associated with lower AMA levels, lower TSF, and lower MAC. Anthropometric measurements of the mid-arm may be a more practical and suitable index not only for nutritional assessment but also for capturing the vulnerable subset of older people living in the community.

40.4.1 Applications to Other Areas of Health and Disease

In the text, we focused on older people in terms of the mid-upper arm anthropometric measurements as nutritional markers and indicators of mortality risk. However, numbers of researches are using upper arm measurements as nutritional as well as growth markers for the children. The World Health Organization (WHO) introduced the Child Growth Standards, which included MAC and TSF, for assessing the growth and development of children, (WHO Multicentre Growth Reference Study Group 2006). In addition, upper arm measurements were also established as an indicator of mortality risk for children (Lapidus et al. 2009).

Summary Points

- Higher average triceps skinfold (TSF) levels were observed in community-dwelling dependent elderly, compared with age-matched (5-year intervals) individuals of the standard Japanese population.
- Lower average arm muscle area (AMA) levels were observed in community-dwelling dependent elderly, compared with age-matched (5-year intervals) individuals of the standard Japanese population.
- AMA levels of community-dwelling dependent elderly were correlated with their physical function.
- TSF levels of community-dwelling dependent elderly were not correlated with their physical function.
- Lower AMA levels of community-dwelling dependent elderly were associated with 2-year mortality.
- Lower TSF levels of community-dwelling dependent elderly were associated with 2-year mortality.
- Lower mid-arm circumference (MAC) levels of community-dwelling dependent elderly were associated with 2-year mortality.

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Chapter 41
The Arm Span to Height Relationship and Its Health Implications

Maw Pin Tan and Sushil K. Bansal

Abstract The Roman architect, Vitruvius, had noted in the first century BC that the arm span closely approximated to height. This relationship has been exploited by medical science by using arm span to estimate height in situations where height measurement is not possible. This can be done by directly substituting height with arm span, a fixed ratio, or specific regression equations. It has also been noted that height decreases with increasing age due to physiological changes, degenerative changes and osteoporosis, while the arm span remains unchanged. The arm span–height difference (AHD) or arm span to height ratio (AHR) can therefore be used as a marker for age-related loss of height. Several studies have also investigated AHD as a predictor for osteoporosis-related vertebral fracture, due to the association of vertebral fractures with height loss. These studies have however yielded conflicting results, probably due to the lack of an agreed definition for vertebral fractures. A recent study demonstrated that AHR is inversely correlated with lung airflow volumes measured with spirometry, and directly correlated with severity of shortness of breath. By using AHR as a quantitative index for loss of height, the authors were able to demonstrate that loss of height is associated with breathing difficulties. The reduction in height with ageing may also result in underestimation of the severity of lung airflow problems and nutritional problems. Involving arm span measurements in the calculation of predicted lung airflow volumes and body mass index may potentially be the solution to overcoming this problem.

Abbreviations

AHD	Arm span to height difference
AHR	Arm span to height ratio
BMD	Bone mineral density
BMI	Body mass index
FEV1	Forced expiratory volume in 1 min
FVC	Forced vital capacity
NYHA	New York Heart Association

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_41,

41.1 Introduction

Arm span is the closest physiological measurement to standing height. In the healthcare setting, the measurement of standing height is crucial in the estimation of nutritional status and in determining the severity of lung airflow limitations. Arm span is therefore sometimes substituted for standing height in clinical situations where the accurate measurement of standing height is not possible. In addition, the discrepancy between arm span and height measurements may also be a useful clinical marker for loss of height in relation to either physiological ageing or pathological processes. Over the past 2 decades, there has been some research activity into the validity and clinical implications of using the discrepancy between arm span and height in assessing loss of height, vertebral deformity and associated health implications.

41.2 Estimating Height with Arm Span

The relationship between arm span and height had been noticed by the Roman architect, Vitruvius, in first century BC, who stated that 'the distance from fingertip to fingertip (arm span) should be equal to the distance from head to heel (height)'. The Vitruvian theory has been most elegantly depicted by Leonardo da Vinci in his drawing of the 'Vitruvian Man'. Assessments of various other anthropometric measures, which include knee height, sitting height, and demispan indicate that arm span has the strongest correlation with standing height (Fig. 41.1). As a result, arm span is often used to estimate standing height in situations where measurements of standing height is not possible, such as in patients with difficulty standing due to neuromuscular weakness, amputees, congenital limb deformities and vertebral deformities. The methods employed for estimating height with arm span include:

1. Direct substitution of arm span for height
2. Correction with a fixed ratio and
3. Gender and ethnicity specific regression equations in increasing order of complexity and accuracy (Table 41.1).

The use of a correction factor for the estimated of height with arm span has been practiced for several decades due to reports by various studies involving predominantly Caucasian adult populations, that the mean arm span to height ratio for their population is 1.03 for men and 1.01 for women (Hepper et al. 1965). However, later studies observed progressive increases in mean arm span to height ratio with increasing age (Hepper et al. 1965; Linderholm and Lindgren 1978). The mean arm span to height ratio also appeared to differ according to ethnicity (Parker et al. 1996). This had lead to the development of specific regression equations in specific geographical areas, taking into account age, gender and ethnic differences. The accuracy of estimated height with regression equations have been consistently shown to be superior to the direct substitution of arm span for height. However, as arm span remains strongly correlated with height, the direct substitution of arm span for height may be acceptable in cultural groups for which regression equations are not available (Aggarwal et al. 1999). In the paediatric age group, there is much higher correlation between arm span and height ($r = 0.97$ for girls and $r = 0.98$ for boys), suggesting that direct substitution may actually be more applicable in children than adjustments with correction factors (Hibbert et al. 1988).

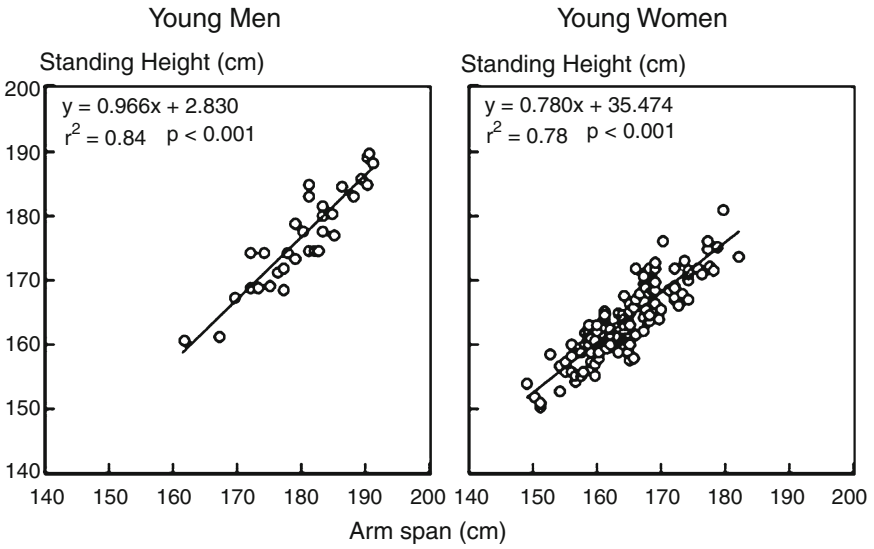

Fig. 41.1 The relationship between arm span and height. A scatterplot demonstrating the strong correlation between arm span and standing height measurements in younger men and women. (With kind permission from Springer Science + Business Media: Wang et al. (2004), Figure 2, © 2003 International Osteoporosis Foundation and the National Osteoporosis Foundation)

Table 41.1 Using arm span to estimate height

Method	Indications
1. Direct substitution of arm span for height	(a) Cultural groups for which no regression equations are available. (b) May be more applicable for children.
2. Calculation using a correction factor or fixed ratio (a) Women: Height = Arm Span/1.01 (b) Men: Height = Arm span/1.03	This method is widely used, but the correction factor has been determined in predominantly Caucasian adult populations and may not be applicable to children, the elderly as well as other ethnic groups and non-Western geographical areas.
3. Calculation using Predetermined Regression Equations (Parker et al. 1996) White males: Height (cm) = 68.7363 + 0.63008 Arm span −0.1010 Age White females: Height(cm) = 33.1453 + 0.79499 Arm span Black males: Height (cm) = 60.1273 + 0.65336 Arm span −0.08399 Black females: Height (cm) = 59.0745 + 0.61442 Arm span	Estimation of height using regression equations is dependent on the availability of gender- and ethnic group-specific regressions. Specific regression equations have not published for some ethnic and cultural groups.

Methods of estimating height with arm span. The methods currently used and available conversion equations are listed in the table above

41.3 Practical Methods and Techniques

41.3.1 Arm Span Measurements

Several methods of assessing arm span have been described. The three most commonly described methods are listed below (Fig. 41.2). The first method of measurement is the one most widely used in published studies and the method used in establishing the conversion equations described above.

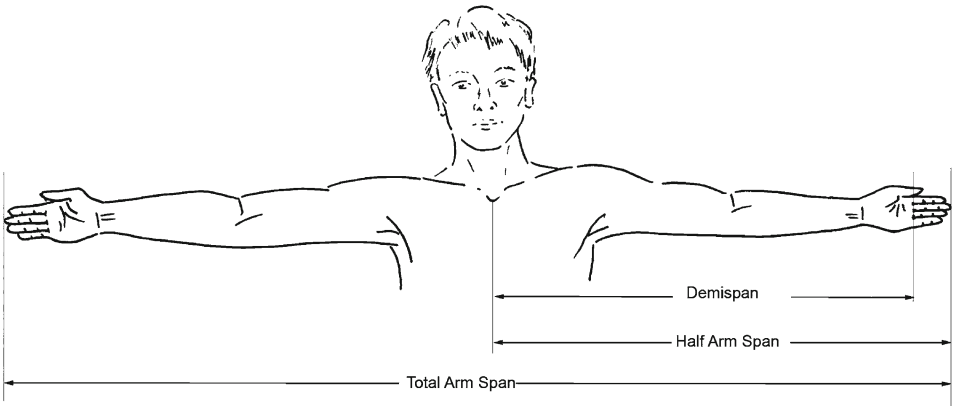

Fig. 41.2 Arm span measurements. The total arm span is considered the maximal distance between the two middle fingers. The half arm span is the maximal distance between the midpoint of the suprasternal notch to the tip of the middle finger. The demispan is the distance between the mid-suprasternal notch to the root of the middle finger

1. Total Arm Span: The maximal distance between the tips of the two middle fingers. The subject is upright with his or her back against the wall. The arms are fully abducted, with straight elbows, at 90° from the torso. Some publications have described a similar technique with the subject facing the wall. The measurement is made with a rigid extended calibrated rule, a flexible metal tape or an adapted stadiometer.
2. Half arm span: This technique is usually performed in the sitting or recumbent position. The distance between the sternal notch and the tip of the middle finger is measured with the arm outstretched at 90° to the body. The measurement is then multiplied by 2 to obtain the full arm span.
3. Demispan: This measurement is also performed usually in the sitting or lying position. It has the advantage of not being affected by subjects with finger deformities, which is particularly common in elderly subjects due to arthritic processes or contractures. It is, however, a less published method. The distance between the suprasternal notch and the root of the middle finger is measured. A height conversation equation for demispan has been devised by Bassey (Bassey 1986):

    - Females: Height (cm) = [1.35 × demispan (cm)] + 60.1
    - Males: Height (cm) = [1.40 × demispan (cm)] + 57.8

41.3.2 Measuring Loss of Height

Actual standing height could be affected by various congenital and acquired conditions, including ageing, congenital kyphoscoliosis, inflammatory arthritis, osteoarthritis and vertebral fractures due to osteoporosis. In individuals with the above conditions, while standing height is usually reduced, arm span may be unaffected. The discrepancy between arm span and height may therefore be a useful measure of the magnitude of height loss.

41.3.3 The Discrepancy Between Arm Span and Height

1. Arm span–height difference [arm span – height]: Most publications have adopted this simple way of calculating the difference between arm span and height. However, this index does not take into account differences in stature. It therefore does not account for the possibility that

taller people have proportionally longer arms and potentially larger differences between arm span and height.

2. Arm span to height ratio [arm span: height] – This index was adopted as a determinant of the discrepancy in arm span and height in a recent publication. It is a unitless measure derived by dividing the arm span in metres with height in metres. An increase in the arm span to height ratio (AHR) is observed with a reduction in height. Unlike arm span–height difference (AHD), AHR assesses the proportion of increase in arm span over height. The additional advantage of using this index is that the AHR has already been extensively studied historically, albeit only in mainly white populations. There are therefore published population norms for AHR, which could be used to determine the presence of loss of height (Hepper et al. 1965), but this practice has yet to be validated scientifically.

41.3.4 Arm Span, Height and Age

Loss of height is a feature of ageing. Data published from the Baltimore Longitudinal Study of Ageing reported a cumulative height loss of 5 cm for men and 8 cm for women, from age 30–80 years (Sorkin et al. 1999). A reduction in vertebral disc spaces, alterations in posture and increases in spinal curvature have been suggested as plausible causes for age-related height loss. The reduction in intervertebral space has been attributed to reduction in disc height as part of a degenerative process. An increase in spinal curvature is also often observed with increasing age. Possible causes of increased spinal curvature include increases in the laxity of the vertebral ligaments, degenerative arthritic processes and osteoporosis. Osteoporosis is very much an age-related condition, which is far more common in women. Vertebral wedge fractures occur in individuals with osteoporosis with little or no trauma resulting in an increase in spinal curvature, which often progresses as the individual sustains further wedge fractures, should the condition remain untreated. Osteoporosis patients may therefore experience extreme reductions in height. Whereas some patients with osteoporosis may present with severe back pain from the vertebral fractures, others with the disease may remain entirely asymptomatic. The prevalence of silent vertebral fractures has not been well established. The overall prevalence of vertebral fractures in European women has been estimated as 23.5% in women aged 65–69 years, and 34.8% in women over 75 years of age (O'Neill et al. 1996). As arm span tends to remain unchanged with age, the discrepancy between arm span and height can be considered a marker of the extent of height reduction associated with age. The relationship between height and arm span with age has been clearly demonstrated in several studies (Fig. 41.3).

41.3.5 Arm Span, Height and Vertebral Deformities

As mentioned earlier, the arm span is often used to estimate standing height in individuals with vertebral deformities. A reduction in standing height is usually observed in individuals with acquired vertebral deformities, whereas the arm span remains unchanged. It can therefore be postulated that an index of the discrepancy between arm span and current standing height could predict the presence or severity of vertebral deformities. The literature behind AHD as a predictor of vertebral deformities has been mixed (Table 41.2). Verhaar et al. (Verhaar et al. 1998) devised a prediction

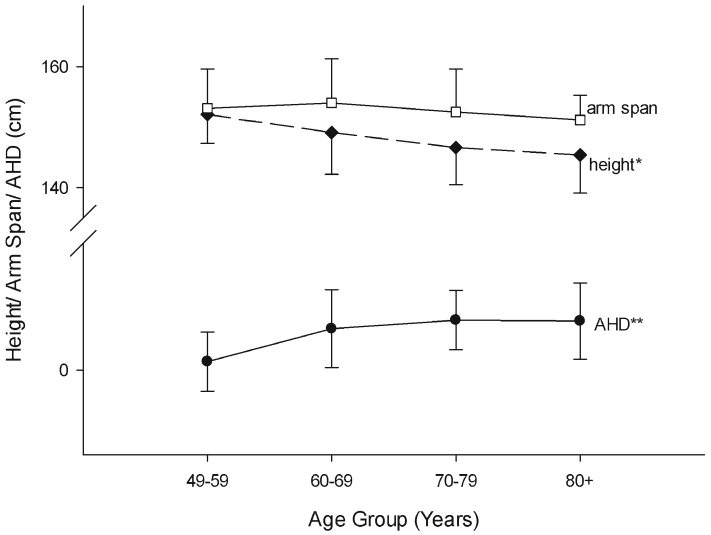

Fig. 41.3 Height, arm span and arm span to height differences according to age. Arm span is unchanged with increasing age, whereas a decline in age is observed, alongside an increase in arm span to height difference (AHD). *$p = 0.001$; **$p < 0.001$. (Figure adapted from Abe et al. (2008). Open access material

curve (Fig. 41.4) and a decision rule for the probability of having osteoporosis (Table 41.3) for which they reported a sensitivity of 81% and specificity of 64% for prediction of osteoporosis (Verhaar et al. 1998). Abe et al. (Abe et al. 2008) reported a sensitivity of 85% and specificity of 52% for the cut-off value for AHD ≥ 4 cm as a predictor of vertebral deformities (Abe et al. 2008). The remaining studies have yielded less convincing results.

The differences in outcomes of the studies may be explained by differences in case selection and the methods used to assess vertebral deformities. The validity of vertebral bone mineral density (BMD) is questionable as a marker for vertebral deformities, as vertebral BMD is no longer considered a useful test for osteoporosis in the presence of vertebral deformities. Clinical diagnoses based on history taking and physical examination have potentially high false negative rates because a large number of osteoporotic vertebral fractures escape clinical diagnosis, whereas radiographic measurements are complex and difficult to interpret. In addition, loss of height may also occur from other causes such as degenerative disc changes and other age-related processes.

Arm span–height difference therefore cannot be recommended as a marker or screening test for osteoporosis-related vertebral fractures at present. While further evaluation may be justified, this is currently limited by the lack of clear diagnostic criteria for vertebral fractures. However, arm span measurements are quick to perform, non-invasive, and cost nothing. It could therefore be a potentially useful screening test, particularly in less wealthy societies, where widespread use of DXA is not economically plausible. Future studies evaluating AHD/AHR with other clinical risk factors, such as age, sex, self-reported loss of height, family history, low body weight, and early menopause may also be justified.

41.3.6 Health Implications of Loss of Height

Congenital kyphoscoliosis is an established cause of respiratory failure due to the presence of a restrictive lung defect and increased work of breathing. The clinical suspicion that respiratory compromise from acquired vertebral deformities from osteoporosis may also occur has been

Table 41.2 Arm span–height difference and vertebral deformities

Authors and References	Subjects	Measurement used for Vertebral deformities	Conclusion	Cut-off	Sensitivity	Specificity
Abe et al. (2008)	116 women aged 69.9 ± 9.3 year	X-ray absorptiometry and BMD	AHD predicts vertebral deformities.	AHD ≥ 4 cm	85%	52%
Twiss et al. (2002)	63 women aged 45–70 years	Osteoporosis risk questionnaire	Almost significant association between risk factor score and AHD ($r = 0.240$, $p = 0.0574$) but significant association with reported height loss ($r = 0.416$, $p < 0.001$).			
Uzunca et al. (2008)	90 women, mean age 59.3 years	L2–4 BMD and hip lateral radiographs	No significant difference between osteoporosis versus non-osteoporosis group			
Verhaar et al. (1998)	36 osteoporotic women, mean age 71.6 years; 25 controls, mean age 68.7 years	Clinical diagnosis of osteoporosis and vertebral fractures (BMD and plain films)	AHD predicts probability of osteoporosis (Fig. 41.3).	AHD> 3 cm Decision rule (Table 4)	58% 81%	56% 64%
Versluis et al. (1999)	449 women aged 55–84 years	X-ray morphometry	Vertebral deformities not detected by AHD	AHD> 5cm	39%	76%
Wang et al. (2004)	34 men and 73 women, aged 46–90 years with vertebral fractures; 112 healthy male and 261 healthy female volunteers aged 18–92 years	20% reduction in vertebral height on lateral X-ray radiograph. (controls did not have X-rays to exclude vertebral fractures)	AHD did not predict vertebral fractures. A multivariate model containing weight, sitting height and arm span as predictors for vertebral fractures in men.*	Men: AHD> 6.6 cm Women: AHD> 2.5cm	62% 48% 83%	37% 48% 80%

BMD bone mineral density.*Men (fracture risk = 18.955 – 0.06 weight – 0.44 sitting height + 0.14 arm span); women (fracture risk = 90.749 + 0.1 age – 0.19 sitting height)
Summary of results of studies evaluating arm span–height difference as a predictor of vertebral fractures or osteoporosis

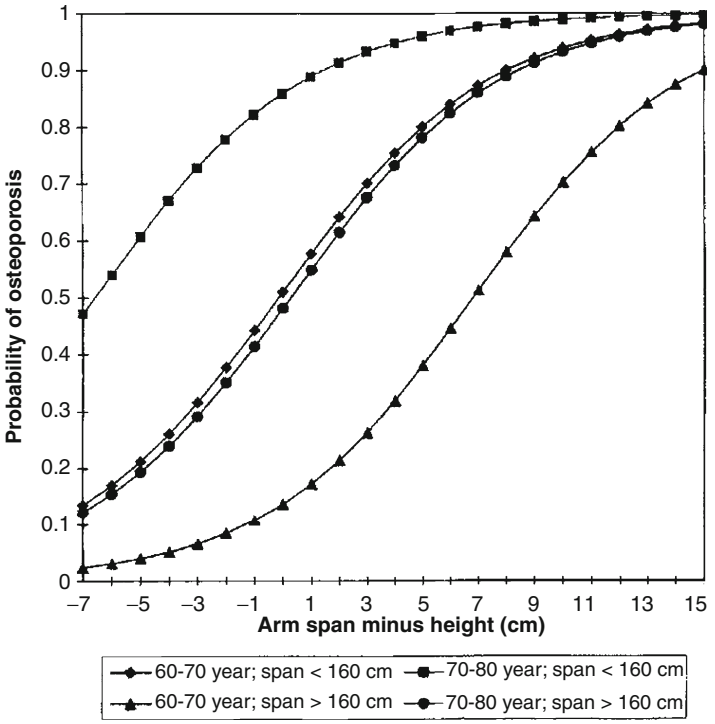

Fig. 41.4 Predicted probability of osteoporosis using arm span–height difference. Probability curves for osteoporosis for arm span–height difference (cm) according to two age categories (60–70 years; 70–80 years) and two arm span categories (<160 cm; >160 cm). (With kind permission from Springer Science + Business Media: Verhaar et al. (1998), Figure 1, © 1998 European Foundation for Osteoporosis and the National Osteoporosis Foundation)

Table 41.3 A decision rule for osteoporosis

		Age (years)	
Arm span–height difference		<70	≥70
Height (cm)	<160	>0 cm	> –7 cm
	≥160	>7 cm	>0 cm

Arm span–height cut-off for osteoporosis

The decision rule devised by Verhaar et al. (1998) for the prediction of osteoporosis. The values in the shaded boxes represent the difference between arm span and height in centimetres. Sensitivity = 81%, specificity = 64%

present for some time. Published studies supporting this clinical observation has been limited, but a recent metanalysis of four small case-control studies suggested that osteoporosis-related kyphosis is associated with impairment in pulmonary function (Harrison et al. 2007). The pattern of pulmonary involvement was mainly restrictive, and the level of impairment is related to the number of vertebral fractures and the clinical severity of kyphosis. This topic is particularly important as osteoporosis is becoming an increasing health problem with the ageing world population.

While the value of AHD as a marker for height loss due to vertebral fractures remains unclear, the arm span to height difference remains a useful marker of age-associated loss of height. Loss of

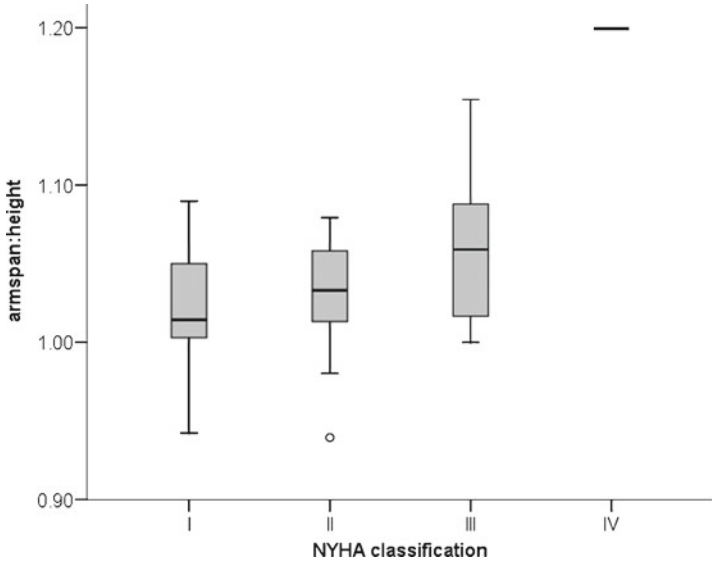

Fig. 41.5 The relationship between arm span–height ratio and the severity of breathlessness. This is a box and whiskers plot, with the thick horizontal line representing the median, the upper and lower borders of the boxes representing the interquartile range and the error bars representing the minimal and maximal values. The severity of breathlessness is measured by the New York Heart Association classification: I = no limitation, II = slight limitation, III = marked limitation, IV = breathless at rest

height, regardless of aetiology (physiological ageing, degenerative or vertebral fractures), may also have potential deleterious effects on respiratory function. A reduction in height by 10 cm is said to correspond to a 700 ml reduction in lung volume in women with osteoporosis (Leech et al. 1990). This problem may be accentuated with old age, due to loss of the elastic recoil of the lung, reduced chest wall compliance and decreased muscle strength. Older people are also more likely to suffer from other coexisting medical problems.

The arm span: height ratio (AHR) has been shown to be negatively correlated with forced expiratory volume (FEV1) and forced vital capacity (FVC) (Tan et al. 2009). FEV1 and FVC are measurements of lung airflow volumes obtained with a spirometer. These measurements are therefore also called spirometry, and are widely used in clinical practice as diagnostic and monitoring tools for obstructive airways diseases, such as asthma and chronic obstructive airways disease (COPD).There was also a significant positive correlation between AHR and the New York Heart Association (NYHA) classification for heart failure, a simple four-point scale widely used to assess the severity of shortness of breath in heart failure patients (Fig. 41.5). Class I on the NYHA classification represents no restriction of activity, whereas class IV indicates severe restriction with symptoms occurring at rest. The authors suggest that the findings of their study imply that loss of height as measured by AHR is significantly associated with reduction in airflow volumes as well as with increasing shortness of breath. Their study was performed on a highly selected population of individuals with suspected heart failure, referred for routine echocardiography by their primary care physicians. As the symptoms of heart failure, dyspnoea and ankle swelling are highly non-specific, the authors claim that the patient group represent individuals being investigated for underlying causes of shortness of breath.

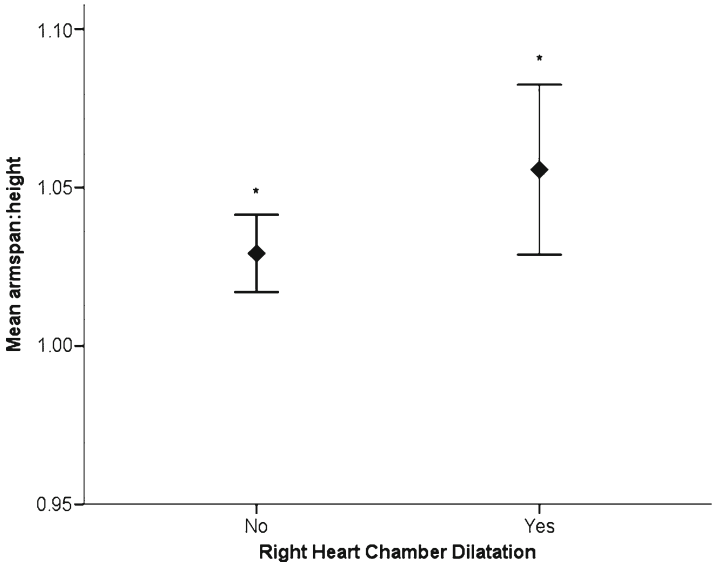

Fig. 41.6 The relationship between arm span–height ratio and right-heart chamber dilatation. The mean arm span for individuals with right-heart chamber (right atrial or right ventricular) dilatation is significantly higher than those with normal right-heart chambers. Error bars represent 95% confidence intervals. *$p<0.05$

In addition to evaluation of respiratory function, as their subjects were recruited from patients attending echocardiography, the authors were also able to determine the association between AHR with cardiac structural changes on echocardiography. The arm span: height ratio was significantly higher in individuals with right atrial and right ventricular dilatation, but not echocardiographically estimated pulmonary arterial pressure (Fig. 41.6). They suggested that this could signify the possibility of right heart failure due to chronic hypoxia as a result of the respiratory compromise associated with loss of height. The generalisability of the above study will have to be assessed in other clinical situations. Arm span: height ratio measurements in individuals with shortness of breath may be a useful indicator of the presence of loss of height, and therefore help identify potential underlying diagnoses, as many cases of shortness of breath remain unexplained at present.

41.3.7 Arm Span-Estimated Height Loss Versus Self-Reported Height Loss

Self-reported height loss is now an accepted risk factor for osteoporosis (Siminoski et al. 2006). Some suggest that the difference between self-reported maximal height and current actual height may also be a useful quantitative marker of height loss. However, this measurement relies on accurate recall of maximal height, which is a subjective process, and research evidence suggests that men tend to overestimate their height, whereas women have a tendency to underestimate their height. One study directly comparing the self-reported height loss and arm span-estimated height loss found the former to be more strongly correlated with osteoporosis risk (Twiss et al. 2002). The authors used an osteoporosis risk questionnaire rather than objective clinical markers of osteoporosis, which would have biased the results against the more objective measurement. However, as both self-

reported height loss and arm span-estimated height loss are less than perfect measurements, and both indices are extremely simple to perform, they are likely to be complementary, and therefore more effective, if used together to identify the presence of height loss.

41.4 Applications to Other Areas of Health and Disease

41.4.1 Pulmonary Function Tests

Assessment of pulmonary function using spirometric measurements requires comparison between the patients' measured airflow volumes against the predicted airflow volumes for their height and age. The current practice is to measure arm span in situations where standing height measurements are not possible as in patients with skeletal deformities, lower limb amputations or neuromuscular weakness. Some experts have suggested that arm span measurements should also be considered in older people, particularly those with osteoporosis, as the severity of airflow limitation could be underestimated, if only height measurements are used to determine predicted airflow volumes in the presence of height loss. Allen (1989) assessed the value of predicting spirometric volumes using arm span in healthy, physically active older women. He concluded that while arm span can be used to replace height, there was little difference between the two measurements suggesting that routine arm span measurement is not justified (Allen 1989). However, in older individuals who have symptoms of breathlessness, the severity of airflow limitation can be underestimated (Tan et al. 2009).

41.4.2 Nutritional Status

The estimation of nutritional status required the use of height as well as weight measurements to estimate the body mass index (BMI). However, in clinical situations where assessment of nutritional status are particularly important, such as in intensive care units and stroke units, patients are often physically obtunded or have significant disabilities such that height measurements are not possible. As a result, demispan or half arm span measurements are often used to estimate standing height. In addition, nutritional assessments are also vital in frail elderly individuals. Frail older people are most likely to experience loss of height due to osteoporosis or other age-related physical changes. Some experts are beginning to recognise that BMI estimation in this group of subjects may be liable to clinically significant overestimation of nutritional status (Hirani and Mindell 2008). The BMI is calculated with the formula: weight/(height^2). As the height measurement is squared in this index, even small reductions in height are magnified, with a small reduction in standing height resulting in a proportionally larger increase in calculated BMI. There have been a handful of studies evaluating the value of replacing standing height with arm span or demispan measurements, but further more conclusive studies are still required.

41.4.3 Limitations

While arm span measurements are highly correlated with standing height measurements, some studies have suggested large variability in arm span to height ratio between individuals, as well as large variability between arm span-estimated height and actual standing height for individuals.

The large interindividual variability of AHR and arm span-estimated height may limit the value of using arm span measurements to replace height measurements in clinical contexts, such as respiratory function tests and nutritional assessments (Hickson and Frost 2003). It is therefore important for clinicians to be aware of this potential limitation, and to exercise appropriate clinical vigilance.

The accuracy of arm span measurements may be affected by congenital and acquired musculoskeletal disorders. Older patients may have difficulty fully abducting the shoulder or fully extending the elbow due to traumatic damage or arthritis. Both inflammatory and degenerative arthritis are associated with finger deformities, which will also affect arm span measurements, but this difficulty could be avoided by measuring the demispan. Genetic disorders, such as Marfan's syndrome and Klinefelter's syndrome, are associated with unusually long arms, which will render any assessments of arm span–height difference or arm span-estimated height inapplicable.

41.5 Conclusion

Arm span measurements are often used in clinical practice to estimated height in situations where actual height measurements are not possible. A reduction in standing height occurs with increasing age, whereas arm span usually remains unchanged. An increase in the difference between arm span and height is therefore observed with ageing. The arm span–height difference can therefore be a useful marker of age-related height loss. While osteoporosis is associated with both height loss and ageing, the evidence for arm span–height difference as a predictor for osteoporosis or vertebral fractures is currently inconclusive. Increases in the arm span: height ratio, which is increased with loss of height, is associated with severity of breathlessness, reducing respiratory airflow and right-sided heart failure. The severity of impairments in lung function and nutritional status in older individuals may be underestimated, if height measurements alone are used in lung function tests and BMI calculations. The role of arm span-estimated heights in these clinical situations needs to be studied.

Summary Points

- Arm span is strongly correlated with standing height.
- Arm span measurements can be used to estimate height in clinical situations where height measurements are not possible.
- Height reduces with age, whereas arm span remains unchanged.
- The difference or ratio between arm span and height is a marker for age-related loss of height.
- The value of arm span–height difference, as a predictor for osteoporosis related vertebral fractures, remains uncertain.
- Arm span to height ratio increases with increasing severity of breathlessness.
- Arm span–height ratio is negatively correlated with lung airflow volumes measured with spirometry, suggesting that increasing height loss is associated with increasing restriction in lung function.
- Age-associated height loss may result in underestimation of the severity of lung airflow problems and nutritional problems in older people, which may be overcome by using arm span-estimated height.

Key Features of the New York Heart Association Classification

The New York Heart Association (NYHA) classification is the system most widely used to assess the severity of symptoms in patients with heart failure. It divides patients into four categories:

Class	Functional impairment
I	No symptoms and no limitation in ordinary physical activity.
II	Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest.

Key Factors Associated with Loss of Height with Age

- Reduction in intervertebral space (reduced disc height).
- Change in posture.
- Increased spinal curvature due to:
  - Ligamentous laxity
  - Degenerative changes and
  - Osteoporosis-related vertebral crush fractures

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Chapter 42
Proximal Femoral Anthropometry by Computed Tomography

Thomas F. Lang

Abstract Age-related and pediatric disorders of the hip are common and confer strong risk factors for current and future disability. Because many of these disorders are associated with variations in proximal femoral structure, the study of the anthropometry of the hip has been of considerable interest to the medical research community. Imaging has become critical to the evaluation of human proximal femoral morphology in clinical research studies and in surgical practice. Using this overall approach, a simple radiograph or a computed tomography (CT) scan may be obtained, and landmarks identified either on radiographic films or digital images. As long as the physical size of the pixels is known, the distance between landmarks may be quantified. In this chapter, we will describe the use of computed tomography (CT) images for morphological assessment of the proximal femur. CT images provide a full three-dimensional assessment of the hip bone, allowing for morphometric analysis of both external and internal structures. Because of the inherently volumetric nature of the data, the orientation of the CT image can be standardized, allowing for reproducible metrics of size and distance. The discussion of CT morphology will be focused on the use of CT to characterize response of the proximal femur to aging, on the limitations of this technique for visualizing anatomic detail, and on practical considerations for using CT in studies of cadaveric specimens and in vivo human studies.

Abbreviations

CT	Computed Tomography
HU	Hounsfield Unit
3D	Three dimensional
kVp	Peak kilovoltage
mAs	Milliamperes
mSv	Millisieverts

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_42,

42.1 Introduction

The femur is the largest and strongest bone in the body, and the structure of its proximal portion allows the leg to move in three dimensions relative to the torso, thus serving as a linchpin of human mobility. Moreover, age-related and pediatric disorders at this skeletal site are common, and confer strong risk factors for current and future disability. Because many of these disorders are associated with variations in proximal femoral structure, the study of the anthropometry of the hip has been of considerable interest to the medical research community. Moreover, variations in hip morphology are also of critical interest to surgical planning, where the ability to take hip morphology into account on a patient-specific basis is crucial for success in choosing designs of implants and other structures used for hip replacements and augmentations of hip stability.

Imaging has become critical to the evaluation of human proximal femoral morphology in clinical research studies and surgical practice. Using this overall approach, a simple radiograph or a computed tomography (CT) scan may be obtained, and landmarks identified either on radiographic films or digital images. As long as the physical size of the pixels is known, the distance between landmarks may be quantified. For example, studies linking variants of hip structure to relatively rare outcomes, such as osteoporotic hip fracture or osteoarthritis of the hip, often require large sample sizes, often thousands of subjects, to estimate risk factors conferred by anatomic measurements. Such measurements must be taken in vivo, with a measurement protocol that can be easily standardized between the different clinical sites at which subjects might be recruited. Similarly, planning of hip surgeries, involving the selection of prosthesis design, or the direction and size of a femoral neck pin, must take into account the specific anatomic features of the subject. The principal manner by which this information can be obtained is through medical imaging.

In this chapter, we will describe the use of computed tomography (CT) images for morphological assessment of the proximal femur. CT images provide a full three-dimensional assessment of the hip bone, allowing for morphometric analysis of both external and internal structures. Because of the inherently volumetric nature of the data, the orientation of the CT image can be standardized, allowing for reproducible metrics of size and distance. In contrast, earlier technologies, such as plain X-rays, compress the three-dimensional anatomy of the proximal femur onto an anteroposterior plane, and, thus, size and distance metrics are confounded by the variable orientation of the subject at the time of the acquisition. Further, although magnetic resonance imaging (MRI) can also provide this information, CT has the advantage that bone anatomy is clearly delineated against the surrounding soft tissue, making it easier to identify bony landmarks. The discussion of CT morphology will be focused on the use of CT to characterize response of the proximal femur to aging. As with all skeletal structures, the proximal femur responds dynamically to its mechanical environment by changing size, shape, and the distribution of bone. In the context of aging, age- and menopause-related bone loss in the presence of continued mechanical loading associated with normal physical activity increases the strain on the hip. The proximal femoral response to age-related bone loss encompasses changes in morphology that have been quantified, and related to endpoints, such as fracture, in research studies carried out in our laboratory and others.

42.2 Key Anatomic Features

The proximal femur consists of the *head*, the *neck*, the *greater and the lesser trochanters, and* several related structures (Fig. 42.1).

The head of the femur serves as the interface between the femur and the acetabulum of the pelvis, forming the *hip joint*. The femur is held in place by the ligament of the head of femur

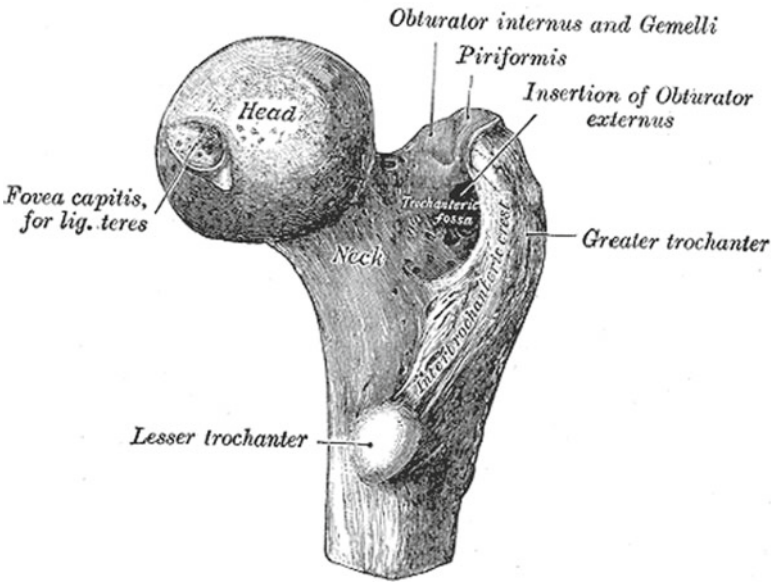

Fig. 42.1 Anatomic landmarks of proximal femur

(*ligamentum capitis femoris*), which is attached to the femur at the *fovea capitis*, a crater-like structure slightly inferior and posterior to the center of the head of the femur, and the *iliofemoral ligament*.

The femoral *neck* is a flattened pyramidal process of bone that connects the *head* to the *proximal femoral shaft*. The *greater trochanter* is a relatively large, quadrilateral projection, oriented slightly inferior and approximately 2 cm lateral to the femoral head in adults. The greater trochanter serves as the point of insertion for numerous muscles of the hip joint, including the *gluteus medius*, *gluteus minimus*, *obturator internus*, *piriformis*, gemelli, and *obturator externus*, which inserts into the *trochanteric fossa*, a deep depression on the medial aspect of the greater trochanter. The *lesser trochanter* is a conical protuberance situated distally and medially from the greater trochanter, and joined via a bony ridge referred to as the *intertrochanteric crest*. The lesser trochanter serves as the insertion of the *psoas major*, a dominant muscle in flexion of the hip.

42.2.1 Types of Bone/Arrangement of Types of Bone/Mechanical Properties

Bone is divided into two types. While bones share a basic chemical composition and contain inorganic matter giving them rigidity, each of the two bone types serve different functions (Pratt 1991). Additionally, its mechanical properties depend on the distribution of the type of bone within a given region. *Compact bone* or *cortical bone* is generally thin and is composed of a very dense arrangement of fibers that makes up the outer layer or shell of long bones. Cortical bone has quite varied mechanical properties, but is very well adapted to providing resistance to shear and compressive forces (Panjabi and White 2001). *Cancellous* or *trabecular* bone is composed of a porous inner layer consisting of

large networks of column-like structures called *trabeculae*. The trabecular bone of the proximal femur functions to uniformly distribute contact stresses at the articular surfaces, and to absorb dynamic loads (such as those in stance/gait). Cancellous bone is found in larger quantity in the proximal femur; however, its density is only about 5–50% that of cortical bone (Panjabi and White 2001).

42.2.2 Movements and Functions

The hip joint is spheroidal, and commonly referred to as a *ball and socket* joint. As such, it has the ability to produce a wide array of movements. Movements of the hip include varying degrees of flexion and extension, internal and external rotation, and abduction and adduction and combinations thereof. For example, the hip may be extended and internally rotated simultaneously when rising from a chair and turning. The primary roles of the proximal femur, in conjunction with the acetabulum of the pelvis, are to support loads related to upright stance and locomotion, and act as a lever for producing muscular force. Loads between 238% and 260% of a person's body weight must be supported at the hip during routine activities, such as walking and stair climbing (Bergmann et al. 2001); higher forces are present during activities, such as running and skiing where loads at the hip can range from 520% to 1,240% of a person's body weight (running and mogul skiing, respectively) (van den Bogert et al. 1999).

42.3 Computed Tomographic Imaging

Computed tomography (CT) is an imaging technique in which information from a set of X-ray measurements obtained at different angles through the body is reconstructed to obtain the distribution of linear X-ray attenuation coefficient in a thin cross section of tissue. Figure 42.2 depicts the geometry of a CT measurement. The patient cross section is contained within a fan of X-rays, defined between the edges of the detector array and an X-ray point source. The X-ray absorption through the patient is measured along rays defined between the individual detector elements and the X-ray source. The thickness of the cross section in which the absorption measurements are obtained can range from 0.5 to 10 mm. The fan of X-rays circumscribes a circular field of view, which is itself contained within a square image matrix, consisting of a square array of square pixel elements, or "pixels." A typical cross section is contained within an array of 512 × 512 pixels. Because the image represents a "slice of tissue," the picture elements have a thickness, and thus are volume elements, or "voxels." The dimensions of the voxels may be adjusted depending on the size of the organ being imaged. For example, in a whole body survey corresponding to a 50-cm field of view, the voxels are typically 1 mm in dimension within the image plane, and 5–10 mm in the slicing dimension. For high-detail bone images, the field of view may be as small as 10–15 cm, resulting in voxel dimensions of 0.2–0.3 mm in the reconstruction plane. The CT image is acquired when the X-ray source and detector rotate around the patient, and the absorption is continuously measured for each detector element. Through a 360-degree source–detector rotation, each voxel is intersected by several ray paths. The X-ray absorption measurements taken at the different angles are recorded in a computer and combined in a process known as back projection to calculate the linear attenuation coefficient at each voxel. In the resulting CT image, the voxel values are based on these linear attenuation coefficients. Because these coefficients depend on the effective X-ray energy (which varies between CT scanner models and different kVp settings of the same scanner),

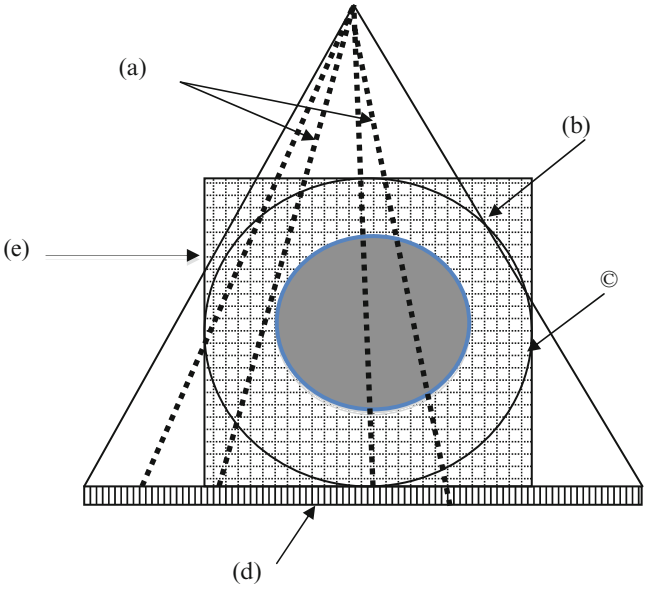

Fig. 42.2 Schematic for CT acquisition

a simple scale, known as the Hounsfield scale, is used to standardize them. The gray-scale value of each voxel is represented as a Hounsfield Unit, given by:

$$HU_T = \left(\frac{\mu_T - \mu_W}{\mu_W} \right) \times 1000$$

where HU_T is the HU of a volume element of tissue and μ_T and μ_w are the linear attenuation coefficients of the tissue and of water, respectively. The HU scale is a linear scale in which air has a value of –1,000, water 0, muscle 30, and bone typically ranging from 300 to 3,000 units.

The value of the Hounsfield unit for a given tissue type depends on several technical factors. First, if the sizes of the structures in the tissue are smaller than the dimensions of the voxel, the HU value is subject to partial volume averaging, in which the HU value is the average HU of the constituent tissues of the voxel, weighted by their volume fractions. For example, a 0.78 × 0.78 × 10 voxel of trabecular bone is a mixture of bone, collagen, and cellular and fatty marrow, and HU is the volume-weighted average of these four constituents. Beam hardening is a second source of variation in HU. Beam hardening occurs because the X-rays used to generate the image have an energy spread. The average energy of the spectrum thus changes as a function of the position within the subject because the lower-energy X-rays are preferentially absorbed. This means that for an object of uniform position, the apparent Hounsfield unit is lower toward the center of the object compared to the periphery, resulting in a cupping artifact. Although manufacturers of CT equipment have implemented beam-hardening corrections, the efficacy of these corrections varies between manufacturers and between technical settings on different machines.

Image data for multiple cross sections are acquired by moving the patient table through the CT gantry (Fig. 42.3). In older models of CT scanners, the patient table stepped in discrete increments, and a 360-degree rotation of the source/detector was performed at each position. Helical CT scanning was introduced in the early 1990s. In this scanning approach, the detector and X-ray tube rotates while the table moves continuously, resulting in acquisition of a volume of data. The X-ray spot describes a spiral trajectory, with use of interpolation to fill in data between the arms of the spiral. Introduction of this technology resulted in significant reductions in image acquisition time (Kalender and Polacin 1991;

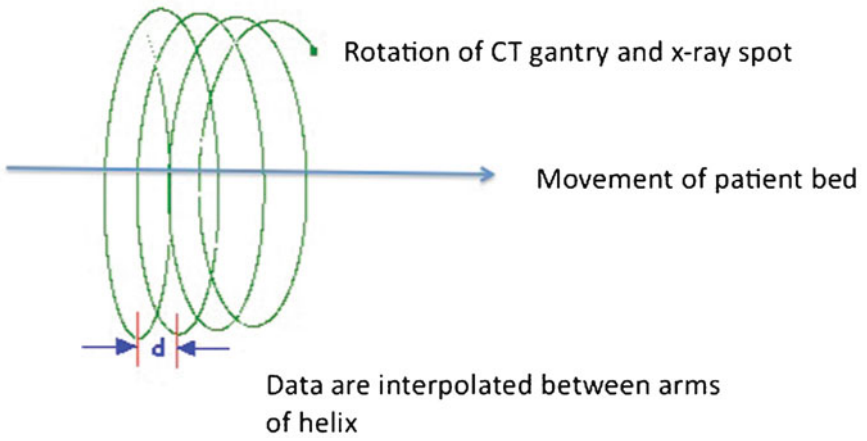

Fig. 42.3 Schematic for helical CT scanning

Kalender et al. 1990) and combined with the advent of powerful inexpensive computer workstations, has enabled the clinical development of volumetric CT analyses of the spine and hip, as will be discussed in the following sections. In the late 1990s and early 2000s, the first multidetector CT systems were introduced, and are expected to have an important impact in skeletal assessment. In multidetector systems, the single detector array is replaced by a series of detector segments, allowing for the reduction of imaging time and improved usage of radiation dose. Initial multidetector systems featured 4–16 detector rows, and the newer systems feature 128–256 rows of detector data. The newest multidetector systems allow for acquisition of CT cross sections of submillimeter thickness, resulting in the ability to acquire high-quality volumetric scans, with the resolution along the table axis comparable to the in-plane spatial resolution (Rubin 2000). As will be described later, this technology will allow for improved analyses of skeletal sites, such as the proximal femur, which must be re-sampled through oblique reformations of the scan data.

42.4 Physical Significance of CT Bone Measurements

CT images provide a three-dimensional depiction of the distribution of bone tissue at a particular skeletal site. The use of CT for quantitative assessments of morphology requires the correct assignment of voxels to bone or to other tissues. In order to standardize the identification of bone voxels based on their image intensity, quantitative CT imaging of bone is often performed with a calibration standard imaged simultaneously within the field of view of the subject (Cann, 1981; Cann and Genant 1981; Faulkner et al., 1993). Bone mineral calibration standards normally consist of a wedge of water-equivalent resin containing cylindrical or square-shaped rods of bone-equivalent materials with different concentrations of calcium hydroxyapatite. During the analysis of the CT image, regions of interest are placed in each of the calibration objects, and linear regression analysis is used to determine a relationship between the mean HU measured in each region and the known concentrations of bone-equivalent material. This calibration relationship is then used to convert the mean HU in a given bone voxel into a concentration (reported in mg/cm^3; i.e., the *mass of bone per unit tissue volume*) of bone-equivalent material within that voxel. The CT image can then be mapped from a distribution of HU onto a distribution of equivalent concentration of calcium hydroxyapatite.

There are two major sources of error that impact the ability to make morphometric measurements from CT images. The first major source of error in the CT bone measurement is the phenomenon of

partial volume averaging. Because the voxel dimensions in CT measurements (0.8–1.0 mm in the imaging plane, 3–10 mm slice thicknesses) are larger than the dimensions and spacing of trabeculae, a CT voxel includes both bone and marrow constituents. Thus, a CT measurement is the mass of bone in a volume containing bone, red marrow, and marrow fat. A single-energy CT measurement is capable of determining the mass of bone in a volume consisting of two components (e.g., bone and red marrow), but not in a three-component system. Resolving the mass fractions of bone, red marrow, and marrow fat in the CT voxel requires a dual-energy CT measurement. Because fat has a HU value of –200, compared to 30 HU for red marrow and 300–3,000 HU for bone, the presence of fat in the CT volume depresses the HU measurement. Thus, the presence of marrow fat causes single-energy CT to underestimate the mass of bone per unit tissue volume, an error which can be corrected using two acquisitions at different energies to resolve a system with more than two tissue components. The effect of marrow fat on CT measurements is larger at the spine than at the hip or peripheral skeletal sites (Gluer and Genant 1989; Goodsitt et al. 1994). Whereas the conversion from red to fatty marrow tends to complete by the mid-1920s in the hip and peripheral skeleton, the vertebrae show a gradual age-related increase in the proportion of fat in the bone marrow, which starts during youth and continues through old age (Dunnill et al. 1967) The inclusion of fatty marrow in CT assessment measurement results in accuracy errors in estimated bone content that range from 5% to 15%, depending on the age group. However, because the increase in the proportion of fat in the marrow is age related, single-energy CT data can be corrected using age-related reference databases; the residual error is not considered to be clinically relevant.

42.5 Processing of CT Data

Measurements of anthropometry from CT images require reproducible orientation of the femur in three dimensions in order to consistently quantify distances between anatomic points of interest. Such procedures can be carried out manually using commercially available 3D display software programs in which the bone can be rendered as a surface, or as a volume, which can be rotated in 3D space. Automated and semiautomated approaches, however, offer much greater reliability in that they remove or reduce the role of human interaction in these measurements.

In our laboratory, and in several others, semiautomated procedures have been developed to assess the morphology of the femoral neck, an important site for age-related hip fractures, as it is affected by aging and by changes in mechanical unloading (Bousson et al. 2006; Camp et al. 2004; Kang et al. 2003, 2004, 2005; Lang et al. 1997; Prevrhal et al. 1997). In the aging process, the femoral neck is the site of extensive age-related bone loss, with extensive resorption of trabecular bone and thinning of the femoral neck cortex (Mayhew et al. 2005; Meta et al. 2006; Riggs et al. 2004). One of the central features of skeletal tissue is its dynamic responsiveness to changes in mechanical loading (Frost 1997, 2003). This responsiveness takes the form of three-dimensional morphological changes on the surface and in the interior architecture of the hip, which can be detected with imaging. In the context of age-related bone loss, the strain experienced by skeletal tissue is increased due to loss of load-bearing skeletal mineral in the presence of continued mechanical loading. Thus, one of the features of aging in the proximal femur is a redistribution of bone from less mechanically loaded to more heavily loaded structures, to best maintain skeletal stiffness in loading conditions associated with normal function. In imaging studies, this can take the form of morphologic changes on the femoral neck, including increased periosteal volume and cross-sectional area, and regional changes in cortical thickness, as well as quantifiable changes in the 3D distribution of imaged bone.

The analytic approaches for proximal femoral morphometry developed in our laboratory (Lang et al. 1997, 2004) and subsequently by others (Camp et al. 2004; Kang et al. 2005), involve

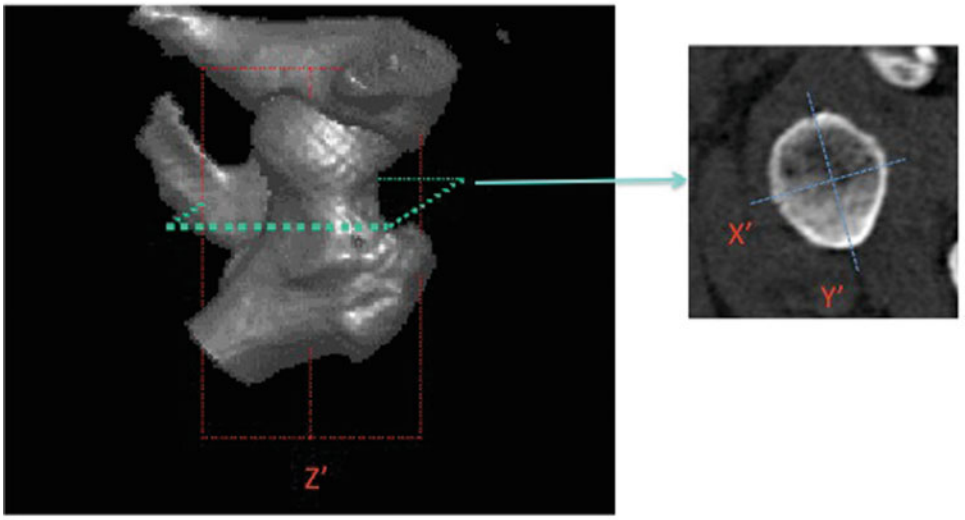

Fig. 42.4 Hip anatomic coordinate system

two primary steps. The first step involves extraction of the structure of interest, the proximal femur, from the CT scan, and the re-sampling of that structure into an anatomic coordinate system, of which the primary axes are based on natural common fixed axes of the bone (Fig. 42.4). In our case, and others, that involves marking the axis of the femoral neck on two planes, coronal and axial. This allows for full 3D specification of a new *z*-axis, permitting re-sampling of the scan along that natural *z*-axis of the bone as opposed to the axis of the scanner, which moves along the femoral shaft. Once the subvolume containing the proximal part of the femur has been rotated, so that the *z*-axis is along the axis of the femoral neck, an image segmentation program then automatically defines the periosteal surface of the bone. Figure 42.4 shows the placement of the anatomic coordinate system on a 3D rendering of a proximal femur from a CT scan.

With the proximal femoral subvolume resampled into an anatomic coordinate system aligned with the femoral neck, and the outer surface of the proximal femur mapped, it is possible to use fully automated landmark detection approaches to divide the proximal femur into anatomic subvolumes. Our approach is based on measurement of the cross-sectional area contained within the periosteal proximal femoral surface as a function of position along the femoral neck axis. In this approach, the femoral neck is bounded by two landmarks: the global minimum of this curve along the axis between the intertrochanteric plane and the lateral aspect of the femoral head, and the maximum of the curve at the plane between the greater and lesser trochanters. We have devised a scheme to subdivide the proximal femoral volume into the femoral neck and trochanteric subvolumes. This subdivision is based on use of the distance between the minimum and maximum cross-sectional area planes, as an intrinsic metric of distance matched to each sample. Thus, each location along the femoral neck axis is parameterized as a function of this intrinsic metric. The femoral neck volume is bounded medially by the cross section having minimum total area and laterally by a plane located 25% of the distance between the minimum cross-sectional area plane and the cross section along the femoral-neck axis having maximum total area. Within the region that encompasses the periosteal volume of the femoral neck, image processing procedures may be employed to isolate the cortical and trabecular compartments for morphologic assessments. These include assessments of total tissue volume, cortical tissue volume, and volume of the medullary space. Although the initial re-sampling of the femoral neck into its anatomic coordinate system involved specification of only a *z*-axis, we can define intrinsic in-plane axes by computing the

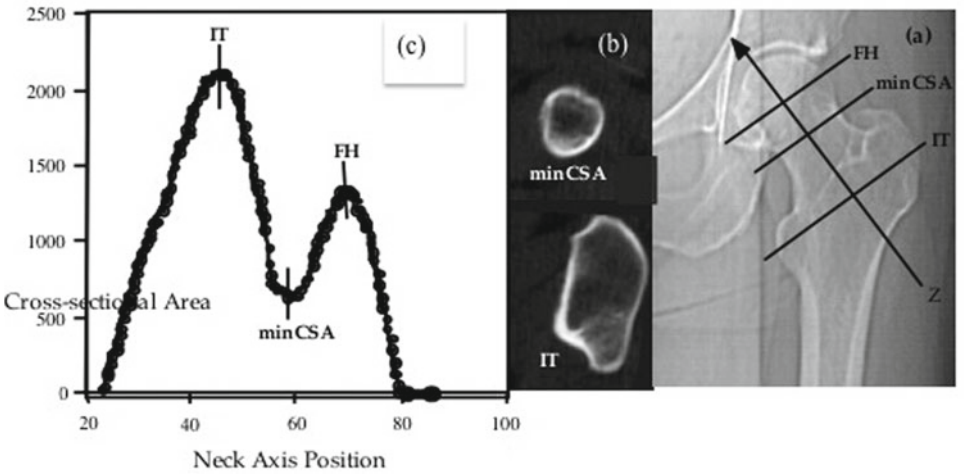

Fig. 42.5 Variation of cross-sectional area along femoral neck axis

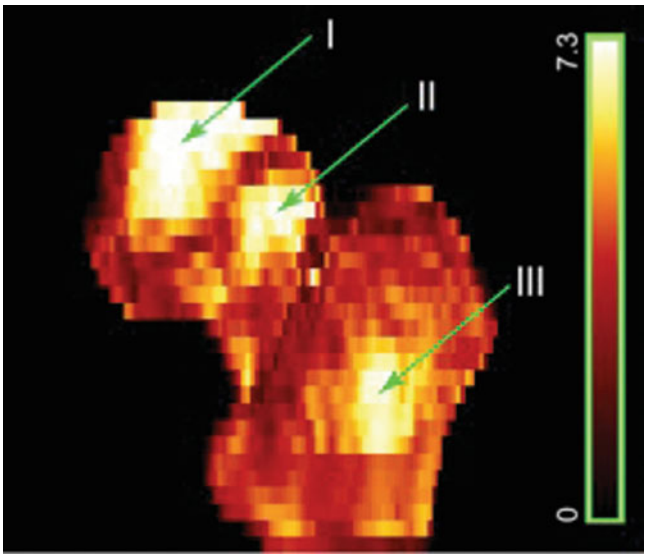

Fig. 42.6 Voxel-based morphometry

axes of inertia of the minimum cross-sectional femoral neck cross section. These axes of inertia may then be employed to define a series of rays, along which the overall bone thickness and the thickness of the cortical shell may be analyzed. Thus, the anatomic coordinate system described earlier may be used for a series of anthropometric and structural measurements that characterize the femoral neck as it changes as a function of age and disease. The method for segmenting the proximal femur into anatomic subvolumes for measurements of morphometry and density is summarized in Fig. 42.5.

In addition to anatomic coordinate system-based measurements, it is also possible to carry out measurements where the proximal femoral surface is defined using the segmentation methods described above, as well as to use three-dimensional image registration techniques in a procedure called voxel-based morphometry (Fig. 42.6) (Li et al. 2007, 2009a, b). In this approach, the surface of the proximal femur is mapped to the surface of a reference femur, or template, using a series of rotations, translations, and scaling to approximately match the two samples, followed by local deformations to achieve the

final fit. With this approach, scans from a study cohort can be warped to a single template, providing a voxel-based statistical model of the cohort. With this model, each voxel of the model contains information from all of the corresponding voxels in the scanned femorae. Thus, within each small subvolume of tissue, it is possible to carry out statistical tests showing three-dimensional morphometric differences between different subgroups of the cohort characterized by different clinical variables. This can include age, gender, fracture status, physical activity, or genotype. Moreover, a cohort may be examined longitudinally by analyzing the statistical significance of voxel values at different time points.

42.6 Applications

Studies of morphologic changes in proximal femur with age and osteoporotic fracture status: Our own group and others have utilized morphometric analysis of computed tomography scans to discern age-related changes in proximal femoral structures. One of the primary findings of this study has been the responsiveness of measures of periosteal cross-sectional area and volume to age. Meta et al. compared young and elderly women in a cross-sectional study, noting that older women had larger cross-sectional areas and periosteal volumes in the femoral neck, even after adjustment for differences in body weight and height. Despite the larger bone sizes, older women had smaller volumes of cortical bone (Meta et al. 2006). This finding agreed with another cross-sectional study of a similar design undertaken at Mayo Clinic (Riggs et al. 2004), which found that, in a thin section of the femoral neck, older men and women had larger cross-sectional areas and smaller cortical thickness measures. While these studies have involved cross-sectional studies of femoral neck morphometry parameters, our own group has utilized another clinical model of bone loss, of long-duration spaceflight, to detect longitudinal evidence for changes in periosteal area and cortical thickness measures. In a study which illustrates the role of bone morphometric measures as descriptors of skeletal adaptation to changing mechanical environment, we followed 16 crew members making long-duration flights of 4–6 months on the International Space Station (Lang et al. 2006). The goal of this study was to examine the changes in the proximal femur, which take place as a function of sustained weightlessness during the flight and re-adaptation of the proximal femur to full weight bearing on return to Earth's gravity. Long-duration spaceflight is associated with extensive bone loss, particularly in the proximal femur, where, on average 1–1.5% of bone mass is lost per month. In our study, we observed that, during the course of the flight, bone loss consisted of loss of trabecular bone and thinning of the proximal femoral cortex, without any change in the outer dimensions of the femoral neck. The loss of trabecular bone density averaged 20%, and, on average, over 10% of the cortical tissue volume was lost. Thus, when subjects were re-exposed to Earth's gravity, they underwent increased mechanical strain on the hips, associated with load bearing in the presence of skeletal atrophy. In our study, we observed increases in femoral neck cross-sectional area and cortical thickness without substantial increases in density. This was consistent with an adaptive process, where new bone formation took place in regions required for optimal load bearing, with reduced accretion of bone in areas that incur less bending load.

42.7 Practical Methods and Techniques

Procedures for carrying out CT-based morphometric measures using CT of the proximal femur vary depending on whether one is scanning a specimen or a human. For human scanning, the scans will typically take place in the clinical radiology department of a hospital. The subject

should typically be dressed in a light hospital gown, with no metal in the field of view of the CT imager. For ideal imaging of the hip, subjects should undergo a localization image, called a scoutview, to first delineate the proximal femoral anatomy, with good coverage of the proximal femur ensured by starting the scan a few centimeters above the acetabulum and ending a few centimeters inferior to the lesser trochanter. In the case of specimens, these can be imaged in a water bath to simulate overlying layers of soft tissue, or simply scanned in air in the case of a dried femoral specimen. In the case of a fresh frozen specimen, biosafety precautions need to be taken into account.

One of the major limiting considerations for analysis of proximal femoral anatomy using CT images is the spatial resolution of the image data as well as noise in the images. The limited spatial resolution affects the detail with which structures of interest can be detected and quantified, and the image noise limits the ability of segmentation programs to isolate the proximal femur for analysis. An additional factor to take into account is partial volume averaging. Partial volume-averaging errors affect measurement of structures that are small compared with the spatial resolution of the imaging device. For thin cortices, such as the superomedial aspect of the femoral neck, this results in underestimation of bone density and overestimation of volume or thickness measurements, with smaller errors for estimation of mass (Augat et al. 1998). Our hip cortical region of interest is primarily composed of the inferomedial cortex of the proximal femur, for which thickness values exceeding 3–4 mm have been reported in humans, and also includes the thin superomedial cortex (thickness 0.3 mm) (Bagi et al. 1997). In a study based on a helical CT scanner similar to our own, Prevrhal et al. reported that detection of changes in cortical thickness is possible for cortices with thicknesses of about 1.2 mm (Prevrhal et al. 1999).

Image noise is a function of the imaging technique used by the scanner and the body size of the human subject being scanned. Noise is essentially determined by the number of X-ray photons used to reconstruct an image, and is reflected in the Poisson-shaped distribution of the brightness values of the reconstructed voxels. For a fixed X-ray tube current, the smaller the voxel size, the lesser the number of photons used to determine the value of a given voxel, and the noisier the image. Thus, there is an effective trade-off between reducing the size of the voxel, which provides higher levels of detail, and the noise.

The trade-off between noise and spatial resolution impacts the techniques chosen for imaging specimens or humans for anthropometric measurements. When imaging specimens, it is important to choose the smallest possible field of view to obtain the maximum resolution possible with the imaging system. It is also important to use the maximum tube current settings to minimize image noise. Settings for human scanners are limited by the radiation dose to which one can ethically expose humans in obtaining the images. Experiments involving scanning of humans must be approved by Internal Review Boards set up for each institution, which are responsible for weighing the experimental risk to the subjects against the value of the knowledge obtained in the experiment. This limits the ability to use high X-ray doses to overcome the noise limitations associated with small pixel sizes and high magnifications. For such protocols, we have found that committees will generally approve imaging with 1-mm slice thicknesses, with 120 kVp and 150–250 mAs, resulting in an effective absorbed radiation dose of 2–4 milliSieverts (mSv) compared to a yearly background of 3.6 mSv. In these cases, we advise carrying out a whole body field of view with roughly 1-mm pixels in plane, but reconstructing the data in magnified fields of view that allow the data to be sampled at pixel sizes corresponding to half of the spatial resolution of the image. Because of the limitations of the CT scanner, it will not be possible to accurately image the superior aspect of the femoral neck, but will be possible to image characteristics, such as inferior neck thickness, total cross-sectional area, and other morphometric parameters of interest.

Summary Points

- Volumetric X-ray computed tomography scans depict the proximal femur in three dimensions, allowing its orientation to be standardized for reproducible morphometric measurements.
- CT images are expressed in units of X-ray attenuation, a measure of the density and atomic number of tissue. These images have limited spatial resolution, and objects less than 0.5–1 mm in dimension are not depicted accurately in size or density.
- CT images of the hip are often sampled into hip-centered anatomic coordinate systems, which provide a position and angular reference for area, width, and distance measures.
- Morphometric studies using CT have documented increases in overall femoral neck size (width and cross-sectional area) with age.
- Morphometric measurements of the femoral neck cortex have documented extensive variability in age-related changes in cortical thickness; sections that are load bearing in normal ambulation and physical activity tend to retain their thickness, whereas sections of the femoral neck that undergo less mechanical stress tend to show extensive thinning.
- Voxel-based morphometry has been used to quantify internal structural variations in the hip that are associated with risk of osteoporotic hip fracture.
- The technical approaches to CT imaging of the hip in living subjects must weigh the need for anatomic detail against the higher amounts of radiation required to visualize these details.

Key Points

Table 42.1 Key points

A. Volumetric Nature of CT Imaging	A1. The 3D orientation of the proximal femur can be standardized, allowing for reproducible definition and measurement of distances between landmarks
B. Volumetric CT Acquisitions	B1. Current CT systems acquire a volume of data, which can be considered as a series of transverse cross-sectional images, which are stacked up to form the CT volume.
	B2. The CT image unit is the Hounsfield unit, a measure of X-ray absorption in a volume of tissue called a voxel
C. Errors in CT	C1. CT images are affected by partial volume averaging, which occurs when the size of the voxels is larger than the structure being imaged. In this case, the Hounsfield unit in a voxel containing multiple unresolved constituents is the volume-weighted average of these constituents
	C2. CT images are sometimes affected by beam hardening, which introduces non-linearities and artifacts into the images
D. Segmentation of Image Data	D1. CT images of the hip can be segmented to remove the bone from the surrounding soft tissue
E. Anatomic Coordinate Systems	E1. To ensure that morphometry is consistently done within and between individuals, standard practice involves resampling the hip image along the axes of a hip-fixed anatomic coordinate system
F. Femoral Neck Morphometry	F1. The cross-sectional area increases with age to preserve its mechanical competence with respect to normal usage
	F2. The cortex of the femoral neck thins with age, with considerable variation depending on femoral neck location
	F3. Voxel-based morphometry can be used to determine differences in the interior architecture of the hip as a function of age, drug treatment, and fracture status
G. Practical Considerations	G1. Imaging approaches must weigh the quality of the image, which allows discernment of smaller features, against increased radiation dose to the human subject

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Chapter 43
Leg Length and Anthropometric Applications: Effects on Health and Disease

Maria Inês Varela-Silva and Barry Bogin

Abstract Decomposing stature into its major components is proving to be a useful strategy to assess the antecedents of disease, morbidity and death in adulthood. Human leg length (foot + tibia + femur), sitting height (trunk length + head length) and their proportions (e.g. leg length in proportion to stature, and the sitting height ratio [sitting height/stature × 100], among others) are used as epidemiological markers of risk for overweight (fatness), coronary heart disease, diabetes and certain cancers. There is also wide support for the use of relative leg length as an indicator of the quality of the environment for growth during infancy, childhood and the juvenile years of development. Human beings follow a cephalo-caudal gradient of growth, the pattern of growth common to all mammals. A special feature of the human pattern is that between birth and puberty the legs grow relatively faster than other post-cranial body segments. For groups of children and youth, short stature due to relatively short legs (i.e. a high sitting height ratio) is generally a marker of an adverse environment. The development of human body proportions is the product of environmental x genomic interactions, although few if any specific genes are known. The short stature homeobox-containing gene (SHOX) is the first genomic region that may be relevant to human body proportions. For example, one of the SHOX related disorders is Turner syndrome. However, in most cases research has been showing that environment is a more powerful force to shape leg length and body proportions than genes.

Abbreviations

BMI	Body mass index
BP	Blood pressure
BW	Birth weight
F	Female(s)
FEV	Forced expiratory volume
FVC	Forced vital capacity

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_43,

H	Height
hr	hour(s)
KH	Knee height
KHR	Knee height ratio = KH/H × 100
IH	Iliac height
LL	Leg length
MRC	Medical Research Council
M	Male(s)
M&F	Males and females
NHANES	National Health and Nutrition Examination Survey
RSLL	Relative subischial leg length = H-SH/H × 100
SES	Socioeconomic status
SH	Sitting height
SHR	Sitting height ratio = SH/H × 100
SLL	Subischial leg length
TL	Thigh length

43.1 Introduction

Leg length has been widely used in biomedical sciences as an indicator of general health, socioeconomic status and propensity for disease. For many years, it was also wrongly used as a racial marker (Bogin et al. 2001; Bogin 2008; Frisancho et al. 2001). However, the concept of 'leg length' has different meanings for different authors, and there is more than one single measurement for leg length. Table 43.1 lists a few key facts about the role of leg length in human biology and evolution.

Table 43.1 Key facts about the role of leg length in human biology and evolution

1. Human beings are distinguished from the non-human primates by several anatomical features and among these are proportions of the arms and legs relative to total body length. The living apes have arms that are longer than their legs, which reflects their adaptations for brachiation (arm swinging). Bipedal fossil hominins of the species *Ardipithecus*, *Australopithecus* and *Homo habilis*, dating from about 4.5 to 1.6 million years ago (MYA) were similar to apes in body proportions, or had long arms in proportion to their legs. Since the evolution of *Homo erectus*, about 1.8 MYA, human ancestors have had essentially modern body proportions.
2. Leg length must approximate 50% of total stature to achieve the lower limits of the biomechanical efficiency of the adult human striding bipedal gait. In modern humans, this happens at the end of the childhood life history stage, which occurs at about 7.0 years of age. By adulthood, human species-specific body proportions allow for not only the bipedal striding gait, but also for long-distance running, which may have been important for hunting and survival to our ancestors.
3. Relatively long legs in modern humans and in human ancestors allows for more efficient thermoregulation in a tropical savannah environment, which was the birthplace of humanity. Long legs allow for greater body surface area for the cooling of the body by evaporation of sweat.
4. Long legs, which allow for human bipedalism, free the hands for carrying objects and infants, for technological manipulation, for gesticulation and communication, and for the type of social–emotional contact that is one of the hallmarks of humanity.

43.2 Leg Length Defined

In principle, leg length (LL) is the length of the femur plus the tibia, and possibly the height of the foot from the tibia-talus articulation to the ground. In a living human being, these lengths are difficult to measure. Consequently, LL is often defined by easier to measure dimensions, such as iliac height (IH) and subischial leg length (SLL). It is also possible to estimate LL via the combination of thigh length (TL) and knee height (KH). Some studies employ only one of these measures as the indicator of LL.

Each of these measurements can be transformed into ratios, generally in relation to total stature (see entry on stature) and sitting height (SH), to give indications of body proportions. In this entry, we will discuss the sitting height ratio (SHR), relative subischial leg length (RSLL) and the knee height ratio (KHR).

43.3 Population Variation in Body Proportions

For many years, there has been the perception that body proportions are genetically determined, immutable and, therefore, a good indicator of 'racial' markers (Eveleth and Tanner 1976, 1990). It is true that, on an average, Native Australians and people of sub-Sahara African origin have the longest leg length in proportion to total stature, followed by people of European ancestry, and those of Asian ancestry (including Native Americans). There is, however, considerable overlap in the range of both absolute and relative leg length values between these general geographic groups (Fig. 43.1).

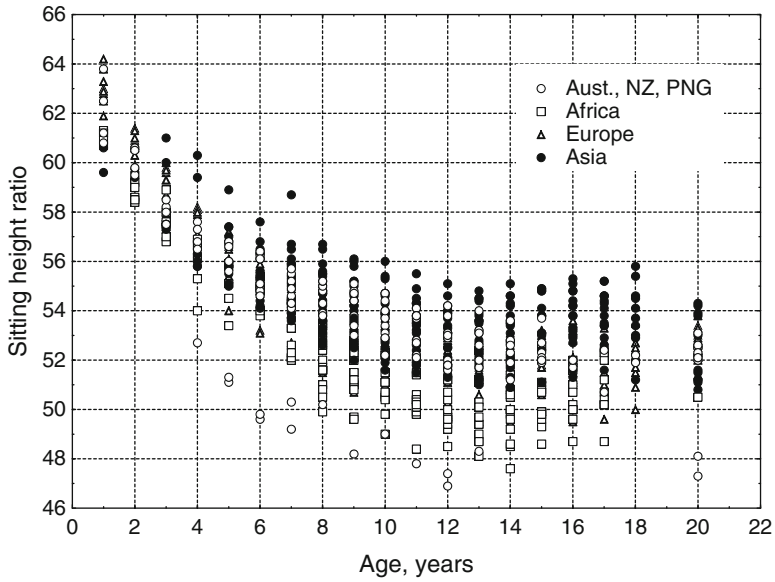

Fig. 43.1 Relative leg length as measured by the sitting height ratio by age for the four geographic groups defined by Eveleth and Tanner (1976, 1990). Age 20 years includes data for adults over the age of 18 years. (From Bogin et al. 2001)

Additionally, socioeconomic factors explain as much of the variation in leg length as does geographic origin or so-called 'race' (Bogin et al. 2001, 2002).

Moreover, leg length and body proportions are plastic, meaning that these phenotypic properties of the human body change in response to external (environmental) factors. Studies conducted in Japan (Kondo and Eto 1975; Tanner et al. 1982; Ohyama et al. 1987) show that environmental improvements in nutrition (mainly the inclusion of milk in the Japanese diet), health and general socioeconomic status are powerful modifiers of body proportions, resulting in longer legs in proportion to total stature in most cases. Between 1957 and 1977, the Japanese population showed a strong positive secular trend in height, and all the increase in height was due to the increase in leg length, with very little increase due to changes in trunk length (sitting height). Bogin et al. (2002) found even greater plasticity in the children of Maya families emigrating from Guatemala to the USA. The Maya families migrated due to precarious conditions in Guatemala, including hunger, poverty and civil war. In the new North American environment, the living conditions improved considerably in terms of basic health care and vaccination, education and availability of clean drinking water. Maya children and adults in Guatemala are typically of very short stature, with disproportionately short legs. Maya-American children experienced a 10–11 cm increase in stature over their Guatemalan living age mates across the ages from 5 to 12 years, and 70% of this increase was due to leg growth. These studies show how body proportions are sensitive to the quality of the environment.

43.4 The Usefulness of Leg Length

The biological and clinical usefulness of LL is based on the cephalo-caudal gradient in growth of all mammals, including humans. The ontogenetic development of human body shape is similar in all human populations, as shown in Fig. 43.2. During the foetal, infant and childhood stages of life, the brain grows faster than the body (Scammon and Calkins 1929). At birth, head length is approximately one-quarter of the total body length, whereas, at 25 years of age, the head is only approximately one-eighth of the total length. There are also proportional changes in the length of the limbs, which become longer relative to the total body length during the years of growth (Scammon 1930). Leitch (1951) was the first medical researcher to propose that a ratio of LL to total stature could be a good indicator of the nutritional history and general health in the early life of an individual. Leitch (p. 145) wrote, '… it would be expected on general principles that children continuously underfed would grow into underdeveloped adults…with normal or nearly normal size head, moderately retarded trunk and relatively short legs.' Leitch found that improved nutrition during infancy and childhood did result in a greater increase in LL than in total height or weight.

A general principle of growth is that those body parts growing the fastest will be most affected by a shortage of nutrients, infections, parasites, physical or emotional traumas and other adverse conditions. The legs, especially the tibia, grow faster relative to other body segments from birth to about the age of 9 years. Relatively short LL in adolescents and adults, therefore, is likely to be due to adversity during infancy and childhood. The alterations in body proportions described by Leitch, and in the studies of Japanese and Maya, are likely due to competition between body segments, such as trunk versus limbs, and between organs and limbs, for the limited nutrients available during growth (Bogin et al. 2001, 2002).

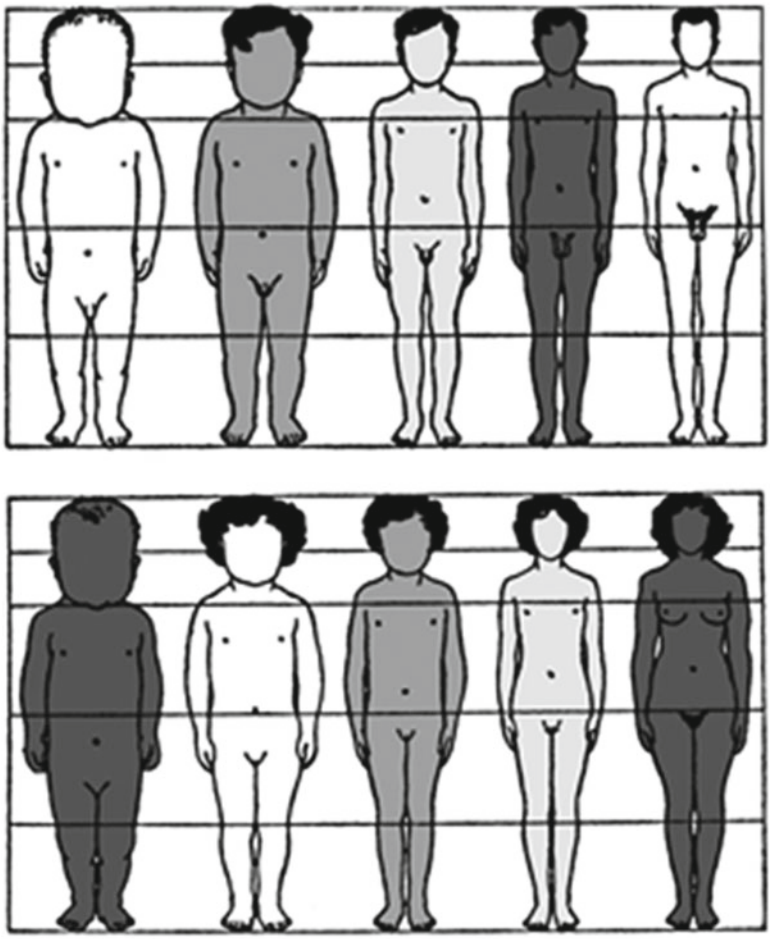

Fig. 43.2 Changes in body proportion during human growth after birth. Ages for each profile are, from left to right, newborn, 2 years, 6 years, 12 years, 25 years. The hair style and shading of the cartoon silhouettes are for artistic purposes and is not meant to imply any ethnic, eco-geographical, or "racial" phenotypic characteristics of the human species [provided courtesy of Dr. J. V. Basmajian]

43.5 Leg Length and Human Health

Table 43.2 summarises several studies that show how leg length and body proportion ratios are powerful indicators of the quality of the environment, and of the plasticity of the human body. The table refers to only a few studies. The table is not a systematic review, and is meant to provide examples of the range of studies available. What is important to note is that regardless of the specific leg measure taken (e.g. IH, SLL, TL and KH), or ratio calculated (SHR, RSLL and KHR), the longer LL is associated with better environments, better nutrition, higher SES and better general physical and psychological health, overall.

Lawlor et al. (2003) present the hypothesis that maternal leg length is associated with birthweight and later health of her infants, meaning that the shorter the maternal leg length, the lower the birthweight of the infant. In turn, low birthweight individuals have increased risk of cardiovascular diseases, among others, as adults. Li et al. (2007) found that taller childhood stature better predicts longer adult leg length than trunk length. Moreover, socioeconomic adversity in childhood

Table 43.2 Summary of studies employing measures of leg length in relation to early life living conditions and health

Measure of leg length	Sample sizes	Sample	Results	Source
IH	Total: 2,209 M: 1,062 F: 1,147	2–14 years Extracted from The Boyd Orr Survey. Children from 1,343 working class families in England and Scotland, measured between 1937 and 1939	M and F: Positive association with length of breastfeeding, decreasing numbers of children in the household and increasing household income. Overall, the individual components of stature mostly associated with childhood environment was leg length (measured as IH) and foot length (not in the scope of this entry).	Whitley et al. (2008)
	Total: 916 M: 376 F: 540	65+ years' inhabitants of Kwangju, South Korea, assessed in 2003.	Shorter limb length is associated with markers of lower early life socioeconomic status and is associated with dementia later in life, especially in women.	Kim et al. (2008)
SLL	Total: 2,338 M: 1,040 F: 1,298	30–59 years (United Kingdom)	M and F: Inverse association with systolic BP, diastolic BP, total cholesterol and fibrinogen. Direct association with FEV, FVC, BW and BMI.	Gunnell et al. (2003)
	Total: 10,308 M: 6,895 F: 3,413	35–55 years (London)	M and F: Strong inverse association with pulse pressure and systolic BP. Strong positive association with lower total/HDL cholesterol ratio, triglycerides and 2-hr glucose M: Strong inverse association with total cholesterol. F: Strong inverse association with diastolic BP.	Ferrie et al. (2006)
	Total: 3,262	Longitudinal study, births from 3–9 March 1946. Twenty-one assessment occasions between birth and 53 years. MRC National Survey of Health & Development (United Kingdom)	M and F: Positive association with mother's and father's height, BW. SLL greater among individuals from the non-manual social class and among individuals who were breastfed.	Wadsworth et al. (2002)
	Total: 5,900	The 1958 British Birth Cohort. Participants assessed at birth and at ages 7, 11, 16, 23, 32, 42 and 45 years.	Adult SLL is associated with parental height and birth weight. Taller prepubertal stature is associated with higher SLL. Maternal smoking during pregnancy resulted in lower adult SLL. Overall, adult SLL is related to a greater extent than trunk length to early life factors and prepubertal height.	Li et al. (2007)
KH	Total: 50 M: 27 F: 23	Infants grouped by gestation time at birth: <28 weeks, 28–31 weeks, 32–36 weeks, >36 weeks. Births occurred in 2004–2005, in the neonatal intensive care, Christchurch, New Zealand.	Changes in KH (using a kneemometer) correlate very well with changes in weight. If gain in weight is achieved, normal linear growth may be assumed. Because of this, kneemometry is not a useful addition to routine measurements of growth in the neonatal unit.	Dixon et al. (2008)

SHR	Total: 2,985 M: 1,465 F: 1,520	2–17 years Mexican Americans (NHANES III, USA)	M and F: Individuals with relatively shorter legs in proportion to total stature are poorer than longer legged individuals (poverty assessed by Poverty Income Ratio)	Frisancho et al. (2001)
	Total: 1,472 M: 747 F: 707	6–13 years, Oaxaca, Southern Mexico Urban settings in 1972: Total:409, M:218, F:173 Rural settings in 1978: Total:363, M:179, F:184 Urban settings in 2000: Total:339, M:173, F:166 Rural settings in 2000: Total:361, M:177, F:184	Positive time trend in leg length from 1972 to 2000 both in rural and urban settings	Malina et al. (2008)
	Total: 2003 M: 2003 F: 0	7–16 years. Two cross-sectional surveys among school aged boys from Kolkata, India. 1982–1983 (n = 816) 1999–2002 (n = 1187)	Positive time trend in relative leg length. Boys measured in 1999–2002 had relatively longer legs in proportion to total stature than their counterparts in 1983–1983.	Dasgupta et al. (2008)
	Total: 1995 M:977 F: 1018	5–12 years. Maya migrants to the USA in 1992 (n = 211), Maya migrants to the USA in 2000 (n = 431) and Maya in Guatemala in 1998 (n = 1353)	Leg length is a sensitive indicator of the quality of the environment. Maya children in the USA show relatively longer legs in proportion to stature than their counterparts in Guatemala. By 2000, Maya migrants to the USA were 11.54 cm taller and 6.83 cm longer-legged than Maya children in Guatemala.	Bogin et al. (2002)
RSLL	Total: 273	Intergenerational sample Parents' generation: Total:165, M:80, F:85 Offspring generation: Total:108, M:49, F:59 From Auckland and Taipei	Is an effective marker of intergenerational changes	Floyd (2008)
KHR	Total: 273	Intergenerational sample Parents' generation: Total:165, M:80, F:85 Offspring generation: Total:108, M:49, F:59 From Auckland and Taipei	Is an effective marker of intergenerational changes. Lower leg growth, as represented by KHR is similar to changes in overall leg length as regards sensitivity to environmental change.	Floyd (2008)

is associated with shorter adult leg length and stature. These two studies are examples of how early life environments, in combination with an intergenerational component, mainly through matrilineal lines, shape body size and proportion.

There are complications in the relationship between LL, health, SES and better environments for growth. One such complication is noted by Schooling et al. (2008a, b), in an analysis of a cross-sectional sample of 9,998 Chinese people aged at least 50 years, and measured in 2005–2006. Sitting height and height were measured and leg length estimated as height-sitting height (SLL). The growth environment for the 50+ year-old adults was estimated via a questionnaire asking about own education, father's occupation, parental literacy and parental possessions. The authors find that leg length and height, but not sitting height, vary with some childhood conditions. Participants with two literate parents, who owned more possessions, have longer legs. The participants' level of education and their father's occupation have no effect on height or leg length, but higher scores for these variables do associate with an earlier age at menarche. The authors explain that earlier menarche for girls, and earlier puberty for boys, will terminate growth at an earlier age. This may explain why higher SES, as measured by education and father's occupation, did not associate with longer LL.

Another complication is noted by Padez et al. (2009), who analyzed the growth status of Mozambique adolescents. The sample comprised 690 boys and 727 girls, aged between 9 and 17 years, from the capital city of Maputo. The sample is divided between those living in the centre of Maputo (higher SES) and those living in the slums on the periphery of the city. Height, weight and sitting height were measured, and the sitting height ratio was calculated. The hypothesis that relative leg length is more sensitive than total stature as an indicator of environmental quality is not uniformly confirmed. Overall, mean stature is greater for the centre group than for the slum group, but relative leg length as measured by the sitting height ratio does not differ. Compared with African-American references (NHANES II), all the girls from the centre group, 9–14-year-old slum girls, all slum boys and the oldest centre boys show relatively shorter legs. These findings show that, within the Mozambique sample, relative leg length is not sensitive enough to distinguish the quality of the living environment between the centre of Maputo (regular housing and higher SES) and the slums in the periphery. A reason for this is that Mozambique was a colony of Portugal until 1975. Civil unrest and warfare characterised the late Colonial period and the post-independence period, until a peace settlement was concluded in 1992. It is possible that all socio-economic status groups within the country, exposed to the war, suffered sufficiently to reduce relative leg length, especially when compared with the better-off African-American reference sample.

43.6 Applications to Other Areas of Health and Disease

The development of human body proportions has a likely genomic basis, although few, if any specific genes are known. *Hox* and homeobox genes are known to regulate the growth of body segments (Mark et al. 1997), and these genes are shared across all taxa. The short stature homeobox-containing gene (SHOX) is the first genomic region that may be relevant to human body proportions. 'SHOX, located on the distal ends of the X and Y chromosomes, encodes a homeodomain transcription factor responsible for a significant proportion of long-bone growth' (Blum et al. 2007, p. 219). One SHOX-related disorder is Turner syndrome (45, XO karyotype), which results in approximately 20 cm deficit in expected stature. Some studies find that legs are disproportionately affected (Neufeld et al. 1978; Ogata et al. 2002), but other studies find no disproportion

(Hughes et al. 1986). Specific candidate genes for body shape are known from some non-human mammals, especially livestock in which body proportions have considerable economic value (Quignon et al. 2009).

Leg length discrepancy (LLD), one leg shorter than the other, poses biomechanical impediments, may predispose people to a variety of musculoskeletal and psychological disorders and may require surgical correction (Gurney 2002). There are several causes for LLD, including *coxa vara*, dislocation of the hip, hemiatrophy or hemihyperatrophy as well as deformities due to rickets or other metabolic diseases. Early and accurate measurement may detect such discrepancy and allow treatment before the period of growth has been completed, when it is easier to correct.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is associated with alterations in body size, composition and proportion. CAH impairs limb growth, especially of the leg, hand and foot. Medical intervention can improve leg growth, especially if the intervention occurs before puberty.

43.7 Practical Methods and Techniques

We define several measurements and ratios of leg length, their anthropometric applications and their biocultural associations with health and disease. We present a brief description of the anthropometric methods required to obtain these measures of leg length. More details of the methods may be found in Lohman et al. (1988) and the NHANES anthropometric manual (http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/NCHS/MANUALS/ANTHRO.PDF).

Table 43.3 shows the usefulness of leg length measurements and ratios in terms of ease of accurate collection, comparison to reference data, as an indicator of body proportions, as an indicator of nutritional status and ease of accurate calculation or interpretation. From all the ratios presented, only the SHR has population-based- and statistically valid reference values (Frisancho 2008).

43.7.1 Iliac height

This is the distance between the summit of the iliac crest and the floor (see Fig. 43.3). The iliac crest is sometimes difficult to find, especially in overweight people. It also may cause ethical concerns as it requires extensive palpation at the hip level to find the landmark required to perform the measurement accurately. There are no reference data available. IH does not easily provide a good indication of body proportions because, by itself, it does not standardise against height or sitting height. This means that comparisons between individuals do not take into account their total stature. Also, as an indicator of nutritional status, it does not provide ready and easy interpretation.

43.7.2 Subischial Leg Length (SLL)

SLL is the distance from the inferior border of the ischium to the floor when the participant is in the standing position. In practice, the border of the ischium is very difficult to locate, and poses serious

Table 43.3 Usefulness of leg length measurements and ratios in terms of ease of assessment, comparison with reference data, as an indicator of body proportions, as an indicator of nutritional status and ease of calculation of the ratio and/or interpretation of the value

	Ease of accurate collection	Comparison with reference data	As an indicator of body proportions	As an indicator of nutritional status	Ease of accurate calculation and/or interpretation
Iliac height	4	4	3	3	4
Subischial leg length	1	4	3	3	3
Thigh length	3	1	3	3	4
Knee height	1	1	2	3	2
Sitting height ratio	1	1	2	1	3
Relative subischial leg length	1	4	2	2	3
Knee height ratio	1	4	2	2	3

1 excellent; *2* good; *3* difficult; *4* very difficult

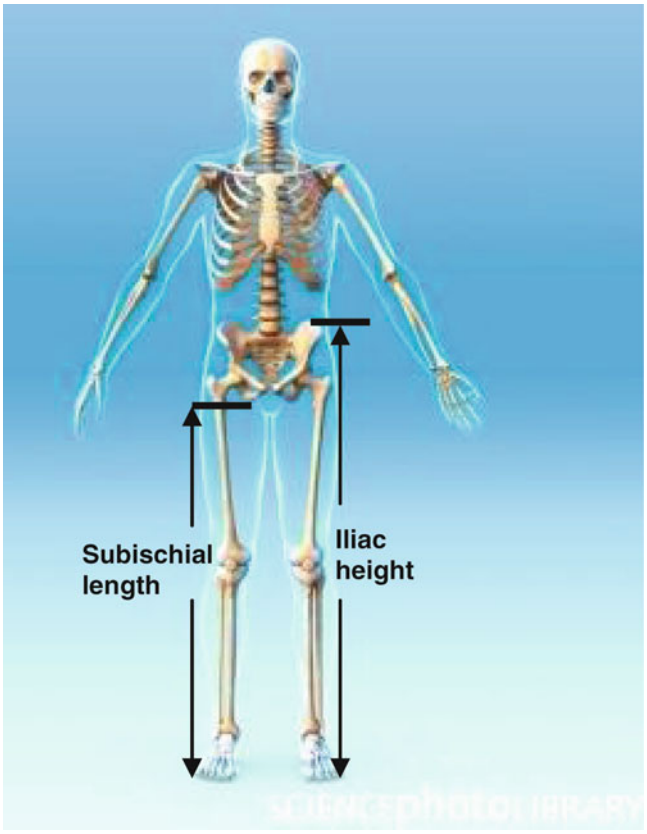

Fig. 43.3 Landmarks for the measurement of iliac height (IH) and subischial leg length (SLL). (Credit: ROGER HARRIS/SCIENCE PHOTO LIBRARY)

ethical concerns (see Fig. 43.3). Therefore, it is a common practice to estimate SLL as the difference between stature and sitting height (see Fig. 43.6). There are no reference data available. It is not a good indicator of body proportions because SLL is dependent on sitting height and it may underestimate leg length values, especially if the participants have high levels of gluteo-femoral subcutaneous fat

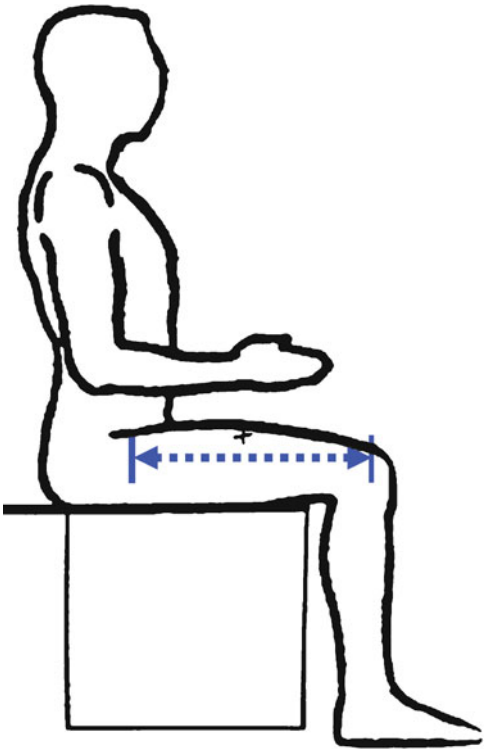

Fig. 43.4 Landmarks and correct body position for the assessment of thigh length

(Bogin and Varela-Silva 2008). Also, it does not take into account the total stature of the individual. As an indicator of nutritional status, it does not provide ready and easy interpretation.

43.7.3 Thigh length (TL)

This is the distance between the hip and the knee. Because in living humans, it is difficult to locate these joints, TL is measured from the midpoint of the inguinal ligament to the proximal edge of the patella (see Fig. 43.4). In overweight or obese people with excessive abdominal subcutaneous fat, it may be difficult to find the inguinal ligament. Also, palpation around the inguinal ligaments may cause ethical concerns. Reference data proposed by Frisancho (2008) are available. TL does not easily provide a good indication of body proportions because, by itself, it does not standardise against height, sitting height or knee height. As an indicator of nutritional status, it does not provide ready and easy interpretation.

43.7.4 Knee Height (KH)

Knee height is the distance between the anterior surface of the thigh (above the condyles of the femur and about 4 cm above the patella) and the floor (see Fig. 43.5). Knee height is regularly used in paediatric assessments, and correlates well with weight during the first month of postnatal life (Dixon et al. 2008). It is relatively easy to collect and does not pose as many ethical concerns as the

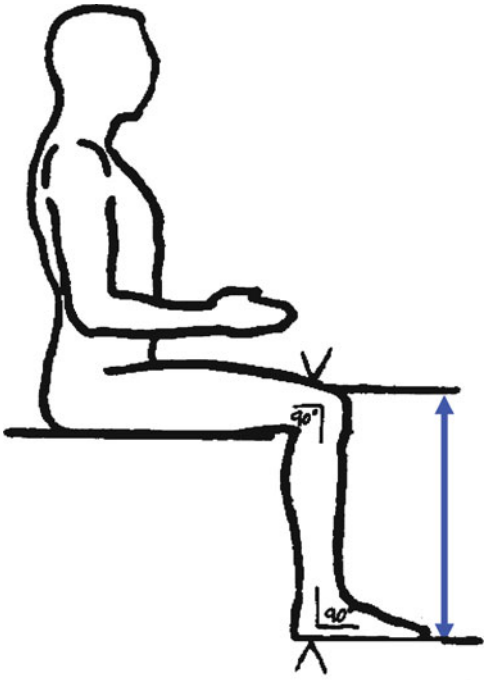

Fig. 43.5 Landmarks and correct body position for the assessment of knee height

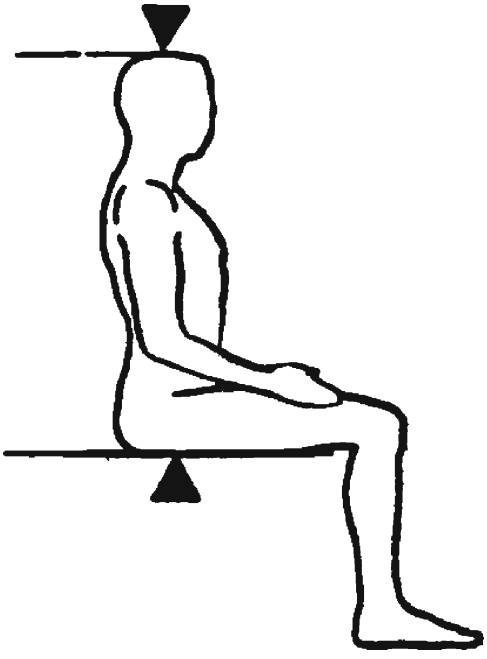

Fig. 43.6 Landmarks and correct body position for the assessment of sitting height

measurements mentioned above. There are reference data proposed by Frisancho (2008). It is a relatively good indicator of body proportions because the tibia grows at the fastest rate and for the longest amount of time relative to the femur and skeleton of the trunk. As an indicator of nutritional status, it does not provide ready and easy interpretation.

43.7.5 Sitting Height Ratio (SHR)

SHR is calculated as SH/H × 100. It defines the percentage of total stature that is comprised by head and trunk (see Fig. 43.6 for details on sitting height measurements). The remaining portion of the body will be the length of the legs. The lower the SHR, the relatively longer the legs are. The ease of accurate collection is high and there are international references (Frisancho 2008) that allow the comparison of any values and the conversion of SHR raw data into percentiles and *z*-scores. SHR is a good indicator of body proportions because it allows individuals with different heights to be compared in terms of the percentage of the body that is composed by the relative length of legs. However, because it is sitting height dependent, this measure can be overestimated in individuals with high levels of gluteo-femoral fat, therefore underestimating the relative contribution of the lower limb to total stature (Bogin and Varela-Silva 2008). It is a good indicator of nutritional status because it allows the classification of the individuals into different degrees of leg stunting, based on the *z*-scores calculated from the references.

43.7.6 Relative Subischial Leg Length (RSLL)

RSLL is calculated as H-SH/H × 100. It defines the percentage of total stature that is comprised by the legs. The lower the RSLL, the shorter are the legs. The ease of accurate collection is high. There are no international reference values. Similar to SHR, RSLL is a good indicator of body proportions because it allows individuals with different heights to be compared in terms of the percentage of the body that is composed by the relative length of legs. However, because it is sitting height dependent, this measure can be overestimated in individuals with high levels of gluteo-femoral fat, therefore underestimating the relative contribution of the lower limb to total stature (Bogin and Varela-Silva 2008). RSLL requires a more difficult computation of values of stature and sitting height than does the SHR.

43.7.7 Knee Height Ratio (KHR)

KHR is calculated as KH/H × 100. It defines the percentage of total stature that is comprised by the lower segment of the leg (tibia + foot height). The higher the KHR, the longer is the leg segment. The ease of accurate collection is high but there are no international reference values. KHR is a relatively good indicator of body proportions because it allows individuals with different heights to be compared in terms of the percentage of the body that is composed by the relative length of legs.

Summary Points

For groups of people:

- Leg length is generally associated with the quality of the environment for human growth and development.
- Longer legs, especially long legs relative to total stature, indicate better quality environments.
- Leg length and body proportions do vary between the major geographic regions of the world, but are not ‘racial’ markers.

- Leg length and body proportions may be useful in the diagnosis of genetic, endocrine and metabolic disorders.
- Different ways of measuring leg length (e.g. IH, SLL, TL and KH) make comparison among studies difficult – if one wishes to compare raw data. However, regardless of what measurement is taken, the overall results are similar, in a sense that longer legs generally show better health status overall and better early life environments.

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Chapter 44
Measures and Application of Lower Leg Length: Fracture Risk Assessment

Jian Sheng Chen

Abstract The standardized measurement of lower leg length (knee height) is easy to perform with a high degree of precision. Lower leg length (LLL) is a reliable index of stature in older people because it is virtually unaffected by aged-related high loss. Height has been identified as a risk factor for fracture in middle-aged men and women. In frail older people, vertebral deformities and muscular contraction are common; and these conditions contribute to height loss and lead to increase risk of fracture. The relationship between height and risk of fracture in older people is therefore confounded, and was investigated using LLL rather than using directly measured height. In a prospective cohort of 2,005 institutionalized older men and women, LLL as a risk factor for fracture was examined in different ways in number of studies. The results showed that LLL was a significant risk factor for hip fracture and any fractures after adjusting for the influences of other risk factors. For residents with LLL ≥ 50.5 cm compared to residents with LLL < 50.5 cm, the adjusted relative risk (RR) was 1.45 (95% confidence interval: 1.07–1.99; $P = 0.02$) for hip fracture and 1.27 (95% confidence interval: 1.00–1.60, $P = 0.05$) for any fractures. The results also demonstrated that LLL affected the risk of fracture through one or two fracture pathways, namely bone fragility and/or the force of the impact of falling. It is most likely that both the mechanical impact of a fall and the correlation between LLL and hip axis length contribute to the fracture effect of LLL. In conclusion, LLL should be considered as a component for inclusion in future fracture risk assessment tools, especially those tools that to be used among frail older people.

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
BUA	Broadband ultrasound attenuation
CI	Confidence interval
FREE	Fracture Risk Epidemiology in the frail Elderly

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_44,

HR Hazard ratio
LLL Lower leg length
OR Odds ratio
PTH Parathyroid hormone
RR Relative risk
SD Standard deviation

44.1 Introduction

Since the end of the nineteenth century, the anthropometric technique has been used by anthropologists to estimate body size. Medical scientists adopted this technique and attempted to regress on height from LLL (knee height) in the last few decades (Chumlea et al. 1985). The height of certain individuals or groups, such as elderly, mobility impaired or diseased people may be difficult or impossible to measure directly. Because of postural problems, vertebral deformities, or confinement to a wheelchair or bed, measuring height with accuracy in many frail, older people poses a great challenge. Height is a component of several nutritional and health indicators, such as body mass index, body surface area, total body water, energy expenditure, and creatinine clearance. An accurate estimation of height is of special importance for specialists in nutritional medicine, geriatrics and pediatric orthopedics, etc. Chumlea et al. (1985) and others have recommended the estimation of height from LLL in older people.

Height has been reported to predict the risk of fracture in middle-aged men and women (Meyer et al. 1993; Hemenway et al. 1995), and the recalled height at the age of 25 has also been reported to predict such risk in older people (Cummings et al. 1995; Gunnes et al. 1996). Age-related height loss may explain this pattern. Height loss is common in older people, mainly due to vertebral deformities; and this loss has been shown to associate strongly with low vertebral and femoral bone mineral density (Bunout et al. 2007). Therefore, the relationship between mature skeletal height and risk of fracture in older people may be confounded. LLL, which is virtually unaffected by the aging process and not subject to recall bias, may be a good surrogate for assessing this relationship in older people. This chapter reviews the application of LLL to health and disease, and specifically addresses its relationship with risk of fracture in older people living in old-age care facilities.

44.2 Measuring Lower Leg Length

Chumlea et al. (1985) and others reported that the estimated height from LLL corresponded well with mature skeletal height in older people, and recommended its use. Key reasons for the recommendation are listed in Table 44.1.

Several stature estimation equations from LLL have been published (Chumlea et al. 1985, 1998; Knous and Arisawa 2002). However, the diversity of these equations has drawn attention to the variation in anthropometric standards among different races. Specific stature estimation equations have been developed by Chumlea et al. (1998) for non-Hispanic white, non-Hispanic black, and Mexican-American ethnic groups (Table 44.2). Accordingly, it is probably appropriate to measure a representative sample of young and older health subjects to obtain a regression equation that can be applied with greater accuracy in very frail, older subjects in the same community.

Table 44.1 Key features of lower leg length (LLL)

1. LLL is highly correlated with mature skeletal stature (Chumlea et al. 1985).
2. Aging process does not affect LLL as it does vertebral height (Mitchell and Lipschitz 1982).
3. Fatness does not bias LLL as it does sitting height (Bogin and Varela-Silva 2008).
4. The standardized measurement of LLL is easy to perform with a high degree of precision and can be applied to almost any persons, including elderly, mobility impaired or diseased people.
5. The estimated height from LLL corresponds well with the measured height in healthy persons (Chumlea et al. 1985) and is a valid surrogate of height in the construction of nutritional and health indicators (Ritz 2004).

This table lists the key reasons for the estimation of height from LLL in frail older people

Table 44.2 Stature estimation equations from lower leg length (LLL) for specific ethnic groups

Targeted population	Estimation equation (Chumlea et al. 1998)
Non-Hispanic white men	Height (cm) = 78.31 + (1.94 × LLL in cm) – (0.14 × Age in year)
Non-Hispanic black men	Height (cm) = 79.69 + (1.85 × LLL in cm) – (0.14 × Age in year)
Mexican-American men	Height (cm) = 82.77 + (1.83 × LLL in cm) – (0.16 × Age in year)
Non-Hispanic white women	Height (cm) = 82.21 + (1.85 × LLL in cm) – (0.21 × Age in year)
Non-Hispanic black women	Height (cm) = 89.58 + (1.61 × LLL in cm) – (0.17 × Age in year)
Mexican-American women	Height (cm) = 84.25 + (1.82 × LLL in cm) – (0.26 × Age in year)

This table lists formulas for calculating height using LLL for specific ethnic groups from Chumlea et al. (1998)

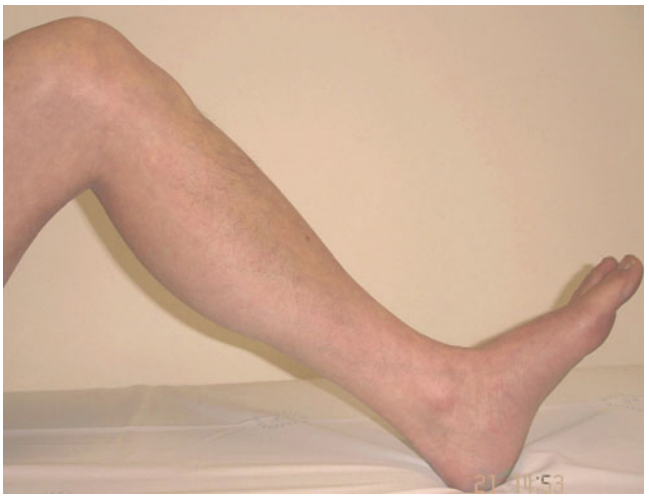

Fig. 44.1 Lying position of lower leg length measurement. Lower leg length (*LLL*) is the distance between the sole of the foot and the apex of the knee with each joint flexed at a 90° angle

44.2.1 Practical Methods and Techniques

LLL is the distance between the sole of the foot and the apex of the knee, with each joint flexed at a 90° angle (Chumlea et al. 1985). It is measured using a sliding caliper. A device designed for this purpose is commercially available. While lying face up with the knee and the ankle at a 90° angle (Fig. 44.1), the flexed blade of the caliper is placed under the heel of the foot, and the mobile blade placed on the anterior surface of the thigh. The shaft of the caliper is held parallel to the long axis of the lower leg, and slight pressure is applied to compress the soft tissue. The measurement can be taken to the nearest 0.1 cm on some calipers. The estimated height (cm) is then calculated from an

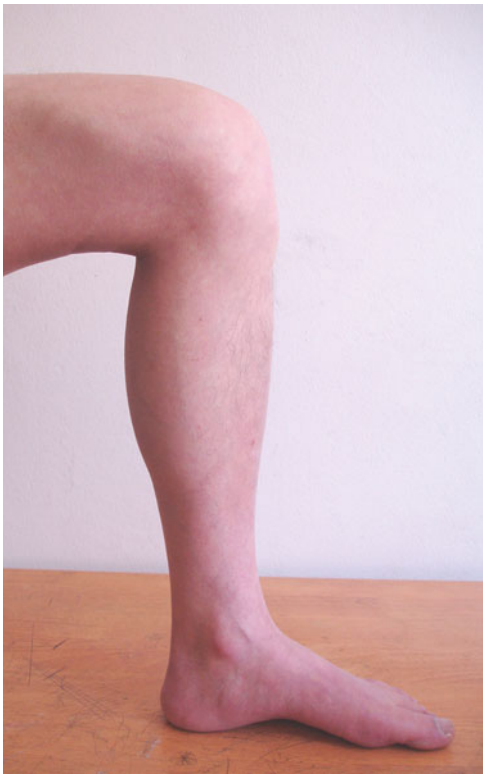

Fig. 44.2 Sitting position of lower leg length measurement. *LLL* is measured from floor to knee (bent at 90°)

estimation equation that best fits the subject. LLL can also be measured from a sitting position (Fig. 44.2). In this case, it is measured from floor to knee (bent at 90°). If there are difficulties in using calipers, the measurement can be taken using flexible tape, which also provides a reliable reading. Repeat measurements may be considered to reduce intra-observer variability, if high accuracy is required.

44.3 Application to Fracture Risk Assessment

44.3.1 Magnitude of Osteoporotic Fractures

Osteoporotic fractures resulting from low trauma events are very common, affecting up to one-half of women and one-third of men after the age of 50 years. Fractures can cause long-standing pain, functional impairment, disability, and death, especially in frail, older people. A rise in crude and sex- and age-adjusted fracture rates over the past century has been observed. For example, in Finnish people, aged 50 years or more, the age-adjusted incidence of hip fractures (per 100,000 people) showed a steady increase from 1970 to 1997: in women, from 292 to 467, and in men, from 112 to 233 (Kannus et al. 1999). The rise has been attributed to the aging of the population and an increased risk of falls-related injuries, which is affected by social and lifestyle changes. However, a secular increase in height, especially leg length (Tanner et al. 1982), in the past century may also contribute to the phenomenon. Table 44.3 presents the key facts of osteoporotic fractures.

Table 44.3 Key facts of osteoporotic fractures

1.	Osteoporosis related fractures are very common, affecting up to one-half of women and one-third of men after the age of 50 years.
2.	Although osteoporosis is a disease affecting the whole skeleton, and any bone may fracture, hip fractures are the most important economically and clinically, being associated with the greatest costs relating to treatment and significant morbidity and mortality.
3.	The lifetime risk of hip fracture at the age of 50 years is about one in six in women and one in 16 in men, and the risk increases exponentially beyond the age of 60 years (Cumming et al. 1997).
4.	In institutionalized older people, hip fracture incidence rate per annum can be as high as 6.2% for females and 4.9% for males (Kannus et al. 1996).
5.	About one in five hip fracture patients will die in the first year and most of the survivors will not fully recover. According to the Royal Australasian College of Physicians' estimation, one in two hip fracture patients will require long-term nursing care.
6.	A rise in the fracture incidence over the past century has been observed (Kannus et al. 1999). This could be attributed to population aging, social and lifestyle changes, and a secular increase in height.
7.	As population ages, it is projected that the worldwide annual number of hip fractures will rise to 6.26 million by the year 2050 from an estimated 1.66 million hip fractures in 1990 (Cooper et al. 1992).

This table lists the key facts of osteoporotic fractures with respect to risk, trend, and consequences

44.3.2 Is height a risk factor for fracture in older people?

Several studies have reported a positive relationship between height and risk of hip fracture in women (Meyer et al. 1993; Hemenway et al. 1995; Cummings et al. 1995; Gunnes et al. 1996). The increasing risk of hip fracture in middle-aged women, who were taller, was reported by Meyer et al. (1993) and Hemenway et al. (1995). However, studies of older women have generally found no relationship of current standing height with risk of hip fracture (Cummings et al. 1995), or a reduced effect of current standing height on risk of hip fracture (Gunnes et al. 1996). On the other hand, recalled height at the age of 25 years or lower extremity length (difference between standing and sitting heights) has been shown to predict the risk in women in all ages (Cummings et al. 1995; Gunnes et al. 1996; Opotowsky et al. 2003). Details of these studies are presented in Table 44.4. The relationship between height and risk of other fractures is less clear as there were few studies available for the evaluation. Gunnes et al. (1996) reported that recalled height at the age of 25 years was a consistent risk factor for all fracture types in a retrospective study of 29,802 post-menopausal women aged 50–80 years. The relationships of current standing height, recalled height at the age of 25 years and lower extremity length with risk of fracture (hip or other fractures) in males appeared to be the same as the relationships observed in females (Meyer et al. 1993; Hemenway et al. 1994).

The apparent discrepancy between older- and middle-aged subjects in the outcomes of fracture risk for current standing height may be due to aged-related height loss. Height loss is common in older people, and the magnitude of the loss is largely dependent on the severity of vertebral deformities and muscular contraction. Chen et al. (2009a) examined risk profiles of osteoporosis for 37,957 patients in primary care settings in Australia, and found that 43.4% of the patients had a self-reported height loss, with the estimated mean loss of 3.9 cm, and 31.8% had a change in spinal posture recorded as "round back" or kyphosis. In many cases, vertebral deformities can be attributed to osteoporotic vertebral fracture, which is a strong indicator of future fracture risk. Also, muscular atrophy can increase response time to a sudden event, resulting in high risk of falls, and reduce the flexibility to protect the body from the impact of the fall, therefore increasing the risk of fracture. Hence, the relationship between height and risk of fracture in older people is confounded; and the chance of finding a positive relationship is therefore reduced or even reversed. In a study of 1,427 white female nursing home residents, with a median age of 86 years, Girman et al. (2002) reported

Table 44.4 Studies of the relationship between height and hip fracture risk

Studies	
Meyer et al. (1993) – a prospective cohort	
Population:	23,270 women and 23,665 men aged 35–49 years
Type of height:	Height measured at baseline
Adjusted effect size:	HR = 3.6 (95% CI: 1.46–8.97; ≥1.7 m vs. <1.55 m) for women HR = 2.96 (95% CI: 0.94–9.05; ≥1.85 m vs. <1.70 m) for men
Adjusted for:	Age
Hemenway et al. (1994) – a prospective cohort	
Population:	49,895 male health professionals aged 40–75 years
Type of height:	Height reported by participants at baseline
Adjusted effect size:	HR = 2.24 (95% CI: 1.14–4.41; ≥1.83 m vs. <1.75 m)
Adjusted for:	Age, BMI, cigarette smoking status and alcohol consumption
Hemenway et al. (1995) – a prospective cohort	
Population:	Over 92,000 female nurses aged 35–59 years
Type of height:	Height reported by participants at baseline
Adjusted effect size:	HR = 2.40 (95% CI: 1.43–4.02; ≥1.73 m vs. <1.57 m)
Adjusted for:	Age, BMI, cigarette smoking status and alcohol consumption
Cummings et al. (1995) – a prospective cohort	
Population:	9,516 white women aged ≥ 65 years with no history of hip fracture
Type of height:	Height measured at baseline and recalled height at the age of 25 years
Adjusted effect size:	HR (adjusted for age only) = 1.0 per 6.0 cm or 1 SD (95% CI: 0.8–1.1) for height measured at baseline HR (adjusted for all risk factors listed below) = 1.3 per 6.0 cm or 1 SD (95% CI: 1.1–1.5) for recalled height at the age of 25 years
Adjusted for:	Age, maternal hip fracture, weight increase since the age of 25 years, self-rated health, previous hyperthyroidism, long-acting benzodiazepine use, anticonvulsant drug use, caffeine intake, exercise, standing time per day, ability to rise from chair, distant depth perception, contrast sensitivity, resting pulse rate, any fracture since 50 years of age and bone mineral density
Gunnes et al. (1996) – a retrospective cohort	
Population:	29,802 post-menopausal women aged 50–80 year (mean 68.3 years)
Type of height:	Height reported by participants at examination and recalled height at the age of 25 years
Adjusted effect size:	OR = 1.22 per 5.6 cm or 1 SD (95% CI: 1.13–1.31) for height reported at examination HR = 1.35 per 5.4 cm or 1 SD (95% CI: 1.24–1.47) for recalled height at the age of 25 years
Adjusted for:	Age
Opotowsky et al. (2003) a prospective cohort	
Population:	4,264 women aged 40–75 years
Type of height:	Height and lower extremity length (difference between standing height and sitting height) measured at baseline
Adjusted effect size:	HR per 6.34 cm or 1 SD for standing height: 1.81 (95% CI: 1.25–2.67) for age 40–59 years, 1.29 (95% CI: 1.05–1.60) for age 60–69 years and 1.10 (95% CI: 0.84–1.44) for age 70–74 years HR per 4.16 cm or 1 SD for lower extremity length: 1.43 (95% CI: 1.05–1.93) for age 40–59 years, 1.30 (95% CI: 1.07–1.58) for age 60–69 years and 1.33 (95% CI: 1.04–1.69) for age 70–74 years
Adjusted for:	age, weight, age at menopause, history of hormone replacement, history of chronic disease, alcohol use, physical activity and history of fracture

This table presents some of the studies that examined whether height is a risk factor for hip fracture and depicts the study population, index of height, and effect size. Abbreviation – *BMI* body mass index, *CI* confidence interval, *HR* hazard ratio, *OR* odd ratio, *SD* standard deviation

that current height from nursing care charts was negatively associated with risk of any fractures. Residents who were taller than 1.60 m had a fracture rate of 11.2% over 18 months, compared to a rate of 15.9% among residents, who were less than or equal to 1.47 m in height.

44.3.3 Lower Leg Length and Risk of Fracture

LLL appears to be a good measure for accessing relationship between height and risk of fracture in frail, older people. LLL is a valid index of mature skeletal stature and can be measured easily with a high degree of precision in almost any frail, older subject. It does not have issues that other measures, such as current standing height, lower extremity length, and recalled height, may have in measuring frail older subjects. Measuring standing height with accuracy in very frail, older people can be difficult or impossible, and in many older people, it is not representative of peak skeleton stature. Self-report of height is inaccurate, and often overestimates the true loss (Arnett et al. 1988), and is not possible for those with dementia. LLL also has advantages over current standing height in older people in expression of body composition by measures, such as body mass index (BMI) (Roubenoff and Wilson 1993), an important risk factor for fracture. LLL should therefore be chosen over other measures as an index of mature skeletal stature in any study of frail, older people. However, this has been uncommon in fracture risk epidemiology studies.

Due to limited data available in the literature, the evaluation of the relationship between LLL and risk of fracture is based largely on a prospective cohort study called the Fracture Risk Epidemiology in the frail Elderly (FREE) study (Sambrook et al. 2007). The FREE study is a study designed to evaluate falls and fracture risk in institutionalized older people in Northern Sydney, Australia. Participants were 2,005 residents (76% female) aged 65–104 years (mean 85.6 years), living in 82 aged care facilities (30 intermediate care nursing care facilities and 52 nursing homes) and were randomly selected from all registered facilities in the region. Individuals, who were bedbound, bilateral amputees, or non-English speaking, were excluded. The participation rate of eligible residents was 54.5% (self-consent, 77.3%; proxy consent, 32.7%). The non-participants were similar in age and gender to the participants, but had higher care needs, and hence a greater likelihood of living in a nursing home. LLL was measured once at baseline from floor to knee (bent at 90°) using a sliding caliper. With slight pressure applied to the blade, the measurement was recorded to the nearest 0.5 cm. Table 44.5 shows the baseline characteristics of the FREE participants. LLL, as a risk factor for fracture, was examined in different ways in number of studies using the FREE study cohort (Sambrook et al. 2007; Chen et al. 2008a, b, 2009b). Table 44.6 presents the key findings of these studies.

44.3.3.1 Any Fractures

In a study aiming to develop and evaluate a simple fracture risk index for use in frail, older people (Chen et al. 2008a), all 2,005 participants were examined. The outcome was 401 fractures, which occurred in 338 participants in two years from baseline. Cox regression modeling was used to identify risk factors for fracture. LLL was a significant and independent risk factor for any fractures after adjusting for institution type, balance, history of fracture since the age of 50 years, cognitive function, number of medications, and weight. Residents with LLL ≥ 50.5 cm were 1.27 (95% CI: 1.00–1.60, $P = 0.05$) times as likely to sustain a fracture consistently over the study period as residents with LLL < 50.5 cm. The effect of LLL on risk of any fractures was not modified by gender. The fracture risk index derived from the independent risk factors, including LLL, was capable of

Table 44.5 Baseline characteristics of the residents from the Fracture Risk Epidemiology in the frail Elderly (FREE) study

Variables	No.	Mean (standard deviation) or %
Demographics		
Age (years)	2,005	85.7 (7.07)
Gender (male: female)	2,005	24: 76
Institution type (intermediate-care facility: nursing home)	2,005	55: 45
Physical measures		
Lower leg length (cm)	1,953	50.6 (2.98)
Walking aids (walks unaided: uses a stick: uses frame: wheelchair)	1,990	30: 22: 32: 16
Balance (good: fair: fair/poor: poor: not capable)	1,993	29: 22: 18: 11: 20
Weight (kg)	1,876	60.1 (14.2)
Broadband ultrasound attenuation (dB/MHz)	1,975	51.6 (22.2)
Medical condition		
No. of medications (0–6: ≥7)	2,001	54: 46
Total hip replacement (yes: no)	1,988	12: 88
Urinary Incontinence (yes: no)	1,961	60: 40
Current smoke (yes: no)	1,998	5: 95
Illness severity rating (no symptoms: mild symptoms: moderate symptoms: severe illness)	1,983	3: 27: 67: 4
Standardized mini mental state examination (0–17: 18–23: 24–30)	1,996	29: 22: 49
Fall in the previous 12 months (yes: no)	1,946	53: 47
Fracture since age 50 years (yes: no)	1,982	45: 55

This table presents baseline information regarding demographics, physical measures and medical conditions collected on the 2005 participants in a cohort study, designed to evaluate falls and fracture risk in institutionalized older people in Northern Sydney, Australia

Table 44.6 Key findings of lower leg length (LLL) as a fracture risk factor

1. LLL was an independent and significant risk factor for any fractures and hip fracture in very frail older people.
2. Compared to residents with LLL < 50.5 cm, residents with LLL ≥ 50.5 cm had a 27% (95% CI: 0–60%) increase in risk for any fractures and a 45% (95% CI: 7–99%) increase in risk for hip fracture after controlling for the influences of other risk factors.
3. LLL was also a significant risk factor for fracture following a fall, indicating a higher fracture risk per fall for residents with longer LLL. For each standard deviation or 2.98 centimeters increase in LLL, the risk of fracture following a fall was increased by 19% (95% CI: 2–39%) for any fractures or by 48% (95% CI: 19–85%) for hip fracture.
4. The effect size of LLL on risk of any fractures increased after adjusting for the falls risk (the falls' incidence rate during the follow-up).
5. The fracture effects of LLL were not dependent on gender or institution type.
6. LLL affected the risk of fracture through one or two fracture pathways, namely bone fragility and/or the force of the impact of falling.

This table lists the key findings of LLL as a fracture risk factor, examined in different ways in a number of studies (Sambrook et al. 2007; Chen et al. 2008a, b, 2009b) using the FREE study cohort
Abbreviation – *CI* confidence interval

identifying higher risk individuals for any fractures in these very frail, older people from both intermediate care nursing care facilities and nursing homes. The fracture risk index had a slightly better fracture discriminating ability among institutionalized older people than the algorithm developed by Girman et al. (2002) (i.e., the area under the receiver operating characteristic curve = 0.69 ± 0.018 and 0.68 ± 0.015 for identifying someone who would have a fracture in 1 and 2 years, respectively, in the FREE study vs 0.63 ± 0.043 for identifying someone who would have a fracture in 1.5 years

in the Girman study). The better discriminating ability of the fracture index from the FREE study might be a result of the inclusion of LLL in the index. However, this cannot be determined, as neither of the two studies measured the same risk factors.

44.3.3.2 Hip Fracture

For hip fracture analysis, 111 residents were excluded [bilateral total hip replacements at baseline ($N = 44$), answering "yes" to the question of total hip replacement but not recording whether it was one or both legs ($N = 50$), or not answering the question of total hip replacement ($N = 17$)], and 1,894 residents (1,433 females, 461 males; mean age 86 years, SD 7.1 years) were then studied (Chen et al. 2009b). Survival analysis with age as a time-dependent covariate was used to analyze the data. Follow-up time was limited to 4 years to maintain the validity of the proportional hazards assumption. During a mean follow-up period of 2.65 years (SD 1.38), 201 hip fractures in 191 residents were recorded, giving an overall hip fracture incidence rate of 4.0% per person year (males 3.6% and females 4.1%). Even in this very high risk population, and after controlling for age, cognitive function, history of fracture since age 50 years, balance, institution type, and total hip replacement, residents with LLL ≥ 50.5 cm were still significantly more likely to sustain a hip fracture compared to residents with LLL < 50.5 cm (i.e., HR 1.45, 95% CI: 1.07–1.99; $P = 0.02$). The effect of LLL on hip fracture appeared to be larger than the effect on any fractures reported above. Also, in this study, broadband ultrasound attenuation (BUA, an indicator of bone fragility) was not a significant risk factor for hip fracture. The result might indicate that, in this very frail older people, the risk for falls played a dominant role in determining the incidence of hip fracture. In a study of the impact of a fall and the breaking point of the proximal part of the femur, Lotz and Hayes (1990) concluded that energy absorbed during falling and impact, rather than bone fragility, may be the dominant risk factors for hip fracture.

44.3.3.3 Influence of Falls

Sambrook et al. (2007) investigated the influence of falls on risk of fracture in the FREE cohort. Negative binomial regression modeling was used to assess the association of LLL with any fractures while adjusting for falls' incidence rate. During a median follow-up period of 1.93 years, 6,646 falls and 375 fractures were recorded, giving a falls' incidence rate of 214 per 100 person years, and a fracture rate of 12.1 per 100 person years. The majority of these fractures (82%) could be attributed to falls. The incidence rate ratio was 1.41 (95% CI: 1.11–1.80, $P = 0.006$) in residents with LLL ≥ 50.5 cm compared to residents with LLL < 50.5 cm in a multivariate model that included risk factors, such as falls' incidence rate, history of fracture since age 50 years, BUA, weight, balance, cognitive function, and institution type. Compared to the effect of $RR = 1.27$ reported above (Chen et al. 2008b), the effect of LLL on risk of any fractures was increased in this study by taking the influence of the falls' risk into consideration.

44.3.3.4 Fracture Pathways

To explore LLL's fracture pathways, the risk of falling was taken out of the fracture risk analysis in a study of risk factors for fracture following a fall (Chen et al. 2008b). This was done by studying only the 1,342 participants (1,035 women and 307 men), who experienced a fall in the follow-up period.

A fall, the mechanical impact of the fall on the skeleton, and the degree of bone fragility usually determine the process leading to peripheral osteoporotic fractures. Risk factors identified in this study are therefore only associated with bone fragility and/or the force of the impact, and not associated with falling. Logistic regression analysis was used to calculate the odds ratio (OR) for fracture for LLL. Each fall was treated as an observation, and lack of independence between falls for the same person (clustering) was taken into account using generalized estimating equations. The analysis was performed separately for any fractures and hip fracture. All 6,646 falls recorded in the FREE study were used. These 6,646 falls resulted in 308 fractures, giving a fracture rate per 100 falls of 4.6. LLL was identified as an independent risk factor for any fractures as well as for hip fracture. For each standard deviation (SD) or 2.98 centimeters increase in LLL, the odds ratio was 1.19 (95% CI: 1.02–1.39, $P = 0.02$) for any fractures and 1.48 (95% CI: 1.19–1.85, $P = 0.001$) for hip fracture after adjusting for other risk factors.

These four studies demonstrate that LLL is an important risk factor for fracture in this very frail older population with high risk of fracture. It has advantages over current standing height as an index of mature skeletal stature in the assessment of fracture risk in frail older people.

44.3.4 Why Is Lower Leg Length a Fracture Risk Factor?

Figure 44.3 presents fracture pathways for some known risk factors, including body height. Two possible fracture pathways of LLL as mature skeletal stature are in its associations with the impact of falling and bone fragility, as demonstrated in the FREE cohort by Chen et al. (2008b).

The effect of height on risk of fracture may be explained by the mechanical impact of a fall. Meyer et al. (1993) suggested that taller people could hit the ground with greater force as they fell from a greater vertical distance and, therefore, had higher risk of fracture. However, a long LLL in frail, older people is not necessary to produce the higher impact from a fall on the upper part of the body. An older person with long LLL, who also has a vertebral deformity due to osteoporosis, may have a similar standing height as that of a healthy older person with short LLL. This could partly explain why the effect size of LLL on hip fracture is larger than on any fractures in the FREE study cohort. Nevertheless, the risk of fracture from an impact with similar force is still higher in a person with osteoporosis than in a healthy person. Also, there are no particular reasons to believe that a tall person is more likely to have height loss due to osteoporosis compared to a short person. As a result, aged-related height loss due to osteoporosis does not obscure the relationship between LLL and risk of fracture in frail, older people. So, the relationship between LLL and risk of any fractures is likely to be a result of the high impact from a high-position fall. The stronger association of LLL with risk of hip fracture, than with risk of any fractures, may be explained by a possible positive correlation between LLL and hip axis length. Faulkner et al. (1993) reported that height was positively correlated with hip axis length, and hip axis length was an independent and significant risk factor for hip fracture. It is quite possible that LLL is also strongly correlated with this femoral geometry. The correlation of hip axis length with LLL is probably higher than that with height. A third explanation is that of genetic differences, with body height as a surrogate for unknown risk factors for fracture propensity, suggested by Gunnes et al. (1996). However, there is no good evidence to support this hypothesis. It is most likely that both the mechanical impact of a fall and the correlation between LLL and hip axis length contribute to the effect of LLL on risk of fracture. Further studies are needed to find out which one is relatively more important in determining a hip fracture when falling.

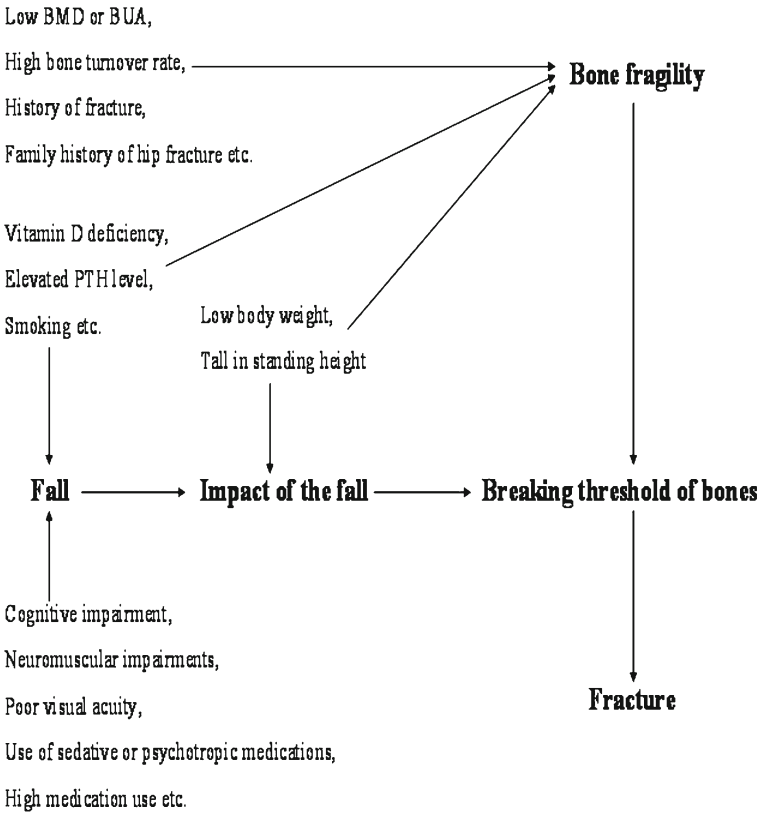

Fig. 44.3 Fracture model showing risk factor pathways. This figure shows fracture pathways for some known risk factors. The occurrence of an osteoporotic fracture usually depends upon first, a fall, second, the nature and impact of the fall, and third, the degree of skeletal fragility. Abbreviations – *BMD* bone mineral density, *BUA* broadband ultrasound attenuation, *PTH* parathyroid hormone

44.3.5 Lower Leg Length as a Parameter in Fracture Risk Index

Many fracture risk factors, such as age, gender, bone mineral density, fracture after 50 years of age, family history of hip fracture, glucocorticoid use, weight or body mass index, current smoking, and alcohol consumption, have been used to construct a fracture risk index. Fracture risk assessment tools, including FRAX (developed by the World Health Organization), are useful in identifying a group of people who are at high risk of fracture. However, the accuracy of these tools in identifying fracture risk at personal level is generally poor. Black et al. (2001) developed a fracture risk index from a large prospective cohort of 7,782 women aged 65 years or older, including parameters, such as age, fracture after 50 years of age, history of maternal hip fracture, weight, current smoking, and use of arms for standing up. They reported a sensitivity of 66.0%, specificity of 66.3%, and positive predictive value of 5.6% for the index at a cut-point of four. To improve fracture discriminating ability, these risk assessment tools may need to include more independent risk factors. Additionally, a useful risk assessment tool should include only risk factors that can be easily assessed and accurately measured in a primary care setting.

Unlike standing height or recalled height, LLL can be measured easily with a high degree of precision in almost any older subject in any setting. More importantly, LLL is an independent and significant risk factor for fracture in very frail, older people. LLL should therefore be considered as a component for inclusion in future fracture risk assessment tools, especially those tools that to be used among frail older people.

44.4 Application to Other Area of Health and Disease

LLL is first considered for older people, who are non-ambulatory or with vertebral deformities, as an estimated height to be included in nutritional status indicators (Chumlea et al. 1985). Its application has been extended to be used as a marker of early life environment, in children with cerebral palsy, and in calculation of height loss, etc. For example, Huang et al. (2008) studied 2,798 men and women for an average of 5.4 years, and found that shorter LLL was associated with higher risk of dementia and Alzheimer's disease in women but not in men. LLL could be considered as a marker of early life environment because most growth before puberty is due to increases in leg length. The authors therefore suggested that LLL might reflect nutritional or other deficits during early development, which could play a role in the determination of future dementia risk. Table 44.7 lists the main medical applications of LLL other than fracture risk assessment.

Summary Points

- LLL can be easily measured with accuracy even in older persons with postural problems, vertebral deformities, or confinement to a wheelchair or bed.
- The estimated height from LLL has advantages over current standing height, lower extremity length or recalled height at the age of 25 years, as an index of mature skeletal stature in older people as it is almost unaffected by aged-related high loss or recall bias.

Table 44.7 Other medical applications of lower leg length (LLL)

LLL as	Area of application
Index of mature skeletal stature	Body mass index (BMI) (Roubenoff and Wilson 1993)
	Body surface area (Ritz 2004)
	Energy expenditure (Cheng et al. 2002)
	Total body water (Ritz 2004)
	Ideal weight (by the Lorentz formula) in the Geriatric Nutritional Risk Index (Bouillanne et al. 2005)
	Creatinine clearance (Schut et al. 2009)
	Height loss (Bunout et al. 2007)
Marker of early life environment	Risk assessment for dementia or Alzheimer's disease in women (Huang et al. 2008)
	Risk assessment for mortality from sex hormone dependent cancers (Gunnell et al. 1998)
	Risk assessment for insulin resistance and coronary heart disease (Smith et al. 2001)

This table lists some applications of LLL as an index of mature skeletal stature or a marker of early life environment in medical fields other than fracture risk assessment

- Institutionalized older people with longer LLL have increasing risk of fracture, and LLL appears to affect risk of hip fracture more than risk of other fractures.
- The effect of LLL on risk of fracture may be explained by the high impact from a high-position fall, and its positive association with hip axis length, which is an independent risk factor for hip fracture.
- LLL should be considered for inclusion in future fracture risk assessment tools to improve the fracture discriminating ability of the tools, especially those tools targeting frail older people.

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Part VII
Regions and Anatomical Areas of the Body: Joints and Digits

Chapter 45
Anthropometry and the Knee Joint

A.J. Teichtahl, A.E. Wluka, Y. Wang, and M. Flavia Cicuttini

Abstract Assessing how human anthropometry (i.e. measures of the size and proportions of the body) influences the knee has provided important information about risk factors for common arthropathies, such as osteoarthritis (OA). Nevertheless, until recently, there has been a paucity of data identifying associations between anthropometric measures and structural aberrations in the knee. This is likely to have resulted from difficulties in assessing knee structures. Previous studies have been largely reliant upon joint radiography to image the knee. Radiographs are limited and provide a two-dimensional assessment of a three-dimensional structure, without the ability to examine the non-radiographically opaque intra and extra-articular structures. New imaging modalities, such as magnetic resonance imaging (MRI), have enabled novel and sensitive opportunities to measure knee structures *in vivo*. MRI has helped to confirm OA to affect the whole joint, enabling a detailed examination of the relationship between human anthropometry and the knee. This chapter seeks to discuss how different dimensions of assessment of knee structure can be related to human anthropometry, and improve our understanding of factors affecting the risk and progression of knee OA. This may facilitate novel preventive strategies for the disease.

Abbreviations

A-P	Anterior-posterior
BMI	Body Mass Index
BML	Bone marrow lesion
JSN	Joint space narrowing
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
WHO	World Health Organisation

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_45,

45.1 Introduction

Assessing how human anthropometry (i.e., measures of the size and proportions of the body) influences the articular knee joint has provided important information about risk factors for common arthropathies, such as osteoarthritis (OA). The most pertinent example of this is the unequivocal link between an increased body mass index (BMI) and the risk for the onset and progression of knee OA (Felson et al. 1997; Gelber et al. 1999; Schouten et al. 1992).

Nevertheless, until recently, there has been a paucity of data identifying associations between other anthropometric measures and structural aberrations in the knee joint. This is unlikely to be a result of the way in which anthropometric measures (e.g., height, weight or body composition) have been collected, as these have proven to be consistently valid, reliable, sensitive and robust. Rather, the lack of association between knee joint structures and anthropometric measures may be attributable to the difficulties in assessing the knee joint.

In both the clinical and research settings, joint imaging provides a non-invasive means of measuring knee joint structures, and therefore assessing the presence and extent of an arthropathy. The most common arthropathy is OA, and radiographic knee OA is estimated to be prevalent in 30% of people aged over 65 years (Felson et al. 1987). Radiographic OA is characterised by joint space narrowing (JSN), osteophytes, subchondral cysts and subchondral sclerosis. While previous radiological measurements have largely been dependent on the joint radiograph, they provide only a two-dimensional assessment of three-dimensional structures, and cannot identify changes occurring in all intra- and extra-articular structures. Some of the limitations associated with joint radiography may have influenced the lack of association between human anthropometry and the knee joint.

The advent of new imaging modalities, such as magnetic resonance imaging (MRI), has, for the first time, enabled the measurement of all knee structures sensitively and non-invasively, in vivo. In particular, MRI enables direct visualisation of joint structures in three dimensions. This has offered a more sensitive quantitative and qualitative alternative to radiographs for examining knee joint arthropathies. Such advances have helped to characterise disease processes, such as OA, as a whole organ phenomenon, and have enabled a more detailed investigation of the relationship between human anthropometry and the knee joint in both health and disease.

This chapter seeks to explore the associations between human anthropometry and the knee joint using OA as a disease paradigm. However, to enable a discussion of how anthropometry is related to the knee joint, an appreciation of how the knee joint can be measured must first be understood.

45.2 Radiological Assessment of the Human Knee Joint

45.2.1 The Joint Radiograph

The World Health Organisation (WHO), in 1961 adopted the Kellgren and Lawrence (K-L) system for grading radiographic OA (see Table 45.1). Although the radiographic features of OA are recognised as osteophytes, JSN, subchondral sclerosis, and cysts, the presence of osteophytes and joint space narrowing have predominantly been used to identify the presence and examine the progression of disease respectively (Fig. 45.1).

Osteophytes are fibrocartilaginous-capped bony outgrowths that can be detected on the joint radiograph. Although the presence of osteophytes is crucial to radiographic grading systems examining the presence and severity of disease, the relevance of osteophytes in the pathogenesis of OA remains unclear.

Table 45.1 Kellgren & Lawrence grading system of knee osteoarthritis

Grade	Classification	Criteria
0	Normal	No features of OA
1	Doubtful	Minute osteophyte, doubtful narrowing of joint space
2	Minimal	Definite osteophyte, absent or questionable narrowing of joint space
3	Moderate	Moderate osteophyte, definite narrowing of joint space, some sclerosis, possible deformity
4	Severe	Large osteophyte, marked narrowing of joint space, severe sclerosis, definite deformity

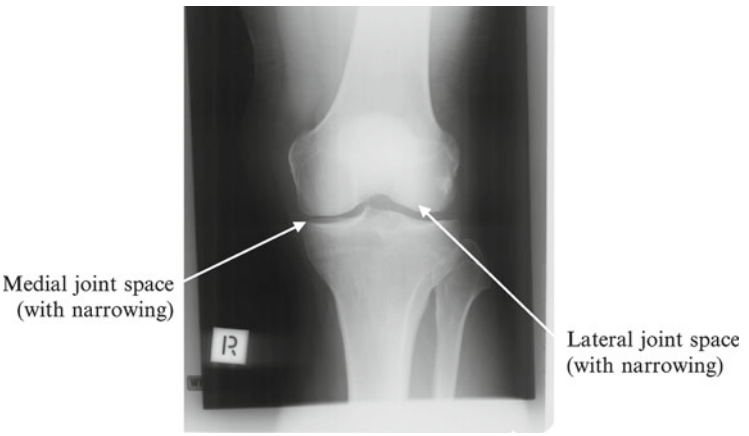

Fig. 45.1 Anterior–posterior knee X-ray

Studies examining individual radiographic features of OA have predominantly reported results related to osteophytes, as their measurement tends to yield better reproducibility than measurements of JSN (Spector et al. 1996). Nonetheless, it has recently been shown that plain radiography may not be the most sensitive means of determining the presence of osteophytes, in particular, central osteophytes. Of 44 asymptomatic volunteer subjects, 25% had osteophytes detected by MRI, of whom three-quarters had no evidence of osteophytes on radiography (Beattie et al. 2005).

According to the K-L grading system, radiographic studies may have therefore under-classified the prevalence of disease by failing to recognise the presence of osteophytes. In contrast, without recognising that other structural changes may not occur in parallel with osteophytes, there has been the potential to underemphasise findings related to other individual radiographic features, such as JSN.

JSN is a continuous radiographic measure used to assess the potential space between opposing bony surfaces (see Fig. 45.1). It has been employed as one of the major outcome variables in studies of disease progression in knee OA (Reginster et al. 2001).

Underlying the measurement of JSN is the assumption that a longitudinal diminution in this potential space is a valid measure of a reduction in articular cartilage volume. This is not necessarily true, as the radiographic joint space is comprised of structures other than articular cartilage (Bruyere et al. 2007; Adams et al. 1999). For instance, mensical extrusion has been shown to account for much early joint space loss at the tibiofemoral joint (Fife et al. 1991). Reliability issues related to JSN are also problematic, primarily because of measurement error related to positioning of the knee. For example, the conventional anterior–posterior knee radiograph is highly observer dependent when determining JSN at the tibiofemoral joint (Gunther and Sun 1999), and measurement error may relate to both the positioning of the knee, and its alignment with respect to the radiograph and source

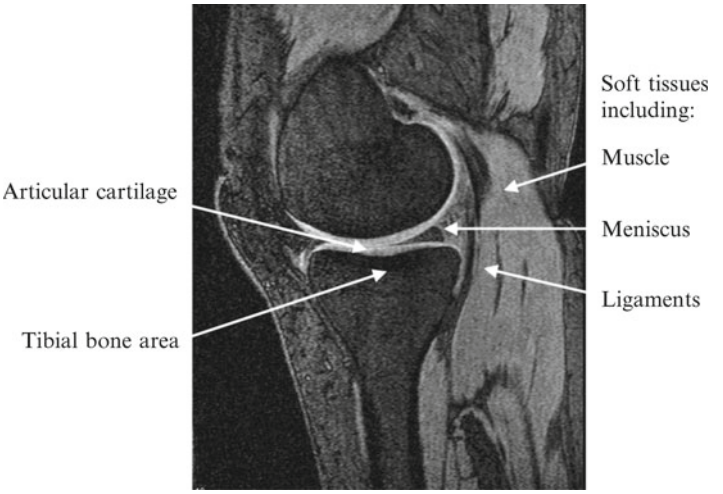

Fig. 45.2 T1 weighted sagittal MRI

of radiation (Altman et al. 1996; Ravaud et al. 1996; Buckland-Wright et al. 1995). Finally, JSN is relatively insensitive to change, and few studies have demonstrated significant change over short-term periods (Raynauld et al. 2004; Vignon et al. 2003).

45.2.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a non-invasive and non-ionising modality, enabling the three-dimensional imaging of all joint structures simultaneously. Thus, MRI enables valid, reliable, and direct measurement of cartilage and bone, as well as other intra- and extra-articular structures (see Fig. 45.2). Since the advent of MRI, OA is more widely appreciated to involve the whole organ, with abnormalities identified in multiple joint structures.

45.2.2.1 Quantitative Measurements of Cartilage

MRI studies examining knee OA initially focussed on the assessment of articular cartilage as the main outcome measure as an extension of the previous radiographic work examining JSN. MRI has been seen as a potentially major advance because it enables the direct assessment of cartilage, rather than the indirect approach allowed by the use of radiography. Epidemiological studies have tended to use cartilage thickness and volume as the main quantitative outcome measures in both cross-sectional and longitudinal studies of subjects with and without established knee OA.

Several limitations have been identified when adopting cartilage thickness as a means for assessing knee OA. In particular, diurnal variability in articular cartilage thickness, but not volume, has been demonstrated (Waterton et al. 2000). Additionally, longitudinal studies examining change in cartilage thickness may be limited by the difficulty in reselecting identical section locations at follow-up assessment (Pilch et al. 1994). Rather than measuring cartilage thickness at a particular geographical location, it is also possible to quantify the entire cartilage plate by measuring cartilage volume.

MRI assessment of knee cartilage volume has been demonstrated to be a valid (Peterfy et al. 1994b; Cicuttini et al. 1999; Burgkart et al. 2001; Graichen et al. 2004) (Cicuttini et al. 2004; Hunter et al. 2003;

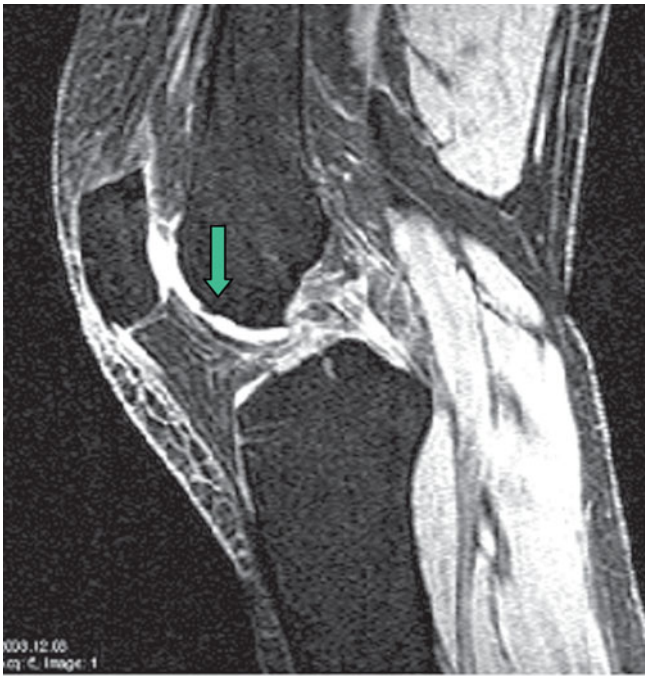

Fig. 45.3 Cartilage defects. *Arrow* demonstrates a tibial cartilage defect

Wluka et al. 2004; Peterfy et al. 1994a; Wluka et al. 2002) and reliable (Marshall et al. 1995; Cicuttini et al. 2000) assessment of the entire geographical cartilage plate. The technique also provides a far more sensitive measure of change in cartilage volume than the joint radiograph, with 11–13% of cartilage volume being lost before the first changes of radiographic JSN can be detected (Jones et al. 2004). Similarly, MRI has demonstrated that, over consecutive 6-month intervals for a period of 2 years, cartilage volume loss occurs, despite no diminution in the radiographic joint space in people with established knee OA (Raynauld et al. 2004).

45.2.2.2 Qualitative Measurements of Cartilage

Although early MRI studies focussed on quantitative measures of cartilage (i.e., thickness and volume), more recent studies have also assessed the quality of cartilage.

Cartilage defects are irregularities on the surface of the usually smooth articular cartilage that can be detected and assessed via MRI (see Fig. 45.3), using a technique developed from arthroscopy (Ding et al. 2006). Histologically, these are highly correlated with the Mankin scale for grading cartilage (McGibbon and Trahan 2003). These lesions are thought to represent early aberrations in the cartilage plate that may be apparent prior to radiographic change (Ding et al. 2005d) and may herald a reduction in cartilage volume, and thus represent a very early form of OA (Ding et al. 2005a, b, c, Cicuttini et al. 2005a).

45.2.2.3 Quantitative and Qualitative Measurements of Subchondral Bone

Once considered primarily a degenerative process of articular cartilage, studies that have employed MRI have enabled greater appreciation that the pathogenesis of OA also involves changes at the articular bone surface.

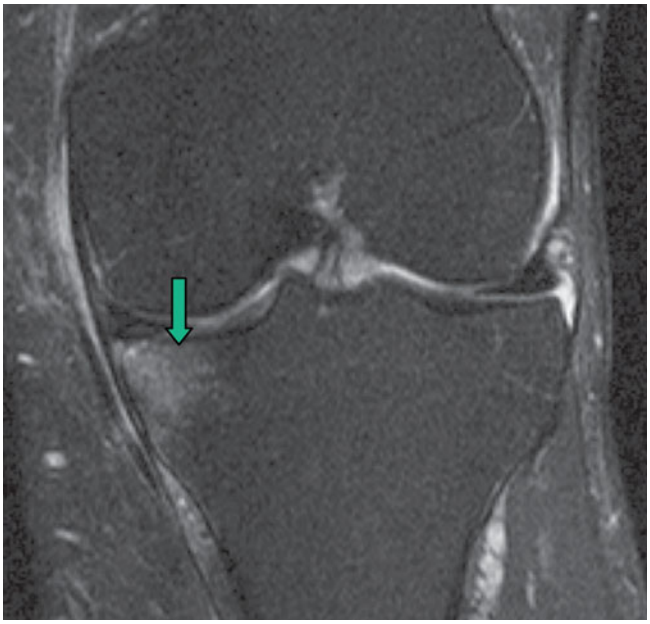

Fig. 45.4 Bone marrow lesions. Large bone marrow lesion identified at medial tibia

Persons with knee OA have been shown to have a larger bone surface area at the tibial plateau than healthy controls, and it has also been demonstrated that the rate of bone expansion is greater in persons with OA than in healthy subjects (Wang et al. 2006, 2005). Radiographically, for each increase in grade of JSN in a compartment, tibial plateau bone area was also shown to be increased (Wluka et al. 2005). In terms of directly assessing cartilage aberrations, it has also been shown that a larger bone area at baseline was predictive of an increase in the severity of knee cartilage defects over 2 years (Ding et al. 2005d). Moreover, increased tibial plateau surface area was a major determinant in mediating reduced knee cartilage volume among people without clinical knee OA (Ding et al. 2007).

Bone marrow lesions (BMLs) are measured via MRI, and are represented by high-signal-intensity areas on fat-suppressed T2-weighted images (see Fig. 45.4). BMLs are correlated with increased bony uptake on bone scintigraphy (Boegard et al. 1999; McAlindon et al. 1991) and, in OA studies, demonstrate histological features consistent with ongoing bone trauma, including marrow necrosis, abnormal bone formation with excessive fibrosis and extensive bony remodelling with reversal lines and areas of osteonecrosis (Zanetti et al. 2000).

BMLs have been shown to be prevalent in approximately 13% of healthy middle-aged subjects with no clinical knee OA (Baranyay et al. 2007). In these healthy subjects, BMLs were positively associated with tibial bone area, and were associated with an increased risk for the presence of cartilage defects (Guymer et al., Baranyay et al. 2007). In subjects with knee OA, BMLs are associated with the radiographic progression of compartment-specific JSN, although some of this progression may have been attenuated by frontal plane knee alignment (Felson et al. 2003). Similarly, knee compartments with a higher baseline BML score also had greater cartilage loss at follow-up, although adjusting for knee alignment attenuated this relationship (Hunter et al. 2006).

Subchondral bone attrition is defined as a flattening or depression of the osseous articular surface. The causes of attrition are unknown, although it is speculated that chronic overload and subsequent remodelling processes may be an important contributor. For instance, bone attrition was associated with knee alignment in a compartment-specific manner, suggesting the importance of biomechanical factors

that increase compartment loads (Neogi et al. 2009). Moreover, in a study of 1,025 knees with or deemed to be at high risk of knee OA, subchondral bone attrition and BMLs were found to coexist, whereby there was an increased risk of bone attrition in areas of prevalent BMLs (Roemer et al. 2009).

45.3 The Relationship Between Human Anthropometry and the Knee Joint

As radiographic OA (assessed by plain radiography) and articular cartilage and bone morphology (assessed by MRI) are the most commonly employed outcome variables in studies examining the articular knee joint, it is important to appreciate how these measures are related to the size and proportions of the human body (see Table 45.2).

45.3.1 Developmental and Gender Differences in the Knee Joint

During development, cartilage accrual is greater in the lateral, rather than the medial knee compartment (Jones et al. 2003). Moreover, paediatric data demonstrates that cartilage volume at the knee peaks during Tanner stage two of development (Jones et al. 2003). Overweight children have lower cartilage volume at all knee sites than their non-overweight counterparts (Jones et al. 2003). Boys have greater increases in cartilage volume than girls, and tibial cartilage volume accrual correlates significantly with height change (Jones et al. 2000). Similarly, adiposity and sedentary lifestyles were related to less bone accrual in children (Wosje et al. 2009). Bone area is also smaller in overweight and obese boys and girls, relative to their body weight (Goulding et al. 2000).

The paediatric trends in cartilage and bone development are also reflected in later life, whereby lateral knee cartilage volume is significantly greater than medial cartilage volume in adults, despite the medial tibial plateau bone area being larger than the lateral plateau bone area (Cicuttini et al. 2002). Adult males have been shown to have greater tibial cortical area and thickness than females (Nieves et al. 2005), as well as greater cartilage thickness and volume at all sites within the knee joint (Cicuttini et al. 1999, 2002). However, although gender has been estimated to account for 33–44% of the variation in adult knee cartilage volume, this estimate is reduced to 8–18% after adjustment for height, weight and bone size (Ding et al. 2003). This suggests that independent of gender, other measures of body size and proportions are key determinants of articular knee joint morphology.

45.3.2 Height and Weight

As the body mass index (BMI) accounts for both height and weight in a single measure, the predominance of studies have tended not to examine height or weight separately. Of the small number of studies examining weight and height separately, weight, including a past history of heavy weight, has been documented as a risk factor for the presence of radiographic knee OA (Abbate et al. 2006; Yoshimura et al. 2004). It has also been demonstrated that increased knee height was associated with an increasing prevalence of radiographic OA, especially among women (Hunter et al. 2005), and is a risk factor for knee joint replacement (Liu et al. 2007). The rationale for knee and body height being an important determinant of knee OA is based on the theory that greater limb length would contribute to larger moments around the knee, producing more torque and subsequent joint load.

Table 45.2 Key features of the anthropometric determinants of joint structure

	ROA	Cartilage volume	Cartilage defects	Metaphyseal bone expansion	Bone marrow lesions
↑ Height	↑ (Hunter et al. 2005)	↑ (Nishimura et al. 2005)	N/A	N/A	↑ (Guymer et al. 2007)
↑ Knee height	↑ (Hunter et al. 2005; Liu et al. 2007)	N/A	N/A	N/A	N/A
↑ Weight	↑↑ (Abbate et al. 2006; Yoshimura et al. 2004)	↑ (Nishimura et al. 2005)	N/A	N/A	↑ (Guymer et al. 2007)
↑ BMI	↑↑↑↑ (Wendelboe et al. 2003; Liu et al. 2007)	↔ (Ding et al. 2005c)	↑↑ (Ding et al. 2005c, 2006)	↑↑ (Ding et al. 2005c)	N/A
↑ Fat mass	↑↑ (Abbate et al. 2006; Yoshimura et al. 2004)	↓↓ (Wang et al. 2007)	↑ (Wang et al. 2007)	N/A	N/A
↑ Fat-free mass	↓↓ (Abbate et al. 2006; Yoshimura et al. 2004)	↑↑ (Wang et al. 2007; Cicuttini et al. 2005b)	↓ (Wang et al. 2007)	N/A	N/A
Static knee alignment	Varus (↑ medial) (Khan et al. 2008) Valgus (↑ lateral) (Khan et al. 2008)	↔ (Teichtahl et al. 2009; Jackson et al. 2004)	Varus (↑ medial) (Issa et al. 2007; Janakiramanan et al. 2008) Valgus (↑ lateral) (Issa et al. 2007; Janakiramanan et al. 2008)	N/A	Varus (↑ medial) (Hunter et al. 2006) Valgus (↑ lateral) (Hunter et al. 2006)

Arrows indicate direction of association (↔ represents equivocal relationship)
N/A data not yet examined, *ROA* radiographic osteoarthritis

Only a small number of MRI studies have examined height and weight separately. Nevertheless, significant correlations have been documented between the tibia and femoral cartilage thickness, and body weight ($R = 0.64$; $P < 0.05$) and height ($R = 0.60$; $P < 0.05$) (Connolly et al. 2008). Likewise, knee cartilage volume is positively correlated with body weight and height (Nishimura et al. 2005). The association between bone and height or weight has not been well examined, but there is some evidence that these anthropometric measures are associated with the presence of BMLs (Guymer et al. 2007).

45.3.3 Body Mass Index and Body Composition

BMI, which is defined by weight (kg)/height (m^2), is an unequivocal risk factor for severe radiographic knee OA and knee replacement (Wendelboe et al. 2003, Liu et al. 2007).

Despite BMI being associated with JSN on radiographs, it has not been consistently demonstrated as a significant determinant of cartilage volume when assessed by MRI (Ding et al. 2005c). Nevertheless, among the small number of studies that have examined the association between BMI and knee cartilage defects, there is a consistent positive association between BMI and the presence of severity of knee cartilage defects (Ding et al. 2005c, 2006). BMI is also positively associated with tibial bone area (Ding et al. 2005c).

However, BMI is only a surrogate measure of obesity, and it cannot discriminate between adipose and non-adipose mass. In a study of 779 females, it was demonstrated that fat mass, percentage fat mass, and waist circumference were associated with the risk of radiographic knee OA, whereas lean mass percentage was associated with lower odds for radiographic knee OA (Abbate et al. 2006). Likewise, in a recent MRI study, it was demonstrated that fat-free mass was associated with an increase in tibial cartilage volume, whereas fat-mass was associated with a reduction in tibial cartilage volume, and weakly associated with an increase in the prevalence of knee cartilage defects (Wang et al. 2007). Indeed, muscle mass has also been demonstrated to reduce the rate of knee cartilage loss (Cicuttini et al. 2005b). No study has examined the associations between body composition measures and bone morphology.

45.3.4 Knee Alignment

In persons with knee OA, radiographic studies have demonstrated that knee alignment is associated with the compartment pattern and severity of disease (Khan et al. 2008). That is, varus alignment is a determinant of medial knee disease, whereas valgus alignment is a determinant of lateral knee disease. Indeed, much of the effect of BMI on the severity of radiographic medial knee OA was explained by varus malalignment (Sharma et al. 2000).

In MRI studies, knee alignment has consistently been associated with compartmental cartilage defects (Issa et al. 2007), both in the presence and absence of established clinical disease (Janakiramanan et al. 2008). Although the association between alignment and cartilage volume is less clear cross-sectionally, change towards genu valgum was shown to reduce the annual rate of medial knee cartilage loss in people with established disease (Teichtahl et al. 2009). Few studies have, however, examined the association between knee alignment and bone size, although the knee adductor moment, a dynamic measure of knee joint loading, is associated with medial tibial plateau bone area (Jackson et al. 2004). In OA, enlarging or new BMLs do, however, occur mostly in malaligned knees, in a compartment-specific manner (Hunter et al. 2006).

45.3.5 The Relationships Between Knee Structures

Within MRI studies, multiple relationships between articular structures have been elucidated. The following examples are non-exhaustive, and provide only an overview of significant findings that indicate that there is a potential continuum of disease in knee OA, whereby the origins of disease may begin in the asymptomatic knee joint devoid of radiographic OA. For instance, prevalent knee cartilage defects are predictive of compartment-specific cartilage loss (Ding et al. 2005a). A larger bone area at baseline was predictive of an increase in the severity of knee cartilage defects over 2 years (Ding et al. 2005d, 2006; Davies-Tuck et al.).Moreover, increased tibial bone area predicts compartmental cartilage volume loss over 2 years (Ding et al. 2007, 2008). BMLs were positively associated with tibial bone area and were also associated with an increased risk for the presence and progression of cartilage defects, as well as cartilage loss in people with and without established knee OA (Guymer et al.; Baranyay et al. 2007, Wluka et al. 2009).

In studies that have combined both radiographic and MRI data, it has been shown that tibial plateau area increased with each increase in grade of osteophyte and joint space narrowing (Wluka et al. 2005). In a separate study, osteophytes were associated with the severity and prevalence of knee cartilage defects and, once again, tibial bone area. The severity of knee cartilage defects was also associated with increased grade of JSN (Ding et al. 2005d).

45.4 Applications to Other Areas of Health and Disease

The acknowledgement of knee OA as a whole-organ disease can predominantly be attributed to advances in imaging, such as MRI. Such progressions have furthered our understanding of how anthropometrical measurements may be related to the knee joint. However, while knee OA has been exemplified in this chapter as the disease paradigm, the principles discussed here are not limited to OA alone. For instance, other arthropathies, including inflammatory processes, such as rheumatoid arthritis and gout, can also be investigated in the context of these anthropometrical measures. Moreover, the application of such principles need not necessarily be limited to the knee joint, and could be examined at other anatomical sites (e.g., hip, carpometacarpal) where different risk factors may be apparent, even for the same disease (e.g., OA). Such investigations will allow a greater understanding of how human anthropometry is related to articular structures in both health and disease.

45.5 Conclusion

Joint radiographs have provided the ability to study important relationships between knee joint structures and measures of size and proportions of the human body. However, newer imaging modalities, such as MRI, have provided a more comprehensive and sensitive means for assessing knee joint morphology. MRI has enabled a more complete appreciation that OA is a disease of the whole joint. Using the sensitive tools facilitated by MRI, the examination of knee structural changes can be made on a continuum, from the normal through to the diseased knee joint. MRI has extended our ability, for the first time, to directly examine all intra- and extra-articular structures non-invasively and three-dimensionally, prior to the development of established radiographic disease. Novel findings include

identification of the potential role of height (total body and knee height) and knee alignment as affecting factors for knee structure, as well as further clarification of developmental and gender differences in the knee joint structure. The importance of body composition (e.g., fat mass), as opposed to obesity per se (as measured by the BMI) in the pathogenesis of knee OA is also becoming increasingly clear. Likewise, the importance of interactions between knee structures (e.g., bone marrow lesions, cartilage defects, metaphyseal bone expansion and cartilage defects) and the continuum from the healthy knee joint to end-stage knee OA are all contributing to our understanding of the pathogenesis of disease. Together, these new findings may lead to improvements in preventive strategies for diseases, such as OA.

Summary Points

- Assessing how human anthropometry (i.e., measures of the size and proportions of the body) influences the knee has provided important information about risk factors for common arthropathies, such as osteoarthritis (OA).
- Until recently, outcome measures at the knee have relied upon the radiograph of the joint to explore the relationships with human anthropometry. However, the joint radiograph provides limited outcome measures in knee OA, and other more valid, reliable and sensitive imaging modalities are now available.
- MRI has provided the opportunity to directly examine intra- and extra-articular structures three-dimensionally prior to the development of clinical disease.
- MRI studies have therefore enabled the associations between anthropometric variables and articular structures to be characterised and help better understand the pathogenesis of knee OA.
- Novel findings include:
    - Height (total body and knee height) and knee alignment being identified as risk factors for radiographic knee OA;
    - Developmental and gender differences in the knee joint structure;
    - The importance of body composition (e.g., fat mass), as opposed to obesity (as measured by the body mass index) in the pathogenesis of knee OA; and
    - Interaction between knee structures (e.g., bone marrow lesions, cartilage defects, metaphyseal bone expansion and cartilage defects) and the potential for a continuum to exist between the healthy knee joint and end-stage knee OA.

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Chapter 46
Knee Anthropometry and Total Knee Arthroplasty: Relationship Between Anthropometry, Surgical Difficulty, and Outcomes

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Abstract The Body Mass Index is usually used to identify patients who may present difficulties during surgery and poor outcomes. In severe and morbidly obese patients some anthropometric parameters may be useful in predicting surgical difficulty and outcomes after total knee arthroplasty surgery. We carried out two prospective studies with an initial hypothesis that the Body Mass Index is not associated with surgical difficulty in obese patients and that knee anthropometry influences outcomes after total knee arthroplasty.

In both studies, consecutive patients diagnosed with knee osteoarthritis with a Body Mass Index equal or more than 35 kg/m^2 scheduled for total knee arthroplasty were prospectively studied. The suprapatellar, infrapatellar and supra/infrapatellar anthropometric indexes were calculated before surgery. The tourniquet time was determined as a measure of surgical difficulty. The health-related quality of life, measured by the disease-specific Western Ontario and McMaster Universities Osteoarthritis Index questionnaire of each patient, was determined before and after surgery.

There was no association between the Body Mass Index and tourniquet time/surgical difficulty. The suprapatellar index was negatively associated with tourniquet time/surgical difficulty ($p = 0.038$). The infrapatellar index percentile < 75 was associated with higher Western Ontario and McMaster Universities Osteoarthritis Index questionnaire pain and function dimension scores after total knee arthroplasty.

The Body Mass Index is not the only parameter that should be considered in order to identify severe and morbidly obese patients who may have more surgical difficulties during total knee arthroplasty. Preoperative determination of the suprapatellar index helped us to classify these patients according to the morphology of the knee and predicted a longer tourniquet time and, therefore, greater surgical difficulty, in patients with a suprapatellar ratio below 1.6 in this study.

Outcomes after total knee arthroplasty surgery are influenced not only by the Body Mass Index but also by the anthropometric characteristics of the knee. An infrapatellar index less than 1.75 predicts worse outcomes after total knee arthroplasty surgery.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_46,

Abbreviations

ATT	Anterior tibial tuberosity
BMI	Body Mass Index
CI	Confidence interval
ES	Effect size
HRQL	Health-related Quality of Life
kg	kilograms
m	meter
MRI	Magnetic nuclear resonance
n	Number
OA	Osteoarthritis
SD	Standard deviation
TKA	Total Knee Arthroplasty
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index questionnaire

46.1 Introduction

Total knee arthroplasty (TKA) in patients with severe and morbid obesity is one of the current challenges in prosthetic knee surgery (Stickles et al. 2001; Bourne et al. 2007; Guss and Timothy 2006; Naik 2006; Gilliespie and Proteus 2007) In our hospital, 15% of patients undergoing primary TKA have a body mass index (BMI) >35 kg/m^2. Various studies have reported greater technical difficulties in operating on these patients (Winarsky et al. 1998; Booth 2002; Rottman et al. 2005; Krushell and Fingeroth 2007) The BMI (Stickles et al. 2001; Miric et al. 2002; Namba et al. 2005; Foran et al. 2004a, b; Amin et al. 2006; Bourne et al. 2007; Patel et al. 2007) is used to identify patients, who may present difficulties during surgery, and may have postoperative complications. However, other reports have not found these differences in TKA outcomes with respect to the BMI (Spicer et al. 2001; Deshmukh et al. 2002). Many patients with a high BMI do not have greater surgical difficulties than the rest of the population (Núñez et al. 2007). The problem is more often focused on the anthropometric profile presented by the obese patient with respect to the distribution of body fat: in some patients, this accumulates in the trunk, whereas in others, it is distributed uniformly, affecting the lower limbs (Booth 2002). Just as the waist-to-hip ratio has been used to predict cardiovascular risk in obese patients in preference to the BMI (Chen et al. 2007), determination of a new anthropometric index in the limb in patients undergoing TKA might help to identify patients, who may present greater surgical difficulties (prolonged tourniquet time (ischemia time)) and worse outcomes, in addition to the BMI.

Reports show a link between knee OA and obesity (Mason 2008), which is reflected by the increased number of TKA in obese individuals (Fehring et al. 2007). TKA can improve the health status of patients with knee OA, reducing pain and increasing functional capacity, when conservative treatment fails. Reports show that the most significant changes in pain and function occur 3–6 months after surgery.

However, reviews have reported that patient characteristics are important determinants of outcomes in TKA. Most studies on TKA outcomes in patients with severe and morbid obesity have concentrated on aspects, such as surgical complications and mechanical failure (Fehring et al. 2007; Gilliespie and Proteus 2007). Few short- or long-term studies have focused on health outcomes or health-related quality of life (HRQL) in these patients and the few that do are heterogenous methodologically.

Measures of the health status or HRQL are useful in evaluating TKA outcomes from the patient's perspective. Disease-specific instruments focus on issues related to a particular health condition, and can be used in therapeutic management. In knee OA, the disease-specific Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK 3.0) questionnaire is valid for assessing functional outcomes in TKA.

We present two prospective studies on whether anthropometry affects surgical difficulty and on outcomes after TKA surgery.

46.2 Relationship Between Knee Anthropometry and Surgical Difficulty

We carried out a prospective study with an initial hypothesis that the BMI is not associated with tourniquet time in obese patients undergoing TKA, and that some anthropometric parameters may be useful in predicting tourniquet time in severely (Class II) and morbidly (Class III) obese patients (Nuñez et al. 2007). A total of 100 consecutive patients diagnosed with knee osteoarthritis with BMI ≥35 kg/m^2 (Miric et al. 2002; Namba et al. 2005), undergoing TKA between November 2005 and November 2006 in the Knee Unit of the Hospital Clinic of Barcelona (Spain), were prospectively studied. Exclusion criteria were joint instabilities or angular deformities of the knee to be operated that required constrained prosthetic models. Radiographic measurement of the limb axis was carried out in the anteroposterior telemetric projection in a standing position by goniometry. Using the data collected during the pre-anesthesia visit carried out 2 weeks before the operation, which determined the weight and the size of the patient, BMI levels were obtained using the formula: BMI = weight (kilograms)/height^2 (meters) (Stickles et al. 2001; Bourne et al. 2007). The tourniquet time, measured from the inflation of the pneumatic cuff, just before the beginning of the operation to its liberation, once the components were cemented to carry out hemostasis, was determined.

The operation was carried out by a specialist surgeon from the knee unit using the same surgical technique and the same prosthetic model in all cases, with cemented implants (Profix; Smith & Nephew Inc., Memphis, TN, USA).

46.2.1 Determination of Knee Anthropometric Parameters

Before the operation, the suprapatellar circumference (measured at 4 cm proximal to the superior pole of the patella), the infrapatellar circumference (measured at the anterior tibial tuberosity (ATT)), and the length of the limb to be operated (measured from the anterior superior iliac crest to the center of the anterior face of the ankle joint) (Fig. 46.1) were determined. The same flexible, inelastic tape measure, calibrated in centimeters, was used for all measurements. The anthropometric indexes calculated were the length of the limb/suprapatellar circumference ratio (suprapatellar index), length of the limb/infrapatellar circumference ratio (infrapatellar index), and the suprapatellar circumference/infrapatellar circumference ratio (supra-/infrapatellar index).

46.2.2 Relationship Between BMI and Knee Anthropometry

Of the 100 patients, 87 were female and 13 male. The mean age was 70.43 years (SD ± 7.73); the mean BMI was 39.81 kg/m^2 (SD ± 3.75). The main sociodemographic and clinical patient variables are shown in Table 46.1. A total of 58% of patients were classified as having Class III obesity (BMI

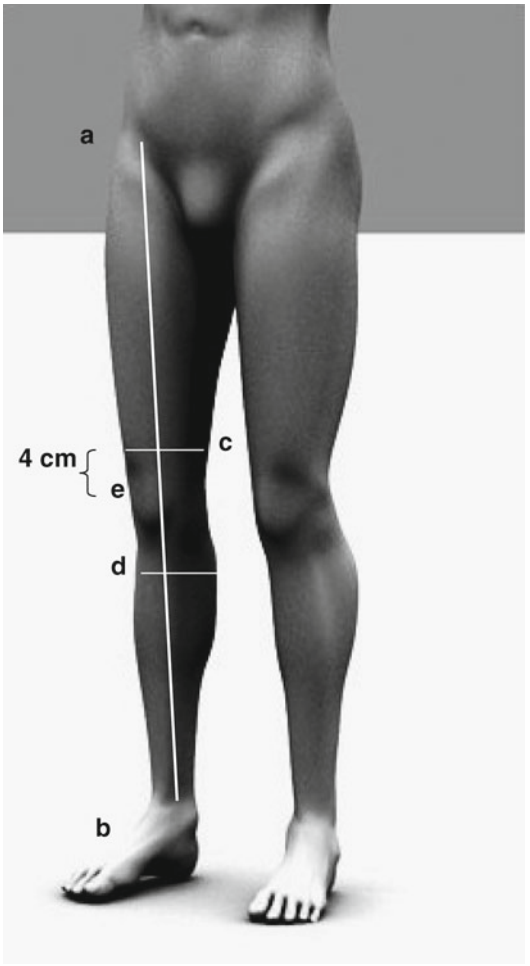

Fig. 46.1 Determination of knee anthropometry. (**a**) anterior superior iliac spine; (**b**) center of the ankle; (**c**) measurement point of the suprapatellar circumference; (**d**) anterior tibial tuberosity; (**e**) superior pole of the patella. This figure shows how the anthropometric parameters of the knee were calculated. The anterior superior iliac spine of the patient and the center of the ankle are palpated, calculating the distance between the two points: this provides the length of the limb. Four centimeters above the superior pole of the knee, the circumference of the knee is measured at the suprapatellar level with a metric tape measure, and the same procedure is carried out at the anterior tuberosity of the tibia to provide the infrapatellar circumference

35–39.99) and 42% as Class IV (BMI ≥40). The mean tourniquet time was 41.67 min (SD± 9.26). The mean values of the anthropometric indexes in the operated knee were:

Suprapatellar index 1.63 (SD ± 0.17)
Infrapatellar index 1.99 (SD ± 0.21)
Supra-/infrapatellar index 1.22 (SD ± 0.08)

There was no association between the BMI and tourniquet time.

When patients were grouped according to a BMI above or below 40 kg/m^2, and above or below 45, non-significant differences, which were not associated with tourniquet time, were found:

BMI < 39.99 kg/m^2:Tourniquet time 40.34 min (SD ± 8.77)
BMI > 40.00 kg/m^2:Tourniquet time 43.27 min (SD ± 9.78).
BMI < 44.99 kg/m^2:Tourniquet time 41.08 min (SD ± 9.04)
BMI > 45 kg/m^2: Tourniquet time 45.70 min (SD ± 10.68)

There was no statistically significant association between tourniquet time and the infrapatellar and supra-/infrapatellar indexes.

The suprapatellar index was negatively associated with tourniquet time ($p = 0.038$). As the suprapatellar index decreased, the tourniquet time increased.

Table 46.1 Sociodemographic and clinical characteristics in the surgical difficulty study

Gender	
Male (*n*)	13
Female (*n*)	87
Age mean (SD)	70.43 (7.73)
BMI mean (SD)	39.81 (3.75)
Class III (IMC 35–39.99)	58
Class IV (IMC ≥ 40)	42
Anthropometric indexes mean (SD)	
Suprapatellar index	1.63 (0.17)
Infrapatellar index	1.99 (0.21)
Supra-/infrapatellar index	1.22 (0.08)
Tourniquet time mean (SD)	41.67 (9.26)

This table shows the demographic characteristics of patients undergoing total knee arthroplasty. The majority were women and the mean BMI was near to the level of morbid obesity. The anthropometric values (indicated by the mean of the indexes calculated) and the ischemia time (tourniquet time) provide an idea of the difficulty of the surgical intervention

n number, *SD* standard deviation

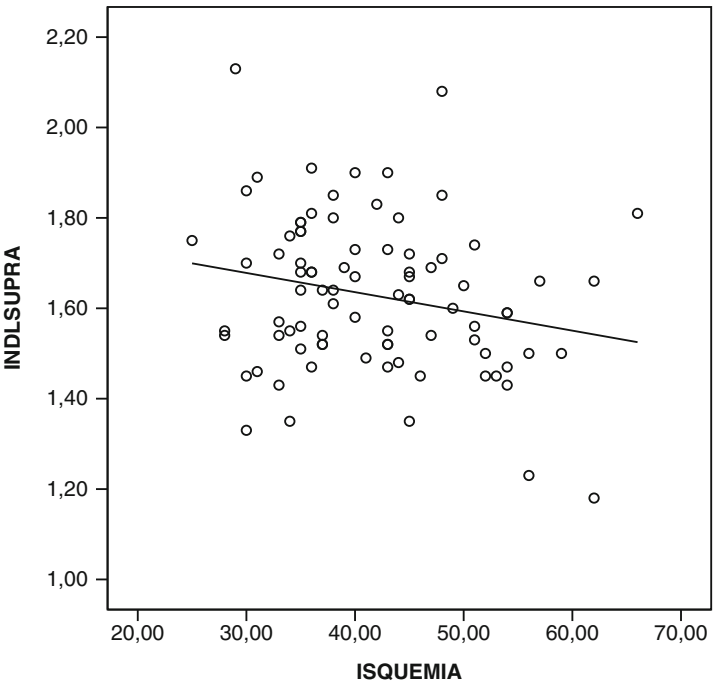

Fig. 46.2 Correlation between tourniquet time and the suprapatellar index. This figure shows the correlation between the ischemia time (variable of surgical difficulty) and the suprapatellar index. The correlation shows that the lower the suprapatellar index, the greater the ischemia time and, therefore, the greater the surgical difficulty. The cut-off value is 1.63. Below this value, the surgery can be forecast to involve greater difficulty

In patients with a suprapatellar index <1.6, the tourniquet time increased significantly (Fig. 46.2).

When the anthropometric indexes were compared according to BMI (<40 kg/m^2 vs. >40 kg/m^2), there were statistically significant differences in the suprapatellar and infrapatellar indexes between the two groups (Table 46.2). In patients with a BMI ≥40 kg/m^2 (Class III obesity) the suprapatellar ($p = 0.001$) and infrapatellar ($p = 0.004$) indexes were significantly lower than in patients with Class II obesity.

Table 46.2 Anthropometric indexes according to BMI in patients undergoing TKA

	BMI < 40 mean (SD)	BMI ≥ 40 mean (SD)	*P*
Suprapatellar index	1.68 (0.15)	1.56 (0.17)	0.001
Infrapatellar index	2.05 (0.18)	1.92 (0.22)	0.004
Supra-/infrapatellar index	1.22 (0.08)	1.23 (0.10)	0.715

This table shows the variations in anthropometric indexes according to the BMI. Both the suprapatellar and infrapatellar indexes vary according to the BMI. The higher the BMI, the lower the anthropometric indexes, suggesting that the limbs to operate are shorter and wider, in accordance with a pattern of uniform obesity. As expected, the supra-/infrapatellar index does not vary, as this index does not take the length of the limb into account
SD standard deviation

46.2.3 Application of Knee Anthropometry in TKA Surgery as a Predictor of Surgical Difficulty

The relationship between obesity and deterioration of the knee joint has been widely reported by many large studies (Nevitt 2002; Focht et al. 2005; Messier et al. 2005; Powell et al. 2005). Obesity is directly related to knee osteoarthritis, and the probability of an obese patient requiring knee replacement increases with the degree of obesity measured according to the BMI (Bourne et al. 2007; Liu et al. 2007). The anthropometric parameters of obese patients that might correlate with deterioration of the knee observed in radiographies have also been studied (Liu et al. 2007).

These studies show that the weight and the BMI are the factors most closely correlated with joint deterioration, and that other anthropometric parameters, such as the waist diameter or the waist-to-hip ratio, are not necessary to predict joint deterioration in obese patients.

The complexity of the obese patient with knee osteoarthritis has also been reported in various studies (Deshmukh et al. 2002; Miric et al. 2002; Foran et al. 2004a, b; Namba et al. 2005; Amin et al. 2006; Fehring et al. 2007; Gilliespie and Proteus 2007; Krushell and Fingeroth 2007; Patel et al. 2007). However, possible surgical difficulties due to the anthropometric type of the knee have not been sufficiently studied.

We often see patients with obesity Class II and III who, in theory, should present more operational difficulties, but whose morphologic characteristics do not differ from those of patients with less (Class I) or no (Class 0) obesity. An explanation could be the various types of distribution of fat in obese patients (Booth 2002). When the fat concentration is predominantly in the thorax and abdomen, following a truncal pattern, the knee to operate (which has suffered osteoarthritic degeneration due to mechanical overload in most cases) (Nevitt 2002; Powell 2005), does not usually present increased subcutaneous fat that would make the operation more difficult.

The opposite situation occurs in patients, whose fat distribution is uniform in the trunk and limbs, following a generalized pattern. In this situation, the knee circumference is increased by the accumulation of subcutaneous fat (Ding et al. 2005). We considered that preoperative identification of these two types of patients could be useful in planning the surgical requirements and the use of resources. The waist-to-hip ratio may be useful in predicting cardiovascular risk in obese patients (Chen 2007), and we hypothesized that a similar type of anthropometric index in the limb might also be useful in predicting surgical difficulties. Thus, in patients with Class II or III obesity, we determined anthropometric parameters at the knee. We hypothesized that determining only the knee circumference at the suprapatellar and infrapatellar levels, without relating them to the length of the limb, would not provide evidence of the anthropometric type, as a high circumference measurement may be accompanied by a long limb in which the fat is not accumulated in the subcutaneous region, creating operating difficulties. Tourniquet time was selected as the objective criterion of operating difficulty, as all operations were carried out by surgeons specializing in knee prostheses, using the same protocol and the same type of prosthesis.

However, in patients with Class II and III obesity, when we studied the anthropometric type of the knee according to the aforementioned indexes, there was a negatively significant association between the suprapatellar index and the tourniquet time, with a lower suprapatellar index being associated with longer tourniquet time. A suprapatellar index <1.6 was significantly associated with longer tourniquet time ($p < 0.038$).

Morphologically, a suprapatellar index <1.6 indicates patients with shorter, wider limbs with greater thickness of subcutaneous tissue in the suprapatellar region and consequent difficulties in various steps of the TKA (in the access route, patellar eversion, positioning of separators, orientation of the cutting guides and positioning of the implants, as well as more complex wound closing) (Winarsky et al. 1998; Booth 2002; Rottman et al. 2005; Krushell and Fingeroth 2007), resulting in a longer tourniquet time. A suprapatellar index > 1.6 indicates patients with longer limbs and smaller suprapatellar perimeters with less operating difficulties.

Although the study had some limitations, including the fact that anthropometric characteristics vary between populations, we believe that the results are valid for our patients. Determination of preoperative BMI, together with evaluation of the knee morphology and determination of the suprapatellar index, identifies patients belonging to a subgroup of obese patients who may present greater operating difficulties. The specific value of 1.6, which determined greater difficulty in our patients, would have to be calculated for each population group with different anthropometric characteristics, but we believe that the manner of determining it may be reproducible in other populations.

46.3 Knee Anthropometry Influencing Health Outcomes in Severe and Morbidly Obese Patients with Knee Osteoarthritis Undergoing Total Knee Replacement

We carried out another study to evaluate general health in severe and morbidly obese patients undergoing TKA and determine whether patient characteristics influenced postoperative WOMAC dimension scores.

46.3.1 Study Design and Setting

A prospective 12-month study was carried out in the Rheumatology Service and Knee Unit of the Hospital Clínic, Barcelona (Spain).

Inclusion criteria. Consecutive patients with knee OA and severe or morbid obesity (Class II BMI ≥ 35 kg/m^2 and Class III BMI ≥ 40 kg/m^2), respectively, according to the World Health Organization [WHO] classification admitted to our hospital for TKA. Patients with functional illiteracy or psychopathology severe enough to prevent complete participation in study procedures were excluded. All patients received a standard (non-constrained) prosthesis.

46.3.2 Study Variables

We determined the following variables:

1. Self-reported general health measured by the WOMAC questionnaire validated for the Spanish population (Escobar et al. 2002). This questionnaire contains three dimensions (pain, stiffness, and

Table 46.3 Baseline patient characteristics of patients undergoing TKA in the outcomes study

Age mean (SD)	70.2 (6.7)
Gender n (%)	
Male	7 (11.7)
Female	53 (88.3)
N of preexisting comorbidities mean (SD)	2.5 (1.5)
Type of preexisting comorbidities n (%)	
Hypertension	42 (70)
Diabetes	14 (23.3)
Respiratory disease	12 (20)
Digestive disease	11 (18.3)
Psychiatric disease/depression	9 (15)
Heart disease	7 (11.7)
BMI mean (SD)	39.9 (3.8)
Class II: 35–39.9 kg/ m^2 *n* (%)	33 (55)
Class III: ≥ 40 kg/ m^2 *n* (%)	27 (45)

This table shows that the patients were mainly women (88%) and that the majority, in addition to presenting knee osteoarthritis, suffered hypertension and that almost half were morbidly obese
SD standard deviation, *N* number, *BMI* Body Mass Index (kg/m^2)

function). WOMAC dimension scores are normalized to a 0 (best)–100 (worst) scale (Escobar et al. 2002).

2. Sociodemographic (age and sex) and clinical (number and type of preexisting comorbidities and BMI) data were recorded.
3. Lower limb anthropometry was measured using the suprapatellar, infrapatellar, and supra-/infrapatellar indexes (Fig. 46.1), which was carried out by an independent researcher.

46.3.3 Anthropometry and Outcomes After TKA

Sixty patients were included in the analyses. Table 46.3 shows baseline patient characteristics. The mean anthropometric index scores were: suprapatellar 1.6 (SD 0.2), infrapatellar 2 (SD 0.2), and supra-/infrapatellar 1.2 (SD 0.1).

The results of the multiple regression models are shown in Table 46.4. An infrapatellar index percentile <75 was associated with worse scores in the WOMAC pain and function dimensions ($p = 0.007$ and 0.025, respectively).

46.3.4 Anthropometry and TKA Outcomes

The health status of our patients improved after TKA. WOMAC dimension scores were negatively influenced by comorbidities and lower limb morphology (infrapatellar index), which were independently associated with worse WOMAC scores at 12 months. Comorbidities were associated with worse functional dimension scores, and the infrapatellar index was associated with worse functional and pain dimension scores. Previous studies have also suggested that comorbidities have an independent negative effect on function (Krushell and Fingeroth 2007) and suggested that therapy and

Table 46.4 Variables independently associated with the WOMAC pain and stiffness and function dimensions at 12 months in the multiple linear regression models in the outcomes study

	Dependent variables								
	WOMAC scores at 12 months								
	Pain			Stiffness			Function		
	R^2 adjusted 0.148						R^2 adjusted 0.232		
	Coefficients	95% CI	*P-value*	Coefficients	95% CI	*P-value*	Coefficients	95% CI	*P-value*
Independent variable									
N comorbidities	–	–	–	–	–	–	6.8	3.5–10.2	<0.001
Infrapatellar index percentile <75	16.2	4.6 – 27.7	0.007	–	–	–	11.5	1.5–21.5	0.025

The coefficients of regression models indicate whether an increase in the independent variables is related with an increase or worse (positive coefficient) or decrease or better (negative coefficient) WOMAC dimensions score. R^2 adjusted is the proportion of variance in the dependent variable explained by the relevant independent variables shown. The three WOMAC scales were normalized to a 0–100 scale for each separate WOMAC dimension, where 0 represents the best health status and 100 the worse health status

This table shows that there is an association between WOMAC scores and the infrapatellar index. This suggests that patients with a lower infrapatellar index have higher WOMAC pain and function dimension scores (worse health status). Likewise, patients with a higher number of comorbidities had higher WOMAC function dimension scores (worse health status)

SD Standard deviation; *CI* confidence interval; *N* number; *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

active control may be required. Studies have shown that severe and morbidly obese patients have more associated comorbidities, and longitudinal studies demonstrate evidence of the relationship between comorbidity and functional limitations. Lower limb anthropometry (infrapatellar index percentile <75) was significantly associated with worse pain and function, and indicated a knee with more difficulties in prosthesis implantation, regardless of the BMI. However, patients with a BMI ≥35 kg/m^2 had greater surgical difficulties, including more subcutaneous fat, and difficulties in patellar eversion, exposing the surgical field and prosthesis orientation.

In conclusion, lower limb morphology influenced WOMAC dimension scores in patients undergoing total knee arthroplasty, and health improved 12 months after TKA surgery.

46.4 Applications to Other Areas of Health and Disease

Our studies show that the morphology of the limb affects the results of surgery and surgical difficulties. This could be applicable to other orthopedic techniques in addition to TKA. Anthropometry can identify groups of patients that need more resources, and its application in improving outcomes may be useful in total hip arthroplasty, arthroscopy surgery, and in trauma surgery of the lower limbs and pelvis.

46.5 Practical Methods and Techniques

46.5.1 Determination of Knee Anthropometry

As shown in Fig. 46.1, the anthropometry of the lower limb takes into account the length of the leg and the circumferences of the knee. The length is determined by two easy-to-locate points: the anterior–superior iliac spine and the center of the ankle. The circumferences are determined at two points: the anterior tibial tuberosity and a point located 4 cm above the superior pole of the patella. The indexes are then calculated using the formulas:

Suprapatellar index: length of leg/suprapatellar circumference
Infrapatellar index: length of leg/infrapatellar circumference
Supra-/infrapatellar index: suprapatellar circumference/infrapatellar circumference.

Low suprapatellar or infrapatellar indexes indicate a short leg with a wide knee and more difficulties. These values are related to the BMI as shown in Table 46.2, although, in itself, the BMI is not a predictor of outcomes and difficulty in orthopedic surgery, as shown by the results of the first study.

Summary Points

- The body mass index is a measurement of body anthropometry, and is calculated as the relationship between weight and height.
- The body mass index classifies patients in four categories. Class II (BMI 35–40 kg/m^2) and III (BMI > 40 kg/m^2) indicate a greater risk of complications and possibly worse outcomes after total knee arthroplasty surgery.

- The distribution of body fat in obese individuals may be truncal or uniform, and the body mass index is not the only parameter that should be taken into account when predicting worse outcomes after total knee arthroplasty surgery.
- The morphology of the knee is important in total knee arthroplasty surgery, and determination of its anthropometry can help to detect patients, who may require more resources.
- When the fat concentration is predominantly in the thorax and abdomen, following a truncal pattern, the knee to operate does not usually present increased subcutaneous fat that would make the operation more difficult.
- In patients whose fat distribution is uniform in the trunk and limbs, following a generalized pattern, the knee circumference is increased by the accumulation of subcutaneous fat.
- The anthropometry of the knee is calculated as the relationship between the length of the leg and various circumferences of the knee, and determines two main indexes: the suprapatellar index and the infrapatellar index.
- A suprapatellar index less than 1.6 predicts more difficult surgery, and an infrapatellar index less than 1.75 predicts worse outcomes in total knee arthroplasty surgery.
- These indexes, together with the body mass index, help to more accurately detect patients at risk of more complications and poorer outcomes after surgery and the possible need for more resources.
- Determination of knee anthropometry before total knee arthroplasty surgery can improve results and patient satisfaction.

Key Features of the Suprapatellar Index

- The suprapatellar index is calculated by measuring the circumference of the knee at a point located 4 cm proximal of the superior pole of the patella with a metric tape measure.
- This value is divided by the length of the limb (obtained by the distance between the anterior superior iliac spine and the center of the ankle) is divided by the suprapatelar circumference to calculate the suprapatelar index.
- The suprapatellar index varies according to the BMI of the patient.
- The suprapatellar index classifies the knee to be operated, as liable to encounter greater or lesser difficulty.
- The lower the suprapatellar index, the greater the expected surgical difficulty.
- In our Western Mediterranean population, a value below 1.6 in the suprapatellar index forecasts greater surgical difficulty (longer surgical time) and the need for greater technological resources in the operating room.

Key Features of the Infrapatellar Index

- The infrapatellar index is calculated by measuring the circumference of the knee at the level of the anterior tibial tuberosity.
- The value of the length of the limb is divided by the infrapatellar circumference.
- The infrapatellar index varies acording to the BMI of the patient.
- Knees with an infrapatellar index less than 1.75 have worse functional results after total knee arthroplasty, as measured by the Western and McMaster Universities quality of life assessment scale.
- Patients with an infrapatellar index below 1.75 should be advised that the results expected after total knee replacement are worse than those expected in the general population.

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Chapter 47
Standardization of Sizes of Knee–Ankle–Foot Orthoses (KAFO) Through Anthropometry

L. Narendra Nath

Abstract Lower limb orthoses enable the locomotor disabled, who have flail or weak lower limbs, to ambulate. The medical causes for these disabilities are many out of which poliomyelitis, cerebral palsy, traumatic paraplegia are common. Though, poliomyelitis is almost eradicated in underdeveloped countries, it still remains a challenge to provide orthosis to the large number of people already affected by polio in childhood. It is also to be noted that such orthosis will need replacement once in 2 years on an average. Hence, there is a huge demand for orthoses year after year. One way to address this problem is to standardize the sizes of orthosis and manufacture cost effective and durable light weight calipers. In order to standardize the sizes of orthosis, there was a need to collect anthropometric data of polio affected lower limbs in different geographical areas and their analysis to arrive at standard sizes for polio affected lower limbs. Towards this, an anthropometric device (AD) was designed and developed to collect anthropometric data of feet and knees of the patients suffering from poliomyelitis. A modular concept in Knee–Ankle–Foot Orthosis (KAFO) was developed making use of this anthropometric data. The modules of this orthosis were essentially foot plate and knee piece in standardized sizes and lateral uprights of universal size which could be cut to the required sizes depending on the length of the lower limb. The anthropometric data led to the development of seven sizes for foot plates and six sizes for knee pieces which could cater to the needs of almost all the patients. These modules of the orthosis were produced by plastic injection moulding and compression moulding processes using glass fibre reinforced polypropylene. These components could be assembled into an orthosis in less than 2 h time whereas a thermoformed KAFO used to take 6–8 h for fabrication. Also, the need to make plaster of Paris replica of polio affected limbs, as in the case of thermoformed KAFO, was done away with saving both, time and cost. The results of field trail of these standardized KAFO were encouraging and it vindicated the concept of standardization of sizes.

Abbreviations

AD	Anthropometric device
CMM	Coordinate measuring machine
EVA	Ethylene vinyl acetate

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_47,

KAFO Knee–ankle–foot orthosis
MRI Magnetic resonance imaging
PoP Plaster of Paris
PP Polypropylene

47.1 Introduction

Mobility and communication are absolute requirements for the survival and welfare of every human being today. Most of the people with locomotor disability are not only deprived of these absolute requirements but also of their dignity because of their disability. In most cases, lack of mobility also makes them suffer from low self-esteem.

It is estimated that t-here are approximately 50 million locomotor-disabled people in the world. The medical causes for these disabilities are many. However, a significant number of them can be helped with their ambulation by providing them with a suitable orthosis. Most of the orthoses available currently are tailor-made, and it is a time-consuming process to make these orthosis for each and every needy person. It is also to be noted that fitment of the orthosis is not a one-time affair, as it has to be replaced at periodic intervals and maintained for effective usage. Hence, there is a huge and repeated demand for these orthoses. This mammoth task can be addressed by the standardization of orthoses, so that they can be provided off the shelf to the locomotor disabled at a low cost, with good quality and durability.

Poliomyelitis is one of the major causes of locomotor disability among the existing locomotor-disabled population in the world. In recent years, effective immunization programs have almost eradicated poliomyelitis. Still, there are millions of people who were victims of this infection in their childhood. Apart from poliomyelitis, people affected by cerebral palsy and paraplegia also form a sizable population of the locomotor disabled. Different kinds of orthoses are needed by these people. Many of them can be helped with the fitment of knee–ankle–foot orthoses (KAFO). Fitment of such a huge number of orthoses is possible only if their production is made easy by standardizing the sizes and also by simplifying the assembly technique. This task of standardizing is more challenging in case of polio-affected individuals, as the development of muscles, bones and joints is significantly affected by the severity of initial infection, and because of which the measurements of girth of limbs at various levels and their length vary grossly from individual to individual. To standardize the sizes for a lower limb orthosis in such individuals, an anthropometric survey of individuals affected by poliomyelitis in different geographical areas was needed. An analysis of these data was needed before standardizing the sizes.

Anthropometry is a branch of science, which has played a major role in understanding the region-wise behavior, functions, lifestyle, etc., of human beings (Churchill and McConville 1976). Anthropometric surveys for weight, strength, etc. are quite common. Generation of data on elderly persons and disabled, for the development of consumer products and devices (Chung and Weimar 1989); calculation of bone mass in the human body (Davis et al. 1999); cross-cultural investigation of the role of foot size in physical attractiveness (Fessler et al. 2005); garment design; calculation of human body surface area (Jianfeng and Hihara 2004), etc., have been reported.

The data generated through anthropometry form the basis for various studies, and benefit the society at large. The design specifications of the workplace have been drawn in the past for employees, based on the anthropometric data obtained regarding their physical ability and limitations (Boussena and Davies 1987). Similarly, the assessment of human obesity through the measurement of body composition has also been carried out (Mahoney et al. 1979). The role of anthropometry in rehabilitation research is quite large. The methods of dynamic anthropometry have been used in

ergonomics, and with suitable modifications, these methods have been used in rehabilitation. The measurements of movement of head, hand, foot, arm, and leg have formed the basis for the assessment of the efficiency of the rehabilitated part of body (Nowak 2003).

Anthropometry provides data on desired points in free space with their interrelation. An anthropometric device (AD) is an instrument, which generates data with respect to a fixed frame of reference of lower limbs of the locomotor disabled. These data could be processed to define various locations of the lower limb in terms of physical measurements. Further, these data could be useful in designing a KAFO in a modular form. In this study, the modular concept of KAFO was developed with standardization of the sizes of its modules. The standardized modules were foot plate, knee piece, and, later, uprights. The knee pieces and foot piece were joined together by universal size lateral uprights to form a KAFO. This standardization and modular concept enabled mass production of orthoses, which are cost-effective and easy of fit. The standardized KAFOs were fitted to sizable polio population to obtain their feedback. Later, the production of standardized KAFOs helped in the fitment of a huge number of individuals in need.

47.2 An Overview of the Locomotor Disabled

Reported disability prevalence rates from around the world vary dramatically, for example, from under 1% in Bangladesh (Bangladesh Bureau of Statistics 1987) and (Kenya Central Bureau of Statistics 1996) to 20% in New Zealand (Statistics New Zealand 1998). This variation is caused by several factors: differing definitions of disability, different methodologies of data collection, and variation in the quality of study design. Therefore, listing disability prevalence rates that are understandable and internationally comparable is a difficult task. This situation is made more complex as there is no comprehensive definition of disability, and the nature and severity of disabilities vary greatly. How the degree of disability is assessed also varies grossly, depending on the purpose for which it is done. The prevalence of disability in some selected countries is tabulated in Table 47.1.

Table 47.1 Prevalence of disability in selected countries

Censuses			Surveys		
Country	Year	Percent of population with a disability	Country	Year	Percent of population with a disability
United States	2000	19.4	New Zealand	1996	20.0
Canada	2001	18.5	Australia	2000	20.0
Brazil	2000	14.5	Uruguay	1992	16.0
United Kingdom	1991	12.2	Spain	1986	15.0
Poland	1988	10.0	Austria	1986	14.4
Ethiopia	1984	3.8	Zambia	2006	13.1
Uganda	2001	3.5	Sweden	1988	12.1
Mali	1987	2.7	Ecuador	2005	12.1
Mexico	2000	2.3	Netherlands	1986	11.6
Botswana	1991	2.2	Nicaragua	2003	10.3
Chile	1992	2.2	Germany	1992	8.4
India	2001	2.1	China	1987	5.0
Colombia	1993	1.8	Italy	1994	5.0
Bangladesh	1982	0.8	Egypt	1996	4.4
Kenya	1987	0.7			

Source: United Nations Statistics Division; IBGR (Brazil), INEC (Nicaragua), INEC (Ecuador), INEGI (Mexico), Statistics New Zealand, INE (Spain), Census of India 2001, SINTEF Health Research (Zambia) 2006

India has a sizable number of locomotor-disabled population. Poliomyelitis, injury other than burns, arthritis, and cerebral palsy are the main causes of locomotor disability in the country. It has been reported that people in the states of south, east, and central India are highly prone to incidence of various causes of disabilities. Overall, poliomyelitis (32%), injury other than burns (28%), other illness (12%), medical/surgical interventions (3%), burns (2%), arthritis (2%), and cerebral palsy (2%) are the major causes of locomotor disability among the working age disabled population (Patel 2009). As on date, approximately seven million poliomyelitis patients and three million amputees form a significant majority of the locomotor disabled in India.

47.3 Anthropometric Measurement

The anthropometric data have proved to be valuable in the field of medical sciences, ergonomics, apparel design, accessories design, automotives, and so on. The anthropometric surveys on range of motion have led to the rehabilitation of people with disabilities (Nowak 1996). There are many techniques for measuring the dimensions of the human body, ranging from usage of a measuring tape or scale, to a coordinate measuring machine (CMM), laser scanning technology, and magnetic resonance imaging (MRI) (Brown et al. 1995; Nishimura et al. 2005), depending upon the need and application. The measurement of external dimensions of the lower limb does not require tight tolerances. The important requirement is that the measurement should be systematic and could be correlated with other measured locations of the limb. Hence, an AD was designed and developed to measure the affected lower limb in a systematic and scientific way. The basic design principle of the AD was to provide data regarding the lower limb in well-defined coordinate system with a fixed frame of reference, so that the positions and locations of various parts of the limb can be correlated. Also, it was so designed that the data obtained from an AD would be useful inputs to design and develop orthoses in standard sizes. Apart from this, ease of portability and maintenance were desired design features of AD.

The materials for the manufacture of AD were chosen on the basis of their functional aspects, processability, durability, and cost, so that lightweight, portable, and cost-effective ADs could be manufactured. All the operations of ADs were mechanical in nature, and the AD provided data for the knee in terms of the cylindrical coordinate system (x, r, θ), and for the foot in terms of the Cartesian coordinate system (x, y, z) including equinus on the foot in degrees (θ) (Dwivedi et al. 2009). The major parts of the AD are listed in Table 47.2 and shown in Fig. 47.1.

The semi-cylindrical canopy assembly was made by fixing it on sliding sockets. The canopy, with the help of sliding probes, could define a point on the knee in terms of the cylindrical coordinate system. However, two side plates were mounted on sliding sockets and placed on the two parallel rails for generating a coordinate, in the Cartesian coordinate system, on any point on the foot. The side plates generated data on the medial and lateral sides of the foot. There was a back plate, which had a tilting mechanism with a protector fitted on its base. This plate was not allowed to slide but tilt. This plate enabled the measurement of degree of equinus of the foot. The pin probe could measure the location and depth of the medial arch.

Apart from the above advantages, the AD had some design limitations. These are mentioned below:

- Limbs having significant contractures were difficult to place in the AD.
- Feet having severe varus or valgus deformity were difficult to measure.

Table 47.2 Major parts of AD

S. No.	Components	Material	Dimension (mm)	No.
1	Base plate	E-glass reinforced polyester composites	1,000 × 275 × 18	1
2	Cylindrical canopy	Poly-methyl-metha-acrylate	Diameter: 200 Width: 80 Thickness: 5	1
3	Side plate	-do-	320 × 60 × 10	2
4	Back plate	-do-	-do-	1
5	Pin probe	Brass	Length: 150	5
6	Sliding rail	Mild steel	Length: 800	2
7	Sliding socket	-do-	Length: 50	4

Reproduced from Dwivedi et al. (2009)

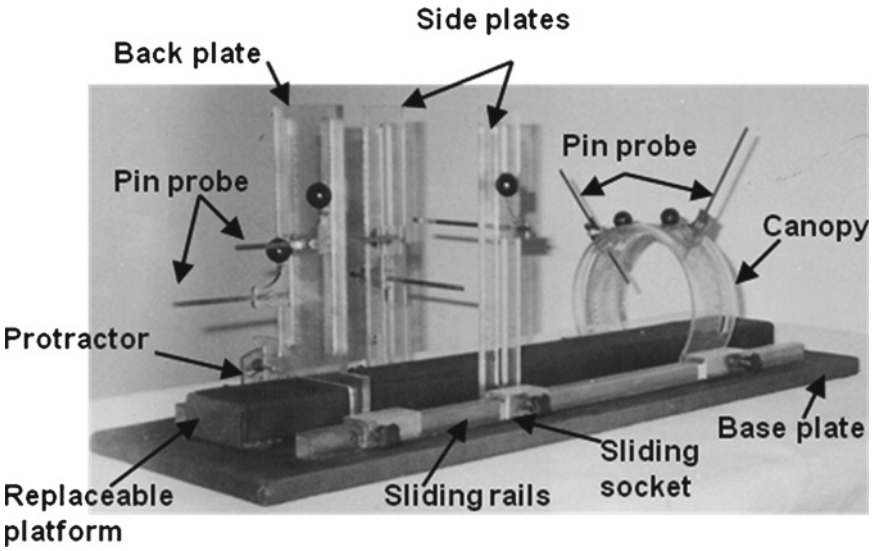

Fig. 47.1 Anthropometric device. (Reproduced from Dwivedi et al.2009)

- No movement of limb was permitted once it was placed and strapped in the AD.
- It was not possible to collect data for the thigh, as there were no well-defined points, such as bony prominences, present.

47.4 Modules of KAFO

The shape of all three KAFO modules originated from the topographical appearance of the knee and foot. Hence, a structure resembling a thin shell over the limb was conceived for the orthosis. The design of the orthosis was not only aimed at its performance but also at minimizing the cost and weight, ease of wearing, air circulation, ability to conceal it in the garment, and esthetic looks. The three modules, that is, foot plate, knee piece, and the lateral uprights, were designed on the basis of pressure-sensitive- and load-bearing parts of the lower limb of the locomotor disabled. Accordingly, enough allowances

were provided in the design of the orthoses. For all the standardized parameters, tolerance values were decided so that, at the time of fitment of an orthosis to a patient, modification and fine-tuning by thermoforming is possible for proper fitment.

47.5 Practical Methods and Techniques

47.5.1 Generation of Anthropometric Data

In order to collect data, the lower limb of a patient was placed on the AD in such a way that the sole of the foot touched the back plate. Then, the limb was tied with two Velcro straps, which were attached to the base plate, as shown in Fig. 47.2. This allowed no relative motion of the lower limb with respect to the AD.

The relevant points of foot and knee were identified. These are tabulated in Table 47.3. These relevant points were mostly the bony prominences.

The side plates and canopy were brought to the desired location on the limb and a pin probe was slid to touch the particular location. The data collection of knee and foot is shown in Figs. 47.3 and 47.4.

The tilt angle on the back plate provided the value of the θ–ordinate for equinus. The length of limb below knee was derived from the difference of the x-ordinate values of the epicondyles and heel. This enabled us to take all the coordinates of relevant points on the lower limb with respect to the fixed frame of reference. The anthropometric data for approximately 1,600 patients, of various age groups ranging from 3 to 60 years at different geographical locations in India, were generated in order to have a broad range of sample size. Accurate sampling is critical to the creation of a database. Sampling involves the process of selecting a group of individuals thought to be representative

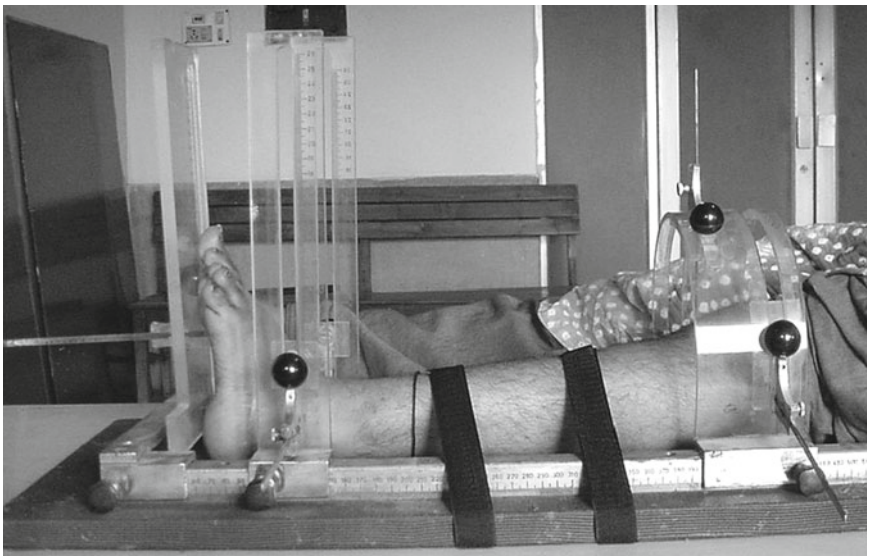

Fig. 47.2 Lower limb placed in an anthropometric device. (Reproduced from Dwivedi et al. 2009)

Table 47.3 Critical locations on foot and knee

S. No.	Foot	Knee
1	Head of first metatarsal	Medial epicondyle
2	Head of fifth metatarsal	Lateral epicondyle
3	Navicular bone	Top of the patella
4	Highest point of medial malleolus	Bottom of the patella
5	Medial point on the heel at bottom of calcaneous	Tibial tubercle
6	Lateral point on the heel at bottom of calcaneous	Head of fibula
7	Highest point of lateral malleolus	Any point on the medial side in the same plane as the tibial tubercle
8	Foot length	
9	Bottom of the medial arch	
10	Top of the medial arch	
11	Depth of the medial arch	
12	Angle of equines	

Reproduced from Dwivedi et al. (2009)

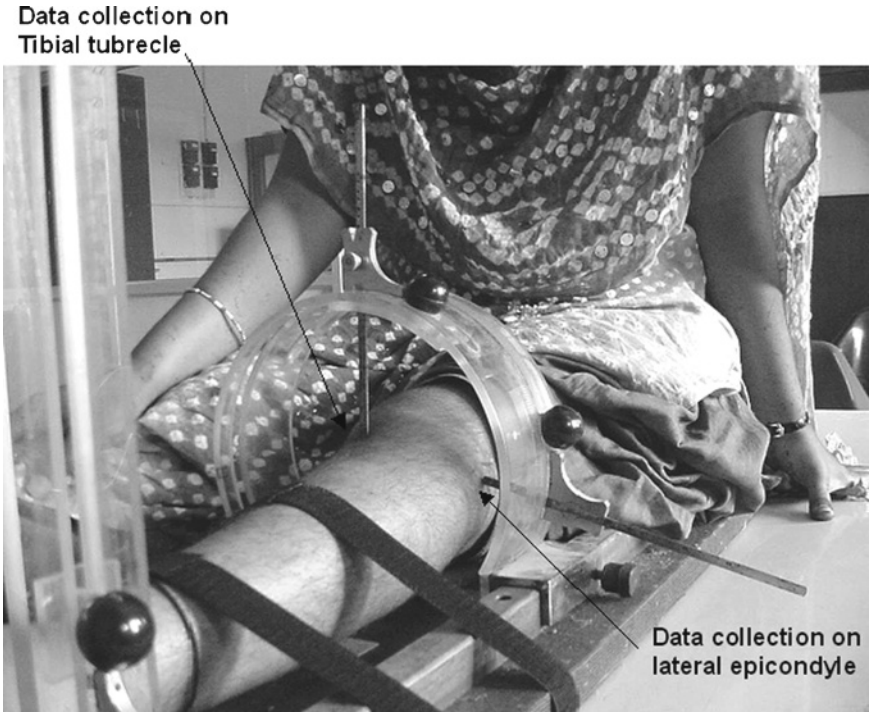

Fig. 47.3 Data collection on knee in an anthropometric device. (Reproduced from Dwivedi et al. 2009)

of an entire population (Churchill et al. 1988). During the collection of data, it was observed that the data collection for the patella was also critical, as it had to be accommodated in the knee piece without any pressure. Hence, the location of the top of the patella, with reference to epicondyles, was extrapolated in the direction of the *x*-axis. In the cases of poliomyelitis, it was observed that the size and location of the patella was not consistent with respect to epicondyles. Similarly, in the

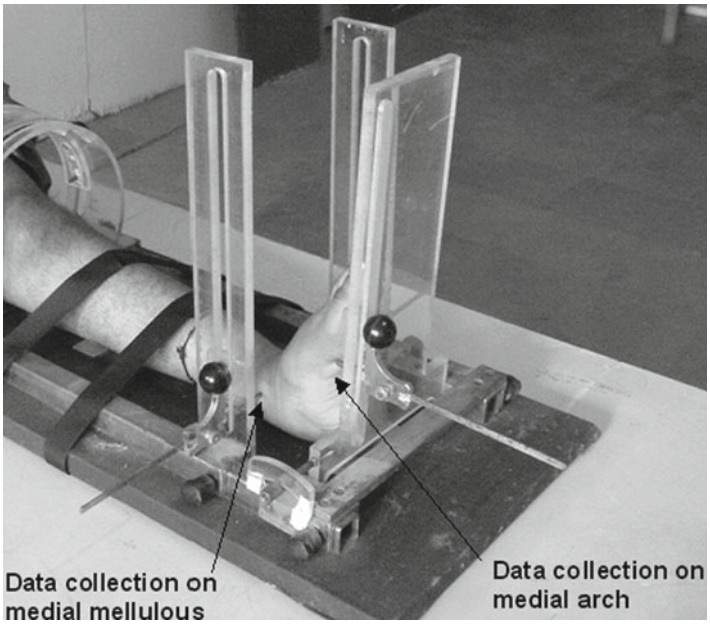

Fig. 47.4 Data collection on foot in an anthropometric device. (Reproduced from Dwivedi et al. 2009)

measurements of the foot, the variation in metatarsal width for the same foot span was observed. Also, variation in malleolus width, and offset between medial malleolus and lateral malleolus for the same heel width was observed. The analysis of these variations of parameters in the foot and the knee led to the finalization and implementation of tolerances in some of the parameters (refer to Tables 47.4 and Tables 47.5).

Two locations, namely navicular bone and head of fibula on the foot and knee, respectively, were pressure sensitive; hence, enough clearance in the orthosis was given at these locations, so that the orthosis did not hurt the users during walking. A point on the medial side was needed to arrive at the below-knee width; hence, any point on the medial side in the same plane as the head of the fibula was taken to arrive at below-knee width. Invariably, it was observed that below-knee width was much lesser than the epicondyle width in the cases of poliomyelitis; hence, this parameter was essential and measured. The knee pieces were designed for left and right sides in order to accommodate the medial epicondyle. These sides were mirror images of each other, whereas, in the foot plate, no side was assigned because the footprint for both the sides matched closely.

47.5.2 Standardization Methodology

Standardization is a method to define any product or system in terms of finite relevant parameters. In the case of locomotor disability, the big challenge is the diversity of the affected population. Disability may be caused by a variety of conditions. The quality of fitment of the KAFO mainly depends upon the fitting of the foot and the knee in the orthosis, and the alignment of orthotic knee joints, if any.

Table 47.4 Knee piece – standard sizes and their standardized parameters

	Standardized parameters				
Size no.	Width EC (mm)	Width BK (mm)	Height TP-ECL (mm)	Distance BP-TT (mm)	Height TP-TT (mm)
K1	38–50	34–44	18±4	17	3–4
K2	45–62	41–52	23±5	18	4–5
K3	63–73	57–67	31±5	19	5–6
K4	74–85	67–77	39±8	19	7
K5	86–98	77–87	47±6	20	8–9
K6	99–113	90–100	56±7	20	10–11

Reproduced from Dwivedi et al. (2009)
EC Epicondyle, *BK* Below knee, *TP* Top of patella, *ECL* Epicondyle line (an imaginary line which connects centers of the medial and lateral epicondyles), *BP* Bottom of patella, and *TT* Tibial tubercle

Table 47.5 Foot plate – standard sizes and their standardized parameters

	Standardized parameter									
				MT offset (mm)			MEL H (mm)		MEL offset (mm)	
Size no.	FL (mm)	HW (mm)	MTW (mm)	M	L	MELW (mm)	M	L	M	L	Equinus (degree)
F1	135	42 ± 3	56 ± 6	85–105	85–105	50 ± 3	85–110	85–110	34	33	8
F2	150	48 ± 3	64 ± 4	95–115	95–115	54 ± 4	90–125	95–125	37	37	10
F3	165	53 ± 3	69 ± 4	105–115	115–135	60 ± 4	105–135	105–135	40	39	15
F4	180	58 ± 2	76 ± 6	110–142	110–155	66 + 4	105–140	105–140	43	42	20
F5	195	63 ± 2	80 ± 5	115–150	125–160	71 + 4	110–140	110–146	44	45	20
F6	210	68 ± 2	87 ± 5	125–165	137–175	76 + 5	115–145	115–147	49	48	22
F7	225	74 ± 3	92 ± 5	137–170	140–185	81 + 4	115–145	120–145	50	50	25

Reproduced from Dwivedi et al. (2009)
FL Foot length, *HW* Heel width, *MTW* Metatarsal width, *MT* Metatarsal, and *MELH* Malleolus height, *M* medial, *L* Lateral.

The generation of specific computer programs for anthropometric surveys, and their analysis to achieve desired results have been reported (Nowak 1992). For this study, a computer program using C language was developed for computing the parameters, as tabulated in Table 47.3, using the coordinates measured from the AD. Appropriate calibration and correction factors relevant to the AD were also incorporated. The parameters so computed were invariant to the foot or knee regarding translation and rotation of the limb on the AD. All the parameters were grouped and categorized. The analysis of these parameters resulted in three modules, namely foot plate, knee piece, and pair of lateral uprights. These modules along with the KAFOs assembled from them are shown in Fig. 47.5.

The foot plate was standardized in seven sizes and the knee piece was standardized in six sizes with left and right sides (Dwivedi et al. 2009). The standard sizes for the knee piece and the foot plate along with their standardized parameters are tabulated in Tables 47.5 and 47.6, respectively. The lateral upright was made in one universal size as per the longest possible length measured in the anthropometric survey.

The three standardized modules for all sizes were mass produced using the materials and technologies mentioned in Table 47.7. The modules of KAFO were assembled by thermoplastic hot-air welding using polypropylene homopolymer filler wire.

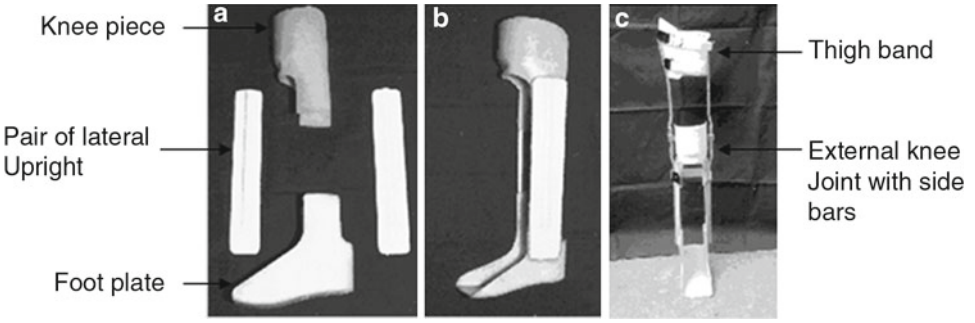

Fig. 47.5 (**a**) Modules of standardized modular KAFO; (**b**) assembled modules of KAFO; and (**c**) KAFO with external knee joints and thigh band. (Reproduced from Dwivedi et al. 2009)

Table 47.6 Material and technologies for the production of standard modules of KAFO

S. No.	Module	Material	Technology
1	Foot plate and knee piece	E-glass staples-reinforced polypropylene	Injection molding
2	Lateral uprights	E-glass fabric-reinforced polypropylene sandwich composite	Compression molding
3	KAFO assembly	Polypropylene homopolymer	Hot air welding

Reproduced from Dwivedi et al. (2009)

Table 47.7 Tabulated periodic feedback

		Periodic feedback (in months)							
S. No.	Parameter	1/2	1	3	6	12	18	24	30
1	No. km. walked per day								
2	Appearance of KAFO								
3	Gait pattern								
4	Wear of sole of the shoe								
5	Breakage or dewelding (specify the location)								
6	Any noise during walking								
7	Any pressure on limb (specify the location)								
8	Any rubbing on the limb (specify the location)								
9	Terrain of walking (flat/uneven/muddy/marshy)								
10	Reaction on walking(staircase/ramp/wet surfaces)								
11	Any other point								

Reproduced from Dwivedi et al. (2009)

47.6 Fitment and Field Trail of Standard Modular KAFO

The modules were assembled into KAFO and fitted to patients after checking the size of the limb of the locomotor disabled. Metallic knee joints and thigh bands were provided where thigh muscles were frail. The total time taken was approximately 1 h for fabrication and fitment of orthosis. It was desirable to wear a pair of shoes with a KAFO, and the locomotor disabled could wear the shoes of their choice, which appealed to them esthetically. They were advised not to wear shoes with high heels.

The medial arch was absent in the majority of polio cases, and wherever it was present, a medial arch carved out of polyethylene vinyl acetate (EVA) microcellular rubber was adhesively bonded on the

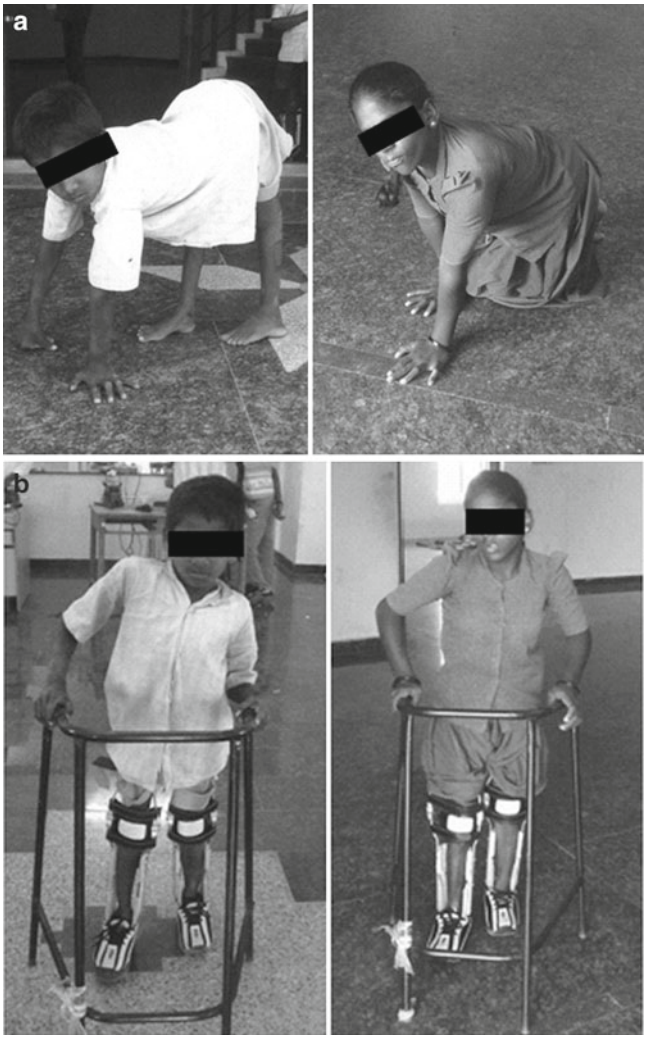

Fig. 47.6 (**a**) Locomotor disabled without orthosis; and (**b**) Walking with KAFO. (Reproduced from Dwivedi et al. 2009)

foot plate at the desired location. Feedback was obtained from a group of captive locomotor disabled persons fitted with standardized modular KAFO, all over the country. The life of a KAFO was predicted to be more than 2 years on the basis of fatigue life of the glass-reinforced polypropylene used for its manufacture. So far, more than 26,000 such orthoses have been fitted all over India. In most of the cases, the KAFO lasted approximately two and half years. The first sign of failure was observed on the foot plate either at the metatarsal or the ankle region. A few failures were reported due to accidents.

A systematic feedback was obtained in a proforma, which had two parts. The first part covered personal details, medical history, muscle chart, previous orthosis used (if any) and tabular periodic feedback along with the comments of the orthotist. The second part consisted of a tabular periodic feedback proforma shown in Table 47.7. This proforma also covered the information on walking terrain (flat/uneven/muddy/marshy) and reaction on walking on staircase, ramp, and wet surfaces.

Two sample cases, suffering from poliomyelitis and fitted with standardized KAFOs, are shown in Fig. 47.6. These patients are satisfied with the standardized KAFO and have started leading a near-normal life. The efficacy of the standardized KAFO is evident by the patients changed postures of walking, as shown in Fig. 47.6b).

The feedback obtained on the standardized KAFO was satisfactory and it indeed helped many in improving their socioeconomic status. Due to the affordable price, light weight, lesser fitment time, durability, and esthetic look, it was accepted and used by the locomotor disabled. It was reported in feedback that many children joined school and adults were able to perform better at the workplace due to the enhanced mobility after the fitment of the standardized modular KAFO. This orthosis has certainly shown a way to tackle the challenge of mass fitment of orthoses in the shortest possible time.

47.7 Application in Other Areas of Health and Disease

The concept of anthropometry, using simple probes and an easy-to-understand mechanism, has shown that ADs could be designed and developed for the collection of data from any part of the body with good accuracy. With some design modifications in the AD, accurate data on the spine could be generated for making suitable splints. This concept of the AD will enable the medical fraternity to map any part of the body, for its topography, in three dimensions. The standardization concept generated for KAFOs may have future applications in solving problems concerning lower limb fractures, walking aids for paraplegics and old aged persons, etc. It helps in designing footwear for diabetics and leprosy patients. The data can also be generated for standardization of sizes for lower limb prosthesis. Similarly, braces and splints for the hand can be fabricated or standardized for orthotic and prosthetic applications.

47.8 Conclusion

Anthropometry is the basis for standardization of clothing, consumer goods, public utilities, transportation, and so on (Tikuisis et al. 2001). Anthropometric data obtained through the AD was utilized in standardization of sizes of KAFO modules. The KAFOs so designed were fitted to thousands of patients with a satisfactory outcome.

The evolution of seven standard sizes in the foot and six standard sizes in the knee has accelerated the pace of the fitment of orthosis to the locomotor disabled. This endeavor has brought many locomotor-disabled persons into the mainstream of life.

Summary Points

The outcome of anthropometry and size standardization is summarized below:

- Anthropometric measurements, with respect to a fixed frame of reference, have provided data of not only the particular location but also their interrelation with other locations.
- The design of the AD is made versatile with an ease of operation so that it could be used to collect anthropometric data of the upper limbs too. If the diameter of the canopy is increased and its platform is extended, then it can provide anthropometric data for the entire human body.
- For the first time, a modular concept was developed in lower limb orthosis through an anthropometric analysis. Also, standardization of sizes of KAFO was made possible through anthropometric data.
- The standardization of KAFO has decreased the fabrication and fitment time from 8 h to less than 2 h. Also, the additional cost and time to make a PoP replica has been eliminated, as the modules of standardized KAFO were made available off the shelf.

- The standardized KAFO is a well-engineered product. It is durable, light in weight, and cost-effective. The life of standardized KAFO is above 2 years.
- The response of the patients using standardized KAFO is quite encouraging.

Acknowledgments The author wishes to thank Mr. Mayank Dwivedi and Mr. K.D. Shetty for their cooperation and support throughout this work. He thanks Dr. A. Sivathanu Pillai, Dr. D. Prasada Rao, Dr.V.B.N. Prasad Rao, Mr. S.S. Chandran, and Mr. G.V. Rao for their invaluable suggestions in completing this work.

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Chapter 48
Sex Differences and Age Changes in Digit Ratios: Implications for the Use of Digit Ratios in Medicine and Biology

John T. Manning

Abstract The term digit ratio is often taken to mean the ratio of the lengths of the second and fourth digits (2D:4D). This ratio has been reported to show sex differences such that on average males have longer fourth digits relative to their second digit than do females. The sex difference in 2D:4D appears in the foetus as early as the ninth week, it is found in infants, children and adults, and the 2D:4D of infants is strongly correlated with their 2D:4D when they become adults. The sex difference results from a different male and female growth trajectory of 4D relative to 2D. It has been suggested that the sex dependent growth trajectory of 4D relative to 2D is the consequence of the effects of prenatal testosterone (PT) relative to prenatal estrogen (PE) on finger growth, such that high PT and low PE may result in low values of 2D:4D. Excluding the thumb, the fingers show six ratios and a number of these show sex differences. However, only 2D:4D, 2D:3D and 3D:4D show both sex differences and are relatively stable with growth in children. Therefore, 2D:4D, 2D:3D and 3D:4D are the most likely digit ratios to reflect levels of prenatal sex steroids. Diseases that show a sex difference in their expression may be influenced by PT and PE. Most work has concentrated on 2D:4D and its links to developmental disorders (e.g. autism, Asperger's syndrome and ADHD), cardio-vascular disorders (e.g. MI), cardiovascular efficiency (e.g. running speed), and cancers (e.g. breast and cervical cancer). Further work is necessary to quantify the strength of such links in order to establish whether 2D:4D may be of predictive value for these diseases. In addition other links with such diseases as prostate cancer are likely to be investigated.

Abbreviations

2D	Second finger or digit, the 'index finger'
3D	Third finger or digit, the 'middle finger'
4D	Fourth finger or digit, the 'ring finger'
5D	Fifth finger or digit, the 'little finger'
2D:4D	The ratio between the length of 2D and 4D
2D:3D	The ratio between the length of 2D and 3D
2D:5D	The ratio between the length of 2D and 5D

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_48,

3D:4D The ratio between the length of 3D and 4D
3D:5D The ratio between the length of 3D and 5D
4D:5D Ratio between the length of 4D and 5D

48.1 Introduction

It has been known for more than 100 years that the relative lengths of the second and fourth digits show a sex difference such that men tend to have longer fourth digits relative to their second digits than do women (Baker 1888). This dimorphism may be seen clearly in some 'extreme' male and female hands. In the male hand, the tip of the fourth or ring finger extends beyond the tip of the second or index finger, whereas in the female hand, the tip of the second finger extends beyond that of the fourth finger. The sex difference may be measured by comparing the distal extents of the second and fourth finger to each other, or by a comparison to the distal extent of the third or middle finger (e.g. Manning 2002; Peters et al. 2002). An alternative method of comparison is to calculate the ratio of the length of the second and fourth digits (2D:4D).

The sex difference in 2D:4D is of small to medium effect size (Cohen's *d*, 0.20–0.50; Manning 2002). However, of late, attention has been directed towards this sexual dimorphism because it has been suggested that it may reflect sex differences in the levels of prenatal testosterone (PT) and prenatal estrogen (PE). That is, high PT and low PE are suggested to be causally related to low values of 2D:4D, and low PT and high PE to be causally related to high values of 2D:4D (Manning et al. 1998; see Table 48.1 for key features of testosterone of PT and adult testosterone). If this proves to be the case, 2D:4D could be a useful biomarker for a number of diseases, such as breast and cervical cancer and myocardial infarction, with an aetiology associated with in utero sex steroid levels (Manning 2002). In support of this suggestion, lower 2D:4D in males compared to females has been described in the 2D:4D of foetuses (Malas et al. 2006), in children (Manning et al. 1998, 2004) and in adults across ethnicities and countries (Manning et al. 2007). In addition, longitudinal studies have shown 2D:4D in infants and children to be strongly related to subsequent 2D:4D after development across puberty and into early adulthood (McIntyre et al. 2005; Trivers et al. 2006).

Of course, there are other finger ratios to consider. Excluding the first digit or thumb (which lacks clearly defined basal creases), there are in total six digit ratios (2D:4D; 2D:3D; 2D:5D; 3D:4D; 3D:5D and 4D:5D). Adult sex differences have been described in a number of these ratios (McFadden and Shubel 2002). However, we do not know whether they show sexual dimorphism in the foetus, or whether they are relatively stable with growth.

Here, I consider sex differences and age changes in digit ratios. In particular, I concentrate on the implications of my findings with regard to the use of digit ratios as biomarkers for diseases that have their origins in utero.

Table 48.1 Key features of testosterone

Key features of testosterone
Testosterone is a steroid hormone, which is synthesised from cholesterol.
It is produced by the testes, the ovaries and the adrenal glands.
In the foetus, testosterone production peaks at 8–12 weeks.
At 8–12 weeks, testosterone levels are higher (3–4×) in males compared to females.
Prenatal testosterone (PT) is thought to have gender-identity effects on the brain.
PT also controls the formation of the genitalia (penis and scrotum) and prostate gland.
The second developmental peak of testosterone is at puberty.
Adult males produce substantially more testosterone (40–60×) than females.

Sites of synthesis and aspects of testosterone produced prenatally (PT) and by the adult

48.2 The Measurement of Digit Ratios and Its Relationship to Sex Differences

I am concerned here with the measurement of digit lengths and their use in the calculation of digit ratios. Digit length may be measured from soft-tissue markers, such as the ventral crease proximal to the palm and the tip of the finger (Manning et al. 1998), or from X-rays of the bones of the finger (McIntyre et al. 2005). With regard to the former method, finger length may be measured directly from the fingers, or indirectly from 2D representations of the finger in photocopies, scans or photographs of the hands. The measurement of digit ratios requires that very small differences between fingers be accurately captured. Widespread inaccuracy in the measurement of finger differences may lead to high frequencies of null findings and failure to replicate studies. In regard to this, there is concern that two-dimensional images of fingers are not sufficiently accurate representations of three-dimensional fingers. Manning et al. (2005), reporting on data from a UK population, have shown that the direct method yields higher mean values of 2D:4D than does the indirect method. This finding has been replicated in populations in the UK (Burriss et al. 2007; Caswell and Manning 2009), Germany (Fink et al. 2006) and the USA (Allaway et al. 2009). However, one 'group' has reported a number of non-replications of these findings in Austrian samples (e.g. Voracek and Dressler 2006). The implications of this discrepancy with regard to the accuracy of 2D:4D are not yet clear, and is likely to be a focus of further study. One particular point of concern that is relevant to this chapter is the finding that the distortional effect of indirect measurement is greater for males than for females. Thus, indirect measurement of finger length may increase the sexual dimorphism of 2D:4D (Manning et al. 2005). At present, we should accept 2D:4D data from indirect measurements of fingers, but avoid mixing such data with 2D:4D from direct finger measurement. However, we need to bear in mind that distortions in data from indirect measurements may be complex and not readily adjusted by simple arithmetical means. Whether similar distortional effects are seen in indirect methods with regard to ratios other than 2D:4D is not yet known. This question will have to be carefully addressed by a number of 'groups' before we get an accurate picture. For the time being, digit ratios from indirect finger measurements should not be mixed with digit ratios from direct measurements.

48.3 Sex Differences in 2D:4D

There have been many studies that have reported significant sex differences in 2D:4D, such that males tend to have lower 2D:4D than females (for reviews see: Manning 2002; Peters et al. 2002). The sexual dimorphism is widespread, and although there are marked ethnic differences in 2D:4D, the sex difference is seen across the macro-ethnic groups of Caucasians, Blacks and East Asians, and across countries with similar ethnicities (Manning et al. 2007).

It has been suggested that lower 2D:4D in males compared to females originates at the end of the first trimester (Manning et al. 1998). The development of fingers and the urinogenital system is under the control of two groups of *Homeobox* genes (*Hoxa* and *Hoxd*). Interaction between hormonal products of the urinogenital system (including PT and PE) and *Hox* genes may then result in patterns of finger growth that correlate with concentrations of PT and PE (Manning et al. 1998). Studies of foetuses have confirmed that 2D:4D is sexually dimorphic, such that males have lower 2D:4D than females (Malas et al. 2006). Therefore, very early growth of 2D relative to 4D does show sex differences at a time when sexual dimorphism of absolute finger length is not strong.

In order to consider sex-dependent patterns of 2D relative to 4D length, I considered sex differences in a sample of adult Caucasian males and females from Hertfordshire. There were 748 participants (344 males) in the sample recruited from a large number of geographically widespread sites. Therefore, for ease of measurement, finger length was measured indirectly from photocopies of the ventral surface of the hands. Repeatabilities for 2D:4D were high, with intraclass correlations for right 2D:4D of $r_1 = 0.96$, $p = 0.0001$, and for left 2D:4D of $r_1 = 0.941$, $p = 0.0001$. As expected, there were sex differences in mean 2D:4D, such that males had lower mean 2D:4D compared to females in both hands (right hand 2D:4D, males 0.949 ± 0.036SD, females 0.961 ± 0.036, $t = 4.7$, $p = 0.0001$: left hand 2D:4D, males 0.939 ± 0.031SD, females, 0.952 ± 0.031SD, $t = 5.48$, $p = 0.0001$). With regard to the relationship of 2D regressed on 4D, there was evidence of sex differences in both the slope and the *Y*-intercept, and these were significant for left 2D:4D and close to significance for right 2D:4D. Thus, for the left hand, the equation for the line of 2D regressed on 4D was $y = 0.74x + 16.069$ for males, and $y = 0.823x + 9.556$ for females (females vs. males: slope −6.513 ± 3.23SE, $t = 2.02$, $p = 0.04$; *Y*-intercept 0.08 ± 0.042, $t = 1.99$, $p = 0.047$: Fig. 48.2). Because males had a higher *Y*-intercept and lower slope than females, the regression lines crossed with the intersection at 4D = 16.069 – 9.556/0.823 – 0.74 = 78.47 mm. For the right hand, the equation for the regression line was $y = 0.722x + 18.239$ for males and $y = 0.805x + 11.492$ for females (females vs. males: slope −6.748 ± 3.501SE, $t = 1.93$, $p = 0.054$; *Y*-intercept 0.08 ± 0.045SE, $t = 1.842$, $p = 0.07$). The intersection of male and female regression lines occurred at 4D = 81.29 mm.

If we know the regression line of 2D on 4D, we can calculate the average 2D:4D for each value of 4D. Figure 48.3 shows this for the left hand. Note that 2D:4D reduced with an increase in 4D; this is because 2D tended to be shorter than expected when 4D was long. The differences in slope and *Y*-intercept of males and females resulted in higher 2D:4D for males compared to females, when 4D was shorter than the 4D point of intersection (4D = 78.47 mm), and in lower 2D:4D for males compared to females when 4D was higher than the point of intersection. Overall, males had longer 4D than females. That is, on either side of the intersection point, there were 350 females and 108 males with 4D < 78.47 mm, and 236 males and 54 females with 4D > 78.47 mm. Therefore, males tended to have lower 2D:4D than females because growth patterns of 2D relative to 4D resulted in sex differences in the slope and *Y*-intercept of 2D on 4D. There was no evidence in this sample for the suggestion that males and females share a common regression line of 2D on 4D, as suggested by Kratochvil and Flegr (2009) (Fig. 48.1).

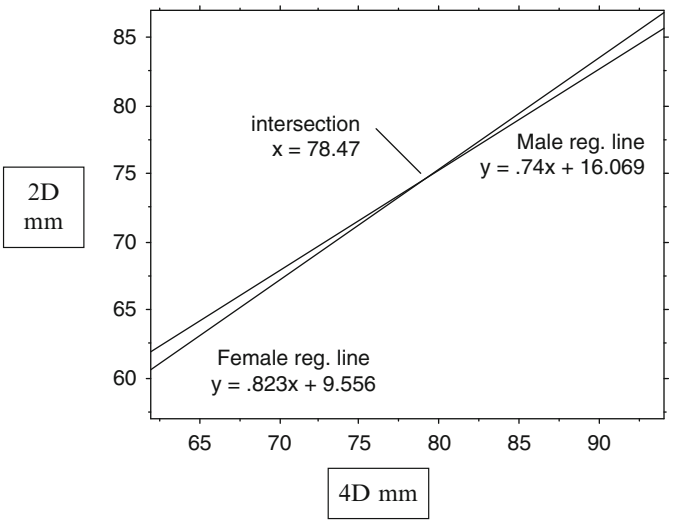

Fig. 48.1 Regression lines of left 2D on left 4D for males and females. The sample consisted of males ($n = 344$) and females ($n = 404$). Males had a significantly lower slope and a significantly higher *Y*-intercept than females. This meant the regression lines intersected (in this case at 4D = 78.47 mm)

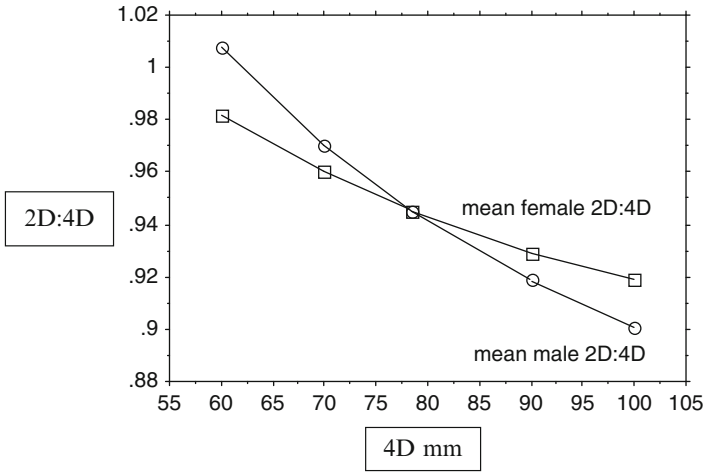

Fig. 48.2 The relationship between 4D length and mean 2D:4D. The sample consisted of 344 males and 404 females. Note that 2D:4D showed no sex difference at the value of 4D where male and female regression lines for 2D on 4D intersect (in this case at 78.47 mm). Below this value of 4D, females had lower 2D:4D than males. Above this value, they had higher 2D:4D than males and the sex difference in 2D:4D increased in size with increasing 4D

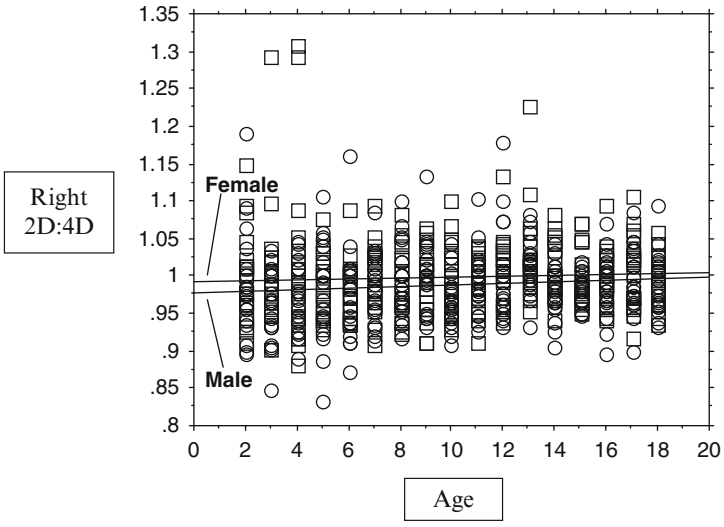

Fig. 48.3 The relationship between right 2D:4D and age (2–18 years). The sample was 340 males and 340 females. Note, there was a significant tendency for 2D:4D to be higher in females compared to males and 2D:4D tended to rise with age, but this tendency was non-significant. Thus, mean 2D:4D from 2 to 18 years showed sex differences but no age differences

48.4 Prenatal Sex Steroids and 2D:4D

Prenatal sex steroids, particularly prenatal testosterone (PT) and prenatal estrogen (PE), are thought to have important organising effects on foetal body systems. The evidence that 2D:4D is a negative proxy for levels of PT, and a positive proxy for PE, derives from studies of direct manipulation of sex steroids in animal foetuses and correlational studies in humans. Here, for brevity, I consider only the more important aspects of this evidence.

Manipulation experiments have been performed in birds and rats. In the former, increases in testosterone in the eggs of pheasants resulted in a significant increase in toe 2D:3D ratio and a non-significant increase in 2D:4D (Romano et al. 2005). With regard to PE, there was significant reduction in 2D:4D and 2D:3D when oestrogen was added to pheasant eggs (Saino et al. 2007).

In rats, exogenous testosterone applied to foetuses increased the length of forelimb 4D, but did not affect 2D. Thus, forelimb 2D:4D was reduced by PT (Talarovicova et al. 2009). In addition, it is known that foetal testosterone is reduced by alcohol, and rat foetuses exposed to alcohol showed a significant reduction in forelimb 2D:4D (McMechan et al. 2004).

A large number of studies of a correlational nature have suggested a link between 2D:4D and prenatal sex steroids. Perhaps most persuasive in this regard are the reports that 2D:4D is linked with congenital adrenal hyperplasia (CAH). Children with CAH have enlarged adrenals and produce high levels of prenatal androgens. In three studies, 2D:4D was reported to be lower in children with CAH than in healthy controls (Okten et al. 2002; Brown et al. 2002; Ciumas et al. 2009).

48.5 Sex Differences and Age Changes in Digit Ratios

In addition to 2D:4D, there are five other digit ratios (I have excluded the thumb because soft-tissue markers for measurement are not easily discerned in 1D). These are: 2D:3D, 2D:5D, 3D:4D, 3D:5D and 4D:5D. Adult sex differences have been noted in some of these ratios (McFadden et al. 2002).

Here, I consider all six ratios for evidence of sex differences and stability with growth. My sample was 680 Caucasian participants (340 males) from the northwest area of England (see Manning et al. 1998 for a description of the sample). The age range was 2–18 years, with 40 participants (20 males) per year group. Finger lengths (2D, 3D, 4D and 5D) were measured directly on the fingers using vernier callipers measuring to 0.1 mm. The influence of sex and age was tested (2 × 17 ANOVA) on all 12 finger ratios (six right hand and six left hand ratios). The results are shown in Table 48.1, and the mean ratios by sex and age are shown in Tables 48.2 and 48.3. If ratios are to be useful as prenatal indicators of sex steroids, they should ideally show significant sex differences but non-significant age changes. I found three ratios that fulfilled or nearly fulfilled these criteria (2D:4D right, sex $p = 0.0008$, age $p = 0.10$; 2D:3D right, sex $p = 0.03$, age $p = 0.06$; 3D:4D right, sex $p = 0.053$, age $p = 0.23$: see Table 48.2 for mean ratios). Note that these ratios are not

Table 48.2 The influence of sex and age on 12 finger ratios

	Sex		Age		Interaction	
Ratio	*F*	*p*	*F*	*p*	*F*	*p*
2D:4D right	11.35	0.0008	1.49	0.10	0.70	0.81
2D:4D left	14.80	0.0001	2.68	0.0004	0.79	0.69
2D:3D right	4.75	0.03	1.60	0.06	0.60	0.89
2D:3D left	15.26	0.0001	6.94	0.0001	3.39	0.0001
2D:5D right	20.96	0.0001	2.82	0.0002	1.27	0.21
2D:5D left	16.86	0.0001	4.15	0.0001	0.98	0.48
3D:4D right	3.76	0.053	1.24	0.23	0.33	0.99
3D:4D left	0.20	0.65	4.59	0.0001	3.25	0.0001
3D:5D right	12.12	0.0005	4.70	0.0001	1.10	0.35
3D:5D left	3.15	0.08	7.95	0.0001	1.04	0.41
4D:5D right	5.11	0.02	3.80	0.0001	1.40	0.14
4D:5D left	2.12	0.15	4.49	0.0001	0.86	0.62

The ratios comprised six from the right hand and six from the left-hand ratios in a sample of 680 Caucasian participants (340 males) aged from 2 to 18 years

Table 48.3 Mean digit ratios (2D:4D, 2D:3D and 3D:4D) across age groups

	2D:4D Right		2D:4D Left		2D:3D Right		2D:3D Left		3D:4D Right		3D:4D Left	
Age	m	f	m	f	m	f	m	f	m	f	m	f
2	0.988	0.999	1.005	1.007	0.911	0.911	0.924	0.910	1.085	1.095	1.090	1.109
	±0.016	±0.014	±0.016	±0.012	±0.011	±0.011	±0.017	±0.012	±0.014	±0.013	±0.014	±0.016
3	0.963	1.002	0.966	0.991	0.888	0.888	0.904	0.894	1.084	1.098	1.071	1.110
	±0.011	±0.018	±0.009	±0.013	±0.007	±0.007	±0.010	±0.007	±0.009	±0.019	±0.012	±0.014
4	0.975	1.006	0.989	0.985	0.904	0.904	0.903	0.914	1.083	10.102	1.097	1.078
	±0.010	±0.025	±0.011	±0.013	±0.015	±0.015	±0.008	±0.014	±0.016	±0.020	±0.012	±0.008
5	0.982	0.988	0.973	0.977	0.898	0.898	0.903	0.901	1.094	1.090	1.077	1.085
	±0.015	±0.009	±0.010	±0.008	±0.011	±0.011	±0.007	±0.007	±0.013	±0.006	±0.009	±0.008
6	0.978	0.979	0.979	0.967	0.906	0.906	0.901	0.896	1.079	1.076	1.088	1.080
	±0.014	±0.009	±0.013	±0.009	±0.012	±0.012	±0.010	±0.008	±0.005	±0.008	±0.013	±0.010
7	0.984	0.999	0.973	0.986	0.903	0.903	0.891	0.898	1.090	1.095	1.094	1.098
	±0.010	±0.010	±0.010	±0.008	0.007	0.007	±0.009	±0.006	±0.007	±0.006	±0.009	±0.007
8	0.995	0.988	0.977	0.992	0.905	0.905	0.894	0.906	1.101	1.096	1.093	1.095
	±0.010	±0.010	±0.007	±0.009	0.007	0.007	±0.007	±0.006	±0.012	±0.011	±0.007	±0.007
9	1.000	0.995	0.971	0.985	0.922	0.922	0.890	0.895	1.085	1.097	1.091	1.100
	±0.010	±0.010	±0.011	±0.010	0.008	0.008	±0.008	±0.006	±0.007	±0.009	±0.008	±0.010
10	0.966	1.000	0.972	0.993	0.896	0.896	0.895	0.901	1.079	1.100	1.086	1.103
	±0.007	±0.010	±0.008	±0.010	±0.005	±0.005	±0.006	±0.008	±0.006	±0.010	±0.011	±0.008
11	0.991	0.992	0.976	0.980	0.911	0.911	0.891	0.906	1.090	1.084	1.097	1.082
	±0.009	±0.008	±0.008	±0.011	±0.010	±0.010	±0.009	±0.008	±0.010	±0.008	±0.010	±0.011
12	1.002	1.014	0.999	1.020	0.916	0.916	0.924	0.926	1.093	1.108	1.082	1.102
	±0.014	±0.010	±0.012	±0.013	±0.009	±0.009	±0.009	±0.012	±0.010	±0.009	±0.016	±0.010
13	1.014	1.026	1.008	1.010	0.918	0.918	0.914	0.920	1.105	1.110	1.103	1.099
	±0.008	±0.013	±0.011	±0.009	±0.006	±0.006	±0.009	±0.008	±0.009	±0.012	±0.009	±0.009
14	0.982	1.010	0.979	1.013	0.907	0.907	0.897	0.923	1.083	1.089	1.091	1.097
	±0.008	±0.008	±0.010	±0.010	±0.005	±0.005	±0.005	±0.006	±0.008	±0.007	±0.008	±0.008
15	0.983	0.997	0.976	1.007	0.913	0.913	0.906	0.922	1.077	1.091	1.078	1.093
	±0.005	±0.009	±0.006	±0.008	±0.004	±0.004	±0.007	±0.005	±0.006	±0.011	±0.006	±0.008
16	0.989	0.998	0.985	1.000	0.916	0.916	0.913	1.000	1.079	1.085	1.078	1.000
	±0.009	±0.008	±0.010	±0.008	±0.007	±0.007	±0.006	±0.008	±0.009	±0.008	±0.006	±0.0004
17	0.994	1.003	0.981	1.004	0.924	0.924	0.914	0.931	1.076	1.078	1.074	1.079
	±0.009	±0.011	±0.008	±0.010	±0.006	±0.006	±0.005	±0.006	±0.004	±0.009	±0.007	±0.008
18	0.990	0.998	0.971	0.991	0.916	0.916	0.910	0.924	1.080	1.085	1.068	1.074
	±0.009	±0.007	±0.007	±0.007	±0.006	±0.006	±0.008	±0.008	±0.006	±0.005	±0.008	±0.007
Mean ratio	0.987	1.000	0.981	0.995	0.909	0.915	0.904	0.916	1.086	1.093	1.086	1.087
	±0.003	±0.003	±0.002	±0.002	±0.002	0.002	0.002	0.002	0.002	0.003	0.002	0.003

Mean digit ratios (±SE) by sex and age across 17-year groups (2–18 years) for right and left digit ratios 2D:4D, 2D:3D and 3D:4D

independent of each other, so that they share at least part of the variance for the influence of sex and age. On this point, the interdependence may also arise because fingers sit next to each other and share developmental trajectories. For example, 2D:4D and 3D:5D do not share fingers, but, in these data, they are positively correlated (right hand, 2D:4D and 3D:5D $r = 0.14$, $p = 0.0002$: left hand, 2D:4D and 3D:5D $r = 0.08$, $p = 0.04$). Considering ratios other than 2D:4D, 2D:3D and 3D:4D, many showed significant age effects, suggesting that they were unlikely to be reliable proxies for prenatal sex steroid levels (for mean ratios see Table 48.4). It is appropriate to point out at this stage that these data are cross-sectional and not longitudinal. It is of course preferable to consider change in ratios in the latter type of data rather than in the former. McIntyre et al. (2005) did

Table 48.4 Mean digit ratios (2D:5D, 3D:5D and 4D:5D) across age groups

	2D:5D Right		2D:5D Left		3D:5D Right		3D:5D Left		4D:5D Right		4D:5D Left	
Age	m	f	m	f	m	f	m	f	m	f	m	f
2	1.234 ±0.023	1.290 ±0.024	1.273 ±0.024	1.287 ±0.024	1.357 ±0.022	1.411 ±0.019	1.380 ±0.019	1.418 ±0.029	1.250 ±0.012	1.291 ±0.016	1.268 ±0.017	1.278 ±0.018
3	1.203 ±0.021	1.236 ±0.015	1.217 ±0.025	1.245 ±0.023	1.357 ±0.023	1.355 ±0.017	1.347 ±0.026	1.393 ±0.024	1.250 ±0.017	1.238 ±0.017	1.260 ±0.027	1.257 ±0.022
4	1.243 ±0.020	1.274 ±0.025	1.237 ±0.021	1.261 ±0.018	1.380 ±0.025	1.398 ±0.027	1.371 ±0.022	1.382 ±0.022	1.277 ±0.024	1.272 ±0.023	1.251 ±0.020	1.283 ±0.019
5	1.204 ±0.018	1.264 ±0.022	1.214 ±0.018	1.240 ±0.016	1.341 ±0.014	1.394 ±0.021	1.345 ±0.021	1.377 ±0.017	1.228 ±0.016	1.279 ±0.018	1.249 ±0.017	1.269 ±0.012
6	1.241 ±0.022	1.244 ±0.017	1.237 ±0.021	1.217 ±0.022	1.369 ±0.017	1.368 ±0.018	1.373 ±0.015	1.359 ±0.022	1.269 ±0.014	1.272 ±0.017	1.265 ±0.020	1.259 ±0.019
7	1.226 ±0.015	1.276 ±0.017	1.210 ±0.015	1.257 ±0.018	1.358 ±0.013	1.399 ±0.018	1.360 ±0.015	1.400 ±0.020	1.246 ±0.012	1.278 ±0.017	1.244 ±0.011	1.275 ±0.016
8	1.210 ±0.016	1.236 ±0.012	1.201 ±0.016	1.248 ±0.017	1.338 ±0.017	1.371 ±0.015	1.343 ±0.016	1.378 ±0.017	1.216 ±0.011	1.252 ±0.010	1.229 ±0.012	1.259 ±0.015
9	1.244 ±0.021	1.235 ±0.016	1.205 ±0.021	1.217 ±0.018	1.348 ±0.019	1.363 ±0.020	1.354 ±0.020	1.360 ±0.022	1.243 ±0.014	1.243 ±0.019	1.241 ±0.020	1.237 ±0.020
10	1.218 ±0.016	1.242 ±0.016	1.192 ±0.012	1.218 ±0.015	1.359 ±0.015	1.366 ±0.015	1.332 ±0.015	1.354 ±0.015	1.260 ±0.014	1.242 ±0.011	1.227 ±0.012	1.228 ±0.012
11	1.217 ±0.012	1.230 ±0.017	1.192 ±0.013	1.216 ±0.012	1.338 ±0.015	1.344 ±0.020	1.339 ±0.013	1.344 ±0.014	1.229 ±0.014	1.240 ±0.019	1.222 ±0.013	1.243 ±0.013
12	1.215 ±0.018	1.237 ±0.012	1.219 ±0.016	1.225 ±0.018	1.327 ±0.016	1.353 ±0.014	1.321 ±0.021	1.324 ±0.018	1.214 ±0.015	1.222 ±0.014	1.223 ±0.019	1.202 ±0.015
13	1.282 ±0.016	1.270 ±0.013	1.256 ±0.019	1.243 ±0.016	1.398 ±0.021	1.376 ±0.014	1.375 ±0.019	1.352 ±0.016	1.265 ±0.016	1.241 ±0.016	1.248 ±0.018	1.231 ±0.012
14	1.181 ±0.013	1.272 ±0.021	1.170 ±0.014	1.239 ±0.015	1.303 ±0.013	1.371 ±0.017	1.306 ±0.015	1.342 ±0.015	1.204 ±0.012	1.259 ±0.015	1.196 ±0.013	1.224 ±0.014
15	1.220 ±0.012	1.218 ±0.021	1.203 ±0.009	1.238 ±0.017	1.337 ±0.014	1.331 ±0.021	1.329 ±0.011	1.343 ±0.020	1.242 ±0.011	1.223 ±0.022	1.234 ±0.010	1.230 ±0.016
16	1.200 ±0.014	1.252 ±0.016	1.183 ±0.012	1.247 ±0.012	1.309 ±0.011	1.361 ±0.016	1.295 ±0.009	1.248 ±0.010	1.214 ±0.013	1.254 ±0.011	1.202 ±0.010	1.248 ±0.011
17	1.201 ±0.014	1.204 ±0.012	1.182 ±0.013	1.184 ±0.013	1.300 ±0.011	1.294 ±0.015	1.294 ±0.015	1.272 ±0.013	1.208 ±0.009	1.201 ±0.014	1.205 ±0.013	1.181 ±0.016
18	1.186 ±0.014	1.208 ±0.013	1.167 ±0.014	1.187 ±0.013	1.295 ±0.012	1.313 ±0.015	1.283 ±0.011	1.288 ±0.021	1.198 ±0.011	1.211 ±0.013	1.202 ±0.012	1.199 ±0.016
Mean ratio	1.219 ±0.004	1.246 ±0.004	1.209 ±0.004	1.233 ±0.004	1.342 ±0.004	1.363 ±0.005	1.338 ±0.004	1.349 ±0.005	1.236 ±0.004	1.248 ±0.004	1.233 ±0.004	1.241 ±0.004

Mean digit ratios (±SE) by sex and age across 17-year groups (2–18 years) for right and left digit ratios 2D:5D, 3D:5D and 4D:5D

this with serial radiographs of the left hand from infancy to age 17 years in the Fels data set. They found that digit ratio sex differences in infancy were maintained through to post puberty despite a tendency for ratios to increase. In partial replication of my findings, this effect was best developed in 2D:4D and 3D:4D. Finally, it should be noted that sexual dimorphism of children's 2D:4D and other ratios is found when sexual dimorphism of finger length is absent. Thus, there is little evidence in childhood ratios for the suggestion by Kratochvil and Flegr (2009) that sexual dimorphism in 2D:4D is determined by sex differences in finger length (Fig. 48.4).

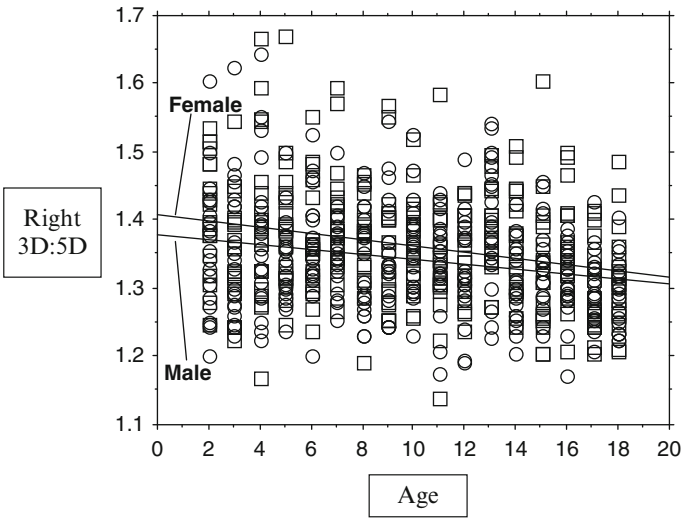

Fig. 48.4 The relationship between right 3D:5D and age (2–18 years). The sample was 340 males and 340 females. Note, there were significant sex differences such that females had higher 3D:5D than males and there was also a significant tendency for 3D:5D ratios to reduce with age. Thus, mean 3D:5D from 2 to 18 years shows both sex differences and age differences

48.6 Applications to Areas of Health and Disease

PT and PE may have important influences on the aetiology of many sex-dependent diseases. Therefore, 2D:4D, 2D:3D and 3D:4D may be useful biomarkers of such diseases (see Huo, Chap. 49). Most work thus far has been conducted with 2D:4D. In particular, the strong links between 2D:4D and sport suggest that 2D:4D may be a proxy for cardiovascular function, musculoskeletal fitness, health and disease (for a detailed consideration of 2D:4D and physical fitness see Honekopp, Chap. 113). I briefly consider here three areas of health: developmental disorders, cardiovascular disease and cancers, in which digit ratios could prove useful as biomarkers for disease.

A number of studies have shown links between low 2D:4D and childhood psychopathologies, such as social difficulties, hyperactivity and poor social cognition (e.g. Williams et al. 2003). In addition, developmental disorders presenting at an early age have also been reported to be associated with low 2D:4D. They include autism and Asperger's syndrome (e.g. Manning et al. 2001; de Bruin et al. 2006) and ADHD (e.g. de Bruin et al. 2006, Martel 2008).

With regard to cardiovascular disease, there is a strong negative association between 2D:4D and running speed over middle- and long-distance races. This suggests that cardiovascular function may be linked with 2D:4D, such that vascular disease is associated with high 2D:4D. Thus, Manning and Bundred (2001) have reported that age at first myocardial infarction (MI) in men is negatively related to 2D:4D. That is, among men, who present with MI, those with low 2D:4D tend to have their MI later in life than those with high 2D:4D. There is some evidence that neck circumference independent of BMI may correlate positively with 2D:4D (Fink et al. 2006). Neck circumference is linked with the metabolic syndrome (a breakdown of normal physiology that includes hypertension and insulin resistance; for further details see Fink, Chap. 36).

With regard to cancers, high 2D:4D in women may be a biomarker for some cancers of the reproductive system. These include cancer of the breast and the cervix. Manning and Leinster (2001) have reported that women with high 2D:4D tended to be younger at presentation of breast cancer than women with low 2D:4D. With regard to cervical cancer, infection with human papillomavirus (HPV)

is a risk factor here, but not all women with this cancer have HPV. Brabin et al. (2008) reported that women with cervical cancer, but without HPV, had significantly higher 2D:4D than controls. Patients with cervical cancer and HPV also tended to have higher 2D:4D than controls, but this was not significant.

It is likely that the potential of digit ratios as biomarkers for disease will be investigated further. Links between 2D:4D and eating disorders, depression, schizophrenia, bipolar disorder, rheumatoid arthritis and cancers (such as prostate cancer) may be strong enough to yield insights into their aetiology. Whether these links will be sufficiently strong enough for 2D:4D to be predictive for these diseases will have to wait on the accumulation of more data.

Summary Points

- 2D:4D (digit ratio) is the ratio of the lengths of the second and fourth digits.
- 2D:4D has been reported to show sex differences such that, on average, males have longer fourth digits relative to their second digit than do females (i.e. they have lower values of 2D:4D than do females).
- The sex difference in 2D:4D appears in the foetus as early as the ninth week, is found in infants, children and adults and the 2D:4D of infants is strongly correlated with their 2D:4D when they become adults. The sex difference results from a different growth trajectory of 4D relative to 2D.
- 2D:4D may be sexually dimorphic as a consequence of the effects of PT relative to PE on finger growth, such that high PT and low PE may result in low values of 2D:4D.
- Excluding the thumb, the fingers show six ratios and a number of these show sex differences. However, only 2D:4D, 2D:3D and 3D:4D show both sex differences and are relatively stable with growth in children.
- Many sex-dependent diseases may be influenced by PT and PE. Therefore, 2D:4D, 2D:3D and 3D:4D could be useful biomarkers for susceptibility to such diseases. Most work has concentrated on 2D:4D. Links have been shown to developmental disorders (e.g. autism, Asperger's syndrome and ADHD), cardiovascular disorders (e.g. MI), cardiovascular efficiency (e.g. running speed) and cancers (e.g. breast and cervical cancer).

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Chapter 49
Correlations Between Digit Ratio and Foetal Origins of Adult Diseases in a Chinese Population: A Focus on Coronary Heart Disease and Breast Cancer

Huo Zhenghao, Lu Hong, Dang Jie, and Francis L. Martin

Abstract Epidemiological studies suggest that impaired foetal growth can promote an adaptive adjustment of metabolism and the morphological development of foetal organs. This may be a significant aetiological factor in adult diseases including coronary heart disease (CHD) or breast cancer; consequently, these modulating factors are defined as foetal origins of adult diseases (FOAD). Digit ratio is determined during foetal life and may be a marker reflecting the development of foetal growth. In order to investigate the relationship between the digit ratio and CHD or breast cancer, we used anthropometric methods to measure the digit length of both hands for every study participant. Digit ratios were scored and compared between right and left hands, for CHD patients (n = 152 cases), breast cancer patients (n = 128 cases) and controls (CHD control, n = 152 cases; breast cancer control, n = 128 cases) respectively; all participants were residents of Yinchuan, Ningxia, China. We observed the following trend 2D:3D < 2D:4D < 3D:4D < 2D:5D < 4D:D < 3D:5D in both the control and the two patient cohorts. However, the digit ratio scores for both CHD and breast cancer groups exhibited higher mean values compared to the control cohort; this was especially the case for 2D:4D. Both CHD and breast cancer cohorts exhibited higher proportions of 2D>4D. These findings suggest that digit ratio, especially 2D:4D, has the potential to be an important and early diagnostic marker for future risk of developing CHD or breast cancer.

Abbreviations

2D:3D	Digit ratio between second to third finger
2D:4D	Digit ratio between second to third finger
2D:5D	Digit ratio between second to fifth finger
3D:4D	Digit ratio between third to fourth finger
3D:5D	Digit ratio between third to fifth finger

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_49,

4D:5D	Digit ratio between fourth to fifth finger
CAH	Congenital adrenal cortical hyperplasia
CHD	Coronary heart disease
FOAD	Foetal origins of adult diseases
L	Left hand
R	Right hand
s.d.	Standard deviation
y	Years

49.1 Introduction: Digit Ratio and Foetal Origins of Adult Diseases (FOAD)

Generally, many chronic adult diseases, such as CHD, diabetes or hypertension, are associated with environmental factors, such as poor lifestyle or specific exposures modulated by polygenic inheritance susceptibility. In the 1990s, Prof. Barker proposed the notion of "foetal origins of adult diseases (FOAD)," which suggests that factors governing fertilisation, embryonic and foetal development, and post-parturition nutritional (over- or undernutrition) status may play a pivotal role in the aetiology of different diseases occurring later in adulthood, or may even influence long-term lifestyle. Included within the FOAD hypothesis is the notion that intra-uterine adverse mechanisms can promote an adaptive adjustment of metabolism and structural development of foetal organs. If undernutrition is not promptly corrected, such adaptive adjustments will induce permanent changes in the metabolic integrity of specific organs, including the vasculature, liver and lung, etc., and the organism; the consequences of these alterations will be borne out in adulthood (Barker 1990; Barker and Osmond 1986). There is increasing epidemiological evidence that impaired foetal growth has long-term effects on the body's morphological development and physiological functions, which in turn are associated with adverse health consequences in adult life. These studies have relied on showing correlations between crude indices of foetal growth, such as overall weight or length at birth and adult health outcomes. There is a need to develop improved morphological markers of impaired foetal growth and, in particular, to identify markers which persist into adult life.

An individual's fingers and toes begin to develop in the 6th week of pregnancy. Digital ratios are determined while the embryo forms, and will then remain the same during individual development. The foetus grows quickly from the 9th week of pregnancy, and this is the sensitive period for foetal development. The major feature of the foetal period is cell differentiation, which is sensitive to external environmental changes. So, during this period, if the foetus encounters changes in the intra-uterine environment, such as intra-uterine undernutrition or hormone level changes, not only will the foetal structures of the organs and organism be modified, but the development of foetal fingers and toes will also be affected. Therefore, studies on digit ratios can reflect development during the foetal period, and indirectly reflect the interference of intra-uterine environment changes. Thus, digit ratio is an important index for studies into morphological development and physiological abnormalities during the foetal period (Manning et al. 2004).

Human fingers are numbered consecutively from one (thumb) to five (little finger). Because thumb length is difficult to measure, digit ratios generally just include the six ratios of digit lengths, 2D:3D, 2D:4D, 2D:5D, 3D:4D, 3D:5D and 4D:5D (Manning 2002). A number of studies have shown that finger and toe development and differentiation of the genitourinary system (including gonads) are related to *HOX* genes (*HOX* A–*HOX* D). Gonads and their foetal products, such as androgens, may influence the morphological development of fingers (and toes) (Manning et al. 2003a).

Among all the digit ratios, the ratio between the length of the second and fourth digits (2D:4D ratio) may be the most important marker during the foetal period. It has been shown in recent studies that human digit ratios (especially 2D:4D) differ between the genders. Generally, the male ring finger is longer than the index finger (4D>2D), and the female index finger is equal in length to or slightly longer than the ring finger (2D≥4D). Thus, the mean female 2D:4D of 1.00 is generally higher than that the male 2D:4D mean of 0.96; as a result, males are designated as having low digit ratios, whilst females have high digit ratios. This gender difference, where females have obviously higher 2D:4D than males, is more pronounced in certain ethnic groups (McIntyre et al. 2006). A large number of studies have indicated such ethnic differences in 2D:4D (Manning et al. 2003b). It has been reported that British, Spanish and Polish populations exhibit higher digit ratios, whereas South African (i.e. Zulu), Chinese (Lu et al. 2008), Finnish and Jamaican population have lower digit ratios; populations in other countries exhibit medial digit ratios (Manning 2002).

Other studies have suggested that 2D:4D is related to individual characteristics such as aggressive behaviour, confidence and competitiveness, and it has been found that 2D:4D also significantly correlates with some abnormal developmental diseases or abnormalities, such as breast cancer, reduced sperm count, and autism (Manning and Bundred 2000; Manning et al. 2003a, b). Ronalds and co-workers studied the correlation between digit ratios and myocardial infarction, HIV susceptibility, foetal dysplasia, leukaemia and tumours, etc., in different ethnic groups in Poland, Spain, Germany and Britain; similar conclusions were obtained (Ronalds et al. 2002). As 2D:4D is related to various gender-dependent diseases, such as CHD (Fink et al. 2006) and breast cancer (Manning and Leinster 2001), we surveyed the digit ratios of a normal control cohort (males and females) and two patient cohorts (CHD and breast cancer) among the Han people in Ningxia, China. We set out to study the 2D:4D correlations of controls compared to patients, to age of onset of the two diseases in order to investigate the relationship of digit ratios and FOAD.

Studies into correlations between digit ratios and abnormalities of different individual characteristics, including morphological development and physiological functions, have drawn much attention from many scholars, and have become extensively debated issues in the fields of developmental biology, anthropology and behavioural science. In 2000, a related paper published in *Nature* introduced studies into digit ratios, and pointed out that "finger length ratio may reveal some surprising information of development" (Williams et al. 2000).

49.2 A Chinese Cohort Sampling: Guidelines

We studied the digit ratios (2D:3D; 2D:4D; 2D:5D; 3D:4D; 3D:5D; and 4D:5D) of the left and right hands from 560 individuals of Han nationality in Ningxia, China, including patient and normal control cohorts. The patient cohorts included CHD cases (n = 152) between the ages of 30–73 years (y) (mean = 47.5 years, standard deviation [s.d.] = 6.7); all CHD patients were male. We selected 152 healthy males as controls with a mean age ± s.d. of 55.9 y ± 7.7. In the breast cancer cohort, there were 128 cases aged between 30 and 73 y (mean = 55.0 years, s.d = 8.2); all the breast cancer patients were female. As such, we selected 128 healthy females as normal controls with a mean age ± s.d. of 54.6 y ± 8.2. Normal control subjects were resident natives of Ningxia, China, and all exhibited healthy physical and mental states. Subjects of the patient group were diagnosed cases in the hospital affiliated to Ningxia Medical University; the parents of all cases were from the same Han ethnic group, and disease had arisen in the absence of either inherited mutations or congenital defects.

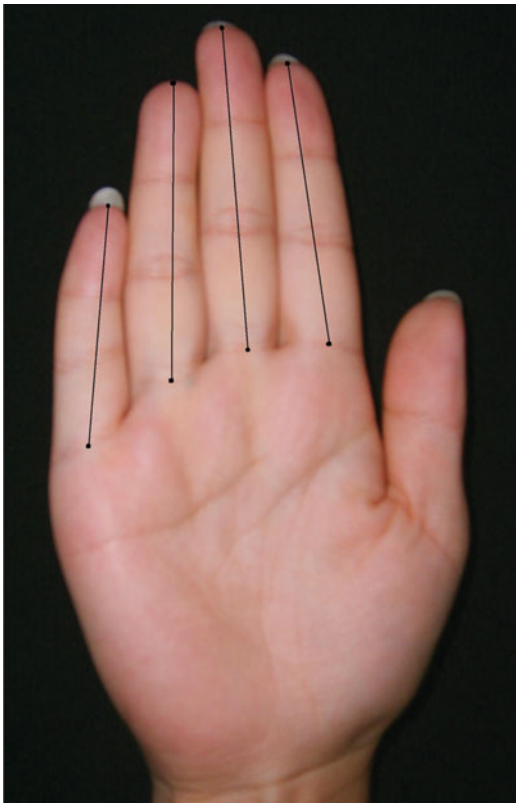

Fig. 49.1 Schematic diagram of digit length measurement. A right hand from a Chinese female; the picture was taken as part of the study

We adopted a photocopy measurement methodology in our study. By using this method, the hand images were captured by using a digital camera and then the images were input into a computer (Fig. 49.1). We then marked all sign spots by ACD image analysis software and measured them by using electronic Vernier callipers; samples with finger injuries were excluded. Samples stored in the computer were either required to have distinctive flexure creases, or repeat imaging was required. All the digits (2D:3D, 2D:4D, 2D:5D, 3D:4D, 3D:5D and 4D:5D) were measured from the basal crease proximal to the palm to the tip of the finger using electronic Vernier callipers capable of measuring to a spatial resolution of 0.01 mm. Repeat measurements were acquired for each finger. We used repeat measures ANOVA to calculate the ratio (F) between measurement error (the differences between successive measures of 2D:4D) and between-participant differences. The t-test and correlation analysis were applied to analyse the results.

49.3 Digit Ratio and Coronary Heart Disease (CHD)

Repeat measures ANOVA was performed on the results of digit ratios of left and right hands in normal control and CHD cohorts of the Han people in Ningxia, China, and the results showed that:

Control cohort: 2D:3D (F = 0.31, P = 0.58); 2D:4D (F = 0.002, P = 0.964); 2D:5D (F = 0.16, P = 0.91); 3D:4D (F = 2.19, P = O.13); 3D:5D (F = 1.08, P = 0.30); 4D:5D (F = 1.49, P = 0.19);
Patient cohort: 2D:3D (F = 0.27, P = 0.62); 2D:4D (F = 0.001, P = 0.973); 2D:5D (F = 1.10, P = 0.37); 3D:4D (F = 145, P = 0.23); 3D:5D (F = 1.07, P = 0.31); 4D:5D (F = 0.27, P = 0.604).

Table 49.1 Mean values of digit ratio and *t*-test results of left (L) and right (R) hands

Digit ratio		Number	Control subjects	CHD patients	*t* value	*P* value
2D:3D	L	152	0.9288 ± 0.0426	0.9290 ± 0.0398	1.950	0.047
	R	152	0.9166 ± 0.0432	0.9169 ± 0.0444	1.390	0.170
2D:4D	L	152	0.9481 ± 0.0351	0.9491 ± 0.0353	2.830	0.005
	R	152	0.9480 ± 0.0321	0.9489 ± 0.0326	2.440	0.020
2D:5D	L	152	1.0814 ± 0.0195	1.0823 ± 0.0193	1.682	0.081
	R	152	1.0813 ± 0.0204	1.0817 ± 0.0348	1.077	0.281
3D:4D	L	152	1.0235 ± 0.0412	1.0238 ± 0.0446	0.476	0.635
	R	152	1.0240 ± 0.0118	1.0244 ± 0.0403	0.480	0.629
3D:5D	L	152	1.1550 ± 0.0575	1.1558 ± 0.0385	0.635	0.525
	R	152	1.1704 ± 0.0740	1.1710 ± 0.0612	0.884	0.377
4D:5D	L	152	1.1314 ± 0.0558	1.1319 ± 0.0508	0.561	0.620
	R	152	1.1350 ± 0.0561	1.1359 ± 0.0511	0.627	0.531

The mean values of digit ratio and paired *t*-test results of both hands (left, *L*; right, *R*) of control and patients diagnosed with coronary heart disease (*CHD*)

Table 49.2 Percentage distributions of 2D:4D patterns of left (L) and right (R) hands between control group and CHD patient group

		2D:4D					
		L			R		
Sample	number	2D < 4D (%)	2D = 4D (%)	2D >4D (%)	2D < 4D (%)	2D = 4D (%)	2D >4D (%)
Controls	152	85.52	1.32	13.16	86.84	0.66	12.50
CHD	152	84.87	0.66	14.47	85.52	0.66	13.82

The comparison of 2D:4D values for both hands (left, L; right, R) between the healthy control and coronary heart disease (CHD) cohorts of Han people in Ningxia, China

P values showed no significant differences ($P > 0.05$) in the digit ratios of both hands of control and CHD subjects between two measurements, indicating that differences of digit ratios of both hands were not induced by measurement errors in the control and CHD cohorts. The mean values of digit ratio and paired *t*-test results of both hands of control and patient cohorts are listed in Tables 49.1.

The results showed that: (1) the mean digit ratios of samples were similar in both hands, and a consistent trend was observed, that is, 2D:3D < 2D:4D < 3D:4D < 2D:5D < 4D:5D < 3D:5D; the mean digit ratios of both hands were higher in the CHD cohort compared to the control cohort; and (2) there were significant differences in 2D:3D (left hand) and particularly 2D:4D (left hand, $P < 0.01$; right, $P < 0.05$) between these two groups. These were the only significant differences between the observed digit ratios.

Relevant studies from other countries have shown that 2D:4D might be correlated with gender-related diseases, such as CHD, breast cancer, etc.; thus, this could potentially be used as a surrogate biomarker as an important early predictor of susceptibility to various gender-related diseases emerging as a consequence of influencing factors occurring during the foetal period. Therefore, we examined further the comparison of 2D:4D values for both hands between the healthy control and CHD cohorts of the Han people in Ningxia, China; the results are shown in Table 49.2.

The results indicated that, in the healthy control cohort and CHD patient cohort, 2D:4D displayed three patterns: 2D > 4D, 2D = 4D and 2D < 4D, with 2D < 4D as the dominant characteristic observation.

Table 49.3 Results of correlation and regression analysis on digit ratios of left (L) and right (R) hands of Han people between control subjects and CHD patients in Ningxia, China

				Statistical results	
Hands	Subjects	Number	Age (years)	*r* value	*P* value
L	Control subjects	152	55.87 ± 7.65	0.043	0.601
	CHD patients	152	47.48 ± 6.70	0.636	0.000
R	Control subjects	152	55.87 ± 7.65	0.055	2.585
	CHD patients	152	47.48 ± 6.70	0.561	0.000
Mean	Control subjects	152	55.87 ± 7.65	0.150	0.059
	CHD patients	152	47.48 ± 6.70	0.561	0.000

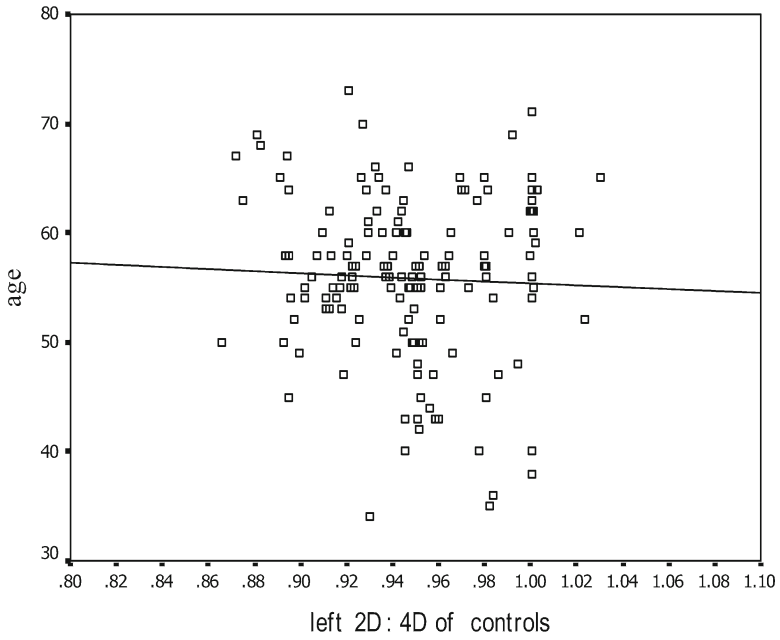

Fig. 49.2 Correlation analysis between 2D:4D of left hands and age in coronary heart disease (CHD) control cohort

There was a higher percentage of 2D > 4D in the CHD group compared to the control group, but without any apparent significant differences ($x^2 = 0.1105$, $P > 0.05$).

In order to investigate whether there were correlations between 2D:4D of both hands and age in normal control and CHD cohorts in the Han people (Ningxia, China), SPSS (version 11.5) was adopted for correlation analysis in our study and the results are shown in Table 49.3, Figs. 49.2 and 49.3.

The results of correlation analysis showed that: (1) there were no significant correlations between 2D:4D or mean 2D:4D of both hands *versus* age in the control cohort; (2) however, the CHD cohort exhibited a negative correlation between 2D:4D or mean 2D:4D of both hands versus age of onset of the diagnosed pathology. However, little is known regarding the reason why the correlation is more significant in 2D:4D and mean 2D:4D of the left hand compared to the right hand.

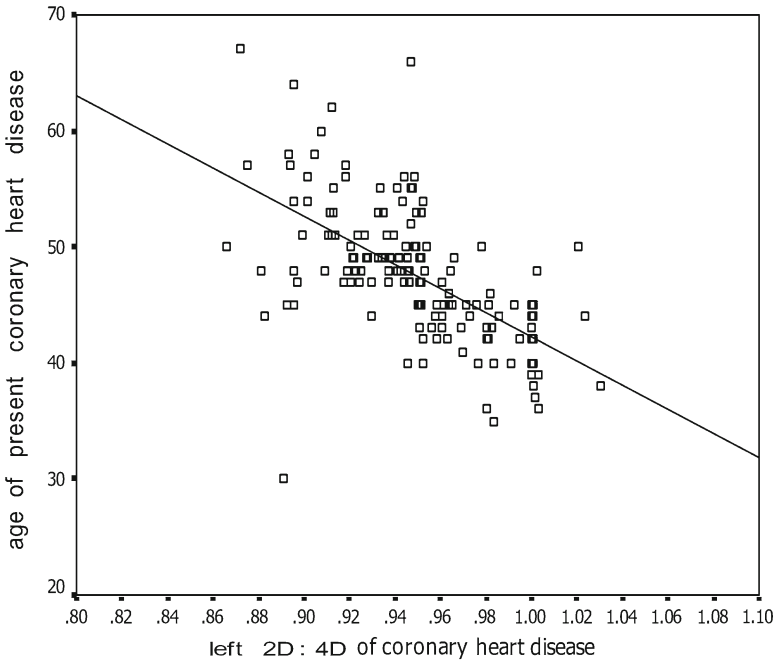

Fig. 49.3 Correlation analysis between 2D:4D of left hand and age of coronary heart disease (CHD) patient cohort

49.4 Digit Ratio and Breast Cancer

Repeated measures ANOVA was conducted on the results of the digit ratios of left and right hands in the normal control compared to the breast cancer cohort of the Han people in Ningxia, China; the results showed that:

Control group: 2D:3D ($F = 0.28$, $P = 0.61$); 2D:4D ($F = 0.005$, $P = 0.943$); 2D:5D ($F = 0.15$, $P = 0.91$); 3D:4D ($F = 2.18$, $P = 0.12$); 3D:5D ($F = 1.09$, $P = 0.29$); 4D:5D ($F = 1.48$, $P = 0.20$);
Patient group: 2D:3D ($F = 0.32$, $P = 0.57$); 2D:4D ($F = 0.001$, $P = 0.975$); 2D:5D ($F = 0.20$, $P = 0.93$); 3D:4D ($F = 0.26$, $P = 0.603$); 3D:5D ($F = 1.07$, $P = 0.31$); 4D:5D ($F = 1.46$, $P = 0.22$).

P values showed no significant differences in digit ratios of both hands of control subjects and breast cancer patients between two measurements ($P > 0.05$), indicating that measured differences in digit ratios of both hands were not a consequence of measurement errors in acquiring the data from the control and patient cohorts. The mean values of digit ratio and paired *t*-test results of both hands of the control group and patient groups are listed in Table 49.4.

The results showed that: (1) the mean digit ratios of samples were similar in both hands, and a similar trend of 2D:3D < 2D:4D < 3D:4D < 2D:5D < 4D:5D < 3D:5D, as previously observed, was noted, and the mean digit ratios of both hands were higher in the breast cancer cohort compared to the control cohort; (2) there were significant differences in 2D:3D (both hands, $P<0.05$), 2D:4D (both hands, $P < 0.01$) and 2D:5D (left hand, $P < 0.05$) in the breast cancer cohort compared to the control cohort, and no significant differences were observed for the remaining digit ratios. We particularly analysed the comparison of 2D:4D values for both hands between the normal control and the breast cancer cohorts of the Han people; the results are shown in Table 49.5.

Table 49.4 Mean values of digit ratio of left (L) and right (R) hands between control subjects and breast cancer patients

Digit ratio		Number	Control subjects	Breast cancer patients	*t* value	*P* value
2D:3D	L	128	0.9387 ± 0.0370	0.9390 ± 0.0398	2.090	0.030
	R	128	0.9267 ± 0.0392	0.9270 ± 0.0404	2.000	0.050
2D:4D	L	128	0.9557 ± 0.0356	0.9582 ± 0.0354	2.870	0.004
	R	128	0.9554 ± 0.0363	0.9556 ± 0.0362	2.270	0.010
2D:5D	L	128	1.0871 ± 0.0285	1.0873 ± 0.0293	1.851	0.035
	R	128	1.0870 ± 0.0209	1.0871 ± 0.0438	1.171	0.241
3D:4D	L	128	1.0325 ± 0.0422	1.0328 ± 0.0326	0.172	0.870
	R	128	1.0340 ± 0.0128	1.0344 ± 0.0303	0.481	0.628
3D:5D	L	128	1.1750 ± 0.0455	1.1758 ± 0.0485	1.272	0.211
	R	128	1.1830 ± 0.0620	1.1836 ± 0.0512	1.394	0.170
4D:5D	L	128	1.1554 ± 0.0548	1.1559 ± 0.0538	0.628	0.531
	R	128	1.1550 ± 0.0551	1.1552 ± 0.0541	0.617	0.533

The mean values of digit ratio and paired *t*-test results of both hands (left, *L*; right, *R*) of control group and patient groups

Table 49.5 Percentage distributions of 2D:4D patterns of left (L) and right (R) hands between the control and breast cancer patient cohorts

		2D:4D					
		L			R		
Sample	Number	2D < 4D (%)	2D = 4D (%)	2D >4D (%)	2D < 4D (%)	2D = 4D (%)	2D >4D (%)
Controls	128	82.81	0.78	16.41	83.59	0.78	15.63
Breast cancer	128	80.47	0.78	18.75	81.25	0.78	17.97

The comparison of 2D:4D values for both hands (left, *L*; right, *R*) between the normal control and the breast cancer cohorts of Han people in Ningxia, China

Table 49.6 Correlation and regression analysis on 2D:4D in left (L) and right (R) hands

				Statistical results	
Hands	Subjects	Number	Age (years)	*r* value	*P* value
L	Control subjects	128	54.57 ± 8.21	0.084	0.171
	Breast cancer	128	47.06 ± 6.35	0.616	0.000
R	Control subjects	128	54.57 ± 8.21	0.062	0.263
	Breast cancer	128	47.06 ± 6.35	0.598	0.000
Mean	Control subjects	128	54.57 ± 8.21	0.065	0.254
	Breast cancer	128	47.06 ± 6.35	0.600	0.000

There was also a higher percentage of 2D > 4D in the breast cancer group compared to the control group, but without significant differences ($x^2 = 0.2427$, $P > 0.05$). The correlation between 2D:4D of both hands and age in the normal control and breast cancer cohorts are shown in Table 49.6, Figs. 49.4 and 49.5.

The results of correlation analysis showed that: (1) there were no significant correlations between 2D:4D and mean 2D:4D of both hands and age in the control group; (2) the CHD group showed a negative correlation between 2D:4D and mean 2D:4D of both hands and onset ages.

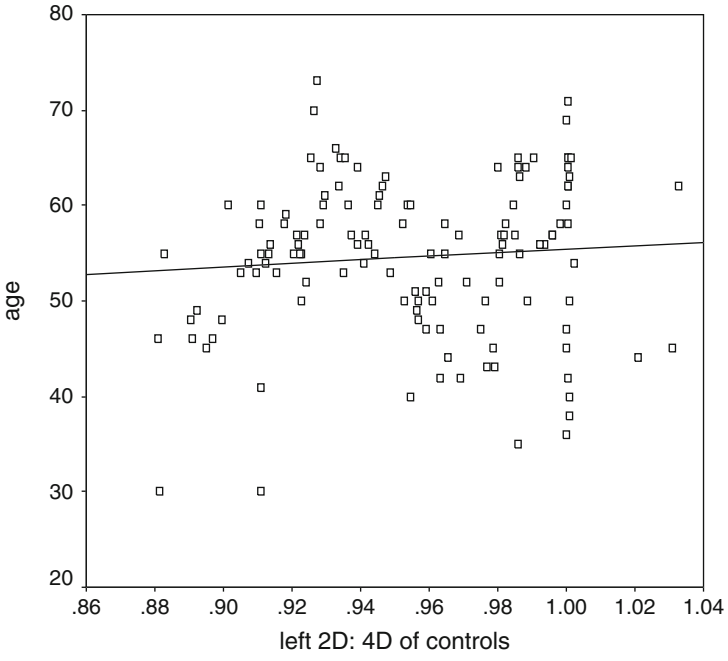

Fig. 49.4 Relationship between 2D:4D of left hands and age in the breast cancer control cohort

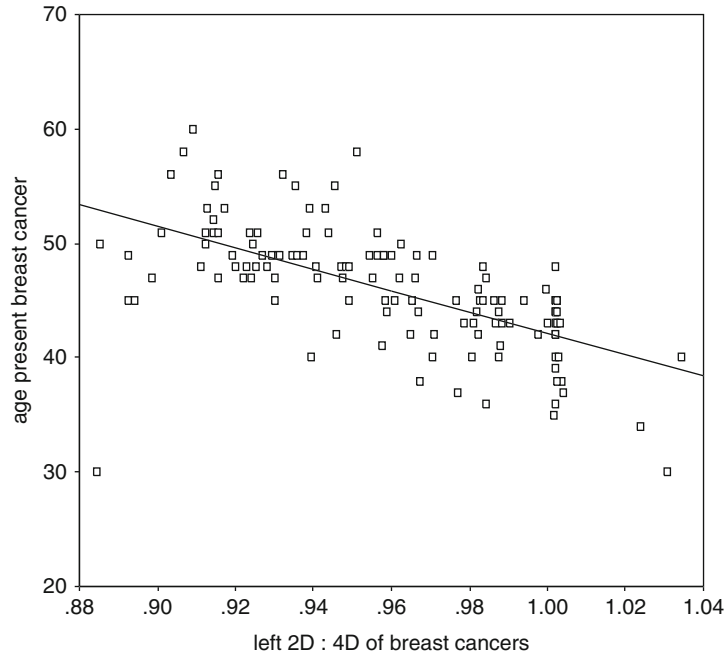

Fig. 49.5 Relationship between 2D:4D of left hands and age in the breast cancer patient cohort

49.5 Applications to Other Areas of Health and Disease

We have used this approach to study CHD and breast cancer in the context of FOAD. These studies also had a control arm consisting of ethnic Han Chinese residents in Ningxia. We intend to advance our studies in order to investigate possible relationships between azoospermia, diabetes and

schizophrenia, amongst other diseases, and digit ratio. Our study's immediate value is that it is an easy-to-obtain potential biomarker of health status that is non-invasive. Such a characteristic allows one to derive data from large cohorts that might then be associated with the presence or absence of particular diseases. This approach can also then be used to compare differences in disease susceptibility between different ethnic groups in greater detail.

49.6 Discussion

CHD is an age-related degenerative disease associated with a variety of genetic influences, environmental factors and poor lifestyle (e.g. smoking and excessive alcohol consumption, etc.), but the underlying aetiological factors remain unknown. Previous studies indicate that the genesis and development of CHD are correlated with age, and that the disease can be accelerated and aggravated by smoking, hypercholesteraemia, hypertension, diabetes, obesity, psychological factors, etc. However, several studies suggest that only 50% of CHD patients can be associated with these classical risk factors. Proposed the hypothesis of the foetal origin of CHD, in which they proposed that if the foetus suffers from undernutrition, it will adapt to the environmental change by physiological and metabolic adaptive responses. These responses persist after birth and will programme susceptibility to a diverse range of diseases. Environmental factors after birth also play very important roles in the development of CHD. Therefore, if a foetus suffers from undernutrition and, then, at a later stage, experience compensatory growth that accelerates the increase in body weight, the risk of developing CHD will increase in adulthood. Epidemiological studies support this hypothesis. Barker conducted an epidemiological survey in England and Wales, and found that populations with low birth weight and low infant body weight exhibited a high mortality induced by CHD in adulthood (Barker and Osmond 1986).

Another study has also indicated that, taking into account aetiological risk factors, intra-uterine sex hormone levels during early pregnancy are closely related with adult diseases, such as myocardial infarction and breast cancer (Manning 2002). Some of these studies strongly suggest that if the foetus is exposed in utero during the first trimester to excess oestrogens, progesterone will induce cardiovascular abnormalities including ventricular septal defects, atrial septal defects and patent ductus arteriosus (Manning and Bundred 2000). Thus, the foetal intra-uterine environment may be a predictor of whether the foetus post parturition will be at a higher risk of developing CHD. As peripheral blood cannot be drawn from a foetus in utero, and is rarely drawn from infants for research purposes, the study of effects of perinatal testosterone in humans had to rely on other methods. One method which has come into focus is the use of digit ratios, especially the second to fourth fingers (2D:4D).

Human digit ratios differ between the sexes, and these are related in the first instance with the effects of perinatal hormones. Perinatal hormone levels, of which the androgen level has the most important effects, affect the development of fingers and toes. The strongest evidence for direct effects of perinatal androgens comes from the study on patients with congenital adrenal cortical hyperplasia (CAH). This disease is initially induced by excess androgens secreted by the perinatal adrenal gland, and a study of digit ratios of these patients has indicated that the 2D:4D of the right hand in female patients is significantly lower than that in control females, whereas 2D:4D of the left hand of the male patient group is obviously lower than that of the non-patient male group (Brown et al. 2002).

In studies on male patients with myocardial infarction and aged-matched healthy control males, it was found that myocardial infarct patients have higher 2D:4D, lower androgen levels and higher oestrogen levels (Phillips et al. 1994; Manning and Bundred. 2000). It has been suggested that high

testosterone concentrations may be a protective factor for males, which can reduce the risk of heart diseases and postpone the age of onset of myocardial infarction (Fink et al. 2006). Some evidence has also suggested that male CHD patients have lower androgen levels, with higher digit ratios and lower androgen levels; this may become an important index to predict male myocardial infarct.

With regard to the relationship between digit ratio and cancer, the relationship between digit ratio and breast cancer has been studied most frequently. Trichopoulos has proposed that higher oestrogen levels in utero during the foetal period are a risk factor for breast cancer after birth (Trichopoulos 1990). Manning and Leinsfer have demonstrated in their study that 2D:4D is positively related with the onset of breast cancer, that is, females with a higher 2D:4D have a higher incidence of breast cancer compared to their aged-matched counterparts with a lower 2D:4D (Manning and Leinster 2001). Therefore, some investigators have proposed that digit ratio could be adopted as a judgement index of susceptibility, diagnosis and therapeutic effects for tumours. They presume that disordered gene regulation induces tumours of the genital system, kidney, intestines, etc., which will be represented morphologically by changes in 2D:4D. Therefore, 2D:4D may be correlated with endometrial cancer, ovarian cancer, and primary renal carcinoma and colon carcinoma, though these correlations need to be confirmed.

Our study revealed that the digit ratios of the patient cohort were higher than those of controls, with significant differences observed in 2D:4D of the left hand between the control and patient groups. However, the underlying reasons for this remain to be further investigated. These results suggest that patients may have lower androgen levels and higher oestrogen levels during their foetal periods compared to healthy controls. In adults, 2D:4D is directly correlated with oestrogen levels. If the foetus is exposed to higher oestrogen levels, the risk of developing CHD and breast cancer will be increased. Higher digit ratios and lower androgen levels (or higher oestrogen levels) may be important indices for screening CHD and breast cancer. The 2D:4D ratios, especially 2D:4D of the left hand, may provide more information for early diagnosis of CHD or breast cancer.

Compared to controls, the two patient cohorts had higher percentages of 2D>4D, which might be a reason for higher mean 2D:4D in the patients. The results suggest that these patients may have had lower androgen levels and higher oestrogen levels during their foetal period. The higher 2D > 4D percentages in the patients suggests that intra-uterine oestrogen levels during the foetal period may have certain stimulating effects on growth of the index finger, whereas androgen levels have certain stimulating effects on growth of the ring finger. So, we can presume that the intra-uterine hormone environment during early pregnancy may be a factor to determine whether there will be a higher risk of developing CHD and breast cancer in adulthood. Compared to reports in the European population, 2D > 4D percentages in CHD or breast cancer patients of the Han people in Ningxia are significantly lower, indicating why the lower digit ratio may be one reason for lower incidences of CHD and breast cancer the Chinese than in the European population.

Correlation analysis indicates that for patients with higher 2D:4D (lower androgen levels or higher oestrogen levels), CHD or breast cancer may arise earlier compared to their aged-matched counterparts with lower 2D:4D (higher androgen levels or lower oestrogen levels). On the other hand, it is also demonstrated that lower androgen levels in the foetus and the corresponding intra-uterine environment may be a risk factor for CHD or breast cancer; the 2D:4D of the left hand provides more effective information for early onset risks of developing CHD or breast cancer.

The hypothesis of the foetal origins of adult diseases provides a new avenue for understanding cardiovascular diseases and metabolic diseases, such as coronary disease and diabetes, and it provides evidence for prevention against these common diseases in the embryonic period and during pregnancy. It also helps to achieve breakthroughs in studies on mechanisms of diseases with unknown aetiological factors. Because the digit ratio can indirectly reflect the interferences of the intrauterine environment on the foetal period, it becomes an effective marker to presume whether individuals

have encountered intra-uterine environmental changes during the foetal period. A large number of studies have confirmed that digit ratios are related to human behaviours, such as aggressive behaviour, cooperation, left handedness, etc., and human diseases, such as autism, dyslogia, infertility, myocardial infarct, breast cancer, etc. So, digit ratios may lend valuable support to early diagnosis and prognosis of many adult diseases. Simultaneously, with the implementation of further studies on 2D:4D, more effective information will be available to postpone the onset of diseases including myocardial infarction by modifying lifestyle, and determine the onset of risk factors for diseases, such as breast cancer.

Summary Points

- Foetal origins of adult diseases (FOAD) are associated with factors governing fertilization, embryonic and foetal development and post-parturition nutritional (over- or undernutrition) status. Such modulating factors may play a pivotal role in the aetiology of different diseases occurring later in adulthood or may even influence long-term lifestyle.
- Digit ratio is an important index for studies into morphological development and physiological abnormalities that may emerge during the foetal period.
- The ratio between the length of the second and fourth digits (2D:4D ratio) may be a good marker of normal development during the foetal period. Previous studies have shown that human digit ratios (especially 2D:4D) differ between genders and different ethnic groups.
- It has also been shown that 2D:4D is related to such characteristics as aggressive behaviour, confidence and competitiveness. Additionally, 2D:4D appears to correlate significantly with some abnormal developmental diseases or abnormalities, including breast cancer, reduced sperm count and autism.
- Our studies revealed that the digit ratios of patient groups are higher than those of control groups. It is suggested that these patients may have had lower androgen levels and higher oestrogen levels during their foetal period.
- Our observations suggest that the intra-uterine hormone environment at early pregnancy may be a factor determining subsequent risk of coronary heart disease (CHD) or breast cancer in adulthood.

Key Features

Table 49.7 Key features of foetal origins of adult diseases (FOAD) and disease susceptibility

Feature number	Foetal origins of adult diseases (FOAD)
1.	Epidemiological studies suggest that impaired foetal growth can promote an adaptive adjustment of metabolism and the morphological development of foetal organs.
2.	It has a potential to be a significant aetiological factor in adult diseases.
3.	Digit ratio is determined during foetal life and may reflect development.
4.	Digit ratio scores for CHD and breast cancer patients are higher compared to those for healthy controls.
5.	2D:4D appears to be the most important digit ratio.
6.	Digit ratio, especially 2D:4D, is potentially an early marker for future risk.

This table lists the key facts associating FOAD and future risk of adult disease

Acknowledgements Our research was supported by the National Natural Science Foundation of The People's Republic of China (Grant No. 30260045 and Grant No. 30960154).

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Part VIII
Regions and Anatomical Areas of the Body: Abdominal and Trunk Regions

Chapter 50
Anthropometry of Abdominal Subcutaneous and Visceral Adipose Tissue with Computed Tomography

Amir Abbas Mahabadi, Pál Maurovich-Horvat, and Udo Hoffmann

Abstract Obesity is a major health care problem with further increasing prevalence in the industrialized world. Multiple studies have outlined the exceptional role of subcutaneous abdominal adipose tissue (SAT) and more importantly visceral abdominal adipose tissue (VAT). VAT is the largest visceral adipose tissue of the human body and drains directly into portal circulation. Both VAT and SAT are strongly associated with other cardiovascular and metabolic risk factors such as hypertension, dyslipidemia, diabetes and the metabolic syndrome. The prevalence of cardiovascular disease is increased with excessive VAT and SAT amount. Moreover, both fat tissues are correlated with systemic markers of inflammation, as they secrete pro- and anti-inflammatory mediators and hormone like peptides. CT imaging of the abdomen is considered the gold standard for VAT and SAT quantification. Three- and two-dimensional measures have been established. Three-dimensional fat volume is more accurate, however, it is relatively time consuming and requires full abdominal CT-imaging. Despite the VAT and SAT volume, the fat area at the level of the umbiculus is most commonly used in the literature. Normative values for different VAT and SAT measures have been established in the literature. However it has to be acknowledged that abdominal adipose tissue distribution differs by age, gender, and ethnicity.

Abbreviations

BMI	Body mass index
CT	Computed tomography
SAT	Subcutaneous abdominal adipose tissue
VAT	Visceral abdominal adipose tissue

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_50,

50.1 Introduction

Obesity is one of the most prevalent cardiovascular risk factors in the industrialized world, promoted by the modern lifestyle with a lack of physical activity and a high-caloric diet. In accord with increasing incidence of obesity, obesity-related disorders such as diabetes, dyslipidemia, and hypertension are of increasing prevalence, leading to an increased risk of cardiovascular diseases. While adipose tissue has simply been considered an energy storing compartment in the past, over the last two decades, it has gained more and more interest, and is now regarded as a complex organ, contributing to energy management of the body, and interacting with systemic and local inflammation. However, there is growing evidence that not only overall adiposity (as assessed by body mass index), but also visceral adiposity is strongly associated with metabolic syndrome, cardiovascular risk factors and present cardiovascular disease, whereas other fat compartments (e.g., hip fat) are of less importance, or may even be protective. Visceral adipose tissue differs from subcutaneous fat in cell size, fatty acid composition, protein content, fatty acid metabolism, enzyme expression, and glucose utilization. Visceral adipose tissue of the abdomen (VAT) is the largest visceral fat depot of the body, and consists of fat deposits in the retroperitoneal, omental and mesenteric spaces. Besides its size, VAT gains specific interest due to its location, directly draining into the portal circulation. In this chapter, we will overview the clinical implications of VAT and subcutaneous abdominal fat (SAT), association with other fat tissues of the body, and changes during growth and lifestyle modifications. Moreover, we will discuss the frequently used measures of pericardial fat, and provide normative values for different measures in different patient populations.

50.2 Practical Methods and Techniques: Planimetric and Volumetric Quantification Techniques of Subcutaneous and Visceral Abdominal Adipose Tissue Compartments

It was previously demonstrated that, for a given BMI or total amount of body fat, the subgroup of patients with excessive intra-abdominal adipose tissue depot is at substantially higher risk of developing insulin resistance and metabolic syndrome (Despres 2006). Other studies demonstrated that the waist circumference correlates with measures of risk, for coronary heart disease, such as hypertension or blood lipid levels (Ledoux et al. 1997; Seidell et al. 1992). Thus, not surprisingly, there has been a great interest during the past decade to develop quantification methods that allow for precise and reproducible assessment of abdominal adipose tissue compartments. Both magnetic resonance imaging (MRI) and computed tomography (CT) allow for three-dimensional, volumetric data collection. Computed tomography is a widely available technique and has several advantages over MRI in adipose tissue quantification. The superior accuracy of CT over MRI for adipose tissue assessment can be attributed thus: (1) in CT images, absolute Hounsfield-unit (HU) values of pixels correspond directly to tissue property, whereas, in MRI, there is no direct association between tissue property and pixel value; (2) MRI-based signal intensities may be inhomogeneous, in particular at a larger field of view (FoV); and (3) CT has better spatial resolution than MRI ($0.4 \times 0.4 \times 04$ mm^3 vs. $1.5 \times 1.5 \times 15$ mm^3 isotropic resolution, respectively). In addition, the feasibility of MRI is limited due to the long acquisition time and high expenses. However, it is important to note that CT utilizes ionizing radiation for image acquisition.

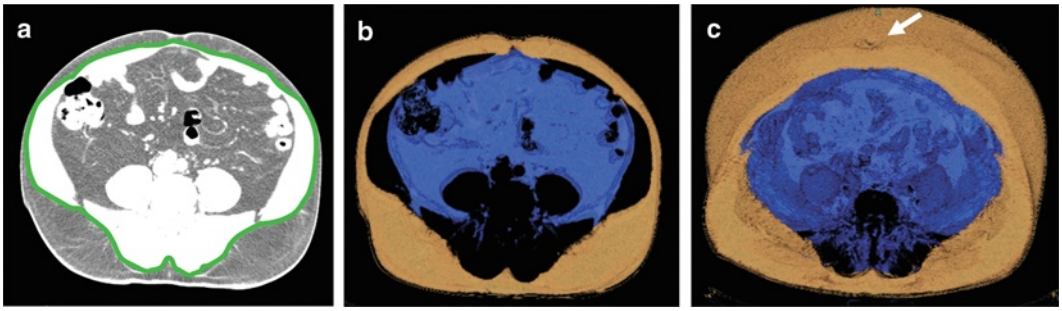

Fig. 50.1 VAT and SAT quantification using CT. *For the black and white image*: Single cross-sectional CT scan at the umbilical level (*panels A and B*) and a 12.5-cm wide volumetric data set (*panel C*). The inner border of subcutaneous abdominal adipose tissue (*SAT*) is traced automatically (*black*). The SAT (*light gray*) area is calculated by subtracting the visceral abdominal adipose tissue (VAT) (*dark gray*) area from the total cross-sectional fat area or total abdominal fat volume. The *arrow* points to the umbilicus in the three-dimensional data set. *SAT* subcutaneous adipose tissue, *VAT* visceral adipose tissue. *For the color image*: Single cross-sectional CT scan at the umbilical level (*panels A and B*) and a 12.5-cm wide volumetric data set (*panel C*). The inner border of subcutaneous abdominal adipose tissue (*SAT*) is traced automatically (*green line*). The SAT (*orange color*) area/volume is calculated by subtracting the visceral abdominal adipose tissue (*VAT*) (*blue color*) area/volume from the total cross-sectional fat area or total abdominal fat volume. The arrow points to the umbilicus in the three-dimensional data set. *SAT* subcutaneous adipose tissue, *VAT* visceral adipose tissue

As the CT attenuation value (Hounsfield unit) of each voxel corresponds directly to the tissue property, a predefined HU range is used for identifying the fat-containing voxels in the CT image. Voxels containing fatty tissue have negative CT attenuation, with values ranging between −100 and −50 HU (Barnes 1992). Several threshold-level settings have been used in the literature for adipose tissue quantification, with an upper attenuation limit of −50 to −30 HU, and a lower attenuation limit of −195 to −150 HU (Maurovich-Horvat et al. 2007; Rossner et al. 1990; Yoshizumi et al. 1999; Table 50.1).

50.2.1 Planimetric or Two-Dimensional Adipose Tissue Quantification

Controversy exists regarding the level of abdominal adipose tissue area measurements. The most commonly used anatomical landmarks for image acquisition are the umbilicus and the level of L4/5, which were highly correlated with the total visceral fat volume (Sjostrom et al. 1986; Yoshizumi et al. 1999; Araki et al. 2010; Chung et al. 2008; Hayashi et al. 2008). Measurement of SAT and VAT area at other anatomical landmarks have been described as well (Hyun et al. 2008; Mundi et al. 2010). Notably, in the Framingham Heart Study cohort, the SAT and VAT area measured at L3/4 provided the best proxy of SAT and VAT burden for both sexes and at different ages (Irlbeck et al. 2010).

The pixels containing fatty tissue are identified in the cross-sectional scan by using predefined HU settings, and the total fat area is calculated by counting the number of pixels. The abdominal muscular wall taken as the inner border of SAT is traced manually or automatically. The SAT area is calculated by subtracting the VAT area from the total cross-sectional fat area (Yoshizumi et al. 1999) (Fig. 50.1, panels A and B).

Table 50.1 Key facts of visceral abdominal adipose tissue subcutaneous abdominal fat

Key facts of visceral abdominal adipose tissue (VAT) and subcutaneous abdominal fat (SAT)
– VAT is the largest visceral adipose tissue compartment of the human body.
– VAT has stronger association with cardiovascular and metabolic risk factor than SAT.
– VAT is associated with increased prevalence of cardiovascular events.
– VAT secretes several adipokines, modulating energy balance, utilization, and metabolism, and also local and systemic inflammation.
– CT is the gold standard for VAT and SAT quantification, with both area and volume measures being established in the literature.

This table summarizes key facts about visceral abdominal adipose tissue (*VAT*) and subcutaneous abdominal fat (*SAT*) and their implication for healthcare-related issues

50.2.2 Volumetric or Three-Dimensional Adipose Tissue Quantification

The inhomogeneous distribution of VAT and SAT throughout the axial length of the abdomen may introduce great variation between the planimetric measurements performed at different anatomical levels. This variation may result in significantly different adipose tissue distribution estimates (Maurovich-Horvat et al. 2007). During volumetric adipose tissue assessment, the SAT and VAT quantities are measured across the total imaging volume (Fig. 50.1, panel C). Using image display settings similar to the previously described planimetric measurements, an automatic or semiautomatic segmentation technique can be performed. The volumetric quantification technique has reproducibility similar to the single cross-section-based planimetric method (Maurovich-Horvat et al. 2007). However, it is important to note that this more robust quantification method comes with an expense of higher radiation dose (2.7 vs. 0.5 mSv).

50.3 Normative Values for Male and Female

As indicated earlier (chapter Measurement Techniques of SAT and VAT), there exist different measurement techniques for the assessment of VAT and SAT mass. Computed tomography is the most commonly used imaging tool for abdominal fat quantification. Three-dimensional volume assessment of VAT and SAT is considered the gold standard. However, it is relatively time consuming, and requires full abdominal CT imaging. Two-dimensional measures may not be accurate (see above). As not a single standard measure for VAT and SAT quantification is established, different normative values have to be acknowledged. Framingham investigators have established normative values for both three-dimensional VAT and SAT volume, as well as fat compartment areas, at multiple specific anatomical landmarks in unselected general population (Table 50.2) (Fox et al. 2007; Irlbeck et al. 2010). When comparing different anatomical landmarks with the fat volume, investigators found close correlation for all investigated landmarks ($r \geq 0.87$, $p < 0.001$), with best performance at the level of L3/4 ($r = 0.96$ for SAT volume in women, 0.99 for VAT volume in women and both fat compartments in men, $p < 0.001$ for all). In contrast, the absolute values for axial fat area differed by more than twofold, depending on location (Irlbeck et al. 2010). These results indicate that axial area measures satisfactorily represent VAT and SAT volume; however, a consistent location for the axial fat measure should be assured.

It has to be acknowledged that normative values, established by investigation of the Framingham cohort, are predominantly based on Caucasian Americans. Therefore, generalization to other ethnic groups may be uncertain. When investigating middle-aged African-American, Hispanic, and white American men and women, Carroll et al. found that African-American men and women had significantly

Table 50.2 Normative values for three-dimensional VAT and SAT volume as well as axial VAT and SAT area at different anatomical landmarks demonstrated as means ± standard deviation, as defined in the unselected general population of the Framingham Heart Study (modified from Fox et al. 2007; Irlbeck et al. 2010)

	Men		Women	
	VAT	SAT	VAT	SAT
Volume (cm^3)	2,159 ± 967	2,603 ± 187	1,306 ± 807	3,071 ± 1,444
L 1/2 (cm^2)	234 ± 99	172 ± 88	104 ± 72	170 ± 86
L 2/3 (cm^2)	208 ± 101	168 ± 79	104 ± 77	192 ± 107
L 3/4 (cm^2)	198 ± 94	215 ± 93	115 ± 81	235 ± 119
Umbilicus (cm^2)	181 ± 78	229 ± 105	118 ± 78	258 ± 137
L 4/5 (cm^2)	158 ± 72	240 ± 115	122 ± 73	297 ± 126
Iliac crest (cm^2)	156 ± 71	241 ± 109	119 ± 69	307 ± 132
L 5/S 1 (cm^2)	108 ± 44	207 ± 110	100 ± 56	320 ± 135

Men tend to have more VAT, whereas women have more SAT. The largest areas of VAT are present at upper parts of the abdomen, whereas the SAT area is higher at lower anatomical landmarks
VAT visceral adipose tissue, *SAT* subcutaneous adipose tissue

Table 50.3 VAT and SAT volume and area in selected studies of different ethnic groups and collectives

Collective	Gender	Measurement site	VAT	SAT	Reference
Non-diabetic Caucasians	Women	L2–L5	40 cm^2	169 cm^2	Mundi et al. (2010)
	Men	L2–L5	74 cm^2	133 cm^2	
Unselected Koreans	Both	Umbiculus	130 cm^2	139 cm^2	Chung et al. (2008)
Insulin-resistant Japanese Americans	Both	Umbiculus	67 cm^2	139 cm^2	Hayashi et al. (2008)
Unselected premenopausal Korean	Women	L1	88 cm^2	147 cm^2	Hyun et al. (2008)
		L4	74 cm^2	207 cm^2	
Obese Japanese children	Both	Umbiculus	63 cm^2	n/a	Araki et al. (2010)
Caucasian American youth	Women	Volume	112 cm^3	899 cm^3	Liu et al. (2010)
	Men	Volume	96 cm^3	621 cm^3	
African-American youth	Women	Volume	67 cm^3	988 cm^3	Liu et al. (2010)
	Men	Volume	96 cm^3	612 cm^3	

VAT visceral adipose tissue, *SAT* subcutaneous adipose tissue
A selected list of publications demonstrating that normal values of VAT and SAT are dependent on age, gender, ethnicity, and measurement technique

less VAT compared to white and Hispanics. In contrast, the amount of SAT was higher in African Americans, and whites had the least total abdominal fat volume (Carroll et al. 2008). Table 50.3 summarizes selected findings of different studies on VAT and SAT in different ethnic groups and collectives.

Moreover, there is a significant gender difference in the amount and distribution of abdominal fat. Men have a significantly larger VAT volume, whereas women tend to have slightly more SAT, especially at lower abdominal regions (L4/5 and below) (Maurovich-Horvat et al. 2007; Fox et al. 2007; Irlbeck et al. 2010).

50.4 Applications to Other Areas of Health and Disease: Association with Metabolic Risk Factors and Cardiovascular Disease

The association of VAT and SAT with cardiovascular risk factors has been investigated in multiple studies. Framingham investigators described that both VAT and SAT were significantly associated with hypertension, dyslipidemia, impaired fasting glucose, and the metabolic syndrome; however,

Table 50.4 Multivariable-adjusted regression for SAT and VAT with metabolic risk factors in the Framingham Heart Study (modified from Fox et al. 2007)

	Women					Men				
	VAT		SAT		*p*-Value	VAT		SAT		*p*-Value
Risk factor	Effect size	*p*-Value	Effect size	*p*-Value	for VAT vs. SAT	Effect size	*p*-Value	Effect size	*p*-Value	for VAT vs. SAT
SBP	4.8	<0.001	3.9	<0.001	0.10	3.3	<0.001	2.3	<0.001	0.01
Log TG	0.23	<0.001	0.14	<0.001	<0.001	0.22	<0.001	0.10	0.003	<0.001
HDL	−5.9	<0.001	−3.9	<0.001	<0.001	−4.5	<0.001	−2.0	<0.001	<0.001
HTN	2.1	<0.001	1.7	<0.001	<0.001	1.9	<0.001	1.5	<0.001	0.006
IFG	2.5	<0.001	2.0	<0.001	0.001	1.8	<0.001	1.5	<0.001	0.005
MetS	4.7	<0.001	3.0	<0.001	<0.001	4.2	<0.001	2.5	<0.001	<0.001

VAT visceral abdominal adipose tissue, *SAT* subcutaneous abdominal adipose tissue, *SBP* systolic blood pressure, *TG* triglycerides, *HDL* high-density lipoproteins, *HTN* hypertension, *IFG* impaired fasting glucose, *MetS* metabolic syndrome

Both VAT and SAT are significantly associated with cardiovascular and metabolic risk factors in women and men. However, associations are stronger for VAT when compared to SAT

when comparing VAT and SAT, the visceral fat volume had significantly stronger association compared to subcutaneous fat (Table 50.4) (Fox et al. 2007). Potential explanations for the specific metabolic risk factors are listed as follows:

- VAT and hypertension: It is estimated that about 70% of cases of hypertension could be attributed to obesity. Besides the liver, adipose tissue is an additional source of angiotensinogen. Therefore, an increased amount of VAT leads to increased levels of angiotensin I and, consecutively, angiotensinogen II. Interestingly, adipocytes themselves express angiotensinogen II receptors, which can hamper the differentiation of preadipocytes to adipocytes. This leads to formation of large dysfunctional adipocytes, which secrete increased amounts of angiotensinogen. Additionally, leptin, which is produced and secreted by adipose tissue, activates the sympathetic nervous system through a melanin-dependent pathway within the hypothalamus (Tallam et al. 2005).
- VAT and dyslipidemia: Due to its location, surrounding the vasculature that drains into the portal vein, VAT can influence hepatic metabolism. It has been suggested that an increased amount of VAT leads to increased delivery of free fatty acids to the liver. This may contribute to the synthesis of triglyceride-enriched very low density lipoproteins (VLDL) and consecutively small, dense, low-density lipoproteins (LDL), one of the key features of visceral adiposity-related risk (Lamarche et al. 1998). Moreover, in viscerally obese individuals, high-density lipoproteins (HDL) levels are decreased, and HDL particles are smaller and denser, resulting in a reduced efficiency in quenching reactive oxygen species (Navab et al. 2005).
- VAT and impaired fasting glucose and diabetes: There is substantial evidence that VAT, and not SAT, is predictive of insulin resistance. For instance, when matching individuals for SAT, the amount of VAT is markedly differentiated by levels of insulin resistance and glucose tolerance, whereas after matching for VAT, the amount of SAT is not of additional value (Ross et al. 2002). It is proposed that the link between VAT and disordered glucose metabolism is a mixture of increased free fatty acid exposure to the liver, the endocrine activity of the visceral adipose tissue itself, and the fact that excessive visceral adiposity is a marker of the relative inability of the subcutaneous fat to store the increased energy surplus.

Consecutively, increased amounts of VAT are associated with presence of cardiovascular disease. It has been acknowledged that VAT is associated with presence of plaque in vascular territories in the whole body, indicating a systemic proatherogenetic effect of VAT (Table 50.5) (Mahabadi et al. 2009).

Table 50.5 Multivariable adjusted associations of VAT with presence of overall cardiovascular disease, coronary heart disease, myocardial infarction, and stroke in the Framingham Heart Study. Multivariable adjustment included age, gender, body mass index, and waist circumference (modified from Mahabadi et al. 2009)

	Odds ratio (95% Confidence Interval)	*p*-Value
Cardiovascular disease	1.46 (1.11–1.92)	0.007
Coronary heart disease	1.36 (1.02–1.82)	0.04
Myocardial infarction	1.38 (0.91–2.08)	0.13
Stroke	1.83 (1.01–3.30)	0.046

Visceral abdominal adipose tissue is significantly associated with the presence of cardiovascular disease and both coronary heart disease and stroke, even after adjustment for general measures of obesity. This suggests a systemic influence of VAT on development of cardiovascular disease

50.5 Diet, Exercise, and Obesity Surgery-Induced Changes of VAT and Total Fat

Because of its implications for cardiovascular disease risk, reduction of visceral adipose tissue is of specific interest. Fortunately, the amount of VAT decreases to a greater degree than total fat mass during negative energy balance. Multiple studies have investigated whether low-calorie diet alone, physical activity alone, or combination of both is most beneficial. However, results from the different studies are conflicting. A meta-analysis of 37 studies on VAT reduction by weight-loss interventions including caloric restriction, endurance exercise, resistance exercise, and bariatric surgery found that changes in VAT are primarily determined by the overall fat mass changes as well as the initial VAT to total fat mass ratio. Interestingly, results were not significantly different for men and women (Hallgreen and Hall 2008).

When investigating factors leading to visceral and subcutaneous adiposity primarily, researchers from the Fels Longitudinal Study found that rapid infant weight gain, male gender, maternal age, and low physical activity were associated with presence of visceral adiposity at a mean age of 47 years. Absolute birth weight as well as maternal weight are associated with later increased amounts of SAT, however, not with VAT (Demerath et al. 2009).

50.5.1 Associations Between Abdominal Adipose Tissue Compartments and Other Adipose Tissue Depots of the Body

Both VAT and SAT are associated to general measures of obesity, such as BMI and waist circumference (Table 50.6). However, in humans, the development of obesity not only leads to an increase in adipose tissue depots in classical locations, such as in the subcutaneous and visceral adipose tissue compartments, but also around specific organs, such as the heart (pericardial), blood vessels (perivascular), and the kidney (renal), or internal organs, such as skeletal muscle (intramuscular) and liver (intrahepatic), which have all been described as locations for ectopic fat storage (Speliotes et al. 2008; Thalmann and Meier 2007). The excessive regional adipose tissue deposits may alter organ function by means of mechanical compression or through secreted cytokines and chemokines (Thalmann and Meier 2007). Visceral adipose tissue assessment requires tomographic imaging

Table 50.6 Association of VAT and SAT with BMI, waist circumference, and waist/hip ratio (modified from Snell Bergeon et al. 2004)

	VAT	SAT
BMI	0.70*	0.88*
Waist circumference	0.78*	0.83*
Waist/hip ratio	0.57*	0.46*
SAT	0.65*	–

Both VAT and SAT are closely associated with general measures of overall and abdominal obesity
VAT visceral adipose tissue, *SAT* subcutaneous adipose tissue, *BMI* body mass index
*$p < 0.001$

techniques, which are expensive and time consuming. By using an "easier to access" adipose tissue depot, such as the pericardial fat compartment, as proxy for visceral adipose tissue quantification, a refined clinical cardiometabolic risk assessment might be feasible.

50.5.1.1 Intrathoracic Adipose Tissue, Pericardial Adipose Tissue, and VAT

Intrathoracic adipose tissue is defined as any adipose tissue located within the thorax from the diaphragm, to the level of the right pulmonary artery; the pericardial adipose tissue compartment is located within the pericardial sac (Rosito et al. 2008). It is about one-tenth of the size of the VAT compartment; however, due to its proximity to the coronary arteries, it might have a significant role in the development of coronary artery disease (Mahabadi et al. 2009). Both intrathoracic and pericardial fat volumes were closely correlated with VAT in women (r = 0.76 and 0.62, respectively) and men (r=0.76 and 0.63, respectively) in the Framingham Heart Study (Rosito et al. 2008). Another study, utilizing ultrasound for pericardial fat assessment, and CT for VAT quantification, showed a similarly good correlation between VAT and pericardial fat compartments (Iacobellis et al. 2003). Thus, pericardial fat may be an overall marker of VAT accumulation. Pericardial fat can be quantified with echocardiography, or during chest CT, without incurring excess abdominal radiation. Pericardial fat may yield additional information on metabolic risk, which may be particularly useful when abdominal imaging with VAT quantification is not feasible (Rosito et al. 2008).

50.5.1.2 Intramuscular and Intrahepatic Adipose Tissue and VAT

Similar to VAT, insulin resistance correlates tightly with the intramuscular and intrahepatic lipid content, which can be quantified non-invasively using computed tomography (Speliotes et al. 2008). With increased lipid content, decreased CT attenuation values are measured in muscle or liver cross-sectional images. This is because CT attenuation values for skeletal muscle, or for the liver, are positive, whereas attenuation values for adipose tissue are negative. Further research is warranted to determine the association between the intramuscular and the intrahepatic adipose tissue and VAT.

50.6 Endocrine Activity of Adipose Tissue

Since the discovery of the first adipokine, leptin, in 1994, the understanding of adipose tissues has changed from a simple energy-storing compartment to a complex organ, contributing to energy management of the body, and interacting with systemic and local inflammation. During the last few years, an increasing number of adipokines, such as adiponectin and resistin, have been discovered. Moreover, associations of adipose tissues with pro- and anti-inflammatory cytokines and chemokines, including tumor necrosis factor alpha, different interleukins, monocyte chemotactic protein 1, and others, were established in the literature. This field of research is of constant novel discoveries; however, certain mechanisms have been established and will be discussed as follows:

- *Leptin*: Leptin is a 16 kDa peptide that is predominantly secreted by white adipose tissue. The levels of circulating leptin are directly proportional to the total amount of fat in the body. Moreover, leptin levels are positively correlated with levels of insulin, and negatively correlated with glucocorticoid concentration. By stimulating receptors in the cortex, the hippocampus, and, most importantly, the hypothalamus, leptin plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. However, it also has been described to regulate pancreatic islet cells, growth hormone levels, immunology homeostasis, osteogenesis, gastrointestinal function, and puberty. Congenital leptin deficiency is a rare but severe cause of early onset obesity, hypogonadism, hyperinsulinemia, hyperphagia, and impaired T-cell mediated immunity, which can be treated with recombinant leptin. In contrast to patients with congenital leptin deficiency, chronically obese patients have enduringly increased levels of leptin, leading to resistance due to leptin receptor signaling defects, downstream blockade in neuronal circuits, and defects in leptin transport across the blood–brain barrier. As a vicious circle, this leads to a lack in the feeling of satiety after eating.
- *Adiponectin*: Adiponectin is a 30 kDa protein that accounts for 0.01% of human plasma protein. It is exclusively secreted by the adipose tissue into the bloodstream, but also locally affects surrounding tissue as well as blood vessels. In contrast to most other adipokines, plasma levels of adiponectin decreases with increasing fat volume. Accordingly, adiponectin is also negatively correlated with VAT and SAT volumes. It is suggested to have an anti-thrombotic effect by acting as an endogenous anti-thrombotic factor; additionally, an anti-inflammatory effect by inhibition of macrophage activation and foam cell accumulation has been described. Moreover, adiponectin has been reported to act as a stabilizer of the inhibitor of nuclear factor kappa B. On a cellular level, adiponectin induces endothelial intercellular adhesion molecule 1 (ICAM-1) and vascular cell-adhesion molecule 1 (VCAM-1) expression and augments endothelial nitrous oxide production. Moreover, hypoadiponektinemia is correlated with increased atherosclerosis-related compounds, such as adipocyte fatty-acid-binding protein (A-FABP), lipoclin-2, and other markers of oxidative stress. Cardiovascular disease, such as stroke and coronary heart disease, and also non-alcoholic fatty liver disease and insulin resistance, are associated with decreased levels of adiponectin, with data suggesting a predictive value of plasma adiponectin levels for cardiovascular disease.
- *Resistin*: Resistin is a 12 kDa protein that is predominantly produced by mononuclear cells, and also by a number of other tissues, including white adipose tissue. Accordingly, it is positively correlated with VAT and SAT volume. Resistin stimulates inflammatory cytokines, such as interleukin 1, 6, and 12 as well as tumor necrosis factor alpha through a nuclear-factor-kappa-B-dependent pathway. Additionally, it reduces the production of intercellular adhesion molecule 1 (ICAM-1), vascular cell-adhesion molecule 1 (VCAM-1), and CC chemokine ligand 2 (CCL-2) in the endothelial cell. In mice, a diabetologic role of resistin has been described; however, whether these results can be assigned to human diabetes remains controversial.

- Further, hormone-like proteins, such as apelin, visfatin, hepcidine, omentin, vaspin, adipsin, and angiopoietin, have suggested association to visceral and subcutaneous adipose tissue. However, more research is needed to define established mechanisms and pathways.
- *Chemokines and cytokines*: Adipocytes secrete numerous pro-inflammatory (interleukin 1, 6, and 8, tumor necrosis factor alpha, and others) as well as anti-inflammatory (including interleukin 4 and 10 and transforming growth factor beta) cytokines and chemokines. Therefore, together with the adipokines, they can influence local and systemic inflammation.

As indicated above, there is a direct relationship between obesity and inflammation. Due to its size, it being the largest visceral adipose tissue of the body and due to its location, thereby draining directly into portal circulation, VAT plays a key role in this association. Accordingly, the amount of VAT was found to be associated with systemic inflammatory markers, including C-reactive protein (CRP), monocyte chemoattractant protein (MCP), intracellular adhesion molecule (ICAM)-1, and plasminogen activator inhibitor type 1 (PAI-1) antigen, with associations to all but CRP reaching statistical significance, even after adjusting for global adiposity (Sam et al. 2009). However, in the same study, SAT was not found to be related to any systemic inflammatory markers after adjustment for body mass index. As inflammation is a key player in the development of atherosclerotic plaque, this may, in addition to the association of obesity with other cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, as demonstrated above, explain the association of obesity and of visceral obesity, in particular, with cardiovascular disease.

Summary Points

- Visceral and subcutaneous adipose tissue of the abdomen differ with respect to cell size, fatty acid composition, protein content, fatty acid metabolism, enzyme expression, and glucose utilization. These differences lead to diverse implications on the metabolic and cardiovascular status.
- Both VAT and SAT are significantly associated with cardiovascular risk factors, such as hypertension, dyslipidemia, impaired fasting glucose, and the metabolic syndrome; however, when comparing VAT and SAT, the visceral fat volume has significantly stronger association compared to subcutaneous fat.
- Increased amounts of VAT are associated with presence of cardiovascular disease. It has been acknowledged that VAT is associated with presence of plaque in vascular territories in whole body, indicating a systemic proatherogenetic effect (of VAT).
- For VAT and SAT quantification using CT, the abdominal muscular wall is manually or automatically traced on axial images. Fat areas and volumes are calculated by summation of pixels, attributable to fat (upper attenuation limit of −50 to −30 HU and lower attenuation limit of −195 to −150 HU).
- Three-dimensional volume assessment of VAT and SAT is considered the gold standard. However, it is relatively time consuming and requires full abdominal CT imaging. Despite the VAT and SAT volume, the fat area at the level of the umbilicus is most commonly used in the literature.
- There is significant gender and ethnicity difference in abdominal fat distribution. Men have more VAT; women have slightly more SAT, especially at lower abdominal regions (L4/5 and below). African Americans have less VAT but more SAT than whites and Hispanics, whereas whites have the least total abdominal fat volume.
- Rapid infant weight gain, male gender, maternal age, and low physical activity are predictors of adult visceral adiposity. Absolute birth weight and maternal weight are associated with later increased amounts of SAT, however, not with VAT.

- Overall fat mass changes as well as the initial VAT to total fat mass ratio are primarily determinants of VAT reduction during weight-loss interventions in both men and women.
- VAT and SAT are correlated with general adiposity measures, such as BMI and waist circumference, and also with other ectopic fat storage, including pericardial, intrathoracic, intramuscular, and hepatic fat.
- Adipose tissue secretes several hormone-like peptides (adipokines), such as leptin, adiponectin, resistin, and others. These modulate not only energy balance, utilization, and metabolism, but also local and systemic inflammation. In addition, adipocytes themselves secrete multiple pro- and anti-inflammatory cytokines and chemokines.
- As inflammation is a key player in the development of atherosclerotic plaque, the relation of obesity with local and systemic inflammation may, in addition to the association of obesity with other cardiovascular risk factors, explain the association of obesity and of visceral obesity, in particular, with cardiovascular disease.

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Chapter 51
Measures of Waist Circumference

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Abstract Waist circumference measurement is recommended in the clinical assessment of obesity and is a useful marker of total and abdominal body fat in genetic and epidemiologic research. Waist circumference measurement is non-invasive and is easily accomplished by trained observers in clinical and research settings. Consensus on the most appropriate measurement location has yet to be reached and several different sites and measurement protocols have been proposed. The importance of developing a systematic approach for identifying and marking the measurement site, positioning the tape, and recording the measurement cannot be understated. In this chapter, we present a description of the measurement of waist circumference. We include information on tape measures, measurement sites, and measurement guidelines. We present a detailed outline that will help clinicians and researchers to efficiently and reliably obtain accurate measurements of waist circumference.

Abbreviations

WAIST Waist circumference

51.1 Introduction

Waist circumference (WAIST) is a measure of abdominal girth. WAIST reflects both total body and central adiposity, predicts intra-abdominal adipose tissue mass better than the body mass index, and is associated with cardiometabolic disease risk (Klein et al. 2007). WAIST measurement is recommended in the clinical assessment of obesity and related metabolic disorders, and has proven to be a highly informative marker of adiposity in genetic and epidemiologic research.

WAIST measurement is non-invasive and is easily accomplished by trained observers in clinical and research settings. Self-measurement of WAIST is not recommended (Bigaard et al. 2005). Observers can routinely take measurements using an accurately calibrated and non-stretch tape measure. Patients must expose their midriff so that measurements can be made on the skin.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_51,

The measuring tape is positioned parallel to the floor and perpendicular to the long axis of the body. Unfortunately, the medical and research communities have not yet reached consensus on the most appropriate measurement location. Several different sites and measurement protocols have been used to determine WAIST. Important anatomical landmarks used in the location of measurement site include the iliac crest and the lower costal margin. Consolidation of WAIST measurement guidelines into a universally accepted methodology would have many advantages; however, further research will be required before consensus is reached (Misra et al. 2005).

In this chapter, we describe the measurement of WAIST from a practical standpoint, by evaluating and synthesizing information from professional consensus statements, original research reports, and online resources. We include information on tape measures, measurement sites, and measurement guidelines. Our objective was to create a detailed guideline that will enable clinicians and researchers to efficiently and reliably obtain accurate measurements of WAIST.

51.2 Measuring Tapes

Body measuring tapes are made of plastic or steel. These tapes have been used to measure head, leg, arm, and WAIST and have a long history of use in anthropometry. An appropriate body measuring tape must be non-stretch, accurately calibrated, durable, portable, and ergonomic. Tapes made from flexible material are often required to take accurate measurements. It is also important that the tape maintains its dimensions through repeated use; this should be evaluated at predetermined intervals. Furthermore, the width of the tape is also an important consideration, given that it must be of sufficient size so that the calibration marks are clearly visible when the tape is placed, with appropriate tension, around the abdominal site. Tape tension indicators and fixed tension tapes have been developed, and should help to minimize observer error.

Steel tapes, such as the Lufkin W606PM, are stretch resistant, and should retain accuracy indefinitely. As steel tapes do not easily adjust to irregular surfaces, plastic fiber tape measures may be more appropriate for use in obese individuals, and are widely available. The Gulick II plus (Fig. 51.1) measuring tape was developed specifically to ascertain body circumferences, and features an indicator device containing a steel spring that purportedly enables the observer to apply a consistent tension during each measurement. Each indicator is calibrated to clearly indicate when 4 oz (100 g) of tension is applied. Similarly, the Figure Finder Tape Measure (Fig. 51.2) also enables a consistent 100 g of tension to be applied during the measurement. The Seca 201 (Fig. 51.3) was also developed specifically for body circumference measurements. The zero end of the tape can be positioned into a slot in the casing, enabling the observer to free one hand during tape placement. This feature also eliminates the need to have the subject hold the casing at any point during the measurement procedure. The tape is then allowed to retract around the abdomen and presumably exert an appropriate tension that is consistent across consecutive measurements. Devices that enable observers to apply a constant tension during measurement are not typically found in measuring tapes and, if accurate, should improve measurement accuracy and precision. Manufacturer details are presented in Table 51.1.

Unfortunately, objective evaluations of the accuracy, precision, and durability of these tapes are unavailable. The details presented above are meant to expose the reader to some of the options available. We encourage observers to test several tapes to determine the one most appropriate for their needs, "*The carpenter who uses a tool is a better judge of its efficiency than the smith who forges it*" (Pearson 1900).

Fig. 51.1 The Gulick II plus measuring tape

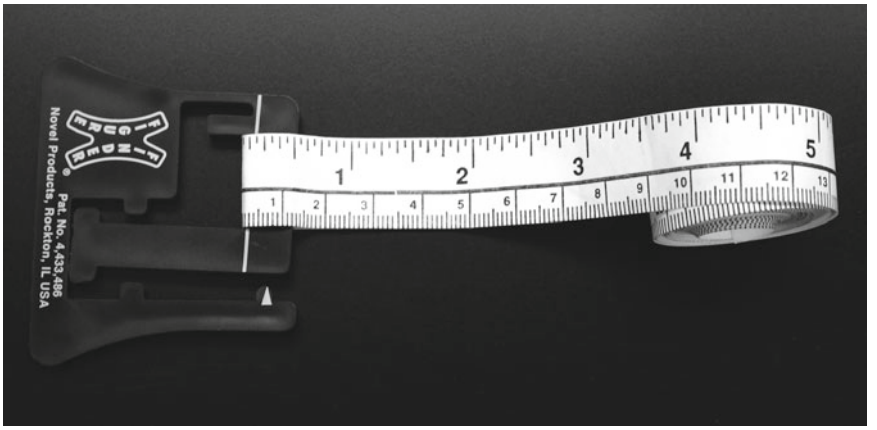

Fig. 51.2 The Figure Finder measuring tape

Fig. 51.3 The Seca 201 measuring tape

Table 51.1 Tape measures for waist circumference (WAIST)

	Manufacturer
Lufkin W606PM	Cooper, www.cooperhandtools.com
Gulick II plus	Country Technology, www.fitnessmart.com
Figure Finder Tape Measure	Novel Products, www.novelproductsinc.com
Seca 201	Seca, www.seca.com

51.3 Measurement Sites

Multiple measurement sites have been proposed. The most commonly used sites are the:

1. Narrowest waist
2. Midpoint between the lower costal region (lowest rib) and the upper border of the iliac crest
3. Upper border of the iliac crest (suprailiac crest)
4. Lower costal margin (lowest rib); and
5. Umbilicus

Sites 1, 2, and 3 have been recommended by Anthropometric Standardization Consensus Group (Lohman et al. 1988), the World Health Organization (www.who.int/chp/steps), and the United States National Institutes of Health (NIH 1998; www.nhlbi.nih.gov/guidelines/obesity), respectively. Studies linking WAIST to disease and disease risk have typically used sites 1, 2, and 4. Reproducibility is generally reported to be high at all of these sites (Wang et al. 2003; Mason and Katzmarzyk 2009). Studies have demonstrated, however, that WAIST can differ significantly depending on measurement site (Wang et al. 2003; Mason and Katzmarzyk 2009), and universal agreement has not been reached regarding the most appropriate site (Tables 51.2 and 51.3). Recently, consensus on the use of the site just above the upper border of the iliac crest has been reached by a number of professional societies in the USA (Klein et al. 2007). The bony landmarks used in the identification of these sites are illustrated in Fig. 51.4.

51.3.1 Narrowest Waist

This measurement must be taken at the narrowest region between the lowest rib and the iliac crest (Fig. 51.5). Although reported to be easy to identify in the majority of subjects (Wang et al. 2003), a single narrowest waist may be difficult to determine in individuals with abdominal obesity. Furthermore, as no anatomical landmarks are used to identify this site, WAIST measures taken at this location may be prone to greater inter- and intra-observer errors than at other sites. Multiple measurements of abdominal circumference may be required to determine this location. These concerns notwithstanding, reproducibility has been reported to be high at the narrowest waist site (Wang et al. 2003; Mason and Katzmarzyk 2009).

51.3.2 Midpoint Between Iliac Crest and Lowest Rib

To accurately identify this site, the lowermost costal region and the upper border of the iliac crest must be located (see later for details on identifying these landmarks). The distance between the two landmarks is measured, and a third horizontal line is drawn at the midpoint where the measurement is taken. Identification of this site is time-consuming, but its use is recommended by the World Health Organization. The location of this site is shown in Fig. 51.6.

Table 51.2 Sources for waist circumference (WAIST) measurement guidelines

- Anthropometric Standardization Consensus Group[a]
- World Health Organization, STEPS instrument[b]
- NHLBI Obesity Education Initiative Expert Panel[c]
- NHANES III, Anthropometric Procedures Video[d]
- Health Canada[e]

[a] Lohman et al. (1988)
[b] World Health Organization, STEPS Surveillance Manual, www.who.int/chp/steps/en
[c] The practical guide for the identification, evaluation, and treatment of overweight and obesity in adults, www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm
[d] NHANES III, Anthropometric Procedures Video, www.cdc.gov/nchs/about/major/nhanes/avideo.htm
[e] Health Canada, www.hc-sc.gc.ca/hpfb-dgpsa/onpp/cg_bwc_introduction_e.htm

Table 51.3 Most widely accepted measurement sites

Site	Origin
Narrowest waist	Anthropometric Standardization Consensus Group[a]
Midpoint between the lowest rib and the iliac crest	WHO guidelines[b]
Above the uppermost border of the iliac crest	NIH guidelines[c]

[a] Lohman et al. (1988)
[b] World Health Organization, STEPS Surveillance Manual, http://www.who.int/chp/steps/en
[c] The practical guide for the identification, evaluation, and treatment of overweight and obesity in adults, www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm

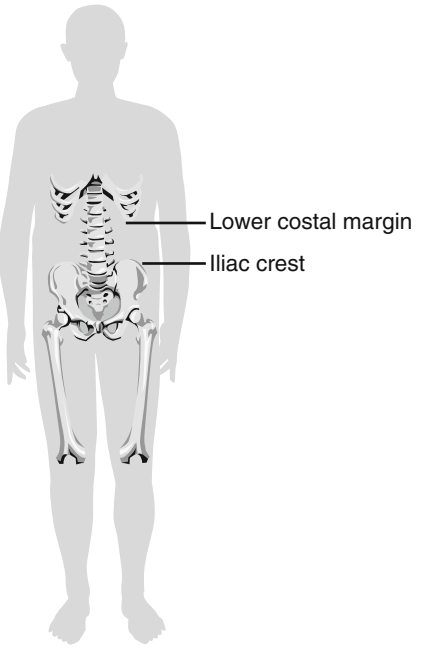

Fig. 51.4 Bony landmarks used to identify waist circumference (WAIST) measurement sites. The lower costal margin, also known as the lowest rib, is located by palpating the anterior region of the right lateral costal margin. The iliac crest is identified by palpating the right hip region to locate the ileum

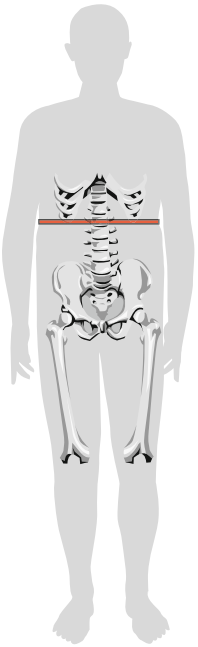

Fig. 51.5 Measuring tape positioned at the narrowest waist location. Measurements at this location are taken on the right side of the body at the narrowest identifiable region between the lowest rib and the iliac crest

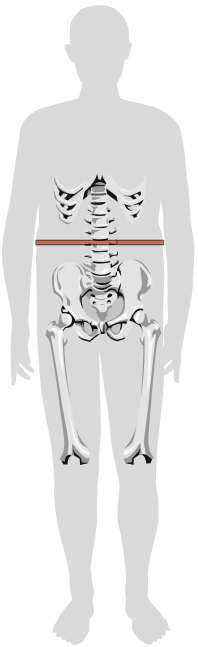

Fig. 51.6 Measuring tape positioned at midpoint between the iliac crest and the lowest rib. Measurements at this location are taken on the right side of the body halfway between the lowest rib (lower costal region) and the uppermost border of the right ileum

51.3.3 Upper Border of the Iliac Crest

This site is readily identified by palpating the right hip bone to locate the ileum. The measurement is taken immediately superior to the uppermost border of the right ileum (Fig. 51.7). Abrupt abdominal curvature often occurs at this location and, consequently, problems with positioning the measuring tape have been reported (Wang et al. 2003). Nevertheless, WAIST measurements taken at this site are

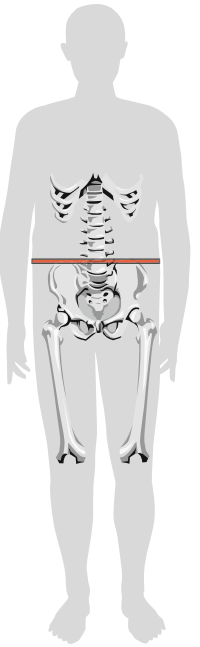

Fig. 51.7 Measuring tape positioned at the upper border of the iliac crest site, Measurements at the upper border of the iliac crest are taken immediately above the uppermost border of the right ileum

reproducible and are strongly related to intra-abdominal adipose tissue and total body adiposity (Wang et al. 2003). This site was used in the National Health and Nutrition Examination Survey (NHANES III), and is recommended by the National Institutes of Health and several other professional medical societies in the United States (Klein et al. 2007).

51.3.4 Lowest Rib

This site is relatively easy to identify and can be located by palpating the anterior region of the right lateral costal margin (Fig. 51.8). If difficulty in locating the lowest rib is encountered, request the subject to inhale deeply, and then palpitate to locate the lowest rib as the subject exhales (www.phenxtoolkit.org). The measurement should be taken immediately beneath the lowest rib (inferior margin of lowest rib). This use of this site is not typically advanced and is likely to correspond to the narrowest waist site in many subjects (Wang et al. 2003).

51.3.5 Umbilicus

Measurement of WAIST at the umbilicus is common, likely due, in part, to the ease at which this site can be identified. Reports also indicate that this site is associated with cardiometabolic morbidity and mortality (Ross et al. 2008). Measurement at this site has not been recommended by any national or international bodies, but is likely to coincide with measurements taken at the upper border of the iliac crest in most subjects.

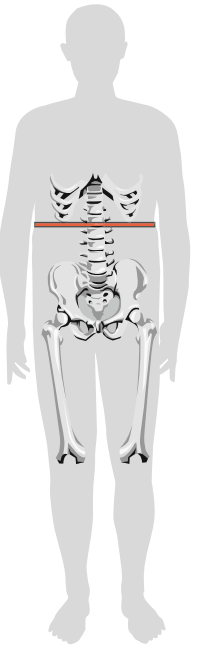

Fig. 51.8 Measuring tape positioned at the lower costal margin. Measurements at this location are taken on the right side of the body immediately below the lowest rib

51.4 Measurement Guidelines

The procedural guidelines detailed here have been adapted from guidelines proposed by the United States National Institutes of Health (National Institutes of Health 1998; www.nhlbi.nih.gov/guidelines/obesity), the Canadian Guidelines for Body Classification in Adults (Douketis et al. 2005), and the World Health Organization (www.who.int/chp/steps; WHO 2000). Furthermore, information from these guidelines has been augmented with details from a recent research report and several online resources (Agarwal et al. 2009; www.phenxtooliit.org; www.cardiometabolic-risk.org; www.hc-sc.gc.ca; and www.cdc.gov/nchs/about/major/nhanes).

51.4.1 Subject Preparation

Measurements should be taken on fasted subjects (Agarwal et al. 2009), preferably after an overnight fast. The observer should fully explain the procedure and request that the subject remove shoes and upper body clothing. Ideally, the subject would wear a hospital gown and minimal underwear during the procedure. All clothing must be removed from the abdominal area.

51.4.2 Subject Posture

WAIST is typically measured in the standing position, barefoot, either with feet touching or separated by shoulder width (25–30 cm). One established protocol recommends that measurements be taken with heels, occiput, and buttocks in contact with a wall (Lohman et al. 1988). Ultimately, feet should be

placed in a position that enables the subject to remain comfortable while standing, with eyes looking straight ahead for the duration of the procedure. The arms can hang freely at the sides or should be crossed over the chest, while the tape is being positioned and the measurement is being taken.

51.4.3 Marking the Measurement Site

The measurement must be made on the skin. A horizontal line of sufficient length should be drawn at the designated measurement site on the right side of the body to intersect the vertical midaxillary line. The midaxillary line runs parallel to the long axis of the body, from the axilla to the hip region. A second line should be drawn at the corresponding site on the left side of the body. If the midpoint of the lower costal region and the upper border of the iliac crest is used, the observer must draw three lines. Observers must ensure that lines are parallel to the floor. A short vertical line should then be drawn at the midaxillary line to intersect the horizontal line at the identified measurement site on the right side. The measuring tape is read on the right side at the intersection of these lines. A cosmetic pencil or washable marker can be used for drawing the lines.

51.4.4 Performing the Measurement

The tape casing should be held in the right hand. Using the left hand, and with the help of the subject, the zero end of the tape should be extended around the thighs and raised to the abdominal level. The zero end is then placed in the right hand so that both ends of the tape are held in the right hand. The left hand is then free to adjust the tape around the abdomen. After the tape is correctly positioned, the left hand can take control of the zero end. The zero end should be placed below the casing end, and aligned with the gradations on the casing end of the tape. Thus, the upper border of the zero end and the lower border of the casing end are juxtaposed at the horizontal line denoting the measurement site. The zero end of the tape is vertically aligned with the marking corresponding to the midaxillary line. Before the measurement is taken, a final check is made to ensure that the tape is appropriately positioned along the right and left markings, and is aligned parallel to the floor. The measurement is taken to the nearest millimeter at the midaxillary line; gradations are read at the lower border of the casing end of the tape.

The tape must be fitted tightly against the skin, but not so tight that the skin and underlying tissue are depressed. These concerns are eliminated by using a tension indicator and fixed tension tapes. Accurate tape placement is better achieved when measurements are taken in front of a wall mirror or when a second observer is present to ensure the tape is correctly positioned on the left side of the abdomen.

51.4.5 Recording the Measurement

The measurement must be taken at eye level to avoid parallax error.

If time permits, two measurements should be taken and averaged. If these differ by more than 0.5 centimeters, a third measurement should be taken. Established protocols offer equivocal guidelines on the respiratory phase at which the measurement should be taken. Given that respiratory phase may influence the measurement (Agarwal et al. 2009), measurements should be taken at a defined

point in the respiratory cycle. The World Health Organization recommends that measurements be recorded at the end of a normal expiration (www.who.int/chp/steps). In general, the subject must be instructed to relax and breathe at tidal volume (Agarwal et al. 2009).

51.5 Conclusions

In the absence of a consensus approach to measurement at this time, we recommend that each clinic or laboratory select an approach proposed by a major professional body. Observers should practice before taking measurements, and determine potential difficulties and obstacles. In particular, it is important to develop a systematic approach to identifying and marking the measurement site, positioning the tape, and recording the measurement.

Summary Points

- WAIST measurements are readily accomplished in clinical and research settings.
- Measurements are taken on the skin using a non-stretch retractable measuring tape; tapes with tension indicators may improve accuracy and precision.
- Subjects should be fasted, barefoot, and in a standing posture with eyes directed straight ahead.
- Universal agreement on the most appropriate measurement site is lacking.
- Commonly used sites include the midpoint between the upper border of the iliac crest and the lower costal margin, just above the upper border of the iliac crest, and the narrowest waist.
- Measurement sites must be clearly marked on the right and left sides of the abdomen and measurements are taken on the right side of the abdomen.
- Two measurements are taken and recorded, if they differ by more than 0.5 cm, a third measurement is made.

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Chapter 52
Trunk:Periphery Fat Ratio

Rachel Novotny

Abstract Overweight and obesity are major health concerns of our time. Body fat has been found to be more predictive of health and disease than overall body mass, central or upper body fat has been more predictive than total body fat, and the distribution of body fat has been found to be more predictive than central or upper body fat. The trunk periphery fat ratio (TPFR) is a measure of the distribution of body fat throughout the body. TPFR is acquired with measures of fat of the body trunk and of the body periphery. TPFR may be measured by subcutaneous skinfold thickness obtained with calipers or by regions of interest from dual energy x-ray absorptiometry (DXA) scans of the whole body. TPFR has been found to vary by sex, ethnicity and rate of maturation where males, Asians, and earlier maturing children have higher TPFR than girls, Whites, African Americans and later maturing children. Birth weight and skeletal breadths (bi-iliac breadth in particular) have been shown to predict TPFR. Earlier versus later maturing boys and girls were also found to have higher TPFR. TPFR may have predictive value for understanding individual and population risk for disease throughout the life span. TPFR variability by sex, ethnicity, birth weight, bi-iliac breadth and maturation rate suggests a possible hormonal or genetic component to the trait. Further research to quantify these risks and protections at different life stages will be valuable to provide targets for research and clinical treatment.

Abbreviations

BMI	Body mass index
DXA	Dual energy X-ray absorptiometry
FAM	Female Adolescent Maturation Study
TPFR	Trunk periphery fat ratio

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_52,

52.1 Introduction

Overweight and obesity are major health concerns of our time, important in the onset of the major chronic diseases. They are often defined using the body mass index (BMI: weight (kg)/height (m^2), Flegal et al. 2009), a measure that reflects lean tissue, in addition to fat tissue. Body fat has been found to be more important than overall body mass, in relation to health; central or upper body fat has been found to be more predictive than body mass, and the distribution of body fat has been found to be more predictive than central or upper body fat (Flegal et al. 2009). Body fat distribution is more relevant to risk for chronic disease, independently of BMI or overall obesity (Calle and Kaaks 2004). BMI is known to be a less valid indicator in older adults, who experience a shift of body fat from the peripheral to the central regions of the body, and in women, who carry more total body fat in peripheral regions than do men. These facts may explain some of the inconsistencies in epidemiologic findings that relate BMI to chronic diseases.

Several measures of central adiposity have been used: especially, waist circumference, computed tomography and magnetic resonance imaging of the central portion of the body, and skinfold thickness of the subscapular, abdominal, and suprailiac fatfolds (Table 52.1). For example, in a study of 421 adult multiethnic women in Hawaii, higher subscapular skinfold thickness was associated with higher diastolic blood pressure (Novotny et al. 1998). These techniques are used to measure central adiposity, which provides important additional information as regards BMI, about risk for health and disease.

Measures of fat distribution are "android" or "gynoid" measurements where, in the former, fat is located around the abdomen, and, in the latter, it is located around the hips. This was first described by Vague (1956, Table 52.2). Vague measured two sets of skinfolds: the nape (of the neck: subscapular) to sacrum ratio, and the brachio (upper arm: triceps) to femoral (thigh) ratio. Together, these gave an index of "masculine" differentiation. Vague noted that the android pattern was associated with increased incidence of premature atherosclerosis, diabetes, gout, and uric calculous disease, whereas gynoid obesity was associated with problems of body mechanics only. More recently, DXA software has defined android and gynoid body regions, of interest (Novotny et al. 2007). Waist (circumference) to height ratio better identified cardiovascular risk than did age-specific BMI percentiles in several

Table 52.1 Techniques to measure central adiposity

Technique
Skinfold thickness: Subscapular, suprailiac, and abdominal
Waist circumference
Computerized tomography
Magnetic resonance imaging

These techniques are used to measure central adiposity, which provides important additional information, about risk for health and disease, as regards body mass index (BMI)

Table 52.2 Techniques to measure of body fat distribution

Measure	Source
Android fat mass/gynoid fat mass	Vague (1956)
DXA: android fat mass/gynoid fat mass	Novotny et al. (2007)
Waist circumference/hip circumference	Lin WY et al. (2002) and Hseih et al. (2003)
Waist circumference/height	Flegal et al. (2009)
Trunk fat mass/peripheral fat mass fat	Novotny et al. (2006), He et al. (2004), Rolland-Cachera et al. (1990), and Frisancho and Flegel (1982)

Measurement of fat distribution and proportion throughout the body provides more information about risk for health and disease than central adiposity measurement alone

populations, including Asians (Lin et al. 2002; Hsieh et al. 2003), and among youth (Kahn et al. 2005). High trunk to extremity fat ratio among youth may increase risk of centralized obesity in adulthood (Rolland-Cachera et al. 1990), serving as an early risk factor that is amenable to modification. Measures of fat distribution and proportion throughout the body provide more information about risk for health and disease than central adiposity measurement alone.

52.2 Practical Methods and Techniques: The Trunk:Peripheral Fat Ratio

A trunk:peripheral fat ratio (TPFR) is acquired with measures of body fat of the trunk and of the body periphery utilizing skinfold thicknesses measured with calipers (subscapular, iliac and/or abdominal for the trunk; and arm, thigh, and/or calf for the periphery), or with output that describes regions of interest from dual energy X-ray absorptiometry (DXA). With either skinfold-thickness measurement or DXA, appropriate calibration, quality control, and standardization of measurements and measurers should be confirmed.

The TPFR is derived from trunk and peripheral (arms plus legs) regions of the DXA output (Fig. 52.1). To calculate the TPFR, DXA measures of body fat from arm and leg regions are first summed from the standard output to estimate peripheral fat. The TPFR is calculated by dividing the DXA trunk regional fat (g) by the peripheral regional fat (g). Thus, TPFR estimates the relative placement of fat in the central portion of the body as compared to the peripheral portion (the limbs). TPFR serves as a tool to examine distribution of body fat throughout the body.

A slightly different formula was used by He et al. (2004), where the pelvic fat mass (i.e., the triangle on the figure) was included in the periphery portion of the ratio. Mueller and Reid (1979) have shown high covariance between the subscapular and the suprailiac skinfolds, and between the triceps and the medial calf skinfolds, suggesting that one of the pair of these measures can be used to estimate trunk and periphery, respectively. Interestingly, they also found that trunk to extremity and upper to lower body fat patterning were essentially the same.

52.3 Population Variability in TPFR

TPFR has been found to vary with sex, ethnicity, and rate of maturation, where males, Asians, and earlier maturing children have higher TPFR than girls, Whites, African-Americans and later maturing children (Tables 52.3 and 52.4). Fat distribution in boys becomes androidal in their late puberty (He et al. 2004). Although increasing evidence points to differences in body fat distribution among ethnic groups (e.g., higher central obesity among Latinos and lower among African Americans, compared to Whites; Wu et al. 2007), evidence is limited for Asian Americans in general (whose obesity-related disease risk appears higher than other ethnic groups), and for Pacific Islanders, whose overall rates of obesity are among the world's highest.

In the Female Adolescent Maturation (FAM) Study, conducted among Asian and White adolescent girls identified through Kaiser Permanente on Oahu in Hawaii, Asians were observed to have smaller total DXA fat mass and anthropometric values compared to Whites or Asian/White mixed girls, but Asians had larger values for the TPFR than both Whites and Asian/White mixed girls (Novotny et al. 2006, Table 52.3). Body fat and weight of the 9–14-year-old FAM girls ($n = 323$) were studied in relation to age, ethnicity, and physical activity. Mean age, calcium intake, weight, and iliac skinfold thickness were 11.5 ± 1.4 years, 736.5 ± 370.7 mg/day, 44.6 ± 13.0 kg, and 12.4 ± 6.1 mm, respectively

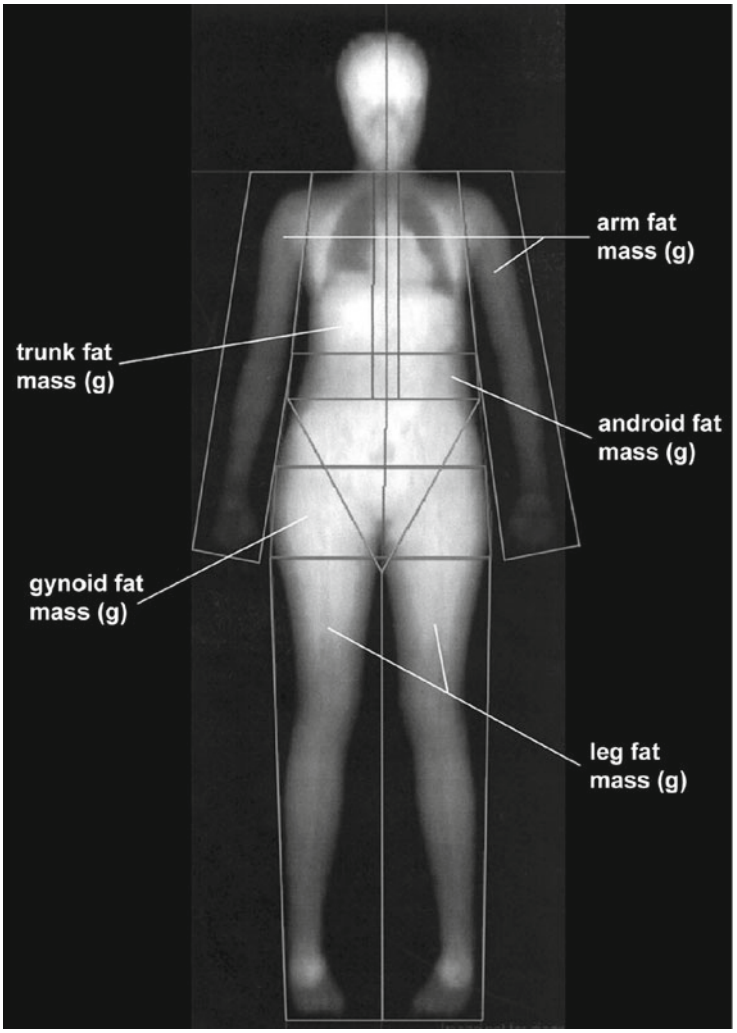

Fig. 52.1 Trunk:periphery fat ratio (TPFR) is derived from trunk (which includes the pentagon-shaped region that includes the upper trunk, android region, and the pelvic triangle) and peripheral (*arm plus leg*) regions of interest, as derived from dual energy X-ray absorptiometry (DXA) by GE Lunar Prodigy. To calculate TPFR, DXA measures of body fat from arm and leg regions are first summed to estimate peripheral fat. Trunk:peripheral fat ratioTPFR is calculated by dividing the DXA trunk regional fat (g) by the peripheral regional fat (g). Thus, TPFR estimates the relative placement of fat in the central portion of the body as compared to the peripheral portion (*the limbs*). TPFR serves as a tool to examine distribution of body fat throughout the body

(Novotny et al. 2004). Multiple regression with age, ethnicity, height, Tanner breast stage, physical activity, energy, soda, and calcium intake explained 17% of the variation in iliac skinfold thickness. Calcium intake, age, and physical activity were significantly negatively associated with iliac skinfold thickness, whereas height, Tanner breast stage, and Pacific-Islander ethnicity were significantly positively associated ($p < 0.0001$, $R(2) = 0.165$). Substituting total calcium with dairy and non-dairy calcium in separate models accounted for 16% and 15% of the variance, respectively ($p < 0.0001$, both models); 1 mg of total and dairy calcium was significantly associated with 0.0025 mm ($p = 0.01$) and 0.0026 mm ($p = 0.02$) lower iliac skinfold thickness. Thus, one additional milk serving was associated with 0.78 mm lower iliac skinfold thickness. The interaction of Asian ethnicity and dairy intake was significant ($p = 0.027$). Non-dairy calcium was not associated with weight or iliac skinfold thickness. Soda intake was significantly positively associated with weight in both models ($p = 0.01$, both models). Thus, decreasing soda and increasing dairy consumption among Asians may help maintain lower central body fat and lower weight during adolescence. Asian ethnicity was an important predictor of TPFR in the FAM study (Novotny et al. 2006). Interestingly, bi-iliac breadth (but not bi-acromial breadth or height) was significantly positively associated, and birth weight was negatively associated, with TPFR.

Table 52.3 Studies examining population differences in Trunk to Periphery Fat Ratio (TPFR)

Author, year	Population	Outcome	Exposures	TPFR
Novotny et al. (2006)	323, 9–14-year-old Asian, White, and mixed Asian/White girls	DXA: Trunk to arm plus leg fat	Ethnicity (Covariates: birth weight and bi-iliac breadth)	Asian = 1, White = 0.84, Asian/White mixed = 0.98
He et al. (2004)	920, 5–18-year-old Asian, African-American, and White children	DXA: Trunk plus pelvic to arm plus leg fat	Sex, ethnicity, and Tanner stage of puberty	Late puberty: African-American boys = 0.48 African-American girls = 0.46 Asian boys = 0.63 Asian girls = 0.52 White boys = 0.49 White girls = 0.46
Rolland-Cachera et al. (1990)	168, 1 month to 21 year old French children	Skinfold: Trunk to extremity ratio in adulthood	Sex	Boys = 1, Girls = 0.76
Frisancho, Flegel (1982) (derived from)	5,012, 1–17 year old White US children	Skinfold: Subscapular to triceps ratio	Early vs. Late maturing (Tanner stage)	Early > late maturing at age 15–16.9; Early boys = 1.0, Late boys = 0.85; Early girls = 0.69, Late girls = 0.50

TPFR has been found to be higher among males, Asians, and earlier maturing children than among girls, Whites, African Americans, and later maturing children

French girls had trunk to periphery fat skinfold ratios similar to White girls in Hawaii (0.76 and 0.84, respectively, Rolland-Cachera et al. 1990), whereas trunk to periphery fat ratio for both French boys and Asian girls in Hawaii had a value of 1. In the French study, early life TPFR was correlated with adult TPFR for girls, but not for boys. In the White children studied by Frisancho and Flegal (1982), early maturers had higher TPFR, with subscapular to triceps ratio (from age 9 years for boys and from age 3 years for girls), than did late maturers, and boys' values were higher than those of girls.

Using a ratio of a skinfold to the total body skinfolds among White children from Michigan, Hattori et al. (1987) showed that obese girls carry more body fat in the trunk, especially the upper trunk, than non-obese girls; though girls generally deposited more fat in the periphery than did boys, who tended to deposit it in the trunk. There were no ethnic differences in waist, hip circumferences, waist-to-hip ratio and subcutaneous fat distribution. Shorter stature in Asian ethnicity compared to White ethnicity was due to shorter legs ($p < 0.001$), as trunk length was not associated with Asian ethnicity ($p = 0.77$).

In a study of Asian, White, and African–American adolescents, Asians had lower gynoid fat than Whites and African Americans (He et al. 2004), among both boys and girls – especially among girls, using either skinfold and DXA measurements.

In a study in the UK, women who were born with lower birth weight were found to have a proportionately lower DXA lean-to-fat mass ratio than women born at a higher birth weight (Skidmore et al. 2009); higher birth weight was associated with a healthier body composition in adulthood. However, they were not able to control for gestational age; shorter length of gestation could explain the finding.

52.4 The Importance of TPFR

The association of larger bi-iliac breadth with higher TPFR in adolescent girls may mark early maturation, which results in broader pelvis at an earlier age, and a skeleton with relatively shorter legs and longer trunk, yielding more physical space for body fat to be placed in the trunkal versus the peripheral region of the body. Thus, early growth pattern is likely important to later distribution of body fat. The fact that central body fat becomes evident during adolescence, as seen with early versus late maturers (Frisancho and Flegal 1982), could indicate that there is mediation of these characteristics by steroid hormones. Environmental influences of late adolescence may bring about expression of genetic factors.

Fat cells in the abdominal region have been thought to be more sensitive to nutritional and/or hormonal factors than fat cells in other regions (Ktotkiewski et al. 1975). In the presence of sex steroid hormones, a gynoid distribution of body fat exists in females. With a decrease in sex steroid hormones, as occurs with aging, there is a tendency to increase central obesity (Garaulet et al. 2004), as is seen in post-menopausal women. Further, women given exogenous androgens or suffering from virilizing tumors or disorders, such as congenital adrenal hyperplasia, develop a more central adipose tissue distribution. This suggests that circulating testosterone favors an increase in trunk adipose tissue (Rosenbaum and Leibel 1997). TPFR was found to be higher in women with higher free testosterone and polycystic ovary disease, controlling for BMI. In the study by Hattori et al. (1987), increased body fat led to a more central or androidal fat patterning. Thus, the higher TPFR seen in Asian girls, as compared to Whites, suggests that Asian girls may have a higher ratio of testosterone-to-estrogen than of White girls of the same stage of pubertal development.

52.5 Applications to Other Areas of Health and Disease

The TPFR is used here to understand obesity and risk for chronic disease. TPFR variability by sex, ethnicity, birth weight, bi-iliac breadth, and maturation rate suggests a possible hormonal or genetic component to the trait. Risk ratios relating TPFR to disease risk may be helpful to clarify prevention and treatment priorities. As DXA is routinely conducted for osteoporosis screening, examination of DXA scans for TPFR may provide information about risk for chronic diseases, such as cardiovascular disease and Type 2 diabetes.

Summary Points

- TPFR measures body fat distribution in a ratio of trunkal body fat to peripheral body fat.
- TPFR may be measured by subcutaneous skinfold thickness obtained with calipers or by regions of interest from dual energy X-ray absorptiometry (DXA) scans of the whole body.
- TPFR is better than central obesity, which is better than BMI, in predicting risk for chronic disease.
- TPFR variability by sex, ethnicity, birth weight, bi-iliac breadth, and maturation rate suggests a possible hormonal or genetic component to the trait.
- TPFR may have predictive value for understanding individual and population risk for disease throughout the life span.
- Further research to quantify these risks and protections at different life stages will be valuable to provide targets for research and clinical treatment.

Key Features

Table 52.4 Key population differences in trunk periphery fat ratio (TPFR)

Greater in males than females
Highest among Asian ethnic groups
Higher among those with lower birth weight
Higher among those with greater bi-iliac breadth
Higher among those who mature earlier vs later
TPFR variability by sex, ethnicity, birth weight, bi-iliac breadth, and maturation rate suggests a possible hormonal or genetic component to the trait

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Part IX
Regions and Anatomical Areas of the Body: Sensory Organs

Chapter 53
Anthropometry of Normal Human Auricle

Ruma Purkait

Abstract The auricle is a defining feature of the face. Its shape, size and position on the face play a key role in facial harmony. Correction of any auricular deformity or facial rejuvenation procedure involves surgical intervention for which a plastic surgeon will require normative data for auricular dimensions. The data is generated by taking various anthropometric measurements and certain visual observations of a normal auricle. For example, to understand the shape and size of a normal adult Indian auricle, six linear dimensions covering various anatomical parts of the auricle are measured. Observations on its anatomy including shape, preauricular area, form of helical fold, lobular shape, size and type of attachment to the cheek are also noted. To explore variation in dimensions of ear structure in an adult population, males ranging in age from 18 to 70 years have been included.

Generally, all auricular features increase in size steadily with age. The lobule contributes the maximum to the overall elongation of the auricle. Its dimensions are dependent on its shape and attachment to the cheek. The lobular and auricular indices decrease with increasing age indicating more elongation than widening of the structures. The data on the auricle is not only useful to physicians as a guideline while performing surgery, but data on ear protrusion above the skull is useful to industries designing hearing aid instruments for the ear. The information that the lobule undergoes rapid elongation after 60 years of age can help law enforcement agencies to update their data on the external ear while using it as a biometric tool.

53.1 Introduction

The auricle plays an important role in the clinical diagnosis of congenital anomalies and syndromes. For a physician a deformation in auricular shape and size or its spatial dislocation on the face can mean a possible anomaly. Patients of Trisomy 13 and 18 syndromes, for example, are reported to have low-set and deformed auricles, while Down's syndrome patients have smaller auricles than healthy person (Vogel and Motulsky 1982). Several studies have reported the relation of the auricle with various syndromes and anomalies (Farkas and Lindsay 1973; Farkas 1978a, b; Della et al. 2001; Beahm and Walton 2002; Chou et al. 2002; Mowlavi et al. 2004).

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_53,

Auricular appearance and symmetry contributes enormously to facial aesthetics. Any auricular defect such as disproportionate size, abnormal elongation of auricular lobe or a missing part can be corrected by surgery. Cosmetic surgery and facial rejuvenation have become quite popular, not only in the west but in other parts of the world as well. For rectifying such abnormalities a plastic surgeon would require information about normal auricular dimensions, its bilateral position on the face as well as general conformation. Such data are collected through studies applying anthropometrical techniques and making certain visual observations of the auricle. So far such studies have been conducted in different parts of the world.

53.2 Short Overview of Available Studies

53.2.1 Simple Anthropometry

The morphology of the external ear has been studied in complete detail in different populations across the world. Schwalbe (1897) was one of the first to invent a method to measure the external ear. He was also the first to attract scientific attention to racial peculiarities in the structure of the ear. He measured ear length and width in cadavers and concluded that auricular expansion occurred after the age of 50 and continued until the age of 70–80 years. Quelprud (1935), adopting the cross-section method, worked along similar lines on subjects ranging from 16–50 years of age, and reported changes in auricular width with age. He also provided a graph on the elongation of the earlobe which helps in judgeing its incremental growth.

Among 1,000 German subjects aged between 1 and 89, Pellnitz (1958) investigated sexual variation in total and cartilaginous ear length. He classified them by sex into various age groups at 10-year intervals. His study was one of the few that demonstrated a significant difference between the rate of expansion of the cartilaginous part and earlobe. A similar study was carried out by Hajnis (1969) on 626 adult Czech subjects aged between 18 and 80. He measured auricular length and width and noticed an increment in both with increasing age. Sexual variation was also obvious in both ear dimensions.

In a study on 100 American adults and 50 children, Rubin et al. (1962) measured ear height, width, scaphoconchal angle, distance of mastoid to helix edge, conchal depth and lobular height. They found that after age 60, the overall ear increased in size and width. They concluded that growth is present in the cartilage as well as in the lobule. A linear regression analysis of auricular length with age was performed by Heathcote (1995), among 206 subjects aged between 30 and 93. His results showed an annual increase of approximately 0.22 mm in auricle length within the studied age interval. Asai et al. (1996) also performed a similar study on 400 Japanese subjects aged between 21 and 94. He reported an annual increase of 0.13 mm in ear length. In another study on 996 males and 992 females, Ito and Imada (2001) compared ear length and width among various age groups using multiple comparison tests. Their results implied a steady increase in auricle length up to the latter half of the 70s in males, while the increment was significant in females even after this age. They explained that auricular expansion could be due to the reduced flexibility of the cartilage.

Brucker et al. (2003) concluded from their study on the ear lobule of Americans that it is the only ear structure that changes significantly with age but does not vary sexually, though ear height was larger in males. They concluded that lengthening of ear lobule with age is due to effect of weight of ear ring as well as the ageing process. This observation was supported by Azaria et al. (2003) in a study on Jews aged between 20 and 80 years. Sexual dimorphism was observed, with a significantly longer ear lobule in males than in females.

An anthropometric study on the adult Turkish external ear was carried out by Bozkir et al. (2006). Their study sample included 341 young adults between 18 and 25. They measured seven ear dimensions viz. ear height, ear width, lobular height and lobular width, distances from tragus to anti helix and to helix and ear projection at tragal level using electronic digital calipers. Sexual dimorphism was observed in ear height and width.

53.2.2 Auricular Growth Study

An anthropometric growth study on normal German children of both sexes (596 boys and 675 girls) aged between 3 and 18 years was carried out by Pelz and Stein (1995). They measured ear length and concluded that the ear grows very slowly from 4th to 18th year of age in both sexes. They described a new anthropometric index the "auriculocephalic index" which according to them is independent of sex and age and helps in syndrome delineation.

One of the most comprehensive growth studies till date has been conducted by Farkas (1978b) among normal and anomalous ears of 1197 North American Caucasian males and females between 6 and 19 years of age. Various measurements, viz. ear length, ear width, length of ear attachment, ear inclination, and ear protrusion, were taken on the left ear. Farkas found that ears grow much slower in width than in length and ear length attained maturation at approximately 15 years in males and at 13 years in females, while ear width developed completely in females at approximately 10 years of age and at 13 years in males.

A similar growth study of the auricle of normal Turkish children (1552) from birth to 18 years was conducted by Kalcioglu et al. (2003). Six ear measurements were taken on the right ear. The frequency of prominent ear deformity and degree of attachment of lobule were computed which provided cut-off points, in years, of development for various ear dimensions among both sexes. The study revealed important implications for the adequate timing of surgical treatment of auricular deformities.

53.2.3 Studies Adopting Indirect Method of Measurement

Apart from directly measuring the auricle, few a studies have adopted various indirect methods. Ferrario et al. (1999) used an electromagnetic digitizer for measuring ear length. They found a significant difference in auricle length between the sexes in their study on 310 Italian subjects classified by sex into three age groups. Their result showed a significant increase in auricle length between each age group.

In a recent study by Meijerman et al. (2006), auricular length, width and earlobe length were measured indirectly on images of both ears of 919 male and 434 female Dutch subjects aged between 18 and 90 years. Helix width was also measured at two positions: the intersection of a line perpendicular to the centre of base and the most posterior point of helix. All these dimensions were found to exhibit sexual dimorphism. They were smaller in females. Age and stature showed a positive correlation with auricle size.

Apart from the above mentioned cross-sectional studies, few longitudinal (follow-up) studies were also conducted in Europe. Sussanne (1977) observed an increment in the auricular length by 4.86 mm over a period of 22 years among 44 male Belgian subjects (average age 32 years at the beginning). Gualdi-Russo (1998) carried out a follow-up study with a gap of 10 years in Italy among 104 males and 58 females. He classified his subjects into four cohorts viz. 31–40 years, 41–50 years, 51–60 years and above 60 years (age at second measurement) and found a significant increase in ear length while ear width remained more or less stable.

Though various populations across the world have been covered in the above surveys, studies from countries inhabited by diverse ethnic groups like India are still scarce. Lakshminarayana et al. (1991) examined ear length and position for syndromology among 850 south Indian children from birth to 11 years of age. They observed that 2% of normal children and 3% children suffering from Down's syndrome had low set ears. In 2007 Purkait and Singh performed a detailed study on the auricle of normal males from central India.

This section will focus on defining and analyzing the anthropometric dimensions of different parts of auricle. The data used for discussion is derived from the above mentioned study conducted on 415 normal males by Purkait and Singh in 2007.

53.3 Methodological Description

Anatomical features of the external ear are shown in Fig. 53.1 (Table 53.1).

A total of nine anthropometric measurements were taken directly on the auricle. The methodology of taking measurements (Table 53.2) and instrument used (Fig. 53.2) are prescribed. The measurements shown in Figs. 53.3–53.5. are as follows:

1. *Length of Auricle* (1–2): It is the straight distance between superaurale (highest point on auricle) and subaurale (deepest point on the free margin of ear lobule) (Fig. 53.3).
2. *Width of Auricle* (3–4): It is the straight distance between preaurale (most anterior point of ear located just in front of the helix attachment to head) and postaurale (most posterior point on the free margin of ear).

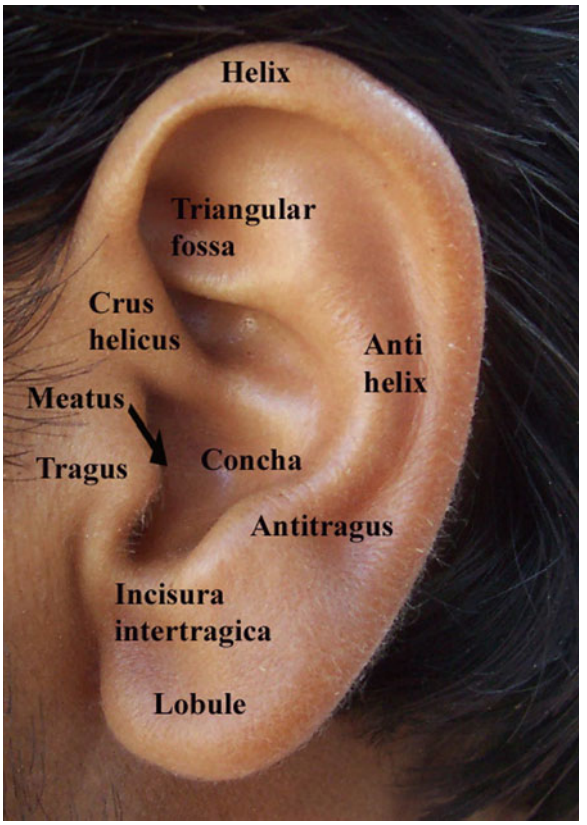

Fig. 53.1 Anatomy of auricle. Various anatomical features of auricle are depicted in the figure

Table 53.1 Key features of human auricle

1. *Auricle* or the external ear, generally ovoid in form is present on the lateral aspect of face. It possesses a cartilaginous framework which gives it its characteristic shape.
2. The outer rim of auricle is *helix* which surrounds a curved prominence, the *antihelix*.
3. A deep capacious cavity located approximately in the centre is the *Concha*. It leads to auditory meatus on its medial aspect.
4. In front of the concha, projecting backward over the meatus, is a small pointed eminence, the *tragus*. Opposite the tragus, separated from it by the *intertragic notch*, is a small tubercle, the *antitragus*.
5. At its inferior aspect is the lobule, the only part of ear that does not contain cartilage. Instead, it is a wedge of adipose tissue (fat) covered by skin. It is the part of ear that is most prone to elongation.

In histology, *adipose tissue* or *fat* is loose connective tissue composed of adipocytes. Its main role is to store energy in the form of fat, although it also cushions and thermal insulation the body. The table lists a short description of anatomical features of auricle

Table 53.2 Guidelines for taking standard measurements on auricle

1. Subject should sit upright with his head in Frankfurt horizontal plane i.e. orbitale and tragion to be in the same plane. Orbitale is the lowest point on the lower margin of orbit and tragion is the point on upper margin of tragus where tangents drawn to anterior and superior margins of the cartilage cut each other.
2. Landmarks on auricle and face to be identified once the head is in Frankfurt horizontal plane.
3. Location of landmark to be marked with skin marking pencil.
4. Standard anthropometric instrument with optimal precision to be used for taking measurements.

The table lists the standard method of taking measurement

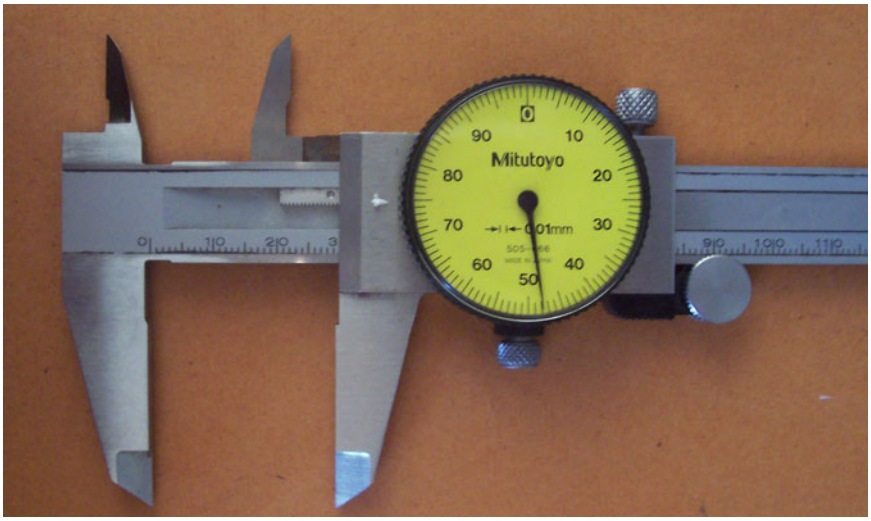

Fig. 53.2 Dial calliper. Calliper used to take linear measurements with an accuracy of 0.01 mm

3. *Lobular length* (6–2): It is the distance between incisura intertragica inferior (deepest point of incisura intertragica) and subaurale.
4. *Lobular width* (9–10): It is the distance between lobule anterior and lobule posterior.

Attachment of ear to cheek is demarcated by drawing a line joining the tip and base of ear attachment. Lobule anterior is the point on this line at midpoint level of lobular length. Lobule

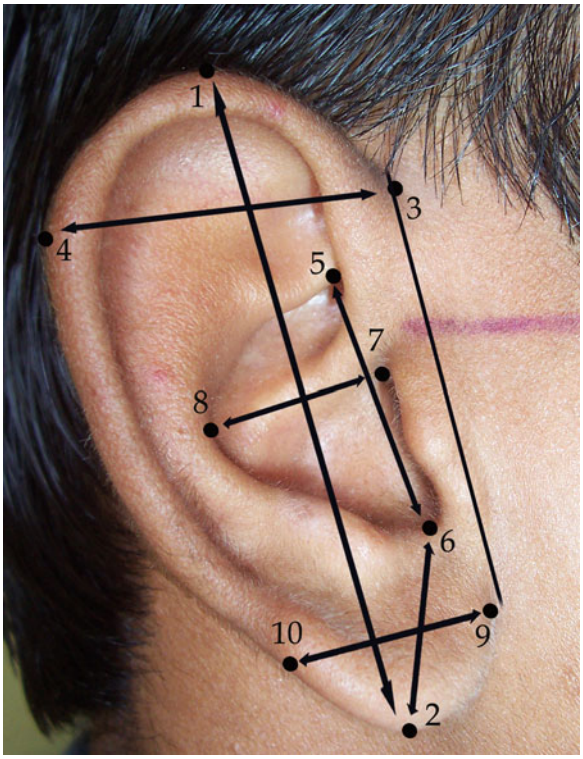

Fig. 53.3 Anatomical landmarks of auricle. (*1*) superaurale, (*2*) subaurale, (*3*) preaurale, (*4*) postaurale, (*5*) concha superior (*6*) incisura intertragica inferior, (*7*) incisura anterior auris posterior, (*8*) strongest anthelical curvature, (*9*) lobule anterior, (*10*) lobule posterior

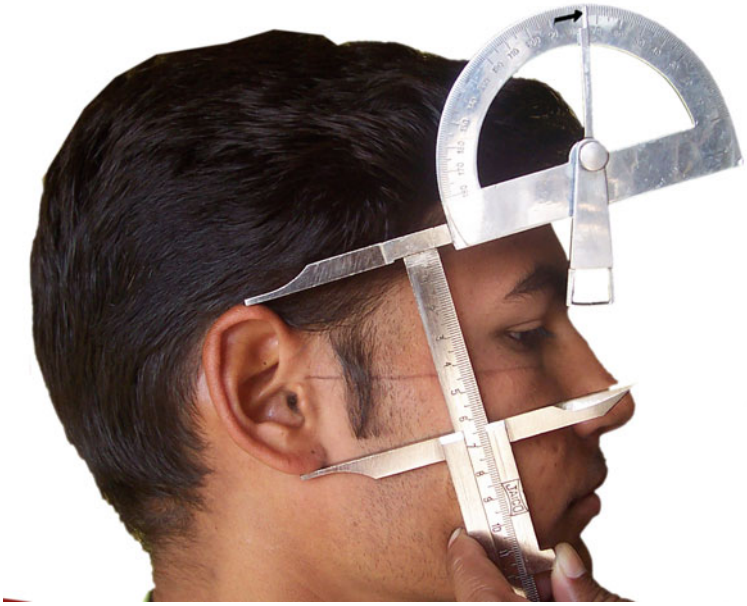

Fig. 53.4 Measuring ear inclination angle. The angle is measured with a goniometer fitted on a sliding calliper. The arrow shows the reading on the goniometer, which is 14°

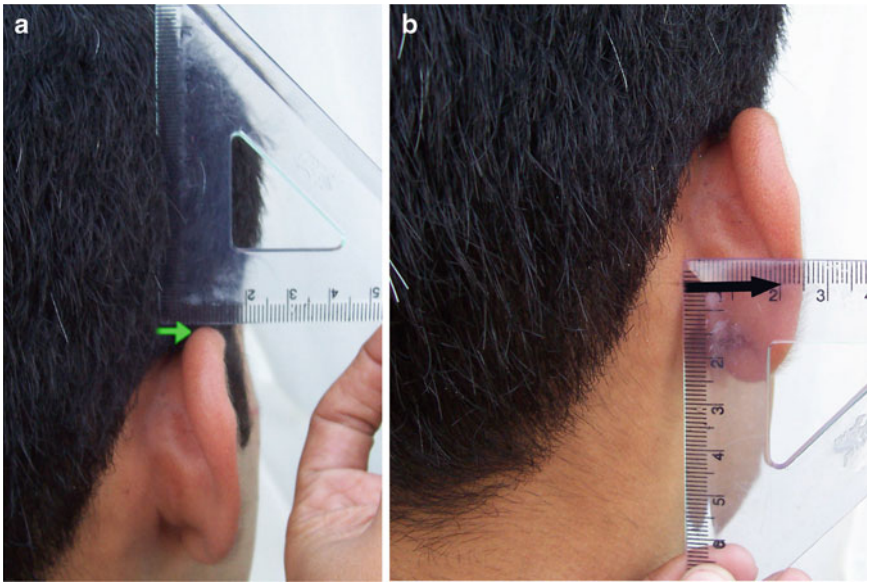

Fig. 53.5 Measuring ear protrusion. Protrusion at (**a**) superaurale and (**b**) tragal levels measured with a geometrical set square. The *arrows* show the protrusion of ear from mastoid bone

posterior is the most posterior point on margin of lobule at same level. Due care to be taken to keep limbs of calliper parallel to the medial longitudinal axis of auricle.

5. *Conchal Length* (5–6): It is the straight distance between concha superior (cross-over of lower edge of anterior end of Crus antihelicis inferius and posterior border of crus helicus) and incisura intertragica inferior.
6. *Conchal width* (7–8): It is the distance of strongest antihelical curvature and incisura anterior auris posterior (most posterior point on the edge of incisura anterior auris).
7. *Auricular inclination angle*: It is the inclination of medial longitudinal axis (line joining superaurale and subaurale) of ear from vertical plane of head and face.

   The perpendicular dropped from vertex to Frankfurt horizontal plane is considered as the vertical plane. The angle is read on the protractor of a goniometer fixed on the immovable limb of a sliding calliper (Fig. 53.4).
8. *Protrusion at superaurale level*
9. *Protrusion at tragal level*

The heights of auricular protrusion are measured with a geometrical set square with its base touching the mastoid area. The vertical limb of the set square thus measures the perpendicular distance between the posterior helical border at superaurale/tragal level and the mastoid area (Fig. 53.5a, b).

Width and length of auricle, concha and lobule can be incorporated into their respective indices to assess their proportion in various age groups.

$$\text{Auricular Index} = \text{width of auricle} \times 100/\text{length of auricle}$$
$$\text{Lobular Index} = \text{lobular width} \times 100/\text{lobular length}$$
$$\text{Conchal Index} = \text{conchal width} \times 100/\text{conchal length}$$

53.4 Analysis of Auricular Morphology

The ear is an important component of the facial complex, and it gives a subtle impression of its bearer's age and sex. Its size, shape and spatial location on the face are not only important from an aesthetic point of view but any abnormality is an indication of possible anomaly in the subject. Knowledge of the normal dimensions of the ear is useful as a guideline for the plastic surgeon while rectifying possible defects. The dimensions would vary in different ethnic groups, which necessitates that the surgeon base his observations on data specific to that ethnic group.

The auricular size continues to increase even during adulthood (Heathcote 1995). This increase is due to reduced resilience and elasticity of skin (Pasquali-Ronchetti et al. 1997), diminutive tensile strength of the connective tissue and gravitational pull (Ito and Imada 2001). The representative data reiterates this observation in almost all linear measurements (Table 53.3). The auricular index, in general, exhibits a decrease down the age groups, indicating faster increase in length than in width with ageing (Table 53.4).

All linear measurements show 6–11% increase in size from youngest to oldest age group, while lobular length registers a 23% increase. Bilateral asymmetry is apparent in all age groups for all measurements but other than auricular length and width and conchal length: none of these reached statistically significant levels. Auricular inclination angle, protrusion at super aurale and tragal levels do not show any definite trend across the age groups. The auricular protrusion increases inferiorly.

Auricular and conchal indices exhibit minor variation compared to lobular index across the age groups. Auricular and lobular indices show a general decreasing trend with advancing age.

Table 53.3 Auricular dimensions in five age groups

	Age groups									
	18–30 years ($N = 121$)		30–40 years ($N = 82$)		40–50 years ($N = 68$)		50–60 years ($N = 74$)		60–70 years ($N = 70$)	
Measurements in mm	R	L	R	L	R	L	R	L	R	L
Length of auricle	58.2	57.7	59.1	58.4	60.4	59.7	62.7	62.7	64.9	64.2
	1.8*	2.2	1.9	2.5	2.4	3.4	3.3	3.1	5.4	5.1
Width of auricle	34.0	33.1	33.9	33.1	34.6	33.4	35.5	35.0	36.4	35.6
	1.6*	1.8	2.1*	1.8	2.4*	2.4	2.0	2.0	2.7*	2.6*
Lobular length	16.9	16.7	18.1	18.3	18.8	19.1	18.9	18.6	20.9	20.6
	2.4	2.7	2.9	2.7	1.9	2.1	1.4	2.8	4.2	3.5
Lobular width	19.6	20.0	20.2	20.9	21.1	21.6	21.8	22.0	21.3	21.5
	2.4	2.9	2.5	2.7	2.9	2.4	3.0	3.4	2.1	1.9
Conchal length	26.8	26.4	27.2	26.7	26.9	26.4	28.0	28.2	28.7	28.6
	2.4*	1.9	2.5*	2.1	2.1*	2.0	2.6	2.3	2.4	2.0
Conchal width	18.7	18.8	19.8	19.6	18.9	18.7	20.1	20.3	20.2	20.1
	2.0	2.0	1.7	1.6	1.9	2.2	1.9	2.0	1.4	1.7
Auricular inclination angle in degrees	14.7	14.6	17.1	16.3	14.2	14.8	16.8	16.5	16.7	16.0
	4.5	4.5	4.0*	3.5	5.2	4.5	3.0	3.1	4.1	2.9
Protrusion at superaurale level	15.7	16.1	15.4	15.5	10.5	11.2	13.5	13.3	13.5	15.5
	4.8*	4.4	4.6	4.5	3.8	3.8	2.9	2.6	4.4	4.5
Protrusion at tragal level	24.8	24.8	24.6	24.0	18.8	18.9	21.8	21.3	22.2	22.8
	4.9	4.9	4.7	5.3	4.2	4.5	3.6	3.6	5.1	4.6

N number of males; *R* right side; *L* left side
*$P < 0.05$ for bilateral difference

Table 53.4 Indices of auricle in five age groups

	Age groups									
	18–30 years		30–40 years		40–50 years		50–60 years		60–70 years	
Index	R	L	R	L	R	L	R	L	R	L
Auricular index	58.5	57.3	57.3	56.9	57.3	56.0	56.7	56.0	57.2	56.4
	3.0	3.2	3.6	3.7	3.9	3.4	3.8	4.1	4.6	4.6
Lobular index	117.4	122.6	115.0	117.1	113.4	116.6	115.7	122.6	105.0	107.0
	9.8	11.3	12.4	12.5	8.9	10.2	10.1	12.3	10.4	9.2
Conchal index	70.3	71.5	73.1	73.7	71.1	71.4	72.3	72.5	70.6	70.9
	4.9	4.9	8.0	7.5	10.8	11.3	8.1	8.8	6.3	6.3

R right side; *L* left side

According to Farkas and Lindsay (1973) and Farkas (1978a), the auricular length and width can be useful in diagnosing syndromes suffering from microtia or disproportionately wide or narrow ears as in craniofacial syndromes. Wide ears are observed in Apert and Crouzon syndromes and narrow ears in cleft lip and palate patients.

53.5 A Note on the Ear Lobule

The ear lobule continues to elongate with age (Table 53.3). The maximum progression of growth was found to be after 60 years of age. The lobular index (Table 53.4) also supported the above observation, exhibiting a decreasing trend with advancing age. This decrease is much more than what is observed in the auricular index, which supports the observation of Brucker et al. (2003) that the lobule is the only ear structure that changed significantly with age.

Brucker et al. (2003) reported a decrease in lobular width with age in their mixed (89 females and 34 males) American data, but when males were only considered, the measurement failed to show any statistical difference across age groups. It is observed that the dimensions of the lobule are dependent on its shape and attachment to cheek. Hence, one should exercise caution while interpreting the result. Among Indians, in the 50–60 years age group, the length remained almost unchanged compared to the earlier group (40–50 years) though the width increased (Table 53.3). When further investigated, it was found that the group contained unusually large proportion (47%) of attached and bow shaped lobules (Fig. 53.6). This explained the shortness of the length and increased width. Farkas (1978b) also found attached earlobes to be hypoplastic in his North American Caucasian data. Great intra and inter-group variation in the shape and attachment of the lobule may also account for the discrepancy exhibited by the lobular index as is reflected in the 50–60 years age group (Table 53.4). Twenty-eight percent of the lobules in the data were either slightly free at the lower end or adherent to the cheek (Fig. 53.7, Table 53.5). It is an already established fact that free earlobes elongate more than its attached counterpart (Azaria et al. 2003). Hence during rectification of earlobe ptosis, an attempt is made to make it adherent to the cheek to stall its further elongation.

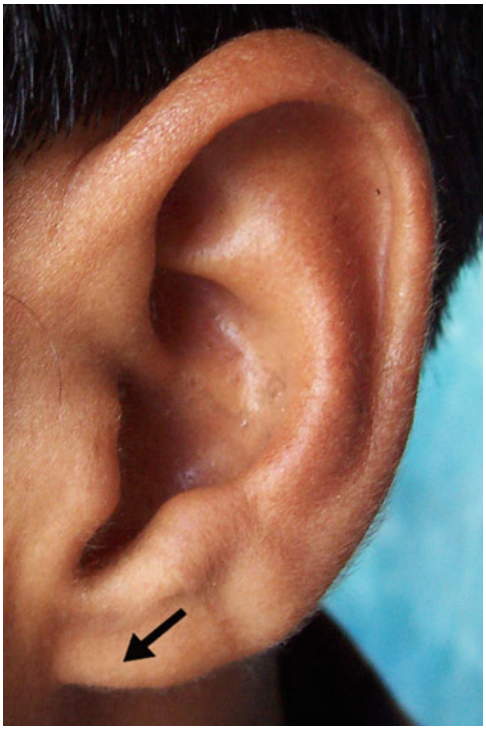

Fig. 53.6 Shape of lobule. *Short* and *bow* shaped lobule

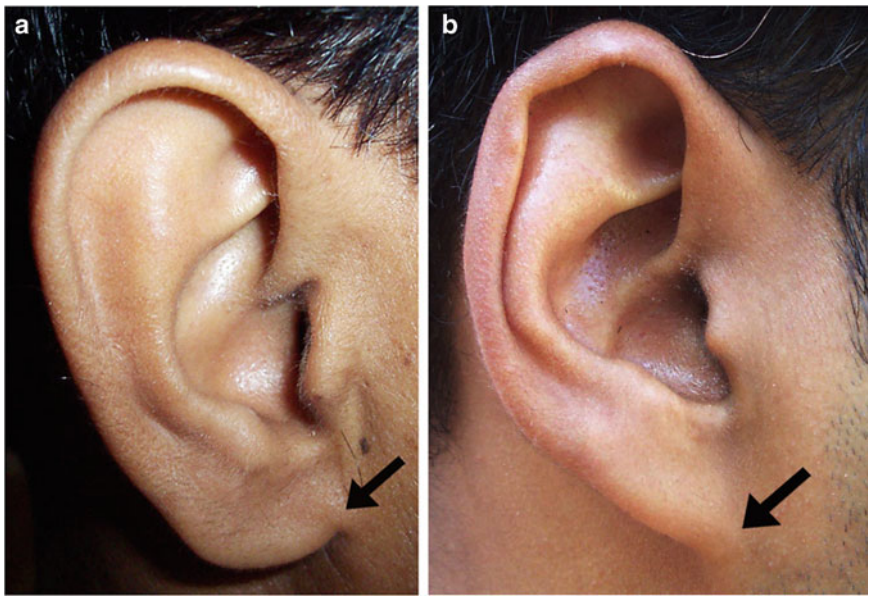

Fig. 53.7 Adherence of lobule. Ear lobule attachment to cheek (**a**) Slightly free and (**b**) completely attached

Table 53.5 Description of auricular features

Features	Classification	Sub classification	Frequency (%) Right	left
Shape of auricle	Normal	Oval	57.3	57.3
		Round	6.5	6.5
		Rectangular	5.4	5.6
		Triangular	30.8	30.6
	Abnormal		–	–
Preauricular region	Clear skin		100	99.6
	Presence of appendages	skin appendage	–	0.4
		Pits	–	–
		Fistula	–	–
Helix	Normally rolled		88.3	88.3
	Wide but not covering the scapha		–	–
	Wide, thin and collapsed above scapha		–	–
	Flat and unfolded		11.4	11.4
	Wide with a concave marginal impression on the junction of middle and upper segment		0.3	0.3
Lobule size	Normal	Large	14.6	14.6
		Proportionate	50.8	46.5
		Small	28.6	31.2
	Hypoplastic		6.0	7.7
Lobule shape	Tongue		41.7	42.6
	Bow		26.3	25.4
	Round		7.8	7.8
	Angular		19.9	19.9
	Pointed		4.3	4.3
Lobular attachment to Cheek	Free	Bilateral	65.5	
		Unilateral	3.8	
	Partially free	Bilateral	12.7	
		Unilateral	1.2	
	Attached	Bilateral	15.9	
		Unilateral	1.9	

The oval is the most common shape of an auricle, followed by the triangular. Normally rolled helices accounted for most of the helix forms. The preauricular area is generally clean. Most lobules are bilaterally free, of proportionate size, generally tongue-shaped among free- and bow shaped among attached lobules. Hypoplasia of the ear lobes is also registered

53.6 Comparative Study

On comparing with data of other populations (Table 53.6), one would find a significant variation in auricular size. Indian auricular length is shorter than any ethnic group depicted in the table. The auricular length of Indian elders (50–70 years) is comparable to young Turkish (18–25 years) (Bozkir et al. 2006) and Italian (Gualdi-Russo 1998; Ferrario et al. 1999) ears. Interestingly, the ear width is similar to Turkish males of same age group (Bozkir et al. 2006).

Among Indians, the lobular length is comparable with Jewish data in the younger age group (Azaria et al. 2003), but in older age groups there is great disparity as unlike Indians elongation continues at a greater pace among Jews. As such it seems that the lobular length is smallest among Indians, though its width is comparable with that of the Americans (Brucker et al. 2003) and Turkish (Bozkir et al. 2006) males. This is further supported by data on auricular features which classified 7.7% right and 6% left lobules as hypoplastic and 31.2% right and 28.6% left lobules as small (Fig. 53.6, Table 53.5).

Table 53.6 Comparison of male auricular dimensions in various ethnic groups

Author	Population studied	Age group	Auricle length in mm	Auricle width in mm	Lobular length in mm	Lobular width in mm	Protrusion at tragal level in mm
Gualdi-Russo (1998)	North Italian	31–40 years	62.4	35.3	–	–	–
		41–50 years	62.5	35.1	–	–	–
		51–60 years	65.9	36.6	–	–	–
		>60 years	68.9	38.2	–	–	–
Ferrario et al. (1999)	North Italian white	18–30 years	R-62.92	R-38.8	–	–	–
			L-63.16	L-38.17			
		31–56 years	R-64.41	R-40.44	–	–	–
			L-65.31	L-39.78			
Azaria et al. (2003)	Ashkenazi and Sephardi Jews of Israel	20–40 years	–	–	R-17.5	–	–
					L-17.3		
		40–60 years	–	–	R-20.4	–	–
					L-20.4		
		>60 years	–	–	R-23.6	–	–
					L-23.4		
Brucker et al. (2003)	American (male)	18–65 years	65.2		18.9	19.6	–
	(Male + female)	15–30 years	61.7	–	17.8	21.0	–
		31–45 years	62.7	–	18.5	19.6	–
		46–65 years	64.5	–	19.9	19.1	
Bozkir et al. (2006)	Turkish	18–25 years	R-62.9	33.1	18.4	19.8	17.6
			L-63.1	33.3	18.3	19.4	17.0
Purkait and Singh (2007)	Indian	18–30 years	R-58.2	34.0	16.9	19.6	24.8
			L-57.7	33.1	16.7	20.0	24.8
		30–40 years	R-59.1	33.9	18.1	20.2	24.6
			L-58.4	33.1	18.3	20.9	24.0
		40–50 years	R-60.4	34.6	18.8	21.1	18.8
			L-59.7	33.4	19.1	21.9	18.9
		50–60 years	R–62.7	35.5	18.9	21.8	21.8
			L–62.7	35.0	18.6	22.0	21.3
		60–70 years	R–64.9	36.4	20.9	21.3	22.2
			L–64.2	35.6	20.6	21.5	22.8

Comparative auricular data in few populations

53.7 Possible Applications of Auricular Data

Exceptionally large auricular inclination is an indication of possible anomaly. Among cleft lip and cleft palate anomaly patients, for example, the ears are set with greater inclination of the longitudinal axis (Farkas 1978b). So it may help for a clinician to be acquainted with the normal range of auricular inclination, which usually falls within a range of 9–29°.

Knowledge of protrusion of the auricle has a two-fold advantage. The first is a possible indication of the presence of a prominent ear when the superaurale distance from the scalp is greater than 20 mm (Kalcioglu et al. 2003). Its incidence is quite common in the general population, ranging from 5.5–38.7% (Preuss and Eriksson 2000). Measuring auricular protrusion also finds its use in designing hearing aid instruments. The aid may be fitted behind the ear or surgically anchored to the mastoid bone. In the bone-anchored hearing aid, a small abutment is exposed outside the skin for transmitting sound vibrations to the bone. Whatever the form of aid instrument, knowledge of the ear projection from the skull, both in the superior and inferior aspect, are essential for designing the instrument; it is also crucial for surgeons planning surgery. The dimensions of the concha can also be helpful in designing a hearing aid instrument which can fit into it.

From the above description on the external ear, one can deduce that the lobule contributes the greatest to the overall increase in ear length. Among Indians, changes in the ear form were found to continue throughout the lifespan but the maximum elongation of the lobule was after the age of 60. This inference is of great use in the field of Ear Biometrics. Ear Biometrics is a machine-based vision system in which databases of ear images are stored. During authentication, the ear image of an individual taken is automatically compared with the ear image already stored in the machine. Since constancy over time is one of the essential requirements of biometrics (Jain et al. 2000), if the ear undergoes rapid change in its form, there are chances of rejection of an authentic person at the time of verification. In other words, the False Rejection rate will be too high with increasing age. Hence it is emphasised that the ear can be used as a biometric tool with a ceiling of 60 years of age. Thus, for using the external ear as a biometric tool, either the law enforcement agencies should limit their database to 60 years or update their data from time to time.

It is essential to remember the statement of Rubin et al. (1962), that there is no ear which can be designated as standard. Even in the same ethnic group, great diversity exists in the shape and size of the external ear (Farkas et al. 1992). Grouping such diverse ears together into various age groups in a cross-sectional study gives us only a crude estimate of their average dimensions. Hence, it is necessary to reiterate to the readers that it may not be the best method for studying changes in ear dimensions with progression of age.

Summary Points

- Though various parts of auricle do exhibit changes with progression of age, the elongation of lobule contributes maximum to the overall increase of auricular length. The progression of growth of lobule was found to be at greatest speed after 60 years of age.
- When compared to other populations, the lobular length of male is found to be smallest among Indians. The observed shortness of the lobule seems to be a characteristic feature of the population of this part of India as 39% left and 35% right lobules are categorized as exceptionally short in length.
- Data on external ear are useful to physicians to detect anomalies in patients while data on ear protrusion above the skull can be used by industries for designing hearing aid instrument for the ear.

Knowledge of the rapid elongation of the lobule after age 60 can help law enforcement agencies to update their data on external ear while using it as a biometric tool.

- Besides providing standards, an objective approach is required to diagnose syndromes or any anomaly by actually measuring features, rather than relying on an impression of physical features. Sometimes, in a routine visual examination, a physician may miss minor defects of the auricle, which will be visible in a metrical analysis.

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Chapter 54
Anthropometric Analysis of the Nose

Abdullah Etöz and İlker Ercan

Abstract Anthropometric evaluation begins with the identification of specific locations, called landmark points, defined in terms of visible or palpable features on the subject. Data from facial landmarks have traditionally been obtained by the direct measurement technique using standard instruments such as callipers, measuring tapes, compasses, protractors and angle finders. However, this requires physical contact by the examiner, which could lead to errors during measurement as many areas on the face are very sensitive to touch. The latest reports on craniofacial anthropometry, therefore, include laser scanning and photogrammetric techniques.

The nose is a person's most defining feature as it is at the centre of the face. The shape of the nose is a signature indicating ethnicity, race, age and sex. Anthropometric methods and surgical practice have now merged to treat congenital or post-traumatic facial disfigurements in various racial or ethnic groups successfully. Nasoplasty surgeons require access to facial data based on accurate anthropometric measurements to perform optimum correction. The photogrammetric anthropometric method will be summarized in this chapter. Anthropometry is said to be the most suitable nasal evaluation method to demonstrate the sharp nasal profile contours and eliminate differences between direct and indirect nasal measurements.

Abbreviations

EDMA	Euclidean Distance Matrix Analysis
NHP	Natural head position

54.1 Introduction

Anthropometric analysis aims to provide the most reliable comparison of body forms by using specific landmarks determined in respect of anatomical prominences. It is now easier to discuss the differences between ethnic and racial groups, and to compare individual variations in both sexes thanks to previous anthropometric studies. Farkas has provided a great body of work in craniofacial

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_54,

anthropometry and established a database of anthropometric norms by measuring and comparing more than 100 dimensions (linear, angular and surface contours) (DeCarlo 1998).

Anthropometric methods and surgical practice have now merged to treat congenital or post-traumatic facial disfigurements in various racial or ethnic groups successfully (Farkas 2005). The nose is a person's most defining feature as it is in the center of the face. The shape of the nose is a signature indicating ethnicity, race, age and sex (Ofodile and Bokhari 1995; Milgrim 1996; Mishima 2002; Ochi and Ohashi 2002; Romo and Abraham 2003; Ferrario 1997; Bozkir 2004; Leong and White 2004; Uzun 2006). Nasoplasty surgeons require access to facial data based on accurate anthropometric measurements to perform optimum correction.

There are several anthropometric studies on nasal anatomy and various methods have been used. We decided to review a landmark-based geometric morphometric technique which can be easily used when analyzing the nasal shape in any condition.

On the other hand, a clinically successful outcome in nasoplasty requires thorough and accurate preoperative planning together with awareness of morphological differences. Anthropometric analysis of the nose is a way for us to provide data which should contribute to satisfactory cosmetic nasal surgery results.

54.2 Anthropometric Measurements

Anthropometric analysis of nasal anatomy is based on the comparison of measurements which are obtained separately from the anterior, lateral and inferior aspects. These measurements can be performed by direct or indirect methods. Direct methods are time-consuming and have several other disadvantages such as difficulty of patient adaptation (especially in children and infants), problems concerning repeatability of measurements and archiving of data. Indirect measurement methods including photogrammetry, cephalometry, stereophotography, laser scanning, and computerized tomography have therefore become increasingly more popular in recent years. The most frequent methods used clinically are photogrammetry and cephalometry. Photogrammetry is a fast and inexpensive method with superior patient compliance. The most important disadvantage of two-dimensional photogrammetry is its inability to assess facial depth. Three-dimensional photogrammetry appears to be a more appropriate technique in this respect.

The following issues are crucial in anthropometric analysis of the nose:

1. Standardization of the method
2. Landmark identification

54.2.1 Standardization of the Method

Details of standardization of the methods used in anthropometric analysis have previously been defined by several investigators and are beyond the scope of this review. It is important to note that a standard head position is essential for any facial measurement. The natural head position (NHP) is the most appropriate since it is the most reproducible and provides a natural face orientation for any clinical planning.

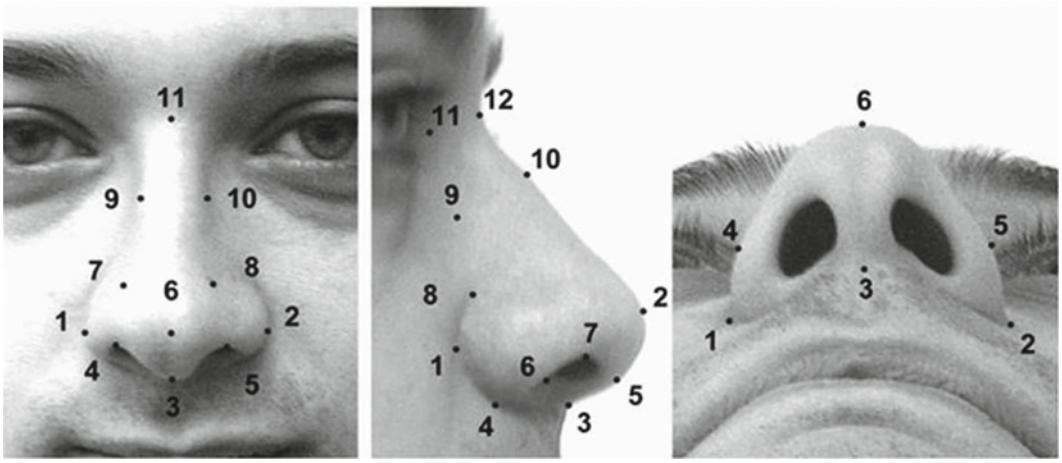

Fig. 54.1 Anthropometric (anterior 1–6, 9–11; lateral 2–4 and 12; inferior 1–3, 6) and constructed (anterior 7, 8; lateral 1, 5–11; inferior 4, 5) landmarks that were used in the anthropometric analysis of the nose (Ercan et al. 2007)

54.2.2 Landmark Identification

The accurate identification and reliability of the landmarks are the most important indicators of the accuracy of anthropometric measurements. One way to increase accuracy is to mark the landmarks before measuring. Many soft tissue landmarks reflect the underlying bony structure. The bony points must be palpated with a finger to find the soft tissue equivalent. While some soft tissue points can be marked with a dermographic pen, other tissue landmarks such as endocanthion, exocanthion, cheilion, and crista philtre can be clearly identified without palpation. Meticulous identification of soft tissue landmarks and marking of the landmarks determined by inspection and palpation before the acquisition of photographs will certainly improve the reliability of measurements in photogrammetry. Nasal landmarks are presented in Fig. 54.1 and Tables 54.1–54.6.

54.2.3 Landmark Reliability

It is important to understand the various sources of error that can affect anthropometric measurements during location of landmarks. Lack of precision results in variability among repeated measurements of the same specimen and has two components:

- Observer error in locating landmarks
- Instrument error in identifying landmark coordinates (Lele and Richtsmeier 1991; Lele 1993)

It is crucial to analyze the reliability of the landmarks. The optimal standard to achieve reliability is that all landmarks should be marked by the same investigator on all subjects. Instrumental errors should be avoided by using standardized digital photographic imaging obtained from anterior, lateral and inferior aspects using a constantly stable digital camera (Hwang and Kang 2003; Uzun 2006).

Table 54.1 Anthropometric landmarks of the nose from the anterior aspect

1–2: al, Alare, the point where the nasal blade (ala nasi) extends farthest out
3: **sn, Subnasale**, the midpoint of the columella base
4–5: c', Columella apex, the most anterior or the highest point on the columella crest at the apex of the nostril
6: prn, Pronasale, the most prominent point on the nasal tip
***7–8:** The estimated junction of the upper and lower lateral cartilages
9–10: mf, Maxilloanteriorale, where the maxilloanterioral and nasoanterioral sutures meet
11: n, Nasion, the point in the midline of both the anatomic nose and the nasoanterioral suture

The numbers, abbreviations and definitions of the examined landmarks are provided. The constructed landmarks are indicated by the "*" sign

Table 54.2 Anthropometric landmarks of the nose from the lateral aspect

***1:** The junction of nasolabial crease and nasal blade (ala nasi)
2: prn, Pronasale, the most prominent point on the nasal tip
3: sn, Subnasale, the midpoint of the columella base
4: **al, Alare**, the point where the nasal blade (ala nasi) extends farthest out
***5:** The most prominent point of medial cruris of the alar cartilage
***6:** The most prominent point of lateral cruris of the alar cartilage
7: **c', Columella apex**, the most anterior or the highest point on the columella crest at the apex of the nostril
***8**: The ending point of the nasolabial fold
***9:** The estimated junction of nasal and maxillary bones
***10:** The most prominent point of the nasal dorsum (nasal hump)
***11:** The estimated insertion point of the medial cantus
12: n, Nasion, the point in the midline of both the anatomic nose and the nasoanterioral suture

The numbers, abbreviations and definitions of the examined landmarks are provided. The constructed landmarks are indicated by the "*" sign

Table 54.3 Anthropometric landmarks of nose from the inferior aspect

1–2: al, Alare, the point where the nasal blade (ala nasi) extends farthest out
3: sn, Subnasale, the midpoint of the columella base
***4–5:** The most convex point of lateral cruris of alar cartilage
6: prn, Pronasale, the most prominent point on the nasal tip

The numbers, abbreviations and definitions of the examined landmarks. The constructed landmarks are indicated by a "*" sign

Table 54.4 The Interlandmark Distances found to be significantly different between males and females (Ercan et al. 2007)

	Anterior aspect	Lateral aspect	Inferior aspect
The greater interlandmark distances in males ($p < 0.05$)	2Y6, 7Y8, 2Y7, 1Y3, 1Y6, 2Y3, 1Y8, 4Y5, 1Y5, 2Y4, 9Y10, 1Y2	4Y10, 6Y10, 8Y10, 7Y9, 3Y9, 5Y11, 5Y12, 3Y10, 7Y10, 2Y11, 4Y6, 2Y12, 3Y5, 4Y7, 5Y10, 5Y9, 6Y7, 2Y4, 6Y8, 2Y9, 2Y10, 2Y6, 2Y7, 3Y8, 1Y2, 7Y8, 9Y10, 4Y5, 1Y7, 2Y8, 1Y6, 5Y8, 1Y5, 3Y6, 5Y6, 1Y4, 3Y4, 1Y3, 5Y7	2Y3, 3Y5, 3Y4, 2Y4, 1Y3, 1Y2, 1Y5, 4Y5
The greater interlandmark distances in females ($p < 0.05$)	4Y9, 3Y9, 1Y9, 2Y10, 6Y9, 5Y10, 3Y10, 6Y10, 7Y9, 3Y11, 6Y11, 8Y10, 4Y11, 5Y11, 4Y7, 5Y8	1Y9, 1Y11, 8Y9	3Y6, 2Y5, 2Y6, 1Y6, 1Y4

These interlandmark distances are shown by bold and thin lines in Fig. 54.2

Table 54.5 The common names for interlandmark distances of the nose

Total nasal bridge length	(n-prn)
Morphological nasal width	(al-al)
Nasal root width	(mf-mf)
Anatomical nasal width	(ac-ac)
Tip protrusion	(prn-sn)

Table 54.6 Data showing the statistical correlations of the interlandmark distances of the nose in both sexes (Etöz et al. 2008)

	Males		Females	
	r	*p*	*r*	*p*
Morphological Nasal Width/Nasal Root Width	0.616	<0.001	0.345	0.001
Morphological Nasal Width/Nasal Bridge Length	0.651	<0.001	0.409	<0.001
Morphological Nasal Width/Anatomical Nasal Width	0.612	<0.001	0.317	0.003
Morphologic Nasal Width/Tip Protrusion	0.299	0.007	0.286	0.008
Nasal Root Width/Nasal Bridge Length	0.492	<0.001	0.439	<0.001
Nasal Root Width/Anatomical Nasal Width	0.392	<0.001	–	$p > 0.05$
Nasal Root Width/Tip Protrusion	0.351	0.001	–	$p > 0.05$
Nasal Bridge Length/Anatomical Nasal Width	0.410	<0.001	0.223	0.039
Nasal Bridge Length/Tip Protrusion	0.405	<0.001	0.378	<0.001
Anatomical Nasal Width/Tip Protrusion	0.527	<0.001	0.761	<0.001

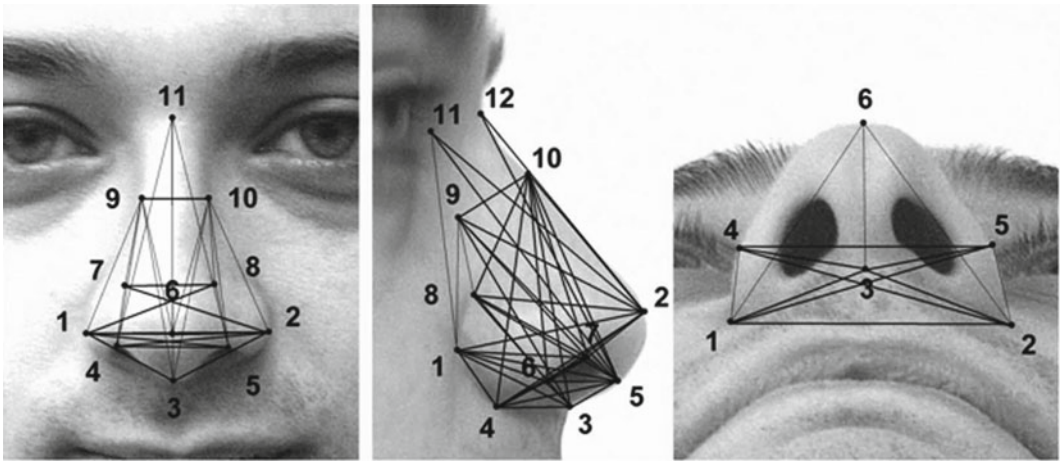

Fig. 54.2 The inter-landmark distances, viewed from anterior, lateral and inferior aspects. These distances can be measured by computer scales in photogrammetric software and the results should be proportionate to each other. For example, the thin lines in this figure indicate the inter-landmark distances that were found to be greater in females while the bold lines indicate those found to be greater in males (Ercan et al. 2007)

54.2.4 Collection of Two-Dimensional Craniofacial Landmarks of the Nose

The data collection procedure should take place in two separate steps, and followed by off-line calculations. Digital photographic images of each subject should first be taken by the same investigator using a digital camera with at least 2.0 mega pixel capacity. The second stage is marking the examined landmarks on these digital images. The anthropometric landmarks are defined in Fig. 54.1. The landmarks shown in the figure have also been accepted in previous anthropometric studies. Some "constructed" landmarks are also used for enrichment of nasal anthropometric analysis. These landmarks are determined by constructing a line tangent to another landmark or a bony edge. The descriptions of the examined landmarks are presented in Table 54.1 and shown in Fig. 54.1.

In the general use of photogrammetry, the common landmarks were selected as follows: Eleven landmarks (five anthropometric and two constructed) in the anterior aspect, twelve landmarks (four anthropometric and eight constructed) in the lateral aspect and six landmarks (four anthropometric and two constructed) in the inferior aspect of nose were defined for each subject. The landmarks were marked on the digital photographs using TPSDIG 2.04 software. This software was developed by F. James Rohlf and is one of the most frequently used software both for marking the landmarks (however, it is recommended to take photos after marking the landmarks on the person) and for determining the inter-landmark distances in pixels (Fig. 54.2). A ruler is used during photography for measurement of the distances between the landmarks on the digital images, and later the unit distance (1 cm) is calibrated with its equivalent in pixels in order to obtain measurement values separately.

This technique has proven to be reliable in studies on facial landmarks by Nechala (1999) and Ferrario (2003) that compared photogrammetry with direct measurements, and showed that sharp facial profile contours could eliminate the differences between the direct and indirect measurements of the nose. The strengths and limitations of photogrammetry must be appreciated but it is ideally suited to the evaluation of proportions, as the magnification factor is eliminated (Weigberg 2005).

Statistical studies of anatomical shape variations in the population are important in understanding the anatomical effects of diseases or biological processes. Several procedures for obtaining shape

information from landmark data have been proposed. The Euclidean Distance Matrix Analysis (EDMA) is used to calculate all possible linear distances between landmarks by creating matrices for each subject (Theodore and Richtsmeier 1998).

Ethnic influences can result in differences in the appearance of the nose, as follows: Caucasian, leptorrhine; African American, platyrrhine; Hispanic, paraleptorrhine; and Asian, subplatyrrine. For example, three types of African American noses are described: African, Afro-Caucasian, and Afro-Indian (Ofodile and Bokhari 1995). There are also variations of nasal shape related to sex in both ethnic groups. Nose shape gives information about race, ethnicity, age and sex. The size, shape, and proportions of the nose provide a personal characteristic vision. Moreover, it is an important key for a natural and aesthetically pleasing human face (Aung 2000). Accordingly, concern about the nasal shape has recently increased with many wanting to undergo nasoplasty. Any surgeon who performs nasal surgery must be keenly aware of the morphological differences in nasal anatomy. The psychological aspects, differences in skin conditions and anthropometric measurements must be taken into consideration when planning nasal surgery.

There are many methods for the anatomic evaluation of the nose and the variations in different racial and ethnic groups. However, there is an easy and reliable method to analyze nose shape: Photogrammetric nasal analysis. This method is believed to be a better way to examine nasal differences than conventional methods.

54.3 Applications to Other Areas of Health and Disease

Anthropometric methods and surgical practice have now merged to treat congenital or post-traumatic facial disfigurements in various racial or ethnic groups successfully. Nasal surgery requires access to facial data based on accurate anthropometric measurements to perform optimum correction for any condition. Cosmetic nasal surgery for men, although not technically different from such surgery for women, requires awareness of additional considerations because of different expectations. Anthropometric analysis is a step in clarifying these important points and a baseline for planning the corrective surgery.

54.4 Practical Guidelines

- The subjects were recruited from a population with no noticeable nasal or facial disfigurement and no history of previous nasal or facial surgery.
- Demographic data obtained included age, place of birth, and parental heritage.
- The subjects were rested for 10 min before the photography.
- A constant, stable three-leg camera holder was used and all subjects were positioned at the same distance from the camera.
- All the data was obtained from standardized digital photographic images taken from the anterior, lateral and inferior aspects using a 5.1-megapixel digital camera.
- Anthropometric landmarks were defined according to a previous report of Farkas et al.
- We used some ‘‘constructed’’ landmarks (the definition of the landmark is determined by constructing a line to another landmark or bony edge) to enhance shape analysis.
- The landmarks were marked on the digital photographs by the same investigator using TPSDIG 2.04 software.

Summary Points

- Statistical studies of anatomical shape variations in the population are important for understanding the anatomical effects of diseases or biological processes.
- Anthropometric analysis of facial asymmetry is based on the comparison of homolog measurements that are obtained separately from the anterior, lateral and inferior aspects.
- The standardization of the method and accurate identification of landmarks to be used in the measurements in nasal anthropometric analysis are important.
- Various anthropometric measurements have previously been used but photogrammetry is a modern and feasible method for nasal analyses.
- Anthropometric analysis is a step in clarifying these important points and provides a baseline for enhancing the corrective surgery plans.

Key Points

Photogrammetry is an easy and effective method for anthropometric analysis of the nose.

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Chapter 55
Three-Dimensional Computerized Anthropometry of the Nose

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Abstract The quantitative assessment of the dimensions of facial soft-tissue structures, their relative proportions, and reciprocal spatial positions is an essential component of the clinical analysis of patients seeking maxillo-facial treatments. In particular, nasal morphology and dimensions play a key role in facial harmony, and modifications of nasal characteristics are among those most asked by patients worldwide. Currently, cosmetic rhinoplasty is the fourth most common surgical procedure in the USA. For a quantitative description of human noses, various methods have been used, both in two (photographs) and three dimensions (direct facial anthropometry, measurements on stone casts, and indirect anthropometry on digital reproductions). Additionally, intrauterine assessments for the prenatal diagnosis of chromosomal alterations and cleft lip are being made by ultrasonography.

In healthy persons, data were reported for nasal linear measurements, angles, external area and volume, nostril dimensions, angles, and symmetry. In both sexes, the fastest child and adolescent growth was found for vertical distances, which doubled their values from birth to young adulthood. Male values were always larger than female values. A large increment was also observed for the antero-posterior distances, with limited sexual dimorphism. The largest sexual dimorphism (males larger than females), and the smallest age-related increments, were found for nasal horizontal measurements. Normal growth and development of the nose did not stop in early adulthood. The cartilaginous tissues of the face continue to grow during maturity and old age, giving older people longer and larger noses. The largest ethnic variations in the nose were found in the descriptors of nasal shape, that is, the angles. During growth, nasal volume progressively increased from childhood to young adulthood, but its modifications continued even after the attainment of skeletal maturity. At 3–4 years of age, nasal volume was approximately 36% (boys) and 42% (girls) of the mean value attained in young adulthood. In old adults, nasal volume was 120% (men) and 118% (women) of the mean value of the 18–30 age group. Nasal size and shape in the different ages and ethnic groups may be usefully employed for clinical assessments, surgical interventions, and forensic reconstructions.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_55,

Abbreviations

3D	Three-dimensional
NURBS	Non-uniform rational B-spline
SD	Standard deviation

55.1 Introduction

The quantitative assessment of the dimensions of facial soft-tissue structures (eyes, nose, mouth and lips, chin, and ears), their relative proportions, and reciprocal spatial positions is an essential component of the clinical analysis of patients seeking maxillo-facial treatments (Yamada et al. 1999; White et al. 2004; Maal et al. 2008; Troncoso et al. 2008). Three-dimensional (3D) quantitative information on the skeleton and soft tissues of the craniofacial complex can be obtained with computed tomography or magnetic resonance (Maal et al. 2008). Unfortunately, both methods have several shortcomings that limit their widespread use in clinics and research: computed tomography uses ionizing radiations, and it cannot be used in healthy, non-patient subjects. Additionally, its use in patients should be limited, and repeated, longitudinal evaluations cannot be proposed even when there are facial alterations and deformities. Magnetic resonance is too time- and money-consuming. Therefore, simpler and less problematic methods, classic direct anthropometry and digital anthropometry, have been proposed and applied (Sforza et al. 2004; Heidari et al. 2009).

Currently, classic direct anthropometry is being coupled and even replaced with various 3D image analyzers (laser scanners, 3D range-cameras, optoelectronic instruments, stereophotogrammetry, and Moiré topography), and contact instruments (electromagnetic and electromechanical digitizers, ultrasound probes), that allow a fast and not invasive assessment of soft-tissue craniofacial morphology (Ferrario et al. 1997, 2003, 2007; Yamada et al. 1999; Aung et al. 2000; Mori et al. 2005; Honrado et al. 2006; Ghoddousi et al. 2007; Schwenzer-Zimmerer et al. 2008a, b; Ozsoy et al. 2009; Plooij et al. 2009). Three-dimensional digitizers provide the x, y, z coordinates of facial surfaces or of landmarks; Euclidean geometrical calculations can then be used to obtain 3D linear distances, angles, surface areas as well as volumes of selected facial structures (Ferrario et al. 1997, 2003).

Nasal morphology and dimensions play a key role in facial harmony, and modifications of nasal characteristics are among those most asked by patients worldwide. Rhinoplasty can improve nasal appearance and proportion, enhancing facial harmony (Troncoso et al. 2008; Heidari et al. 2009). Currently, cosmetic rhinoplasty is the fourth most common surgical procedure in the USA. In 2008, over 152,000 operations were performed, with an increase of 0.4% on 2007 data (http://www.consultingroom.com/, accessed on July, 12th 2009).

Normal, reference data for nasal morphology are therefore necessary, together with detailed information about the age-related charges in nasal dimensions and proportions, to plan a proper treatment for the surgical correction of nose dysmorphologies, traumatic disfigurements, or aesthetic imbalances.

55.2 Assessment of Nasal Morphology

In healthy persons, data were reported for nasal linear measurements, angles, external area and volume (Spalding and Vig 1990; Farkas et al. 1994; Ferrario et al. 1997, 2007; Yamada et al. 1999; Aung et al. 2000; Zankl et al. 2002; Porter and Olson 2003; Sforza et al. 2004; Troncoso et al. 2008; Heidari et al. 2009),

Table 55.1 Nasal landmarks

Landmark	Definition
Midline landmarks:	
Nasion (n)	Innermost point between the forehead and nose
Pronasale (prn)	Most protruded point of the apex nasal
Columella (c′)	Midpoint between the columella crests, level with the top of the corresponding nostril
Subnasale (sn)	Midpoint at the union of the lower border of the nasal septum and the upper lip
Labiale superius (ls)	Midpoint of the upper vermilion line
Paired landmarks (right and left sides noted $_r$ and $_l$):	
Alare (al)	Most lateral point on each alar contour
Nasal alar crest (ac)	Most lateral point in the curved base of each alar
Inferior terminal of the nostril (itn)	Inferior point of the nostril axis
Superior terminal of the nostril (stn)	Superior point of the nostril axis

The table lists and defines the most used soft-tissue nasal landmarks

nostril dimensions, angles, and symmetry (Spalding and Vig 1990; Yamada et al. 1999; Russell et al. 2000; Porter and Olson 2003; Uzun et al. 2006; Rosati et al. 2009; Troncoso et al. 2008). Tables 55.1 and 55.2 report a list of the most commonly used nasal landmarks (Fig. 55.1) and measurements.

55.2.1 Asymmetry

Additionally, several investigations reported data on nasal symmetry, using both simple, clinically based, right–left indices (Yamada et al. 1999; Rosati et al. 2009), and more complex mathematical calculations (Russell et al. 2000; White et al. 2004; Baeyens et al. 2006; Daelemans et al. 2006). Asymmetry can be divided into directional and fluctuating: directional asymmetry indicates a differential development favoring one side of the body consistently over the other, while fluctuating asymmetry does not favor one side of the body over the other (Rosati et al. 2009). In morphological contexts, directional asymmetry seems to depend from repeatable effects of environment or genotype on the analyzed structures. In contrast, fluctuating asymmetry seems to reflect developmental stability (Rosati et al. 2009): subjects with a lower level of fluctuating asymmetry should possess a healthier and stronger structure (Ercan et al. 2008).

Therefore, the assessment of asymmetry is of both clinical and theoretical interest: the definition of the level of asymmetry in the normal population can be used to set intervention guidelines and treatment goals (Russell et al. 2000; Ferrario et al. 2003; Schwenzer-Zimmerer et al. 2008a, b). At the same time, facial symmetry is always associated with perceptions of health: present theories of perceptual psychology underline the importance of a reduced fluctuating symmetry for esthetic appraisal (Ercan et al. 2008). In this context, phenotypic symmetry is used as a cue reflecting a better genetic background (Table 55.3).

55.2.2 Methods of Analysis

For a quantitative description of human noses, various methods have been used, both in two (photographs, Porter and Olson 2003; Liou et al. 2004; Baeyens et al. 2006; Daelemans et al. 2006; Troncoso et al. 2008) and three dimensions. In particular, direct facial anthropometry (Farkas et al. 1994; Zankl

Table 55.2 Anthropometric nasal measurements

	Landmarks	References
Distances (mm)		
• Nasal width	al_r-al_l	Farkas et al. (1994) and Ferrario et al. (2007)
• Alar base width	ac_r-ac_l	Farkas et al. (1994) and Ferrario et al. (2007)
• Height of the nose	n-sn	Farkas et al. (1994) and Ferrario et al. (2007)
• Length of the nasal bridge	n-prn	Farkas et al. (1994) and Ferrario et al. (2007)
• Philtrum length	sn-ls	Zankl et al. (2002)
• Nasal tip protrusion	prn-sn	Farkas et al. (1994) and Ferrario et al. (2007)
• Nasal tip protrusion	prn-(al_r-al_l)	Ferrario et al. (2007)
• Right and left lengths of the nostrils	stn-itn	Ferrario et al. (2007)
• Superior width of the nostrils	stn_r-stn_l	Ferrario et al. (2007)
• Inferior width of the nostrils	itn_r-itn_l	Ferrario et al. (2007)
• Right and left alar length	prn-al	Rosati et al. (2009)
Angles (degrees)		
• Alar slope or inter-alar angle	al_r-prn-al_l	Aung et al. (2000) and Ferrario et al. (2007)
• Nasal tip	n-prn-sn	Farkas et al. (1994) and Ferrario et al. (2007)
• Nasolabial angle	prn-sn-ls	Farkas et al. (1994) and Ferrario et al. (2007)
• Nasal convexity or nasal prominence	sn-n-prn	Ferrario et al. (2007)
• Inter-axial angle	stn_r-itn_r^stn_l-itn_l	Aung et al. (2000)
• Right and left angles between nostril and alar axes	(stn-itn)^(prn-al)	Rosati et al. (2009)
Volumes (mm^3)		
• Nasal volume	Approximated from the volumes of two tetrahedra: the first tetrahedron had the plane ac_r, ac_l, prn as its base and vertex in n, the second had the same base and vertex in sn	Ferrario et al. (1997), (2007)
• Nasal volume	Total volume from digital reproductions	Ferrario et al. (2007)
Areas (cm^2)		
• External nasal surface	Sum of the areas of the triangles n-prn-ac_r, n-prn-ac_l, prn-sn-ac_r, and prn-sn-ac_l	Ferrario et al. (1997), (2007)
• External nasal surface	From digital reproductions	Ferrario et al. (2007)
• Nostril area	Between two lines connecting itn and stn; lateral limit on the lowest profile of ac; medial limit on the most lateral-inferior border of the columella crest	Rosati et al. (2009)

The table lists and explains the most used nasal measurements as reported by literature. The landmarks are shown in Fig. 55.1 and defined in Table 55.1

et al. 2002; Porter and Olson 2003; Heidari et al. 2009), measurements on stone casts (Spalding and Vig 1990; Russell et al. 2000; Ferrario et al. 2007; Rosati et al. 2009), as well as indirect anthropometry on digital reproductions (Yamada et al. 1999; Aung et al. 2000; Sforza et al. 2004; White et al. 2004; Ferrario et al. 2007; Schwenzer-Zimmerer et al. 2008a, b) have all been successfully used.

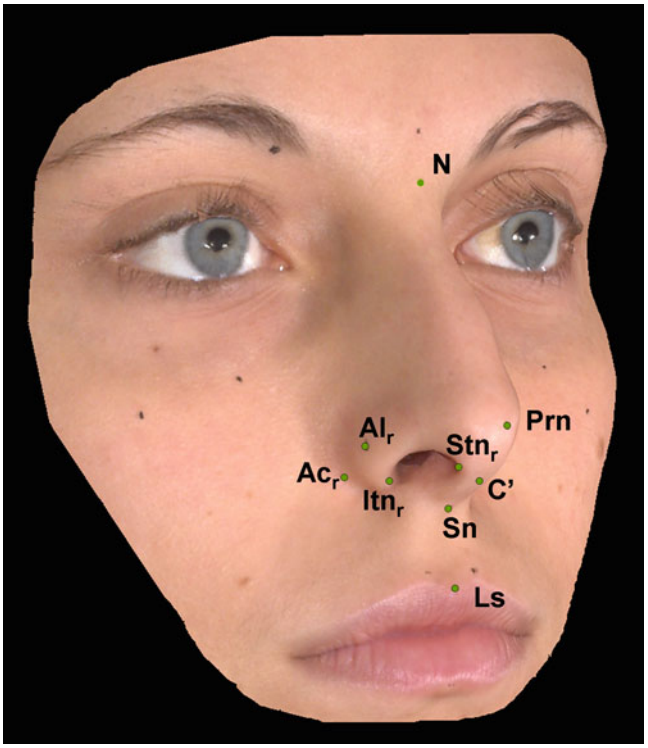

Fig. 55.1 Nasal landmarks. The landmarks are defined in Table 55.1. The image shows the most used soft-tissue facial landmarks in the nose region

Table 55.3 Nasal asymmetry in healthy persons

Subjects	Side	Directional asymmetry	Fluctuating asymmetry	Reference
Caucasian infants	Variable	–	✓	White et al. (2004)
Japanese children	Variable	✓	–	Mori et al. (2005)
Caucasian adolescents	R > L	✓	✓	Russell et al. (2000)
Caucasian young adults	L > R	✓	✓	Rosati et al. (2009)
Japanese adults	L > R	–	✓	Yamada et al. (1999)
Turkish adults	L > R	✓	–	Ercan et al. (2008)

R right; *L* left
Several authors analyzed nasal asymmetry in healthy people, and found that some degree of asymmetry is a common finding at all ages of life

Among the others, considering their position, the assessment of nostril dimensions and shape can often be difficult, when using both direct and indirect anthropometry (Schwenzer-Zimmerer et al. 2008a, b). Therefore, researchers have developed several methods for the reproduction of noses, and their subsequent measurement. The use of stone casts allows the performance of detailed analysis even of the nostrils (Rosati et al. 2009). The casts can be analyzed directly, or they can be reproduced with digital instruments, using reverse engineering methods (Ferrario et al. 2007; Rosati et al. 2009).

55.2.3 Nose Reproduction: Stone Casts and Digital Models

Nasal morphology can be evaluated from 3D reproductions (Ferrario et al. 2007; Rosati et al. 2009). The method developed in our laboratory uses silicon impressions that are cast in dental stone. Subsequently, plaster nasal models are digitized using a computerized electromechanical

digitizer (Microscribe G2, Immersion Corporation, San Jose, CA). Point clouds obtained from the digitization of the plaster casts can subsequently be elaborated to create virtual surfaces using a commercial software for the 3D modeling of solids (Rhinoceros 3.0; Robert McNeel & Associates, Seattle, WA).

All procedures are made with the subject supine in a dental chair.

For each subject, a custom metal mesh is shaped using three 1-mm wires: two horizontal wires, one passing through pronasale and one approximately 1 cm below nasion, and a vertical wire connecting the horizontal wires on the nasal midline. The wires are individually modeled to follow nasal morphology. The mesh needs to be somewhat larger than the actual nose to allow space for the impression material.

The first stratum of impression material (polyvinylsiloxane) is put on the nasal surface, avoiding the formation of bubbles. The entire nasal surface, from glabella (forehead) and endocanthi (medial eye fissure) to subnasale, is gently covered. Some additional impression material is poured at the nostrils. The metal mesh is directly included in the first stratum of impression material. Immediately, a second stratum of polyvinylsiloxane is added, and the metal wires are completely covered.

During the hardening of the impression material (approximately 5 min), the subject breathes through the mouth with no facial movements. The negative cast impression is then gently removed from the skin starting from its uppermost part (nasion), and a positive model is obtained by filling the impression with dental stone. To avoid deformations, stone filling is done in two steps: at first, a thin layer of stone is put in the negative cast; when the layer is hardened, the filling is completed with care. During hardening, the model is kept within a box filled with sawdust that allows a correct positioning of the impression without any local deformation.

Subsequently, the plaster nasal models are digitized using a computerized electromechanical digitizer that provides metric data independent from external reference systems (Ozsoy et al. 2009). The electromechanical digitizer is a multi-joint arm digitizer with a terminal stylus (or tip); within each joint, an optical encoder works with a microchip and instantly sends the joint angle to a host computer; the 3D coordinates of the stylus are therefore provided. The instrument has an accuracy of 0.38 mm within a 50-in. sphere workspace, and its calibration is controlled before each data collection session using 3D objects of known dimensions.

Each stone cast is covered with a grid of lines, and several points on standardized horizontal and vertical lines are digitized. Seven principal horizontal lines are drawn: through landmarks pronasale, nasion, subnasale, columella, at the inferior and superior borders of the nostrils, and at mid-way on the nostrils. Four-to-six additional horizontal lines (according to nasal dimensions) are drawn between nasion and pronasale. Three principal vertical lines are drawn: on the midline through nasion, pronasale, and subnasale; on the right and left sides of the lateral nasal surface through endocanthion, the lateral contour of the nose, and the nasal alar crest. Subsequently, four additional lines for each side are drawn parallel to these three. Overall, each nostril should be crossed by three or four horizontal lines.

Point clouds obtained from the digitization of the nasal casts are subsequently elaborated to create virtual surfaces using the commercial software for the 3D modeling of solids (Rhinoceros 3.0; Robert McNeel & Associates, Seattle, WA).

Non-uniform rational B-spline (NURBS) geometry is used for the digital reproductions. These B-splines are mathematical illustrations of 3D geometry, and can represent geometric objects in two and three dimensions. These surfaces are the mathematical equivalent of elastic sheets, and can be modeled to adapt to any form. Because of their flexibility and accuracy, NURBS models are widely used in several industrial processes from computer-aided design, manufacturing, and engineering, to computerized illustration and virtual animation.

55.3 Nasal Growth, Development, and Aging

Normal growth and development of the nose does not stop in early adulthood. The cartilaginous and skeletal tissues of the face continue to grow and modify during maturity and old age, giving older people longer and larger faces (Zankl et al. 2002; Sforza et al. 2009). This observation is well known even to lay people: for instance, according to a Chinese belief, long ears indicate longevity (Sforza et al. 2009). Indeed, both in cross-sectional and in longitudinal studies, older people tend to possess bigger ears (Zankl et al. 2002; Sforza et al. 2009). Unfortunately, the coexistence of two conditions is not sufficient to demonstrate their association, and we cannot relay on a simple anthropometric measurement to predict health and longevity.

Nasal dimensions and characteristics are currently being measured in utero by ultrasonography: indeed, fetuses with chromosomal alterations (in particular, trisomy 21) tend to have a significantly larger incidence of nasal bone absence (delayed ossification) or hypoplasia than fetuses with a normal karyotype. The intrauterine assessment of nose dimensions is therefore one of the "soft markers" used to detect fetuses with an increased risk of altered karyotype. The matter is further presented and discussed in the chapter "Anthropometric indices of facial features in Down's syndrome subjects" in this book. Nasal alterations are also found in fetuses with cleft lip.

55.3.1 Linear Distances

Postnatal measurements of nasal dimensions were made by several authors; one of the most known cross-sectional databases is that provided by Farkas et al. (1994) for North American white Caucasian persons. In their investigation, they analyzed approximately 1,800 persons from birth to 25 years of age using conventional anthropometry.

In both sexes, nasal height (a vertical distance) had the fastest growth (Fig. 55.2), and it doubled its value from birth to young adulthood. Male values were always larger than female values. A large increment was also observed for the antero-posterior distance prn-sn (nasal tip protrusion); for this measurement, male and female values were very similar at all ages (Fig. 55.3), with female to male ratios all larger than 94% (except in the first age group). The largest sexual dimorphism (males larger than females) and the smallest age-related increments were found for nasal width (al-al), a horizontal measurement (Fig. 55.4).

These growth patterns are well in accord with the general modifications in craniofacial growth: at birth, horizontal dimensions are always more advanced in their development than vertical ones.

Some nasal measurements for the subsequent age groups were provided by Zankl et al. (2002), who analyzed 2,500 white Caucasians of central European descent living in Switzerland. Cross-sectional data were obtained by conventional anthropometry on persons from birth to 97 years. Overall, nasal growth continued also after 20 years of age, but modifications went on with much reduced speed: for instance, nasal protrusion in men changed from 2.2 cm at 20 years of age, to 2.45 cm at 88 years of age. In the same period, the length of the nasal bridge (n-prn) modified from 5.25 cm to 6.8 cm. Modifications were even smaller in women. As expected, the largest modifications were found for vertical measurements: at 88 years of age, philtrum length (sn-ls) was 1.6 (men) and 1.26 (women) times larger than at 20 years of age.

The age-related modifications found in our laboratory were smaller than those reported by Zankl et al. (2002). We analyzed 859 healthy white Caucasians living in northern Italy (519 men, 340

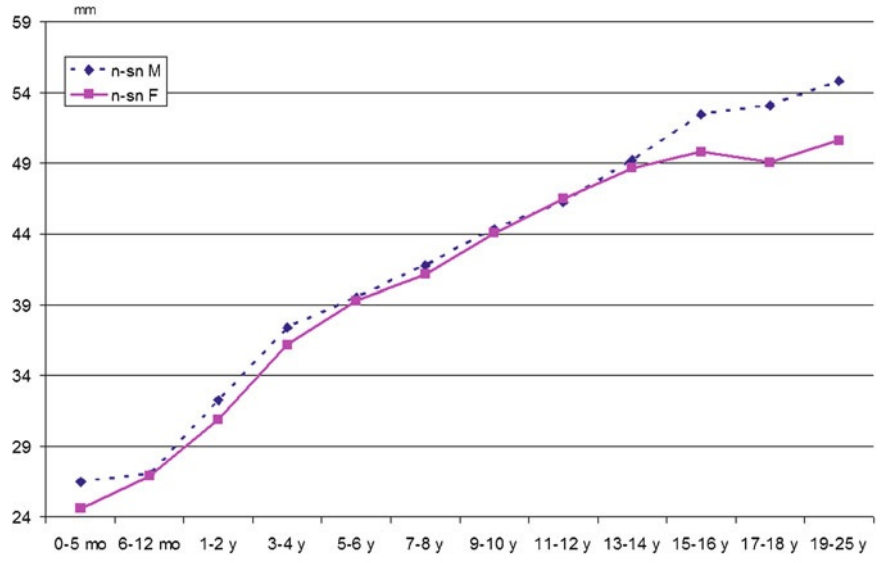

Fig. 55.2 Height of the nose (*n-sn*) in healthy white Caucasians from northern America (Data from Farkas et al. 1994). Continuous line, women (*F*); interrupted line, men (*M*). From birth to young adulthood, nasal vertical dimensions grow in both sexes, with a clear sexual dimorphism

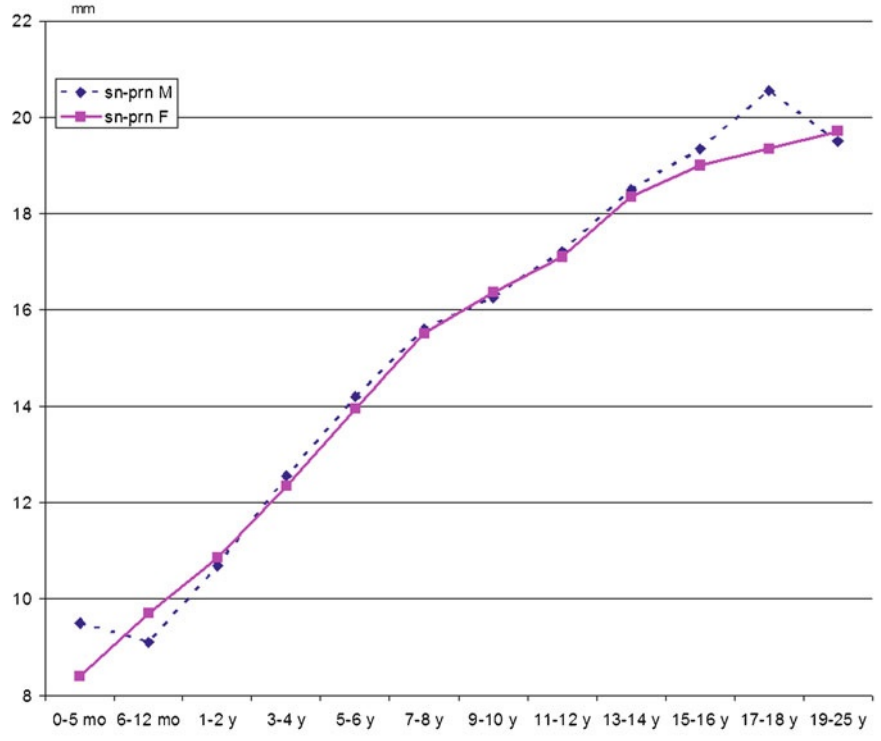

Fig. 55.3 Nasal tip protrusion (*sn-prn*) in healthy white Caucasians from northern America (Data from Farkas et al. 1994). Continuous line, women (*F*); interrupted line, men (*M*). From birth to young adulthood, nasal antero-posterior dimensions grow in both sexes, but male and female data are very similar

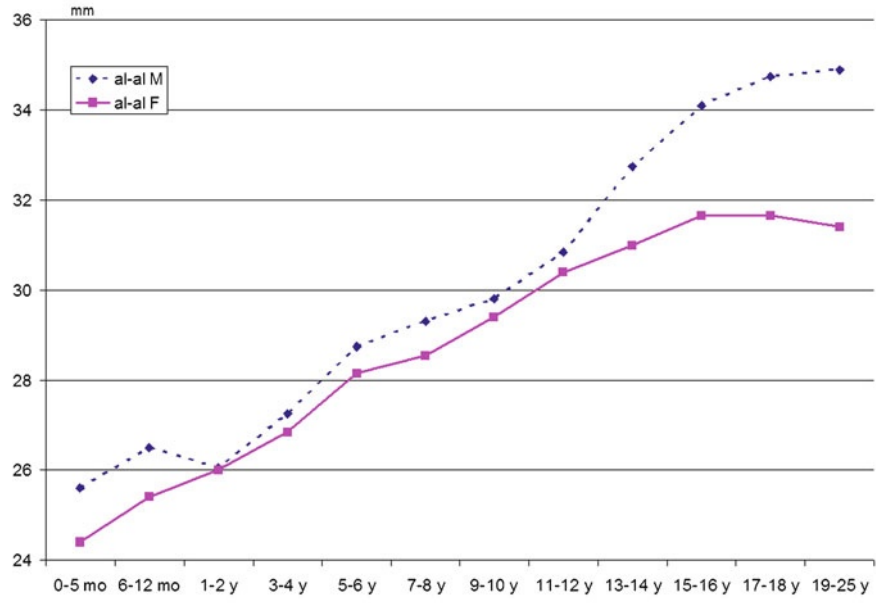

Fig. 55.4 Nasal width (al_r-al_l) in healthy white Caucasians from northern America (Data from Farkas et al. 1994). Continuous line, women (*F*); interrupted line, men (*M*). From birth to young adulthood, nasal horizontal dimensions grow in both sexes; sexual dimorphism becomes larger after adolescence

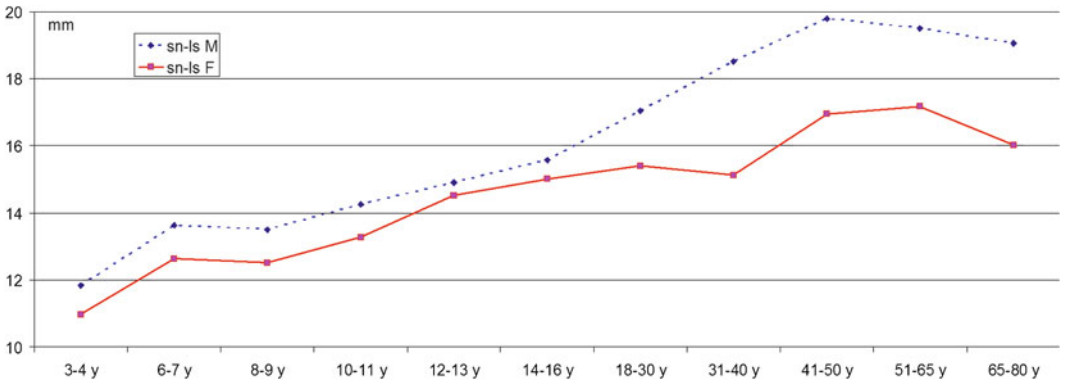

Fig. 55.5 Philtrum length (*sn-ls*) in healthy white Caucasians from northern Italy. Continuous line, women (*F*); interrupted line, men (*M*). From childhood to old age, nasal vertical dimensions grow in both sexes, with a clear sexual dimorphism

women) from 3 to 73 years of age, using digital anthropometry (details are provided in the chapter "Three-dimensional facial morphometry: from anthropometry to digital morphology" in this book). Overall, from young adulthood (18–30 years of age) to old age (65–80 years of age) philtrum length increased 1.12 (men) and 1.04 (women) times (Fig. 55.5). Also, the values reported by Zankl et al. (2002) were somewhat larger than those found in our laboratory.

Data collected in our laboratory were also smaller than those reported by Farkas et al. (1994), even if similar age-related trends were observed: the largest modifications were found for the vertical distance (nasal height, Fig. 55.6), intermediate variations for the antero-posterior dimension (nasal tip protrusion, Fig. 55.7), and the smallest ones for the horizontal nasal width (Fig. 55.8).

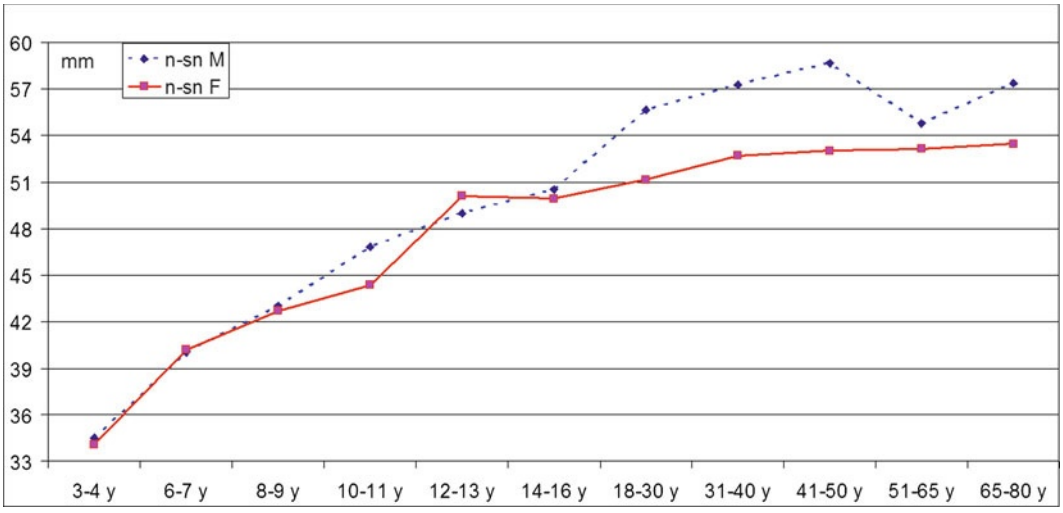

Fig. 55.6 Height of the nose (*n-sn*) in healthy white Caucasians from northern Italy. Continuous line, women (*F*); interrupted line, men (*M*). From childhood to old age, nasal vertical dimensions grow in both sexes; sexual dimorphism is more evident after young adulthood

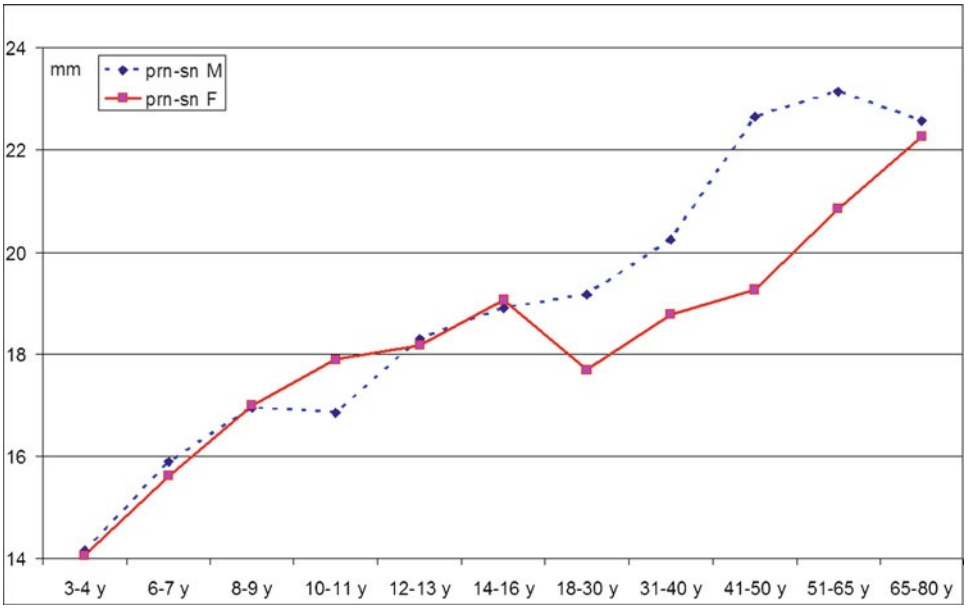

Fig. 55.7 Nasal tip protrusion (prn-sn) in healthy white Caucasians from northern Italy. Continuous line, women (F); interrupted line, men (M). From childhood to old age, nasal antero-posterior dimensions grow in both sexes; sexual dimorphism is more evident after young adulthood

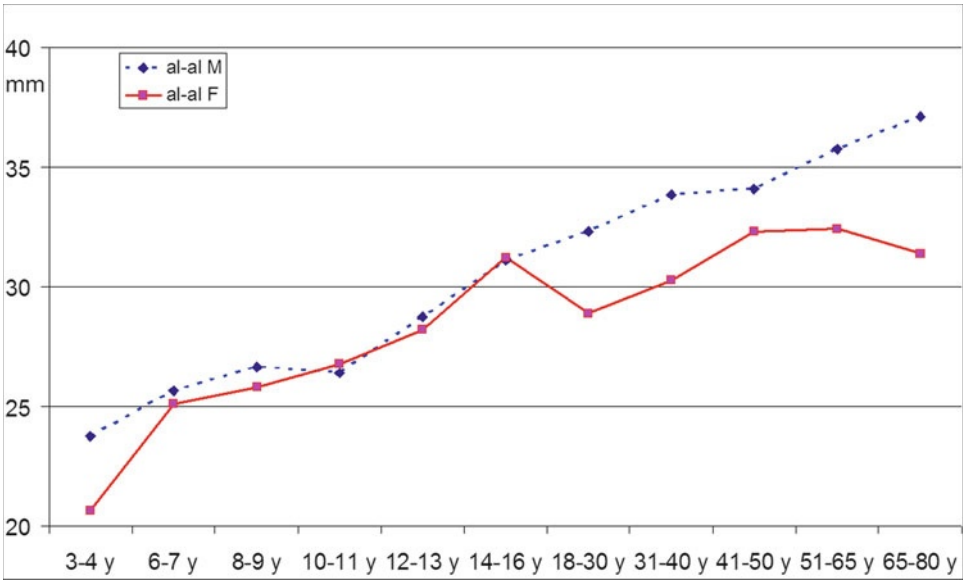

Fig. 55.8 Nasal width (al_r-al_l) in healthy white Caucasians from northern Italy. Continuous line, women (F); interrupted line, men (M). From childhood to old age, nasal horizontal dimensions grow in both sexes; sexual dimorphism is more evident after adolescence

Indeed, differences in the age range, methods, and ethnic origin of the analyzed persons may explain these discrepancies (Aung et al. 2000).

55.3.2 Angles

The largest ethnic variations in the nose are expected in the descriptors of nasal shape, that is, the angles. In young adults, nasal angles were measured both directly by conventional anthropometry, indirectly by digital instruments and photographs, and on stone casts. Direct measurements were made by Farkas et al. (1994) on Northern American white Caucasians (100 men and 200 women), and by Porter and Olson (2003) on 107 African American women. Standardized photographs were taken by Troncoso et al. (2008) in 90 men and 90 women who had at least three generations of Chilean ancestry. Aung et al. (2000) laser scanned the noses of 90 Chinese men and women, while in the current study an electromagnetic digitizer was used on Northern Italian white Caucasians (126 men and 65 women). Rosati et al. (2009) measured the nasal casts of 15 women and 5 men from Northern Italy (Table 55.4).

Overall, the largest nasal tip angle was found in the Italian persons, while the smallest in the Chinese persons. The smallest nasolabial angle was measured in Afro-American women, and the largest in Northern Italian women; intermediate values were reported for Chinese and Northern American persons. In Chinese persons, inter-alar angle was approximately 15° larger than in white Caucasians, while the difference in interaxial angle reached 25–30°. Adult Chileans had the smallest interalar angles.

Table 55.4 Nasal angles in healthy young adults in different ethnic groups

Angles (degrees)		Chinese (Aung et al. 2000)	North America (Farkas et al. 1994)	North Italy (current study)	North Italy (Rosati et al. 2009)	Chilean (Troncoso et al. 2008)	Afro-American (Porter and Olson 2003)
Nasal tip	M	82.55	71.7	93.84	–	–	–
(n-prn-sn)	F	83.87	67.4	94.99	–	–	–
Nasolabial angle	M	99.91	99.8	126.84	–	104.8	86
(prn-sn-ls)	F	97.71	104.2	127.06	–	109.9	–
Inter-alar angle	M	89.07	–	75.43	77.5	67.84	–
(al_r-prn-al_l)	F	90.89	–	74.45	–	68.62	–
Inter-axial angle	M	75.07	–	–	49.6	–	–
(stn_r-itn_r^stn_l-itn_l)	F	80.67	–	–	–	–	–

Each ethnic group possesses a specific nasal shape that can be described by a set of angles. The table reports some examples in several ethnic groups

55.3.3 Volume

Nasal volume was assessed only in a limited number of investigations. Ferrario et al. (1997) reported data collected on 402 children aged 6–14 years, and on 101 young adults, using a simplified mathematical calculation. Starting from the 3D coordinates of five soft-tissue facial landmarks (ac_r, ac_l, prn, n, and sn), they reconstructed nasal morphology using two tetrahedra: the first tetrahedron had the plane ac_r, ac_l, prn as its base and vertex in n, the second had the same base and vertex in sn. Euclidean geometry provided the volumes of the two tetrahedra, and reference data for healthy children and adults were calculated. Data were used to assess the final surgical outcome of a group of patients operated for cleft lip and palate (Ferrario et al. 2003).

Heidari et al. (2009) measured the nose characteristics of 200 Baluch and 200 Sistani adult women from Iran, and estimated nasal volume using the same method proposed by Ferrario et al. (1997). On average, the noses of their women were 1.3–1.4 times larger than those estimated from Northern Italian women (Fig. 55.9).

More recently, Ferrario et al. (2007) compared their simplified calculations with values obtained from a surface-based NURBS approach, as detailed in the section "*Nose reproduction: stone casts and digital models*" of this same chapter. In the simplified landmark-based approach, nasal volumes ranged between 3.2 and 8.1 mm^3, and between 12.6 and 23.8 mm^3 in the surface-based approach. On average, nasal volumes obtained by the surface-based approach gave values that were 3.5 times larger than those computed with the landmark-based approach (ratios ranging between 2.8 and 4.7 mm^3/mm^3). The two measurements were highly related to each other, and a linear regression equation was obtained to convert landmark-based values to surface-based volumes. Indeed, the surface-based nasal volumes should directly correspond to the actual nasal volumes.

During growth, nasal volumes progressively increased from childhood to young adulthood, but their modifications continue even after the attainment of skeletal maturity (Fig. 55.9). In children aged 3–4 years, nasal volume is approximately 36% (boys) and 42% (girls) of the mean value attained in young adulthood (between 18 and 30 years of age). In old adults aged 65–80 years, nasal volume is 120% (men) and 118% (women) of the mean value of the 18–30 age group.

If the equation proposed by Ferrario et al. (2007) for young adults is applied to the all adult groups measured in the current study, mean adult nasal volumes should range between 16.6 mm^3 (18–30 years old women) and 19.17 mm^3 (51–64 years old men). Obviously, this equation was tested

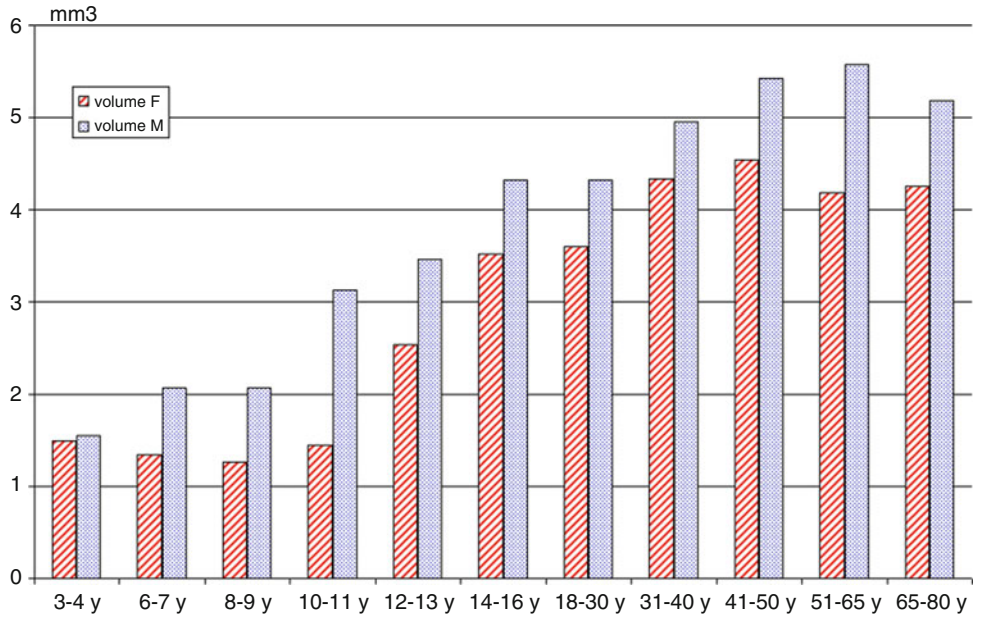

Fig. 55.9 Nasal volume in healthy white Caucasians from northern Italy. Lines, women (F); dots, men (M). From childhood to old age, external nasal volume grows in both sexes; sexual dimorphism is always evident

only in a small group of young adults within a limited age range, and further analyses are necessary to develop conversion algorithms that could provide the actual values of nasal volumes at all ages and in both sexes.

55.4 Applications to Other Areas of Health and Disease

Anatomical and anthropometric descriptions of humans (both living and dead) and clinical applications, both need a quantitative assessment of facial characteristics. The clinical, qualitative description of facial alterations should be supported by well-selected quantitative data that may provide appropriate information for diagnosis, treatment planning, and the evaluation of results (Yamada et al. 1999; Russell et al. 2000; Ferrario et al. 2003; Liou et al. 2004; Baeyens et al. 2006; Daelemans et al. 2006; Honrado et al. 2006; Schwenzer-Zimmerer et al. 2008a, b; Troncoso et al. 2008). In plastic, reconstructive, and cosmetic surgeries, a quantitative approach can be useful to compare the outcome of different surgical procedures or intervention schedules, and it may also assist in the identifications of those facial areas susceptible of surgical intervention (Ferrario et al. 2003).

Nasal size and shape in the different ages and ethnic groups may also be usefully employed for forensic reconstructions (Troncoso et al. 2008). Considering that the nose continue to modify even after the attainment of biological maturity, its age-related variations may help in the aging of both living and dead persons, as well as in personal identification (Rynn and Wilkinson 2006; Sforza et al. 2009). The definition of age-, sex- and ethnic-specific databases may help in the identification of those individual facial features that best discriminate among persons. Facial reconstructions from

skeletal remnants and artificial aging also need data collected from living persons of the widest possible age span, supplying information that may help in simulating the modifications of facial features during normal growth and aging (Troncoso et al. 2008).

55.5 Conclusions

Quantitative data should always come with qualitative anatomical description to allow a deeper understanding of the processes that regulate growth and development, normality, and alterations (Spalding and Vig 1990; Ferrario et al. 1997). In a clinical context, a quantitative description of the outcomes, both immediate and during longitudinal evaluations, gives support to the improvement of surgical procedures, allowing the choice of the best timing of intervention (Honrado et al. 2006; Schwenzer-Zimmerer et al. 2008a, b). In particular, the use of current digital 3D methods adds to linear dimensions and angles (those given by direct anthropometry, Farkas et al. 1994; Zankl et al. 2002), areas, and volumes.

Literature reports several studies about nasal morphology; quantitative investigations underlined that nasal growth does not stop in early adulthood, but it continues even in old age (Zankl et al. 2000). Nasal dimensions do not modify at the same rate: vertical distances tend to increase more and faster than antero-posterior and horizontal ones. These characteristics should be considered when planning plastic, reconstructive, and cosmetic surgeries (Honrado et al. 2006; Schwenzer-Zimmerer et al. 2008a, b), as well as when reconstructing facial characteristics in forensic anthropology (Rynn and Wilkinson 2006; Troncoso et al. 2008).

Most previous studies found a moderate level of asymmetry even in normal, healthy individuals (as reviewed by Rosati et al. 2009). In particular, directional asymmetry may be the effect of possible repeatable environmental factors.

The nostrils had the largest asymmetry (Rosati et al. 2009). This part of the nose was often assessed from nasal stone casts, as described in this same chapter. The principal limit of the method for nose casts was that it requires labor, and a lot of collaboration from the subjects (Ferrario et al. 2007). Alternative procedures that directly digitize nasal morphology using optical devices (Yamada et al. 1999; Aung et al. 2000; White et al. 2004; Mori et al. 2005) have been used by some investigators. It has to be underlined that the nose itself produces a shadow that limits nostril imaging. Additionally, nose hairs (especially in men) produce artifacts, making the final 3D reconstruction inaccurate (see the chapter "Three-dimensional facial morphometry: from anthropometry to digital morphology" in this same book). Indeed, a recent study where the faces of patients with cleft lip were imaged using portable laser scans, found that only two thirds of the scans were free from imaging artifacts in the nasolabial area (Schwenzer-Zimmerer et al. 2008b). Therefore, the use of plaster models still maintains its validity when a detailed analysis of nostrils is needed.

Nonetheless, direct contact with calipers, as well as the effect of the impression material during the production of a nasal cast, may artificially increase nasal asymmetry, especially in the nostril area, where the cartilaginous support is more limited, and deformations may become larger.

Additionally, the use of less invasive optical instruments may provide the best patient compliance, especially when repeated, longitudinal measurement should be made (Yamada et al. 1999; Baeyens et al. 2006; Daelemans et al. 2006; Honrado et al. 2006; Schwenzer-Zimmerer et al. 2008a, b). Unfortunately, their actual performance for selected nasal base measurements is still unknown.

A further question is the effect of race/ethnicity on nasal dimensions and shape. Surgeons and forensic anthropologists should use reference, normative data collected on the population most similar to the individual patient (Table 55.5).

Table 55.5 Key points in age-, sex- and ethnic-related variations in nasal dimensions

	Adult dimensions at	Old age increment	Sexual dimorphism	Ethnic/racial variations
Vertical dimensions	13–14 years (females) 18 years (males)	104–126% (women), 110–160% (men)	✓	✓
Horizontal dimensions	15 years (females), 20 years (males)	109% (women), 115% (men)	✓	✓
Antero-posterior dimensions	15–16 years	115%	=	✓
Angles	12–13 years	Variable	Variable	✓
Volume	14–16 years (females), 16–18 years (males)	118–120%	✓	?

The various nasal dimensions modify in different ages of life, with different patterns in the two sexes and in the various ethnic groups

Summary Points and Practical Methods

- Together with conventional anthropometry, digital anthropometry as well as plaster casts can be used to investigate nasal morphology from a quantitative point of view.
- Less invasive optical instruments may provide the best results, but their actual performance for selected nasal base measurements is still unknown.
- To provide a complete evaluation of any patient, individual values should be compared to those collected in healthy subjects of the same age, sex, race, and ethnic group.
- Surgical reconstructions should attentively consider the different growth potentials and timing of the various nasal structures.
- Three-dimensional nasal reconstructions can be profitably used in several medical and forensic fields.

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Part X
Regions and Anatomical Areas of the Body: Internal Organs, Other Tissues and Regions

Chapter 56
Imaging Techniques for the Measurement of Liver Volume

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Abstract Assessment of liver volume may be of great relevance in the clinical management of several hepatic diseases as well as systemic disorders associated with liver involvement. With the increasing use of innovative strategies in liver resection and partial transplantation, in vivo measurement of liver volume has become of major interest. Liver volume has also been proposed as a sensitive indicator of ectopic adiposity and associated metabolic disorders in obese subjects. Several formulae have been developed for the estimation of standard liver size, based on anthropometric measures. Most data have been generated in the research areas of liver transplantation and computation of the body surface area, body weight, age, and/or gender. Several methods for measuring liver volume using Computerized Tomography (CT) or Magnetic Resonance (MR) have been described, which apply automatic or semiautomatic segmentation and subsequent reconstruction by the summation of the products of section thickness and area of the segmented liver in each section. Ultrasonography has also been employed for the estimation of liver volume. The left lateral segment of the liver can be easily visualized in its entirety by ultrasound examination, and measurement of the hepatic left lobe volume has been employed to objectively evaluate the extent of liver involvement in nonalcoholic fatty liver disease of obese subjects.

Abbreviations

ATP III	National Cholesterol Education Program Adult Treatment Panel III
BH	Body height
BSA	Body surface area
BW	Body weight
CC	Craniocaudal
COR	Coronal
CRP	C-reactive protein
CT	Computerized tomography
HLLV	Hepatic left lobe volume
IDF	International Diabetes Federation

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_56,

LV	Liver volume
MR	Magnetic resonance
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
SD	Standard deviation
US	Ultrasound
VD	Ventrodorsal

56.1 Introduction

The liver is a large organ located in the upper right-hand portion of the abdominal cavity, extending from the right lateral aspect of the abdomen transversely toward the xiphoid. The weight of the adult liver varies from 1,200 to 1,800 g, depending on the body size, and constitutes about 2–3% of the total body weight of an adult. Based on external appearance, four lobes are traditionally described: right, left, quadrate, and caudate. The 2 main lobes (right and left) are anatomically divided by the falciform ligament on the anterosuperior surface and by the fissures for the ligamentum venosum and ligamentum teres on the visceral surface (Skandalakis et al. 2004). Liver weight increases with age, reaching the highest values in the fifth to sixth decades, with males showing greater volumes (Choukèr et al. 2004).

Assessment of liver volume may be of great relevance in the clinical management of several hepatic diseases as well as systemic disorders associated with liver involvement. It may be useful to evaluate the progress of hepatic failure, to plan radiotherapy dosimetry, and to assess the responses to treatments. With the increasing use of innovative strategies in liver resection and partial transplantation, in vivo measurement of liver volume has become of major interest (Reiner et al. 2009). Successful liver transplantation is the result of several factors, including reliable volumetric estimation of the hepatic segments of living donors. This is crucial to provide suitably sized grafts for the recipient, without compromising liver function of the donor after resection. Sedentary lifestyle and poor dietary choices have led to an obesity epidemic associated with the risk for developing metabolic syndrome and nonalcoholic fatty liver disease (NAFLD) (Table 56.1). Liver disease of metabolic origin, associated with obesity, is now recognized as the most prevalent liver disease in Western countries. The histological spectrum of NAFLD ranges from simple steatosis, which in general

Table 56.1 Key features of Nonalcoholic fatty liver disease (NAFLD)

1. The term Nonalcoholic fatty liver disease (NAFLD) has been introduced to indicate a clinicopathologic syndrome that encompasses a broad spectrum of hepatic lesions, ranging from simple steatosis to necroinflammatory lesions and fibrosis
2. NAFLD is a common finding in obese subjects.
3. Among obese subjects, NAFLD is frequently observed in patients with the metabolic syndrome.
4. Visceral adiposity and insulin resistance are viewed as the key factors in the development of the metabolic syndrome.
5. The metabolic syndrome represents a clustering of risk factors for cardiovascular diseases.
6. Increasing evidence has been provided suggesting that NAFLD represents the hepatic component of the metabolic syndrome.

This table lists the key facts of NAFLD. Liver enlargement due to diffuse accumulation of triglycerides in hepatocytes is a common finding in obese subjects. NAFLD is the result of a multi-factorial process, and there is increasing evidence that NAFLD represents the hepatic component of the metabolic syndrome

follows a benign nonprogressive clinical course, to nonalcoholic steatohepatitis (NASH), which is a more aggressive form of liver injury that may progress to cirrhosis and end-stage liver disease (Marchesini et al. 2008; Myers 2009). At present, liver biopsy represents the most reliable tool to establish the severity of hepatic involvement. However, due to the complexity of this procedure and the growing prevalence of NAFLD, the identification of effective noninvasive tools for the diagnosis and staging of this liver disease has emerged as a major clinical and research priority. Furthermore, liver enlargement appears related to the extent of the metabolic derangement that is associated with visceral obesity, and liver volume has been proposed as a sensitive indicator of ectopic adiposity and related metabolic disorders in obese subjects (Santini et al. 2007).

Manual assessment of liver volume by palpation and percussion lacks both accuracy and reliability, especially in obese subjects. Formulae based on anthropometric measures can calculate the expected normal liver volume, which can be taken as a standard reference to assess adequacies of graft size in living donor before liver transplantation or remnant liver after major hepatectomy. An accurate noninvasive in vivo volumetry of individual livers may be performed by imaging techniques.

56.2 Estimation of the Standard Liver Volume by Formulae Based on Anthropometric Measures

Several formulae have been developed to estimate normal liver size, the ultimate goal being to find the method that most often leads to appropriate clinical decision-making. Most data have been generated in the research area on liver transplantation. An accurate pretransplant estimation of standard liver volume is indeed crucial to provide an adequate hepatic mass to the recipient while ensuring donor safety. Most formulae include the body surface area (BSA), as the best index that correlates with liver volume. Other formulae compute the body weight, age, and/or the gender (Table 56.2). Yet, several differences have been observed among formulae derived from various ethnic groups, thus suggesting that a formula may be necessary for each local population.

Table 56.2 Reported formulae for the estimation of standard liver volume (LV), based on anthropometric measures

Author	Formula	LV (mL) ± SD
DeLand and North (1968)	LV = 1,020 × BSA - 220	1400.41
Urata et al. (1995)	LV =706.2 × BSA + 2.4	1195.34 ± 112.64
Lin et al. (1998)	LV = 13 × BH + 12 × BW – 1,530	1364.41 ± 212.94
Heinemann et al. (1999)	LV =1072.8 × BSA – 345.7	1466.52 ± 171.11
Lee et al. (2002)	LV = 691 × BSA + 95	1022.95
Vauthey et al. (2002)	LV = 1267.28 × BSA - 794.4	1355.77 ± 200.95
Choukèr et al. (2004)	LV = 16.98 × BW + 591.82	1666.55 ± 152.09
Yu et al. (2004)	$LV = 21.585 \times BW^{0.732} \times BH^{0.225}$	1414.67 ± 160.17
Chan et al. (2006)	LV = 218.32 + BW × 12.3 + gender × 51 (M = 1; F = 0)	927.54 ± 168.78
Hashimoto et al. (2006)	LV = 961.3 × BSA - 404.8	1219.07 ± 153.33
Yuan et al. (2008)	LV = 949.7 × BSA - 48.3 × age-247.4 (<40 years = 1; 41–60 years = 2; >61 years = 3)	1290.18 ± 156.40
Yoshizumi et al. (2008)	LV = 772 × BSA	1308.84 ± 122.41

Several formulae have been developed for the estimation of the normal liver size. Most formulae include the BSA as the best index that correlates with liver volume. Other formulae compute the body weight, age, and/or the gender. Yet, several differences have been observed among formulae derived from various ethnic groups, thus suggesting that a formula should be created for each local population

56.3 Measurement of Liver Volume by Computed Tomography (CT)

Several methods for measuring liver volume using CT have been described. Early methods require manual tracing of the entire liver contour on every CT slice. The area of each slice is calculated by a computer using mathematical algorithms and the volume is reconstructed by summation of the products of the section thickness and area of the segmented liver in each section (Heymsfield et al. 1979; Fritschy et al. 1983; Emiroglu et al. 2006). While yielding very accurate results, manual methods are time-consuming processes that require considerable user involvement in the segmentation of the liver on each section.

More recent methods apply automatic or semiautomatic segmentation (Gao et al. 1996; Sandrasegaran et al. 1999; Schroeder et al. 2002; Hermoye et al. 2005; Nakayama et al. 2006). These systems use mathematical computerized models that provide an estimation of CT value of the liver to determine the boundaries of liver in each section. The results of liver volumetry are dependent on the slice thickness, and a 6-mm slice has been proposed as the preferred slice thickness for CT imaging (Reiner et al. 2009). Because the liver density is similar to the density of surrounding tissues, automatic techniques have been developed after intravenous or intra-arterial infusion-iodinated contrast material to provide better delineation of the liver edge.

56.4 Measurement of the Liver Volume by Magnetic Resonance (MR)

As for CT, MR imaging offers an accurate means of determining adult liver volume, and it now plays a major role in the evaluation of the living donor before liver transplantation. MR imaging of the liver has evolved in recent years mainly due to the development of fast imaging techniques that provide superior-quality, high-resolution images in a breath hold. By using the generated data, 3D reconstructed images of the liver and its vascular anatomy can be created (Marcos et al. 2000; Bassignani et al. 2001; Cheng et al. 2001, Fulcher et al. 2001, Lee et al. 2001; Sahani et al. 2004). A comprehensive MR imaging examination includes parenchymal assessment for focal or diffuse abnormalities; MR angiography for delineation of vascular anatomy; MR cholangiography for biliary branching anomalies. Diffuse liver diseases like fatty infiltration and hemochromatosis can be diagnosed at MR imaging due to the signal intensity changes they produce with the different pulse sequences.

A simple, diameter-based formula, applied to CT and MR cross-sectional images has recently been proposed for calculation of total liver volume (Muggli et al. 2009). The volume formula for a tetrahedron was used as a starting point to define a new formula. The ground area was defined as the product of the maximal craniocaudal (CC), ventrodorsal (VD), and coronal (COR) liver diameters. A quotient was calculated and the following formula was obtained: Liver volume = CC × VD × COR × 0.31. The estimated volumes showed a highly significant correlation with the virtual volumetric measurement obtained by a dedicated computer software.

56.5 Measurement of the Liver Volume by Ultrasound (US)

Ultrasonography represents an easy and reliable tool for the estimation of visceral adiposity through measurement of visceral fat thickness. Ultrasonography may also provide semi-quantitative information on the degree of liver steatosis (Joseph et al. 1991; Mathiesen et al. 2002), and it has been

Table 56.3 Key features of liver ultrasonography

1. Liver ultrasonography may be of great relevance in the clinical management of several hepatic diseases as well as systemic disorders associated with liver involvement.
2. Ultrasonography may provide semi-quantitative information on the degree of liver steatosis.
3. Ultrasonography can be employed for the detection of liver masses.
4. Ultrasonography can be employed for the estimation of liver volume.
5. The left lateral segment of the liver can be easily visualized in its entirety by ultrasound examination.
6. Measurement of the hepatic left lobe volume (HLLV) has been employed to objectively evaluate the extent of liver involvement in nonalcoholic fatty liver disease of obese subjects.
7. HLLV can be used as an anthropometric marker of visceral obesity and related co-morbidities.
8. Ultrasonography is handy, little expensive, and easily feasible in an ambulatory setting.
9. Ultrasound measurement of HLLV is a reliable and simple tool for the estimation of liver enlargement in several clinical circumstances.

This table lists the key facts of liver ultrasonography. Ultrasonography represents an easy and reliable tool for the estimation of visceral adiposity through the measurement of visceral fat thickness, may provide semi-quantitative information on the degree of liver steatosis and it has been employed for the estimation of liver volume

employed for the estimation of liver volume (Carr and Duncan 1976; Fritschy et al. 1983; Van Thiel et al. 1985; Leung et al. 1986) (Table 56.3). Sonographic preoperative assessment of liver volume before major liver resection has been recently performed (Kitajima et al. 2008). In that study, liver was divided into three main compartments: segments II–III (left lateral segment) were configured as a quarter of an ellipsoid, segments V–VIII (right lobe) were configured as an ellipsoid, and segment IV was configured as a section of a cylinder. The volume of each compartment was calculated from three measures obtained by ultrasound examination. A fair correlation was observed between estimated volumes and the volume of actual specimens after hepatectomy. However, ultrasonographic measurement of liver volume presents objective difficulties. Indeed, the liver shows wide individual variation, and the scanning fields may be hindered by the bowels or the lungs, particularly in obese subjects. The left lateral segment of the liver can be easily visualized in its entirety by ultrasound examination, even in subjects with severe abdominal obesity. Measurement of the hepatic left lobe volume (HLLV) has been employed in patients scheduled for liver transplantation (Hatsuno et al. 2002). In a recent study (Santini et al. 2007), the ellipsoid formula (width × height × length × 0.52) was applied to calculate the hepatic left lobe volume in obese subjects. The height (longitudinal diameter) of the lobe was obtained on an epigastric-longitudinal scan, considering the distance between the diaphragm and the lower margin of the left lobe. The length of the lobe (lateral–lateral diameter) was calculated on the axial scan by drawing a line between the round ligament and the lateral margin of the hepatic lobe. Thickness was obtained on both the axial and the longitudinal scans, measuring the distance between the anterior and the posterior borders of the liver. To validate the ultrasound procedure, sonographically measured HLLV was compared with the total liver volume as measured by MR and dedicated software. A highly significant positive association was demonstrated. The mean ± SD value of HLLV in obese women was 431 ± 214 mL (range = 46–1,019 mL) while it was 187 ± 31 mL (range 143–258 mL) in the normal weight group. A close association between HLLV and several anthropometric and serologic parameters that may be altered in obese subjects was demonstrated. In particular, in a multiple logistic regression analysis, intra-abdominal fat was the only anthropometric measure independently associated with HLLV (Fig. 56.1). Furthermore, a significant association was observed between HLLV and serum liver enzymes, fasting glucose, insulin, uric acid, CRP, triglycerides, and HDL-cholesterol (Fig. 56.2). Finally, a positive association between HLLV and systolic or diastolic blood pressure was observed. For all these parameters, the association with HLLV was stronger than that observed with ultrasound measured intra-abdominal fat. Using the linear regression formulas, the values of HLLV corresponding to the

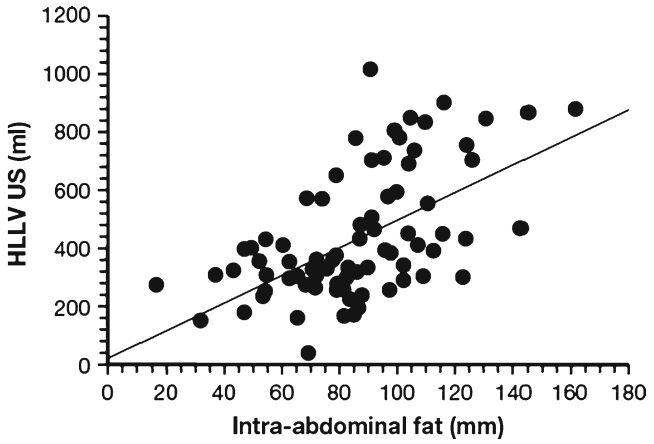

Fig. 56.1 Correlation between hepatic left lobe volume (*HLLV*) and intra-abdominal fat in obese women. A highly significant ($p < 0.0001$, $R = 0.572$) positive association between HLLV and intra-abdominal fat was observed. In a multiple logistic regression analysis including BMI, weight, and intra-abdominal fat, the latter was the only anthropometric measure independently associated with HLLV (From Santini et al. (2007). With permission)

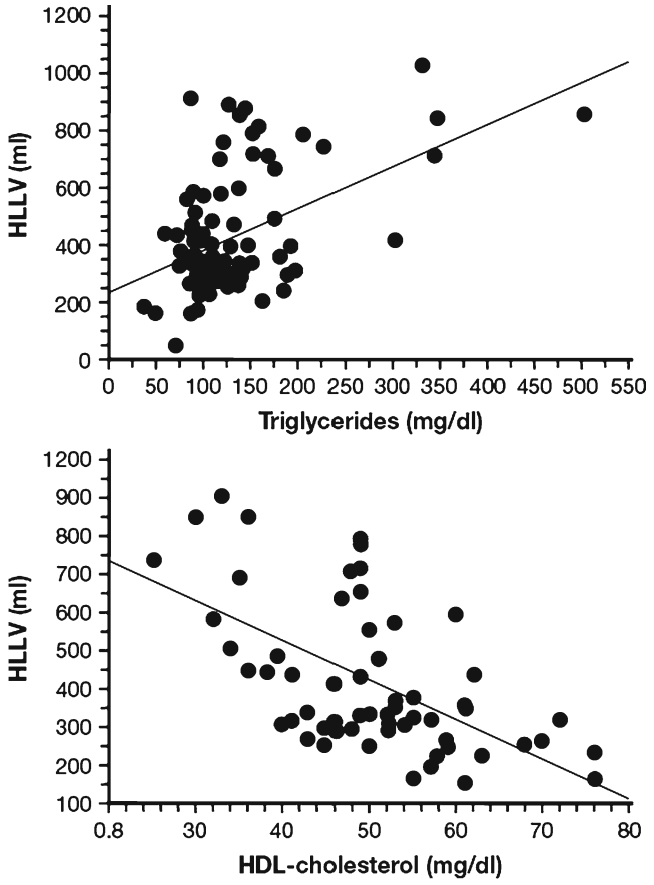

Fig. 56.2 Correlations between hepatic left lobe volume (*HLLV*) and serum indexes of lipid metabolism in obese women. A positive correlation between HLLV and triglycerides ($p < 0.0001$, $R = 0.485$) and a negative correlation between HLLV and HDL-cholesterol ($p < 0.0001$, $R = -0.583$) were observed (From Santini et al. (2007). With permission)

Table 56.4 Cut-off values of the risk factors for the metabolic syndrome and HLLV

Risk factors for the metabolic syndrome (cut-off value)	HLLV (mL)
Triglycerides (≥150 mg/dL)	452
High Density Lipoprotein Cholesterol (≤50 mg/dL)	422
Glucose ATP III (≥110 mg/dL)	549
Glucose IDF criteria (≥100 mg/dL)	478
Systolic blood pressure (≥130 mmHg)	443
Diastolic blood pressure (≥85 mmHg)	457
Mean HLLV ± standard deviation (ATP III)	465 ± 49
Mean HLLV ± standard deviation (IDF)	450 ± 20

Modified from Santini et al. (2007)
This table shows the estimated hepatic left lobe volume (HLLV), as assessed by linear regression, at each cut-off point of various risk factors for the diagnosis of the metabolic syndrome, defined according to the criteria of the Adult Treatment Panel III (ATP III) or the International Diabetes Federation (IDF)

cut-off values of various risk factors for the diagnosis of the metabolic syndrome, as proposed by the National Cholesterol Education Program Adult Treatment Panel III or the International Diabetes Federation, were calculated. A mean value of 465 mL (450 mL according to the criteria of the International Diabetes Federation) as the threshold volume matching the outbreak of the syndrome was calculated (Table 56.4). These results suggest that HLLV can be used as an anthropometric marker of visceral obesity and related co-morbidities. While CT and MR are sophisticated techniques unlikely accessible for routine management of obese subjects and, due to technical limitations, they may not be available for the most severely obese patients, ultrasonography is handy, little expensive, and easily feasible in an ambulatory setting. This makes ultrasound measurement of HLLV a reliable and simple tool for the estimation of liver enlargement in several clinical circumstances (e.g. preoperative evaluation of obese candidates to laparoscopic bariatric surgery, follow-up of patients undergoing weight-loss programs).

Summary Points

- The liver is a large organ located in the upper right-hand portion of the abdominal cavity, extending from the right lateral aspect of the abdomen transversely toward the xiphoid.
- The weight of the adult liver varies from 1,200 to 1,800 g, depending on the body size.
- Assessment of liver volume is of great relevance in the clinical management of several hepatic diseases as well as systemic disorders associated with liver involvement.
- Sedentary lifestyle and poor dietary choices have led to an obesity epidemic associated with the risk for developing metabolic syndrome and nonalcoholic fatty liver disease (NAFLD).
- At present, liver biopsy represents the most reliable tool to establish the severity of NAFLD.
- With the increasing use of innovative strategies in liver resection and partial transplantation, in vivo measurement of liver volume has become of major interest.
- Manual assessment of liver volume by palpation and percussion lacks both accuracy and reliability, especially in obese subjects.
- Formulae based on anthropometric measures can calculate the expected normal liver volume.
- An accurate noninvasive in vivo volumetry of individual livers may be performed by imaging techniques.
- Several methods for measuring liver volume using CT have been described.

- MR imaging offers an accurate means of determining adult liver volume, and it now plays a major role in the evaluation of the living donor before liver transplantation.
- Ultrasonography represents an easy and reliable tool for the estimation of visceral adiposity, may also provide semi-quantitative information on the degree of liver steatosis and it has been employed for the estimation of liver volume.

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Chapter 57
Epicardial Adipose Tissue Measured by Multidetector Computed Tomography: Practical Tips and Clinical Implications

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Abstract Epicardial adipose tissue (EAT) is the fat depot surrounding the heart and is confined within the pericardial sac. It accounts for approximately 20% of the total heart weight and covers 80% of the cardiac surface, mostly in the grooved segments along the paths of the coronary arteries. To clearly delineate the asymmetric distribution of EAT and explore its pathophysiological significance, EAT should be measured in three dimensions using multidetector computed tomography (MDCT): regional thickness, cross-sectional areas, and total volume. Details regarding MDCT measurements of EAT are introduced in this chapter. Regardless of differences in ethnicity and body habitus, EAT thickness in the grooved segments is greater than in the non-grooved segments. Among the grooved segments, the right atrio-ventricular groove (where the right coronary artery is located) has the thickest fat, followed by the left atrio-ventricular groove (where the left circumflex artery and great cardiac vein are located). The maximal EAT thickness surrounding the left anterior descending coronary artery, measured in the superior inter-ventricular groove in the basal short-axis plane, is less than that surrounding the right coronary artery or the left circumflex artery. The average volume of EAT is generally between 110 and 125 cm^3.

Although EAT constitutes only 1% of the total fat mass, several clinical studies have shown that the amount of EAT is associated with obesity, the amount of intra-abdominal visceral fat, cardiometabolic risk factors, cardiac structural changes, coronary atherosclerosis, and the incidence of coronary heart disease events. However, it is still a matter of debate as to whether these associations with EAT are direct or indirect, and which EAT measurement provides the best correlate. It appears that EAT thickness in the left atrio-ventricular groove provides a more accurate assessment of its metabolic and atherogenic risks and is therefore a better indicator of its metabolic risk and a stronger coronary risk factor than total EAT volume. Future studies are critical to elucidate whether there is indeed regional variation in the molecular characteristics of EAT and whether this variation confers any clinical, prognostic, and therapeutic implications.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_57,

Abbreviations

BMI	Body-mass index
EAT	Epicardial adipose tissue
MDCT	Multidetector computed tomography

57.1 Introduction

Fat surrounding the heart resides in two distinct depots separated by the parietal pericardium: the epicardial and paracardial adipose tissues (Rabkin 2007; Sacks and Fain 2007). Epicardial adipose tissue (EAT) is situated on the surface of the heart, especially around the epicardial coronary vessels, and it is confined within the pericardial sac. Paracardial adipose tissue is located on the external surface of the parietal pericardium within the mediastinum and has alternatively been termed mediastinal fat. Pericardial adipose tissue is defined as EAT plus paracardial adipose tissue (Fig. 57.1).

Epicardial and paracardial adipose tissues have different embryological origins (Ho and Shimada 1978). EAT shares a common embryological origin, the splanchnopleuric mesoderm, with intra-abdominal visceral fat depots (mesenteric and omental fat depots). Paracardial adipose tissue originates from the primitive thoracic mesenchyme, which then forms the parietal pericardium and the outer thoracic wall. The vascular supplies of both depots are also different. EAT obtains its vascular supply from the coronary arteries, which together with the epicardium (visceral pericardium) originate from mesothelial cells migrating from the septum transversum (the embryological source of the diaphragm). Paracardial adipose tissue derives its blood supply from non-coronary vessels such as the pericardiacophrenic branch of the internal mammary artery.

Unlike the isolation of paracardial adipose tissue from the heart by the parietal pericardium, there are no fascia-like structures separating EAT and the underlying myocardium (Iacobellis et al. 2005). It is commonly observed that a small amount of EAT extends from the epicardial surface into the myocardium, often following the adventitia of the coronary arteries. This close anatomical relationship between EAT and the myocardium suggests that it may play a role in the development of coronary atherosclerosis and the functional alterations of cardiac structures. Moreover, a growing body of evidence indicates that EAT is a metabolically active visceral fat depot, like intra-abdominal visceral fat. The rate of fatty acid breakdown and the secretion of pro-inflammatory cytokines are even higher in EAT compared with subcutaneous and omental fats (Marchington and Pond 1990; Mazurek et al. 2003; Kremen et al. 2006; Baker et al. 2009). These observations have prompted a resurgence of interest in EAT and its pathophysiological significance.

Several clinical studies have explored the association of EAT with anthropometric indices, the amount of intra-abdominal fat, cardio-metabolic risk factors, and coronary atherosclerosis (Chaowalit et al. 2006; Ahn et al. 2008; de Vos et al. 2008; Gorter et al. 2008a; Rosito et al. 2008; Sarin et al. 2008; Wang et al. 2009a, b). In most of these studies, they either measured the local thickness of EAT over the right ventricular free wall using echocardiography or the total volume of EAT using multidetector computed tomography (MDCT). As the distribution of EAT is asymmetric and mostly localized in the perivascular atrio-ventricular and inter-ventricular grooves (Abbara et al. 2006; Gorter et al. 2008b; Wang et al. 2009b), it is reasonable to question whether global or focal EAT measurements are more appropriate to assess the clinical significance of EAT. Furthermore, how many and which focal EAT measurements should be obtained is still controversial. Among the three imaging modalities (echocardiography, magnetic resonance imaging, and MDCT) used to assess EAT, MDCT offers a novel opportunity to assess the in vivo distribution of EAT in high-resolution three-dimensional

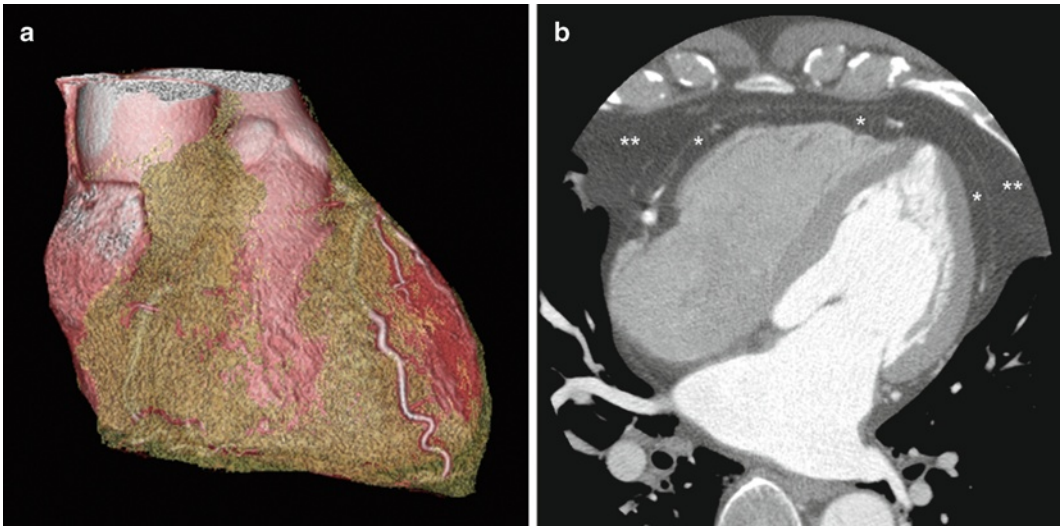

Fig. 57.1 Computed tomographic images of epicardial adipose tissue. (**a**) A three-dimensional volume-rendered computed tomographic image showing the distribution of epicardial adipose tissue around the heart. Epicardial adipose tissue is primarily concentrated in the atrio-ventricular and inter-ventricular grooves along the major branches of the coronary arteries. (**b**) Epicardial and paracardial adipose tissues are separated by the parietal pericardium. *Single asterisk mark* (*) denotes epicardial adipose tissue and *double asterisk mark* (**) denotes paracardial adipose tissue

views. Echocardiogram is dependent on acoustic windows and cannot provide an adequate window to assess all of the cardiac segments, whereas magnetic resonance imaging has spatial resolution limitations in the through plane dimension.

In this chapter, we first introduce the anatomical and physiological characteristics of EAT. Second, we describe how to measure EAT and which measurements should be made by MDCT, together with various EAT topographic data reported in subjects of different ethnic backgrounds. Third, we discuss the clinical significance of EAT by describing the association of various MDCT measurements of EAT with anthropometric indices, metabolic risk factors, coronary atherosclerosis and prevalent cardiovascular diseases, and cardiac structural changes. Finally, we delineate the future perspectives of EAT topographic measurements in different medical research fields.

57.2 Anatomical and Physiological Characteristics of Epicardial Adipose Tissue

Autopsy studies have shown that EAT accounts for approximately 20% of the total heart weight (Corradi et al. 2004). Although left ventricular mass far exceeds that of the right ventricle, the amount of EAT is equally distributed on the surface of the right and left ventricles. As a result, the ratio of EAT to the weight of the myocardium for the right ventricle is more than 3 times that of the left ventricle: 0.54 for the right ventricle and 0.16 for the left ventricle.

The low specific gravity of adipose tissue compared with myocardium indicates that EAT comprises an even higher percentage of the mass volume of the heart. It covers approximately 80% of the cardiac surface area and is primarily present in the grooved segments (Shirani et al. 1995). In normal adults, EAT is concentrated in the atrio-ventricular and inter-ventricular grooves and along the major

Table 57.1 Key features of epicardial adipose tissue

1. EAT is the fat surrounding the heart and within the pericardial sac.
2. EAT accounts for approximately 20% of total heart weight and covers 80% of the cardiac surface, mostly in the grooved segments along the paths of the coronary arteries.
3. The volume of EAT (~120 cm^3) accounts for approximately 20% of total cardiac volume, including the chambers.
4. EAT often extends from the epicardial surface into the myocardium and the adventitia of coronary arteries since there are no fascia-like structures separating EAT and the underlying myocardium.
5. EAT constitutes only 1% of the total body fat mass.
6. EAT shares a common embryological origin, the splanchnopleuric mesoderm, with intra-abdominal fat depots (mesenteric and omental fat) and is also a metabolically active visceral fat depot.
7. The putative physiological functions of EAT include:
   (a) A cushion to buffer the coronary artery against the torsion induced by the arterial pulse wave and cardiac contraction
   (b) A buffering system against toxic levels of fatty acids between the myocardium and the local vascular bed by its ability to rapidly scavenge excess fatty acids
   (c) A local energy source by providing free fatty acids to meet increased myocardial demands, especially under ischemic conditions
   (d) Protecting the ganglia of the intrinsic cardiac nervous system residing in EAT

This table lists the anatomical, embryological, and physiological properties of epicardial adipose tissue. *EAT* epicardial adipose tissue

branches of the coronary arteries, and, to a lesser extent, around the atria, over the free wall of the right ventricle and over the apex of the left ventricle (Fig. 57.1).

The putative physiological functions of EAT are listed in Table 57.1. First, because the coronary arteries and their major branches are embedded in EAT, it has been proposed that EAT functions as a cushion to buffer the coronary artery against the torsion induced by the arterial pulse wave and cardiac contraction. Second, high circulating levels of fatty acids in the coronary microcirculation can interfere with the generation and propagation of the contractile cycle of the heart, causing ventricular arrhythmia and alterations in repolarization. In young adult guinea pigs, the rate of fatty acid synthesis, release, and breakdown in response to catecholamines by EAT is markedly higher than in other adipose depots (Marchington and Pond 1990). Therefore, the second putative function of EAT is that it may act as a buffering system against toxic levels of fatty acids between the myocardium and the local vascular bed by its ability to rapidly scavenge excess fatty acids. Third, the increased lipolytic activity of EAT suggests that this fat depot may serve as a local energy source by providing free fatty acids to meet increased myocardial demands, especially under ischemic conditions. Fourth, EAT is the anatomical site where the intrinsic cardiac nervous system, including numerous ganglia and interconnecting plexuses, are located. Stimuli, such as transient coronary artery occlusion, can modify the activity generated by the intrinsic cardiac nervous system and thereby mediate the pain of angina pectoris. EAT may have a protective role for these ganglia (Rabkin 2007).

57.3 Practical Methods and Techniques: Measurements of Epicardial Adipose Tissue by Multidetector Computed Tomography

Before introducing how to measure EAT by MDCT, the geographical characteristics of EAT should first be reiterated. The distribution of EAT is characterized by its asymmetric distribution and its primary accumulation around the base of both ventricles, especially in the perivascular atrio-ventricular and inter-ventricular grooves, rather than in the non-grooved cardiac surfaces (Abbara et al. 2006; Sacks and Fain 2007). It is obvious that the measurement of total EAT volume alone cannot provide

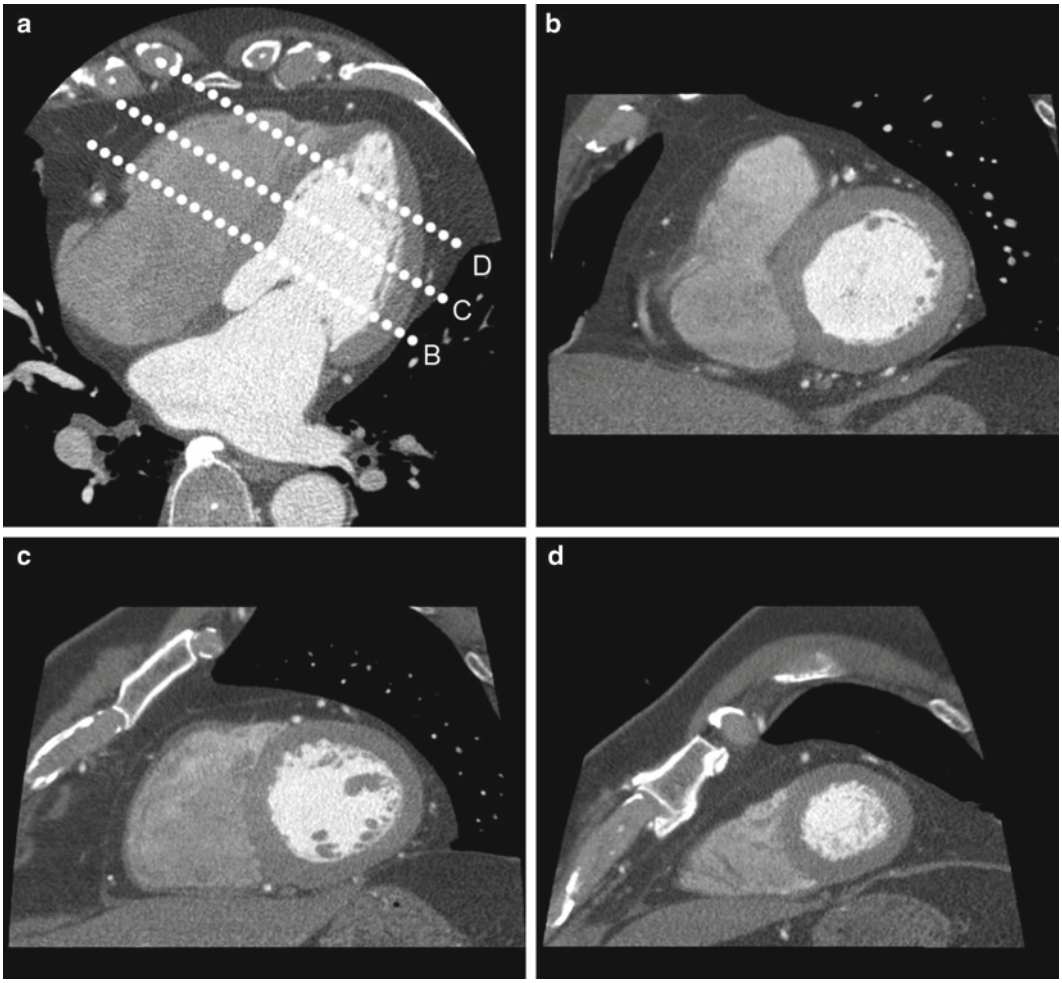

Fig. 57.2 Multiplanar reconstructions of multidetector computed tomographic images of epicardial adipose tissue. Multiplanar reconstructions of multidetector computed tomographic images in the horizontal long-axis (**a**) and short-axis (**b**–**d**) planes are shown. Anatomical landmarks for the selection of the basal (**b**, tips of the mitral valve leaflets), mid-cavity (**c**, papillary muscles), and apical (**d**, beyond the papillary muscles but before the end of the cavity) short-axis slices are displayed. The horizontal long- and short-axis planes are at 90º relative to the long-axis of the left ventricle

relevant information. To clearly delineate the asymmetric distribution of EAT and explore its pathophysiological significance, we propose that EAT should be measured in three dimensions: regional thickness, cross-sectional areas, and total volume (Wang et al. 2009b). Details of how to measure EAT in these three dimensions are described accordingly.

57.3.1 Regional Thickness of Epicardial Adipose Tissue

In order to measure the regional thickness of EAT, the first step is to obtain multiplanar reconstructions of the MDCT data in the standardized ventricular short-axis planes at the basal, mid-cavity, and apical levels, and in the horizontal long-axis plane, as defined by the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association (Fig. 57.2) (Cerqueira et al. 2002).

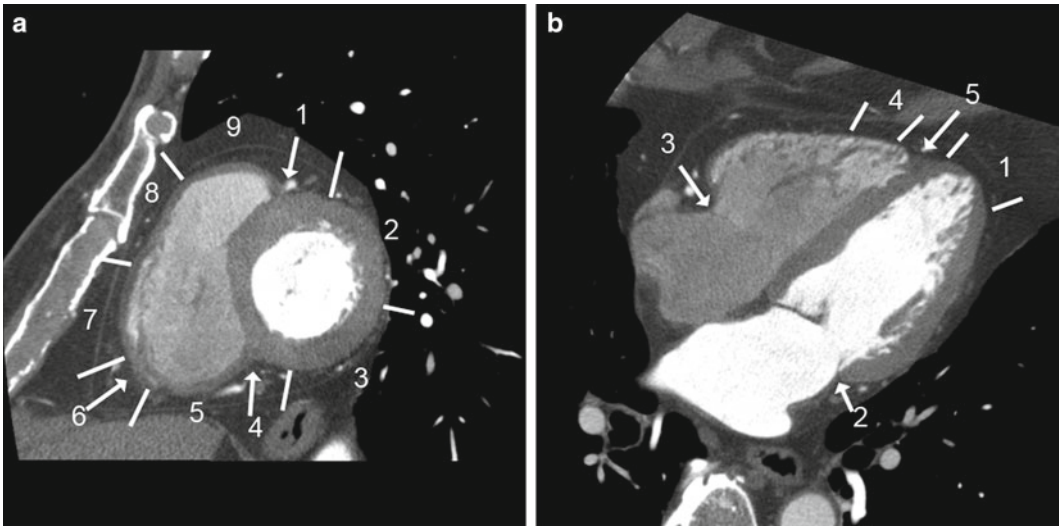

Fig. 57.3 Comprehensive segmentation system for the measurement of regional thickness of epicardial adipose tissue. The segmentation system, proposed by Abbara et al., for the measurement of the regional thickness of epicardial adipose tissue in the short-axis (**a**) and horizontal long-axis (**b**) planes are shown. The 9 short-axis segments are: *1* superior inter-ventricular groove, *2* left ventricular superior lateral wall, *3* left ventricular inferior lateral wall, *4* inferior inter-ventricular groove, *5* right ventricular diaphragmatic wall, *6* acute margin, *7* right ventricular free wall inferior, *8* right ventricular free wall superior, and *9* right ventricular superior wall. The 5 segments in the horizontal long-axis plane are: *1* left ventricular apex, *2* left atrio-ventricular groove, *3* right atrio-ventricular groove, *4* right ventricular apex, and *5* anterior inter-ventricular groove

The short-axis and horizontal long-axis planes are at 90º relative to the long axis of the left ventricle that transects the apex and the center of the mitral valve plane. The MDCT short-axis plane corresponds to the parasternal short-axis plane traditionally used in echocardiography, whereas the horizontal long-axis plane corresponds to the echocardiographic apical 4-chamber plane. The basal level of the short-axis plane is acquired from between the mitral annulus and the tips of the papillary muscles at end-diastole. The mid-cavity level is selected from the middle of the entire length of the papillary muscles. The apical level is selected from the area beyond the papillary muscles to just before the end of the cavity. The slice thickness is set to be 3 mm in our protocol. Image reconstructions are performed at 75% RR intervals (Lee et al. 2008).

The second step is to divide the cardiac surfaces, as shown in the above-mentioned reconstructed MDCT images, into segments. Abbara et al first reported their segmentation system for mapping EAT to facilitate transepicardial arrhythmia ablation (Fig. 57.3) (Abbara et al. 2006). In their system, 9 segments were made at each level of the short-axis slices (27 segments overall), including the superior inter-ventricular groove, left ventricular superior lateral wall, left ventricular inferior lateral wall, inferior inter-ventricular groove, right ventricular diaphragmatic wall, acute margin, right ventricular anterior free wall inferior, right ventricular anterior free wall superior, and right ventricular superior wall. In the horizontal long-axis plane, five segments, including the left ventricular apex, left atrio-ventricular groove, right atrio-ventricular groove, right ventricular apex, and anterior inter-ventricular groove, were obtained. This segmentation system is comprehensive but relatively complex and may exceed practical clinical application. To simplify the segmentation system without sacrificing essential information about the distribution of EAT, we designed a modified segmentation system as described below (Fig. 57.4) (Wang et al. 2009b). As EAT is mostly distributed around the base of both

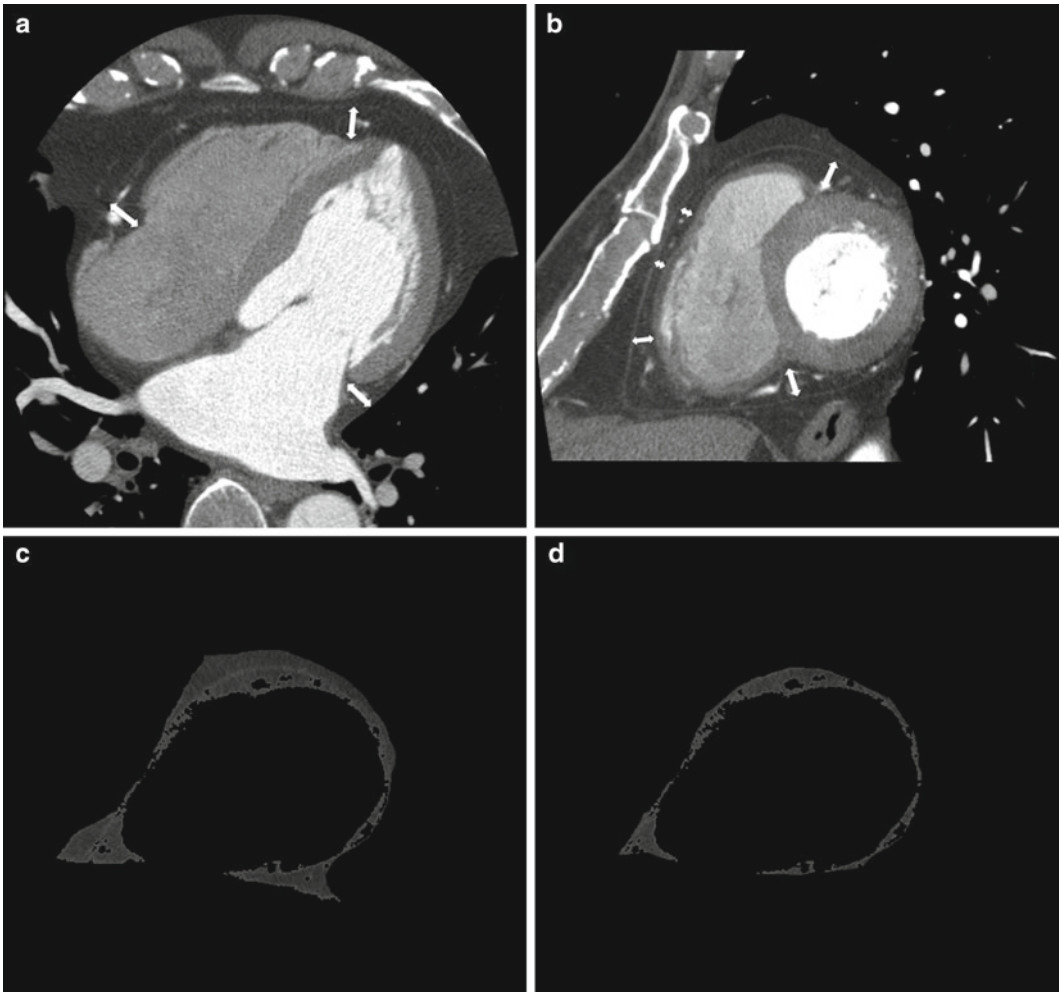

Fig. 57.4 Simplified segmentation system for the measurement of regional thickness of epicardial adipose tissue. Simplified segmentation system for the measurement of the regional thickness of epicardial adipose tissue (**a**, **b**) and cross-sectional areas of intra-thoracic adipose tissues (**c**, **d**) are shown. (**a**) Epicardial adipose tissue thickness in the grooved segments is measured at three sites in the horizontal long-axis plane (right atrio-ventricular groove, left atrio-ventricular groove, and anterior inter-ventricular groove). (**b**) Epicardial adipose tissue thickness in the superior inter-ventricular groove and the inferior inter-ventricular groove and over the right ventricular free wall is measured in the basal short-axis plane. Epicardial fat over the right ventricular free wall is measured at three equally spaced points along the right ventricular free wall (25%, 50%, and 75% of the full length). (**c**) Measurement of the cross-sectional area of pericardial (paracardial plus epicardial) adipose tissue is made by tracing the mediastinum boundary in the short-axis plane. A density range between –30 and –190 Hounsfield Units is used to identify adipose tissue. (**d**) Measurement of the cross-sectional area of epicardial adipose tissue is made by tracing the pericardium

ventricles, only the basal short-axis plane, rather than all three short-axis levels, is used for the measurement of regional EAT. Segmentation is simplified to include only the right ventricular free wall and two grooved segments (superior inter-ventricular groove and inferior inter-ventricular groove), where EAT primarily accumulates. Likewise, three grooved segments in the horizontal long-axis plane (right atrio-ventricular groove, left atrio-ventricular groove, and anterior inter-ventricular groove), rather than non-grooved cardiac surfaces, are chosen. Overall, six segments (five grooved

segments and the right ventricular free wall) are measured in our system. The segment of the right ventricular free wall is selected because this is the only EAT segment that can be assessed reliably using echocardiography, and all previous echocardiographic assessments of EAT were made in this specific location (Iacobellis et al. 2003; Ahn et al. 2008). Given that all coronary vessels are present in the grooved segments and EAT primarily accumulates at the base of both ventricles, the "maximal" pericoronary EAT thickness could be obtained from measurements in the five grooved segments selected in our simplified segmentation system (Fig. 57.5). According to our MDCT findings and those of Abbara et al., the maximal EAT thickness around the left anterior descending artery is found at the superior inter-ventricular groove in the basal short-axis plane, the maximal EAT thickness around the left circumflex artery approximates the thickness measured in the left atrio-ventricular groove in the horizontal long-axis plane, and the maximal EAT thickness around the right coronary artery is close to the thickness measured in the right atrio-ventricular groove in the horizontal long-axis plane (Abbara et al. 2006; Wang et al. 2009b), further ensuring the clinical applicability of our simplified segmentation system. In the report of de Vos et al., maximal EAT thickness surrounding each individual coronary artery was measured in the axial cut that is not perpendicular to the long-axis of the left ventricle and may therefore overestimate EAT thickness by obliquity (de Vos et al. 2008).

The third step is to measure EAT thickness in the pre-defined segments. Maximal EAT thickness perpendicular to the pericardium is recorded in the grooved segments. In the only non-grooved segment chosen in our system (the right ventricular free wall), the averaged thickness orthogonal to the myocardial surface at three equally spaced points is recorded (Fig. 57.4).

Regardless of differences in ethnicity and body habitus, it is consistently observed that EAT thickness in the grooved segments is greater than in the non-grooved segments, including the right ventricular free wall (Table 57.2). Among the grooved segments, the right atrio-ventricular groove has the thickest fat where the right coronary artery is located, followed by the left atrio-ventricular groove where the left circumflex artery and great cardiac vein are found. The maximal EAT thickness surrounding the left anterior descending coronary artery, measured in the superior inter-ventricular groove in the basal short-axis plane, is less than that surrounding the right coronary artery or the left circumflex artery.

57.3.2 Cross-Sectional Areas of Epicardial Adipose Tissue

Measurements of abdominal fat depots usually take the form of cross-sectional areas. Likewise, measurements of EAT cross-sectional areas could be of clinical value. We propose that cross-sectional areas of EAT should be measured in all four MDCT planes (the short-axis planes at the basal, mid-cavity, and apical levels, and the horizontal long-axis plane) for regional EAT thickness measurements.

To obtain EAT cross-sectional areas, measurements of a thin slab volume of EAT from two contiguous images are made by tracing the pericardium. A density range between –30 and –190 Hounsfield Units is employed to identify adipose tissue. The cross-sectional area is determined by dividing the thin-slab volume by the slab thickness (4 mm in our protocol).

Aside from the EAT cross-sectional areas, cross-sectional areas of the pericardial and paracardial adipose tissues can be obtained in the same way (Fig. 57.4). the thin-slab volume of pericardial (epicardial and paracardial) adipose tissue from two contiguous images can be measured by tracing the mediastinum boundary. The thin-slab volume of paracardial adipose tissue is obtained by subtracting the volume of EAT from that of pericardial adipose tissue. Dividing the thin-slab volume by the slab thickness produces the cross-sectional area.

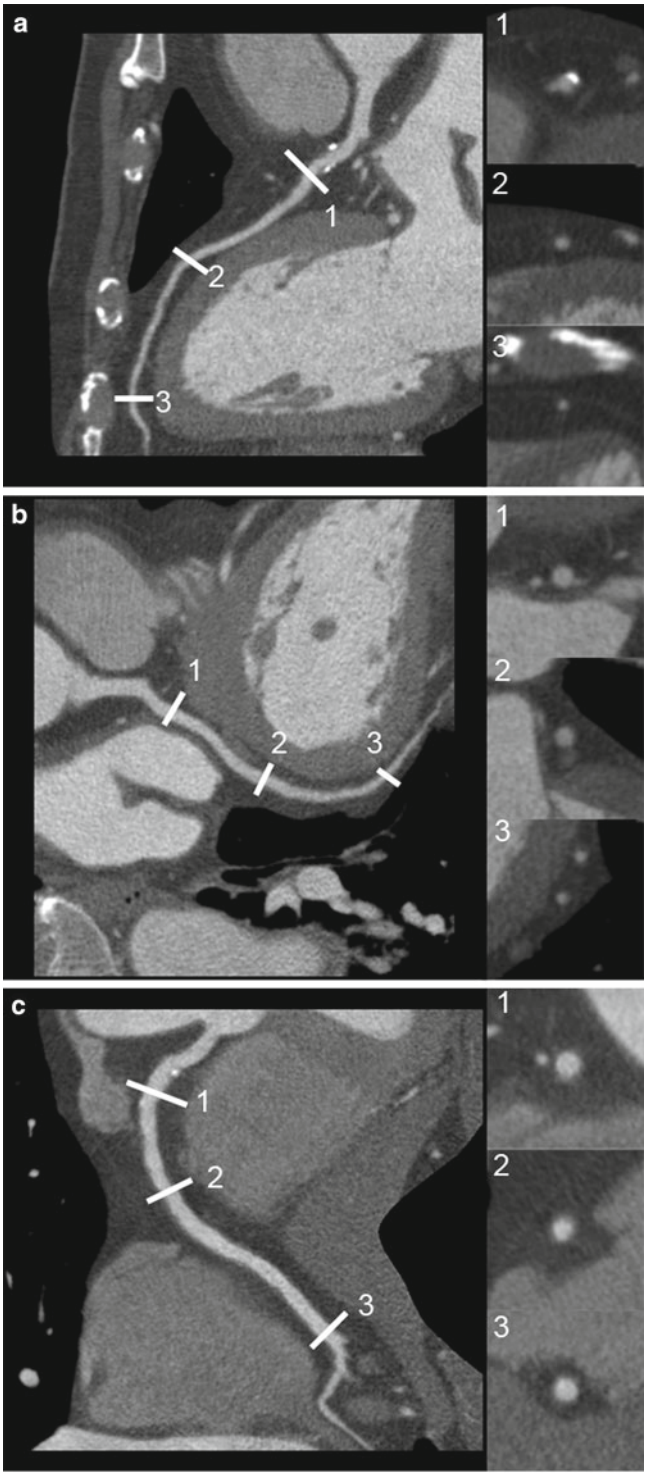

Fig. 57.5 Thickness of epicardial adipose tissue around the coronary arteries at different segments. Thickness of epicardial adipose tissue surrounding the left anterior descending (**a**), left circumflex (**b**), and right (**c**) coronary arteries at the arbitrarily defined proximal (*1*), mid (*2*), and distal (*3*) segments are shown. The maximal epicardial adipose tissue thickness around the left anterior descending artery is in the proximal segment located at the superior inter-ventricular groove in the basal short-axis plane (**a**). The maximal epicardial adipose tissue thickness around the left circumflex artery is also in the proximal segment, approximating the thickness measured in the left atrio-ventricular groove in the horizontal long-axis plane (**b**). The maximal epicardial adipose tissue thickness around the right coronary artery is in the proximal segment, close to the thickness measured in the right atrio-ventricular groove in the horizontal long-axis plane (**c**)

Table 57.2 Regional thickness and cross-sectional areas of epicardial adipose tissue in different studies

	Authors			
	Wang et al. (2009b)	Abbara et al. (2006)	de Vos et al. (2008)	Gorter et al. (2008a)
Number of cases	148	59	573	128
Age (year)	59 ± 9	58 ± 13	67 ± 6	61 ± 6
Men (%)	85	69	0	70
Ethnicity	Chinese	American	European	European
BMI (kg/m^2)	26 ± 3	–	27 ± 4	28 ± 3
Waist circumference (cm)	92 ± 8	–	86 ± 10	–
Hypertension (%)	61	–	51	90
Diabetes mellitus (%)	30	–	5	19
Previous myocardial infarction (%)	7	–	4	23
Adipose tissue parameters				
Epicardial adipose tissue thickness (mm)				
Right ventricular free wall	4.3 ± 1.8	6.6 ± 3.1	–	
Horizontal long-axis plane				
Left atrio-ventricular groove	12.7 ± 3.2	12.7 ± 3.3	10.8 ± 3.0	10.0 ± 2.2
Right atrio-ventricular groove	13.9 ± 4.0	14.8 ± 4.6	16.5 ± 4.3	15.9 ± 3.1
Anterior inter-ventricular groove	6.9 ± 2.5	7.7 ± 2.5	–	–
Basal short-axis plane				
Superior inter-ventricular groove	10.1 ± 2.3	11.2 ± 3.3	6.4 ± 2.2	5.2 ± 1.9
Inferior inter-ventricular groove	6.7 ± 2.9	9.2 ± 3.5	–	–
Mean grooved segments	10.1 ± 2.0	–	11.2 ± 2.2	10.4 ± 2.0
Epicardial adipose tissue cross-sectional area (cm^2)				
Horizontal long-axis plane	10.7 ± 4.4	–	–	–
Short-axis plane				
Basal	12.2 ± 4.9	–	–	–
Mid-cavity	7.8 ± 3.5	–	–	–
Apical	7.5 ± 3.2	–	–	–
Mean	9.2 ± 3.7	–	–	–
Paracardial adipose tissue cross-sectional area (cm^2)				
Horizontal long-axis plane	8.5 ± 5.3	–	–	–
Short-axis plane				
Basal	20.5 ± 9.5	–	–	–
Mid-cavity	5.9 ± 3.3	–	–	–
Apical	6.7 ± 3.8	–	–	–
Mean	11.0 ± 4.8	–	–	–

Regardless of differences in ethnicity and body habitus, the thickness of epicardial adipose tissue in the grooved segments is greater than in the non-grooved right ventricular free wall. Values are mean ± SD for quantitative variables and *n* or % for qualitative variables

The cross-sectional areas of epicardial, paracardial, and pericardial adipose tissues have been reported only by our group. We demonstrated that the distribution of EAT is primarily located at the base of both ventricles, with the greatest area obtained in the basal short-axis plane. The distribution of paracardial adipose tissue is similar to that of EAT. However, the amount of paracardial adipose tissue is slightly greater than that of EAT in the parasternal short-axis plane (Table 57.2).

57.3.3 Total Volume of Epicardial Adipose Tissue

To calculate the entire volume of EAT, as well as the other intra-thoracic adipose tissues, all the axial images should be loaded into a workstation, with the pericardium manually traced in these images.

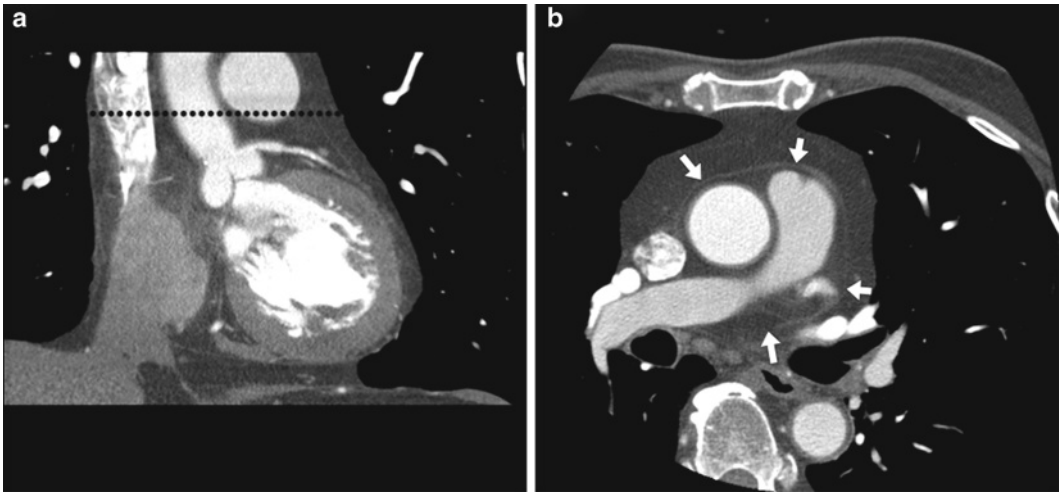

Fig. 57.6 The top boundary for the measurement of total epicardial adipose tissue volume. Method of selection of the top boundary for the measurement of total epicardial adipose tissue volume is shown. (**a**) The top boundary is set to 1 cm above the superior extent of the left coronary artery (*dotted line*). (**b**) The axial cut of the top boundary shows the presence of the right pulmonary artery. The surrounding pericardium is identified by four *white arrows*.

To measure the volume of EAT, the selected top boundary is somewhat different between studies. We set the top boundary at 1 cm above the superior extent of the left coronary artery, and others chose the level of the right pulmonary artery or the bifurcation of the main pulmonary artery (Greif et al. 2009; Mahabadi et al. 2009). In fact, the level we set was approximately at the level of the right pulmonary artery (Fig. 57.6). Conversely, the "exact" level of the right pulmonary artery or the bifurcation of the main pulmonary artery is ambiguous and may vary within the width of the pulmonary artery (~2 cm). The visceral pericardium reflects back near the origins of the great vessels and a few centimeters proximal to the junctions of the caval vessels with the right atrium. Therefore, the top boundary we selected is close to the uppermost level of the pericardium. In the areas above our top boundary, the volume of EAT between the great arteries is minimal and almost negligible. We thus suggest setting the top boundary to 1 cm above the superior extent of the left coronary artery to simplify the measurement procedure and to retain accuracy. The diaphragm is generally set as the lower boundary.

To measure the pericardial adipose tissue volume, the anterior border is defined by the sternum and the ribs, whereas the posterior border is defined by the esophagus and the descending aorta. The volume of paracardial adipose tissue is then derived by subtracting the volume of EAT from that of pericardial adipose tissue.

The average volume of EAT is generally between 110 and 125 cm^3 (ml), despite tremendous heterogeneity in ethnic background, anthropometric features, and underlying medical conditions (Table 57.3). Despite the low specific gravity of adipose tissue and the widespread coverage (~80%) of the cardiac surface, the volume of EAT accounts for approximately 15–20% of the total cardiac volume, including the chambers (Sarin et al. 2008). Intriguingly, this number is close to the ratio of total EAT weight to total heart weight (~20%).

On the basis of a random sample of 60 images evaluated by 2 investigators, we previously demonstrated that intra- and inter-observer reproducibility for all adipose tissue measurements were >0.95 (Wang et al. 2009b).

It is worth mentioning that although the total volume is an overall measure of EAT, the volume of EAT is only moderately correlated with various regional EAT thicknesses. This phenomenon is

Table 57.3 Total volume of epicardial adipose tissue in different studies

	Authors				
	Wang et al. (2009b)	Wang et al. (2009a)	Mahabadi et al. (2009)	Sarin et al. (2008)	Gorter et al. (2008a)
Number of cases	148	127	1,267	151	128
Age (year)	59 ± 9	55 ± 8	60 ± 9	51 ± 12	61 ± 6
Men (%)	85	80	46	55	70
Ethnicity	Chinese	Chinese	American	American	European
BMI (kg/m^2)	26 ± 3	26 ± 3	28 ± 5	32 ± 7	28 ± 3
Waist circumference (cm)	92 ± 8	86 ± 12	94 ± 14	–	–
Hypertension (%)	61	61	29	54	90
Diabetes mellitus (%)	30	39	10	11	19
Previous myocardial infarction (%)	7	0	3	–	23
Epicardial adipose tissue volume (cm^3)	107 ± 43	140 ± 49	124 ± 50	121 ± 47	110 ± 44

Values are mean ± SD for quantitative variables and *n* or % for qualitative variables

consistent with the fact that EAT is asymmetrically distributed. Moreover, it indicates that the measurement of regional thicknesses could not be replaced by the total EAT volume since it reflects the region-specific characteristics of EAT that might have particular clinical significance.

57.4 Applications to Other Areas of Health and Disease

Although EAT constitutes only 1% of the total fat mass (Rabkin 2007), several clinical studies have shown that the amount of EAT is associated with obesity (generalized and abdominal), cardiometabolic risk factors, cardiac structural changes, coronary atherosclerosis, prevalent cardiovascular diseases, and the incidence of coronary heart disease events. However, it is still under debate as to whether these clinical associations of EAT are direct or indirect. We discuss each of these associations in this section.

57.4.1 Association with Obesity (Generalized and Abdominal)

It has been consistently observed that the volume of EAT is positively related to the extent of obesity. However, the strengths of the associations of total EAT volume with different measures of obesity are varied. Most MDCT studies show that total EAT volume is highly correlated with the amount of intra-abdominal visceral fat (correlation coefficient 0.6–0.8) and is moderately correlated with body-mass index (BMI) – the index of general adiposity – waist circumference – the index of abdominal adiposity (correlation coefficient 0.4–0.6) (de Vos et al. 2008; Rosito et al. 2008; Wang et al. 2009b) (Fig. 57.7). Compared to BMI, total EAT volume is more closely related to waist circumference. These observations are in line with the fact that EAT and intra-abdominal visceral fat depots, but not subcutaneous fat, share a common embryological origin, and therefore a closer quantitative relationship. Among all MDCT measurements of EAT, total EAT volume is most closely related to various obesity measures and is therefore the best indicator of visceral obesity.

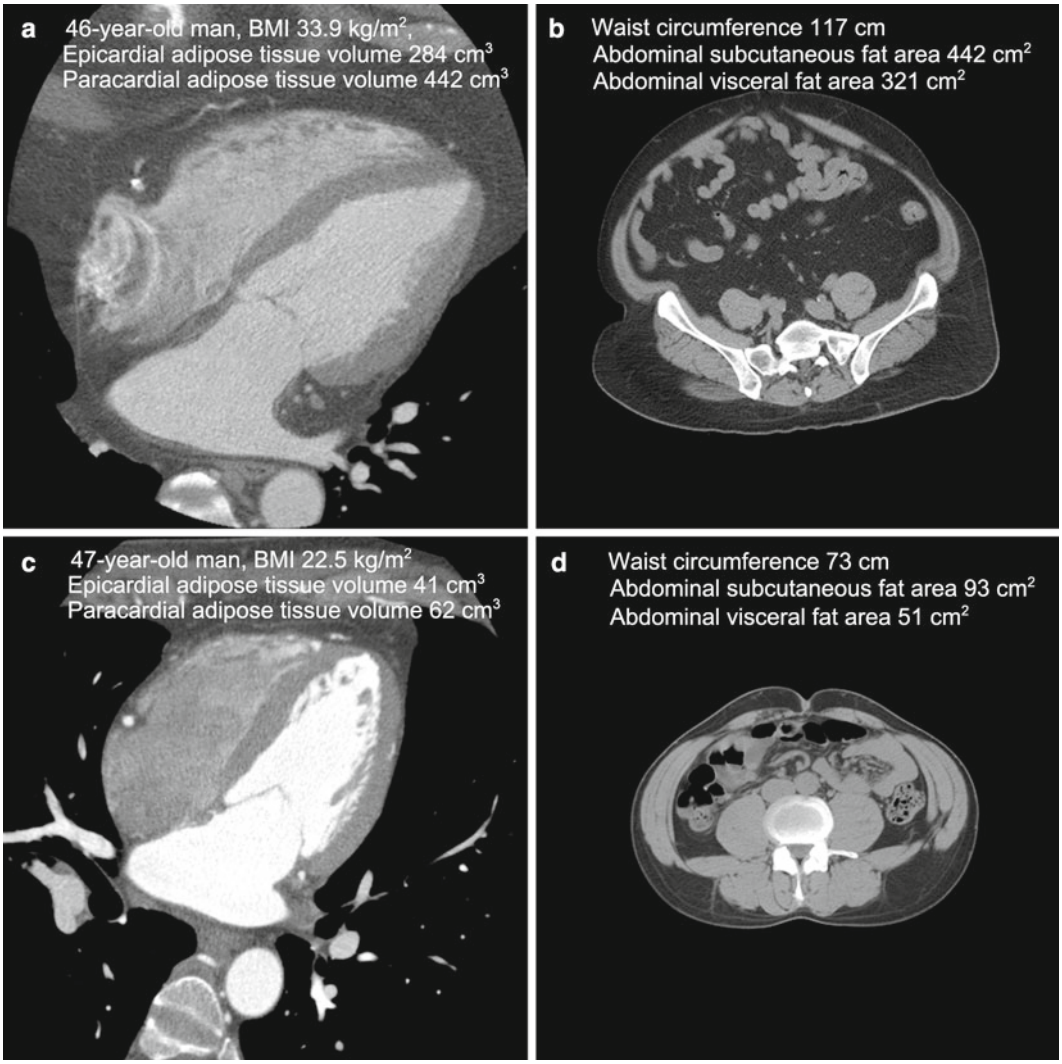

Fig. 57.7 Cases demonstrating the positive association of the total volume of epicardial adipose tissue with other anthropometric indices and intra-abdominal adiposity. (**a**, **b**) are the axial cuts at levels of the mitral valve and the umbilicus, respectively, in a 46-year-old man with hypertension, diabetes mellitus, and coronary artery disease. (**c**, **d**) are the axial cuts at levels of the mitral valve and the umbilicus, respectively, in a 47-year-old man with no coronary risk factors or prior history of coronary artery disease. The positive association of the total volume of epicardial adipose tissue with other anthropometric indices and the amount of intra-abdominal visceral fat is clearly exemplified in this figure. *BMI* body-mass index

57.4.2 Association with Cardio-Metabolic Risk Factors

Obesity often coexists with a number of cardio-metabolic risk factors, including hypertension, atherogenic dyslipidemia, insulin resistance, and impaired glucose tolerance, which are collectively referred to as the metabolic syndrome. Adipocytes and the surrounding adipose tissue, especially intra-abdominal visceral fat depots, have been ascribed to be the underlying pathogenic factor mediating the links between obesity, insulin resistance, and other components of the metabolic syndrome

(Van Gaal et al. 2006). Given the shared embryological origin of EAT and intra-abdominal visceral fat, several recent studies have demonstrated that the amount of EAT is quantitatively associated with various cardio-metabolic risk factors, even after adjustment for intra-abdominal visceral adiposity (Iacobellis et al. 2003; de Vos et al. 2008; Gorter et al. 2008b; Rosito et al. 2008; Wang et al. 2009a, b). Intriguingly, the strengths of associations between peri-coronary EAT thickness (averaged EAT thickness in the grooved segments) and total EAT volume with three different components (blood pressure, lipid, and glucose parameters) of the metabolic syndrome are varied. For peri-coronary EAT thickness, the correlation is strongest with the glucose parameters, then with the lipid parameters, and less strongly with the blood pressure parameters (de Vos et al. 2008; Wang et al. 2009b). For total EAT volume, the significant association is often observed only with the lipid parameters, but not with the other two parameters (Rosito et al. 2008). Consistent with these observations, a stronger correlation between peri-coronary EAT thickness and clustering of metabolic syndrome components than with total EAT volume has been demonstrated (Gorter et al. 2008b). We further clarify this by demonstrating that the association between the increasing number of metabolic syndrome components and EAT is primarily related to regional EAT thickness in the left atrio-ventricular groove, with a moderate magnitude of correlation (correlation coefficient ~0.4) (Wang et al. 2009b). The underlying mechanisms for this region-specific association of EAT and cardio-metabolic risk factors remain elusive. However, it has been speculated that this association might be related to the well-developed venous drainage system and great cardiac vein traversing the left atrio-ventricular groove, and its role as an arena for communications between EAT and systemic circulation. Moreover, although echocardiographic EAT thickness over the right ventricular free wall correlates with the circulating levels of C-reactive protein and several adipokines (Iacobellis et al. 2003; Malavazos et al. 2008), we demonstrated that the correlations between EAT and inflammatory markers and adipokines are also specifically related to the thickness of EAT in the left atrio-ventricular groove, thereby providing a mechanistic link. By using receiver-operating-characteristic analysis, the optimal cutoff point for left atrio-ventricular groove thickness to predict the metabolic syndrome was determined to be 12.4 mm for men and women of Chinese ethnic origin (Wang et al. 2009b). Whether this cut-off point can be applied to other ethnic groups still awaits confirmation.

In summary, EAT thickness in the left atrio-ventricular groove, but not total EAT volume, is the best indicator of metabolic risk.

57.4.3 Association with Cardiac Structural Changes

Several echocardiographic studies have shown that the thickness of EAT over the right ventricular free wall is associated with measures of the left ventricular mass, left atrial size, and impaired right and left ventricular diastolic filling (Iacobellis and Willens 2009). However, these associations are not independent of other ectopic fat stores, the only exception is the left atrial size. In the Framingham Offspring Study, total EAT volume was also independently associated with increased left atrial dimension, measured in the anteroposterior direction from an axially oriented image, in white men (Fox et al. 2009). Generally speaking, for cardiac structures and functions, the effects of EAT are mostly outweighed by the systemic effects of obesity.

57.4.4 Association with Coronary Artery Disease

A number of clinical studies have shown that the amount of EAT, measured by either echocardiography or MDCT, was correlated with coronary atherosclerosis and the prevalence of cardiovascular

disease (Chaowalit et al. 2006; Ahn et al. 2008; de Vos et al. 2008; Gorter et al. 2008a; Rosito et al. 2008; Sarin et al. 2008; Greif et al. 2009; Wang et al. 2009a). However, in studies showing a positive association between total EAT volume and the "presence" of coronary artery calcification or atherosclerotic plaques, the EAT volume was paradoxically not related to the severity of coronary atherosclerosis or plaque burden in a dose-dependent manner (Gorter et al. 2008a; Rosito et al. 2008; Greif et al. 2009). Additionally, the positive association between averaged peri-coronary EAT thickness and coronary artery calcification is not significant after adjustment for waist circumference in healthy post-menopausal women (de Vos et al. 2008). As observed for the relationship between EAT and the metabolic syndrome, we found that the quantitative association between EAT and coronary atherosclerosis primarily stems from EAT thickness in the left atrio-ventricular groove, which is the only EAT measurement unanimously associated with all different measurements and definitions of coronary atherosclerosis (correlation coefficient ~0.3). This association remains significant even after adjustments for conventional risk factors, such as BMI, waist circumference, C-reactive protein, and intra-abdominal visceral adiposity. Therefore, it is conceivable why only modest associations are observed between "global" EAT measurements (total EAT volume and averaged peri-coronary EAT thickness) and coronary atherosclerosis. The consistent region-specific associations of EAT thickness in the left atrio-ventricular groove with the metabolic syndrome, inflammatory markers, and coronary atherosclerosis further strengthen the reliability of this intriguing finding. Moreover, there is a preferential association between EAT thickness in the left atrio-ventricular groove and atherosclerosis in the embedded left circumflex artery, indicating a local atherogenic role of EAT accumulated in the left atrio-ventricular groove. Using receiver-operating-characteristic analysis, 12.2 mm was determined to be the optimal cutoff point for left atrio-ventricular groove thickness to predict the presence of significant coronary stenosis (≥50% diameter stenosis) for men and women of Chinese ethnic origin.

Apart from the cross-sectional association between EAT and coronary atherosclerosis, it has been shown that "pericardial" adipose tissue volume predicts the occurrence of coronary heart disease in white adults who participated in the Multi-Ethnic Study of Atherosclerosis (Ding et al. 2009). However, it has not been determined whether this association is independent of other ectopic fat depots. Moreover, it is not known whether EAT thickness in the left atrio-ventricular groove has a greater power to predict coronary heart disease than pericardial or epicardial fat volume. To date, it appears that the thickness of EAT in the left atrio-ventricular groove provides a more accurate assessment of its atherogenic risk and is therefore a better coronary risk factor than total EAT or pericardial adipose tissue volume.

57.5 Future Perspectives

In recent years, EAT has attracted wide attention from clinicians and medical researchers, and is no longer regarded as an indolent bystander in the human body. EAT as a whole has generally been viewed as an integral ectopic fat depot and assumed to behave similarly, although the distribution of EAT around the heart is obviously asymmetric and mostly concentrated in the grooved segments around the epicardial vessels. However, our recent cross-sectional association studies demonstrated that there are substantial variations in the metabolic and atherogenic risks of EAT in different locations. Therefore, it is mandatory to examine whether there is indeed regional variation in the molecular characteristics (adipokine secretion, inflammatory activity, brown/white adipose tissue distribution, etc.) of EAT, whether this variation is a primary or secondary (responsive to coronary atherosclerosis) event, and whether it confers any clinical significance, such as contributing to the systemic levels of inflammatory markers, clustering of metabolic risk factors, and local coronary atherogenesis.

Although a number of cross-sectional association studies demonstrated that EAT, using either regional or global measurements, is correlated with measures of obesity, cardio-metabolic risk factors, and coronary atherosclerosis, larger studies are still needed to verify these findings and further examine: (1) whether these EAT measurements provide incremental information compared to conventional risk factors, other anthropometric indices, and ectopic fat measurements; (2) the threshold values of EAT measurements to predict the presence of various pathological conditions; and (3) whether there are any ethnic and gender differences in the clinical significance and threshold values of EAT. More importantly, information regarding the prognostic significance of various EAT measurements is still lacking and desperately needed.

After obtaining the above-mentioned information, it would be worthwhile to evaluate the effects of non-pharmacological (weight reduction, caloric restriction, exercise training, etc.) and pharmacological interventions on EAT measurements. Moreover, it would be interesting to assess whether local treatment for specific EAT regions may provide any benefits in stabilizing the progression of coronary artery disease.

Summary Points

- Epicardial adipose tissue (EAT) is situated on the surface of the heart and confined within the pericardial sac.
- The distribution of EAT is characterized by its asymmetric distribution and its primary accumulation around the base of both ventricles, especially in the perivascular atrio-ventricular and inter-ventricular grooves, rather than in the non-grooved cardiac surfaces.
- To clearly delineate the asymmetric distribution of EAT and explore its pathophysiological significance, EAT should be measured using multidetector computed tomography (MDCT) in three dimensions: regional thickness, cross-sectional areas, and total volume.
- The first step to measure the regional EAT thickness is to obtain multiplanar reconstructions of MDCT data in the standardized ventricular short-axis planes at the basal, mid-cavity, and apical levels, and in the horizontal long-axis plane. The second step is to divide the cardiac surfaces in the reconstructed MDCT images into segments. The final step is to measure EAT thickness in the pre-defined segments. In grooved segments, maximal EAT thickness perpendicular to the pericardium is recorded, whereas in non-grooved segments, EAT thickness orthogonal to the myocardial surface is recorded.
- Regardless of differences in ethnicity and body habitus, EAT thickness in the grooved segments is greater than in the non-grooved segments, including the right ventricular free wall.
- Among the grooved segments, the right atrio-ventricular groove has the thickest deposits of fat where the right coronary artery is located, followed by the left atrio-ventricular groove where the left circumflex artery and great cardiac vein are located. The maximal EAT thickness surrounding the left anterior descending coronary artery, measured in the superior inter-ventricular groove in the basal short-axis plane, is less than that surrounding the right coronary artery or the left circumflex artery.
- The average volume of EAT is generally between 110 and 125 cm^3 (ml), despite high levels of heterogeneity in the ethnic background, anthropometric features, and underlying, associated medical conditions.
- Although EAT constitutes only 1% of the total fat mass, several clinical studies have shown that the amount of EAT is associated with obesity, cardio-metabolic risk factors, cardiac structural changes, coronary atherosclerosis, and the incidence of coronary heart disease events. However,

it is a matter of debate as to whether these associations of EAT are direct or indirect and which EAT measurement represents the best correlate.

- Among all MDCT measurements of EAT, total EAT volume is most closely related to various obesity measures and is the best indicator of visceral obesity.
- To date, it appears that EAT thickness in the left atrio-ventricular groove provides a more accurate assessment of its metabolic and atherogenic risks, and is therefore a better indicator of its metabolic risk and a better coronary risk factor than total EAT volume.
- Further studies are desperately needed to elucidate whether there are indeed regional variations in the molecular characteristics (adipokine secretions, inflammatory activities, brown/white adipose tissue distributions, etc.) of EAT and whether this regional variation confers any clinical, prognostic, or therapeutic implications.

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Chapter 58
Breast Volume Determination in Breast Hypertrophy

Laszlo Kovacs and Maximilian Eder

Abstract In the last few decades, several surgical techniques have been presented to decrease the symptoms of breast hypertrophy by removing a specific amount of breast tissue and reshaping the breast. Reliable and objective breast volume determination could be a helpful pre- and intraoperative assistance for the surgeon to achieve an aesthetic result, especially in breast asymmetry. But thus far no generally accepted method exists. In this paper, the advantages and disadvantages of classical techniques for breast volume determination (anthropomorphic measurements, conventional 2D radiological imaging, Archimedean methods, moulding techniques, measuring devices, modern radiological imaging) are critically analyzed and compared to an innovative alternative technique using 3D surface imaging. The technical background of 3D surface imaging is presented, underlining the reliability and accuracy of this innovative breast volume determination technique. Furthermore, a comparison of 3D surface imaging with the classical techniques of breast volume determination reveals the more comprehensible and transparent character of the 3D surface imaging method that permits a non-invasive, risk-free, non-contact, non-deformable patient assessment and delivers high-resolution 3D virtual, colored models of the breast region. Precise and accurate pre- and postoperative 3D quantitative calculations of shape, volume, surface changes, symmetry, projection, swelling tendency, contour and deformation are feasible. Finally, postoperative follow-up examinations at close intervals and optimizations of the preoperative surgical planning are possible. The clinical applications in the field of plastic, reconstructive and aesthetic breast surgery show promising results, but further implementations in other related fields should be performed.

Abbreviations

2D	Two dimensional
3D	Three dimensional
CT	Computer tomography
MRI	Magnetic resonance imaging

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_58,

58.1 Introduction

Breast hypertrophy patients often suffer from physical and psychological discomfort because of their heavy breasts. Physical symptoms of mammary hypertrophy (neck and shoulder strain, headaches, back and breast pain, persistent rashes in the intertrigo areas and sometimes musculoskeletal degenerations) combined with psychological disorders (minor self-esteem and self-confidence because of their breast or rather shame and aversion against their breast) aggravates the desire of these women for breast reduction surgery (Birtchnell et al. 1990). Different studies have demonstrated the medical benefits with regardto the improvement in physical and psychological well being after breast reduction (Blomqvist et al. 2000). In the last few decades, several surgical techniques have been presented to decrease the symptoms of breast hypertrophy by removing a specific amount of breast tissue and reshaping the breast (Bostwick 1999). Besides improvement in clinical symptoms, the aesthetic appearance (shape, volume, and symmetry) of the breast is also a decisive reason for patient's satisfaction and quality of life after surgery. The correlation between breast shape and breast volume for achieving postoperative symmetry is essential (Hudson 2004; Kovacs et al. 2004). Especially, breast volume estimation in mamma hypertrophy patients with large and pendulous breasts is challenging and purely intuitive. Reliable and objective breast volume determination could provide helpful pre- and intraoperative assistance for the surgeon to achieve an aesthetic, pleasing result, especially in breast asymmetry (Eder et al. 2007). Further, a reliable method of determining postoperative volume, shape and resulting symmetry in sense of an outcome analysis or quality assurance could guarantee a more transparent and objective evaluation (Kovacs et al. 2006a, b, 2007).

Therefore, this contribution will give an overview of the existing classical techniques of breast volume determination and will provide a critical analysis of the advantages and disadvantages of each method. Further, we will present an innovative alternative technique using 3D surface imaging and its potential clinical application in comparison with the established breast volume determination techniques.

58.2 Main

Breast volume determinations are not regularly performed in a clinical routine because thus far no generally accepted method exists (Bulstrode 2001). The classical techniques for breast volume determination can be assigned to one of the following presented categories.

58.2.1 Classical Breast Volume Determination Techniques

58.2.1.1 Anthropomorphic Measurements

Anthropomorphic measurements in plastic surgery were primarily used to describe anatomical relations between specific landmarks of the thoracic region to support the surgeon in optimal breast shaping (Penn 1955; Smith et al. 1986). Later, anthropomorphic methods were followed to derive correlations between breast volume calculations and standardized direct end-to-end measurements of the thoracic region (Westreich 1997). With regard to statistically relevant conformity, specific formulas mainly based on geometrical bodies have been developed to determine the breast volume. A modified anthropomorphic method, for example, equates breast volume to a half-ellipse. The

parameters of the mathematical formula of a half-ellipse are measured directly on the patient or indirectly using two-dimensional (2D) photographs of the breast region (Qiao et al. 1997).

Calculated breast volumes using anthropomorphic methods are based only on individually determined values (end-to-end measurements) and a predefined geometrical breast shape which hardly corresponds to the individual anatomical breast conditions. The reported mean breast volume measurement deviations of 3.61 percentage by Westreich et al. and 3.89 percentage by Qiao et al. are surprisingly small taking into account the known uncertainties caused by individual uneasiness during an investigation and compared to Kovacs et al. with a mean deviation of 6.26 percentage (Kovacs et al. 2007).

Anthropomorphic methods are relatively easy and inexpensive (tape measure, calculator, and working time) and can be used with the patient standing. But calculation of the formulas is quite cumbersome and the methods require subjective determinations because breast landmarks are extremely arbitrary and not well defined. Variability of manual measurement increases with less anatomically well-defined landmarks or those which are located in the submammary region (Kovacs et al. 2006a). Additionally, manual interaction of the observer with the patient can cause decreased acceptance of this method. The abovementioned individual feeling of uneasiness related to anthropomorphic methods affects reproducibility, and clearly shows observer dependency of volume determination.

58.2.1.2 Conventional 2D Radiological Imaging

Breast volume determination methods using conventional 2D radiological imaging such as mammography and ultrasound are comparable to the abovementioned modified anthropomorphic measurement using 2D photographs (Malini et al. 1985; Kalbhen et al. 1999). Different geometric parameters (e.g. partial ellipse) are projected onto the 2D image or ultrasonic layers and the volume is calculated according to the applied mathematical formulas. A major disadvantage is caused by the compression of the breast during the assessment. The resulting images do not provide the natural shape and appearance of the breast. Therefore, the calculations are questionable and, in addition, the patient's acceptance due to personal discomfort is very low (Bulstrode et al. 2001).

58.2.1.3 Archimedean Methods

The technique is based on the Archimedes' principle of water displacement. The patient bends over a water-filled vessel, lowering her breast into the water and the breast volume is calculated based on the displaced water (Bouman 1970). Modified methods use calibrated cylinders placed against the thoracic wall. The rigid thoracic wall forms the dorsal border of the breast and the ventral soft-tissue portion is measured as the displaced breast volume (Wilkie 1977). Patient's acceptance is poor because of cumbersome feasibility and impracticable measurement systems with low reliability (Bulstrode et al. 2001).

58.2.1.4 Moulding Techniques

Moulding materials (plaster or thermoplast) are placed on the upright seated patient and generate a negative cast of the breast. The cast model is filled with water or sand in order to determine the breast volume (Campaigne et al. 1979). During the assessment the breast is deformed and compressed against the thoracic wall. The relatively inflexible moulding material cannot perfectly model the breast shape and is distorted under the manual pressure of the examiner (Kovacs et al. 2007). By

filling up the casts with water or sand, the rear demarcation of the chest is defined as a flat level. Breast portions above this flat rear wall are not included into volume calculations and therefore smaller volumes are computed (Kovacs et al. 2007). Moreover, manual evaluation is quite subjective, arbitrary and extremely difficult to perform because of not clearly defined breast boundaries. The precision of the breast volume calculation using thermoplastic casts has been reported as relatively constant with a mean deviation of 6 percentage (Edsander-Nord et al. 1996) and 7.97 percentage (Kovacs et al. 2007). Besides high material costs of approximately US$ 150 per breast, inflexible moulding, resulting breast tissue deformation and cumbersome manual volume assessment affect reproducibility. Therefore, thermoplastic casts should be used with caution for breast volume assessment (Bulstrode et al. 2001; Kovacs et al. 2007).

58.2.1.5 Specific Measuring Devices

Strömbeck et al. used transparent, non-deformable containers of different sizes to cover the breast and to measure the volume before surgery (Strömbeck and Malm 1986). The method is fast, practicable and not expensive. But by using rigid containers the breast is deformed and compressed. The proper breast shape is not taken into consideration. Grossmann and Roudner developed a cone shaped, adaptable device which shows the corresponding volume on a lateral placed scale (Grossman and Roudner 1980). But according to Palin et al. the "Grossmann-Roudner-Device" delivers only acceptable reproducibility in a certain breast volume range and is therefore limited in its clinical functionality (Palin et al. 1986).

58.2.1.6 Modern Radiological Imaging

Computer tomography (CT) and nuclear magnetic resonance imaging (MRI) offer an alternative to visualize and to calculate breast volumes in 3D (Kovacs et al. 2006b). The patient is placed in the scanner in a prone or supine position. The breast volume is calculated by the summation of segmented mono-layers.

Breast volume calculation is based on clear, visible anatomical structures and landmarks. Therefore, manual segmentation is easy and precise. MRI provides the most precise volume assessment method with a mean deviation varying from 4.3 percentage (Fowler et al. 1990) to 1.56 ± 0.52 percentage (Kovacs et al. 2007). Because of its time and cost-intensive acquisition ($1.400 per assessment) and its invasive character, MRI is not suitable for routine preoperative breast volume measurements (Caruso et al. 2006). Another disadvantage of the MRI is the resulting deformation of the breast tissue in the supine or prone position. The reconstructed 3D models do not correspond to the real anatomical shape of the breast and are of little help to clinicians (Eder et al. 2008).

58.2.1.7 Intermediate Review

The hitherto presented various breast volume determination techniques exhibit variable reliability. Furthermore, these techniques are sometimes difficult to perform because of cumbersome feasibility or even limited practicability, of low patient acceptance and are often cost-intensive (Table 58.1). These reasons limit the application in daily clinical routine and, therefore, breast volume determination is used for preoperative surgical planning only in some exceptional cases (Kovacs et al. 2007).

Table 58.1 Key facts of different breast volume determination techniques

	Reliability	Practicability	Costs	Patients acceptance	Overall rating
Anthropomorphic measurements	- -	+	- - -	+	+
2D Radiology	- -	+	+	- -	- -
Archimedean method	- -	- -	-	- - -	- -
Moulding techniques	-	- -	+	- -	- -
Measuring devices	-	++	- -	+	-
MRI/CT	+++	++	+++	+	+
3D Surface imaging	+++	++	+++	+++	++

+, high; -, low

58.2.2 Innovative Breast Volume Determination in Three Dimensions

These insufficient breast volume determination methods show the necessity to supply clinicians with additional comfortable evaluation methods that guarantee fast, noninvasive, routine clinical follow-up examinations at close intervals and objective and patient-specific quantification of the breast geometry. Optical measurement systems for three-dimensional (3D) body surface imaging fulfill these requirements. Their potential applications in the field of breast surgery have been presented (Eder et al. 2007, 2008, Kovacs et al. 2006a, b, 2007). Three-dimensional surface imaging permits a noninvasive, risk-free, noncontact, nondeformable patient assessment and delivers high-resolution 3D virtual color models of the breast region. Precise and accurate pre- and postoperative 3D quantification of shape, volume, surface changes, symmetry, projection, swelling tendency, contour and deformation are possible. Furthermore, 3D surface imaging enables postoperative follow-up examinations at close intervals and optimizes specific steps in preoperative surgical planning (Eder et al. 2007). The stored digitalized 3D data guarantee reliable, well-structured patient documentation that allows a computer-aided detailed evaluation even in the absence of the patient. Time-consuming patient measurements are not needed any longer, and the possibility to work with different data sets concerning different clinical questions applying different software solutions pre-, intra- and postoperatively is provided as well (Kovacs et al. 2004, 2006).

58.2.2.1 Technical Background

The technical principle of 3D optical measurement systems is based on triangulation and consists of a transmitter unit (light source) and a receiver unit (camera). The transmitter unit projects a point upon the object to be assessed whereas the receiver unit detects the reflected light. The geometric shape and the measured angle between the light source and the camera enable the precise definition of the accurate object point in space and the resulting surface geometry (Breuckmann 1993). The captured surface is accumulated as a point cloud (different single points). Each point has a respective *x*-, *y*-, and *z*-coordinate, and precise visualization of the whole body surface is possible (Kovacs et al. 2006a, b). The mathematically precise 3D quantification of the body region in a Cartesian coordinate system allows the creation of a virtual 3D surface computer model using different algorithms and software. This virtual 3D model offers several advantages compared to conventional 2D photography: apart from color information, spatial computation of individual points on the basis of the respective *x*-, *y*-, and *z*-coordinates and rotation of the 3D model in all three dimensions is possible.

A large variety of 3D surface geometry acquisition systems exist and are based on varying physical principles (stereo (-photo) grammetry, Moiré topography, pattern/structured light, linear laser scanner, etc.). They all have in common that a virtual digitalized 3D model of the body surface is created in a short time without any deformable body contact. Different body surface imaging systems were tested in our preliminary studies with regard to their potential medical application, and we concluded that the 3D linear laser scanner was the most suitable method (Brockmann et al. 2006).

Before applying this 3D technology to clinical routine it is necessary to standardize the 3D capturing process of the breast region in a normal standing position and to evaluate the precision and accuracy of the method in order to optimize the data reproducibility (Kovacs et al. 2006a). Accuracy of existing scanning systems depends on the capturing speed and their capability to assess larger body regions in one or more steps (Brockmann et al. 2006). Current 3D imaging systems vary enormously in fulfilling these requirements. It is often necessary to accomplish multiple surface scans from different angles to capture the whole breast region. The capturing process for one single shot takes 1–2 s. More complex scanning systems with multiple combined scanning modules are expensive but allow a 360° assessment with one single shot. Depending on the scanning system and the region of interest, the whole capturing process takes from seconds until several minutes.

In a test series, scanner-related factors (scanner position, number of scanners and single shots), as well as the influence of the breast region (variable breast shapes) were investigated. The accuracy of measurements on the virtual models was compared with manual measurements through a coincidence analysis (Kovacs et al. 2006a). By respecting standardized settings for 3D imaging of the breast region with a laser scanner, an acceptable degree of accuracy and reproducibility can be achieved, and is therefore clinically applicable (Kovacs et al. 2006a).

58.2.2.2 Three-Dimensional Breast Volume Determination: Reliability and Accuracy

The pre- and postoperative assessment of the breast and thoracic regions can be accomplished sufficiently precisely and accurately using a 3D linear laser scanner according to a standardized scanning protocol (Kovacs et al. 2006) and presented as a virtual 3D model for further computer-aided evaluation with appropriate software (Fig. 58.1). To establish an easily reproducible investigation protocol for reliable breast volume determination, a standardized procedure was defined and evaluated (Fig. 58.1). The breast volume of interest was labeled on the virtual 3D model (Fig. 58.1a and b). The labeled area was deleted and by applying specific software algorithms the defective curvature surrounding the deleted area (Fig. 58.1c) was used to compute the surface to be filled. The mean curvature of the thoracic wall at skin level was interpolated (Fig. 58.1d). The overlaid congruent areas were subtracted to obtain a closed volume corresponding to the breast volume (Fig. 58.1e and f).

The standardization of this 3D breast volume determination method showed a mean deviation of breast volume measurements (reliability) expressed as a percentage of volume over 2,420 measurements of 2.86 ± 0.98%. The highest measurement reliability was found between a breast volume range from over 250 cm^3 to 1,600 cm^3 (Fig. 58.2). Reasons for decreased reliability outside this range are on the one hand large and ptotic breasts, and on the other hand smaller breasts which are not clearly visible on the thoracic wall (Kovacs et al. 2006b). For further validation these 3D breast volume determinations were compared with reference MRI volume measurements obtained from test subjects; they showed significant ($r = 0.995$, $p < 0.001$) correlation (Kovacs et al. 2006b).

In addition to the evaluation of reliability, studies were performed focusing on the precision of measurement. In order to examine the accuracy of the 3D method, Losken et al. analyzed the mean

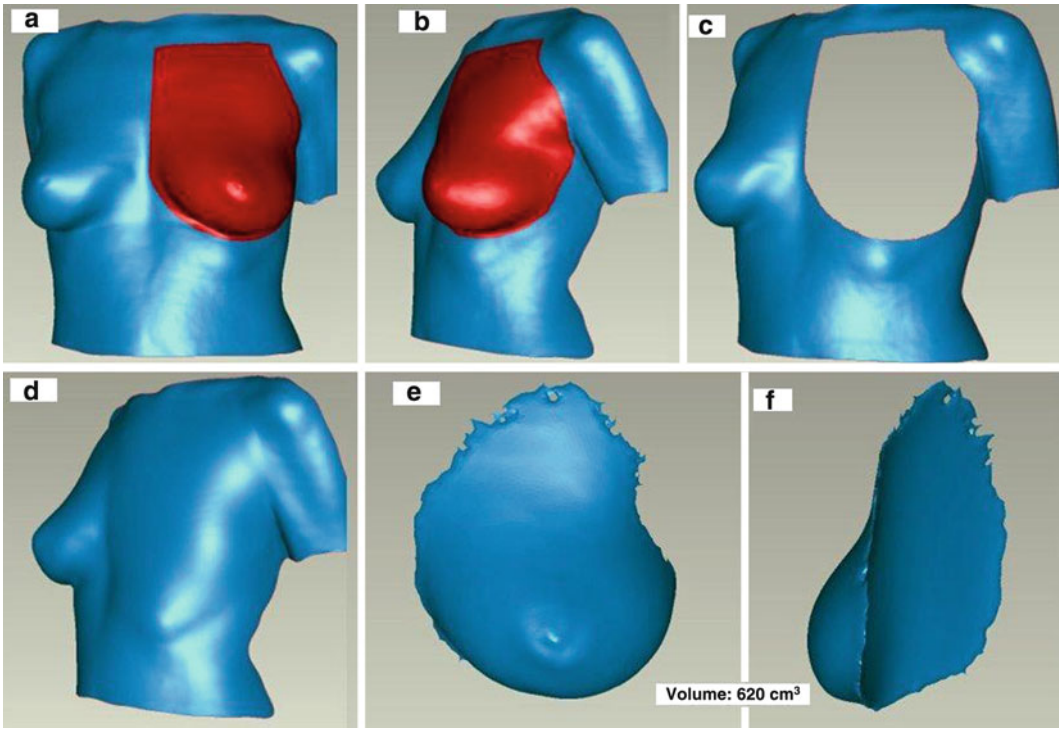

Fig. 58.1 Standardization of 3D breast volume determination. Procedure for standardized breast volume measurements: (**a**, **b**) labeled breast region; (**c**) erased breast region; (**d**) interpolated chest wall curvature as dorsal boundary of the breast volume; (**e**) measured breast volume: ventral and (**f**) dorsal aspect

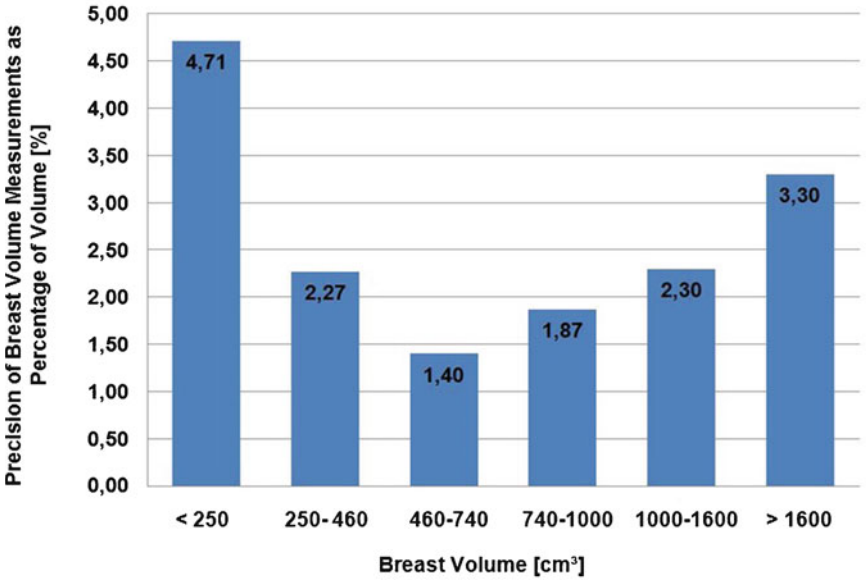

Fig. 58.2 Reliability of 3D breast volume determination. Reliability (precision) of 3D breast volume determination according to breast volume (mean deviation of the breast volume measurements expressed as percentage of volume over n = 2,420 measurements of 2.86 ± 0.98 percentage)

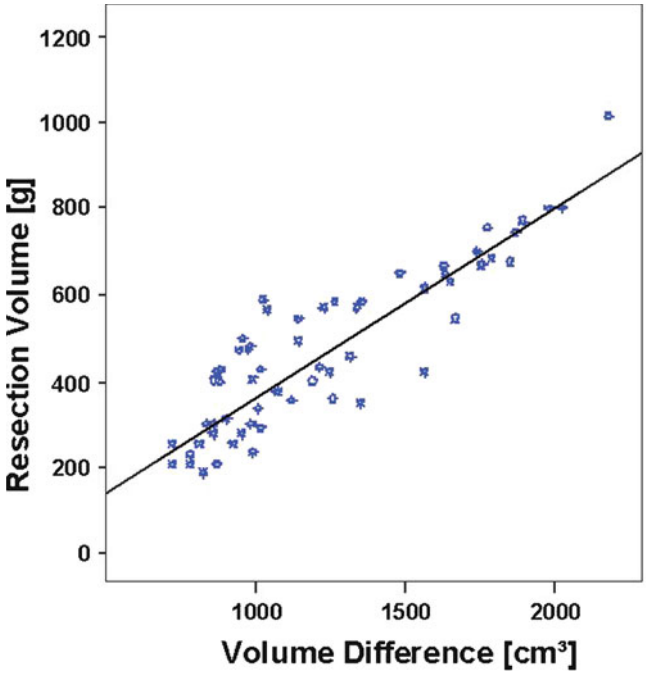

Fig. 58.3 Accuracy of 3D breast volume determination. Correlation ($r = 0.804$, $p < 0.001$) between the breast resection weight [g] and measured difference between pre- and postoperative breast volumes [cm^3]

relative difference between the breast resection weight and the measured difference between pre- and postoperative calculated breast volumes using 3D surface imaging in breast reduction patients: a mean relative difference of –2 ± 13–16 percentage is described (Losken et al. 2005). In our preliminary findings we described a mean relative difference of –1.80 ± 5.92 percentage (Kovacs et al. 2006b). Our actual findings show a significant, high correlation between the resection weight and the measured difference between pre- and postoperative volumes ($r = 0.804$, $p < 0.001$); it delivers a mean relative difference of 0.75 ± 6.75 percentage (Fig. 58.3).

58.2.2.3 Comparison to Classical Techniques

Breast volume determination using 3D surface imaging is sufficiently precise and accurate, but to what extent are these findings comparable to other determination techniques? Until today, only one comparison has been made between breast volume calculations using 3D imaging versus classical techniques (Kovacs et al. 2007) and only two cross-comparisons of the classical volume computation methods were performed (Palin et al. 1986; Bulstrode et al. 2001). These analyses have shown that the different breast volume calculation methods include different areas of breast tissue (Kovacs et al. 2007). Therefore, differences in the measured absolute volume values across the analyzed methods were found. Because different methods measure different breast volume areas, a meaningful comparison can be made only by applying the precise level of measurement (Kovacs et al. 2007).

We compared the most common techniques of anthropomorphic measurements, MRI, and thermoplastic casts with 3D surface imaging (Kovacs et al. 2007), and MRI showed the best agreement

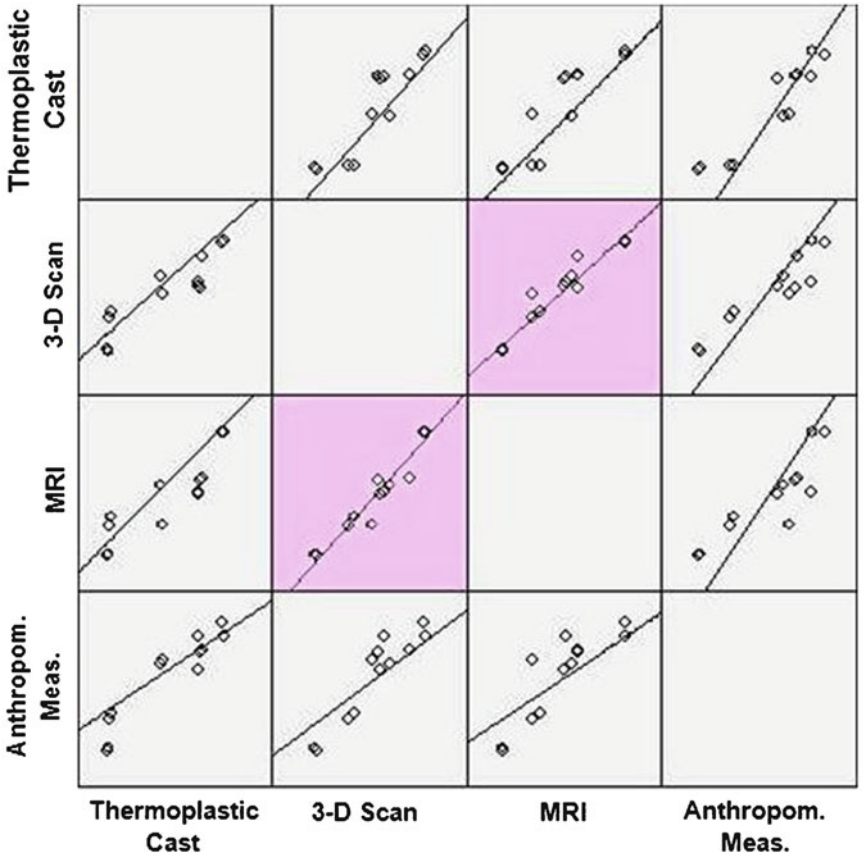

Fig. 58.4 Comparison of different breast volume determination techniques. Regression lines between breast volume determinations from 3D scanning, MRI, anthropomorphic measurements and thermoplastic casts

with 3D surface imaging ($r = 0.990$, $p < 0.001$), followed by the anthropomorphic method ($r = 0.947$, $p < 0.001$) and thermoplastic casts ($r = 0.727$, $p = 0.017$). To compare classical breast volume determination with 3D surface imaging, regression equations were calculated which enabled conversion of all determination units into those of 3D surface imaging (Fig. 58.4). The regression equations showed the following relations: (a) 3D scan = 9.83 + 0.75 × MRI, (b) 3D scan = –47.69 + 1.22 × thermoplastic casts, and (c) 3D scan = 141.03 + 0.70 × anthropomorphic measurement (all units in cm^3). The regression equations can compare absolute values of the specific volume calculation methods and permit comparison of the innovative 3D surface imaging technique with other classical techniques (Fig. 58.4).

58.2.2.4 Objective Breast Region Evaluation

In contrast to conventional 2D photographs, direct linear measurements can be performed directly on the surface using virtual 3D models. Breast projection, degree of ptotic breasts, thoracic circumference, etc. can be documented and visualized precisely (Fig. 58.5a). Objective breast volume and breast surface determinations (Fig. 58.5b and c) are fast, noninvasive and precisely quantifiable (Kovacs et al. 2006a, b; Eder et al. 2007, 2008). It is possible to compare the whole breast region

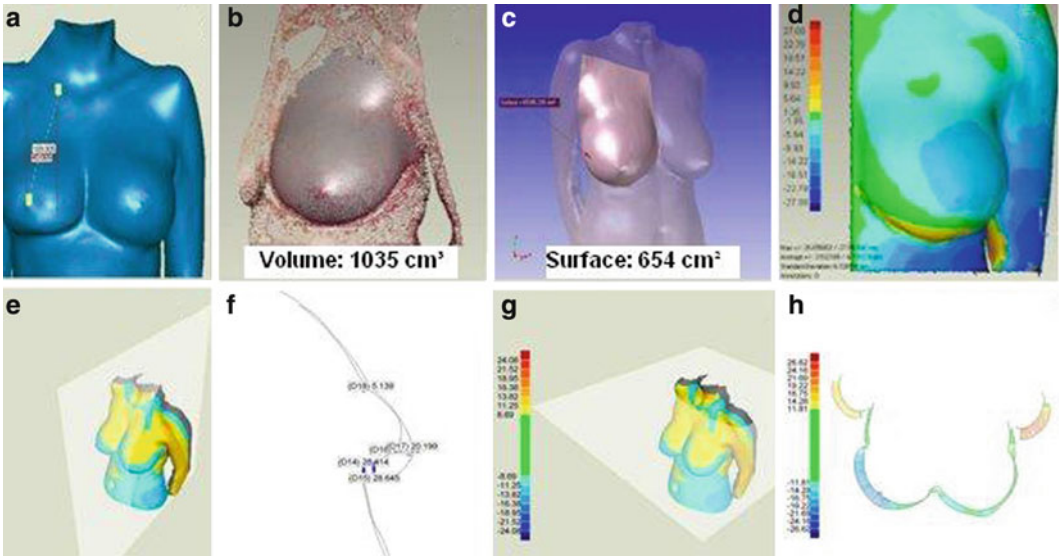

Fig. 58.5 Objective breast region evaluation. Different 3D quantification methods of the breast region: (**a**) linear on surface measurements [cm]; (**b**) volume measurements [cm^3]; (**c**) surface measurements [cm^2]; (**d**) placing symmetric mirror plane and color-coded quantification of breast asymmetry by superimposed mirrored 3D model on the non-mirrored 3D model; (**e**) and (**g**) superimposed preoperative 3D model and the postoperative 3D model and color-coded deviation visualization [cm]; (**f**) vertical and (**h**) horizontal slice at nipple–areola-complex height with color-coded 2D deviation between the pre- and postoperative 3D model [cm]

surface by mirroring the region of interest and to evaluate the symmetry (Fig. 58.5d). By superimposing the preoperative 3D model onto the postoperative 3D model, precise color-coded quantification of surgically induced breast shape changes is possible in horizontal (Fig. 58.5e and f) and vertical (Fig. 58.5g und h) axes. The noninvasive and fast technique of 3D surface imaging provides the possibility for routine follow-up examination at close intervals. 3D surface imaging permits postoperative long-time analysis regarding swelling and soft tissue shape changes over time. By superimposing standardized 3D surface scans accomplished at different postoperative examination dates and by applying the above-described analyzing tools, the results can be automatically generated in an evaluation report which allows objective breast region quantification to optimize surgical procedures. It also allows an objective quality assurance of postoperative results and long-term postoperative follow-up studies.

58.2.3 Application to Other Areas of Health and Disease

Efforts in the field of cranio-maxillo-facial surgery enabled the expansion to related medical fields (Brockmann et al. 2006; Kovacs et al. 2004, 2006b). Clinical applications in the field of plastic, reconstructive and aesthetic breast surgery are well known and show promising results (Kovacs et al. 2004; Losken et al. 2005). Further promising implementations in other related fields, especially in breast surgery, is feasible in the future. One potential future application should be the implementation of noninvasive 3D surface technologies in the field of oncologic breast surgery. In particular, oncologic breast surgery pursues the challenge of operating being as minimally invasive as possible

and performing breast-preserving surgery. Current surgical planning regarding the quantification of tumor size and the correlation between tumor size and breast volume/breast shape are based on 2D radiographic diagnosis (mammography and ultrasound) or MRI/CT, which do not take the normal breast shape into account. By combining tumor location, size and expansion using current diagnosis systems with 3D surface imaging while respecting the normal breast geometry, it would be potentially possible to reduce soft tissue resection in tumor surgery to a minimum, with the result that the original breast shape is preserved. Another application could be in the field of breast reconstruction with patient-specific designed implants. For the non-operated, healthy breast, a virtual 3D breast implant could be designed on the basis of 3D surface imaging data and be produced using modern manufacturing techniques like rapid prototyping. In combination with other innovative techniques, it would be possible to introduce 3D surface imaging as an objective technique for quality assurance in oncologic breast surgery.

Besides surgical application, efforts have been undertaken in the clothing industry (Lee et al. 2004). Every kind of brassiere (underwire, jogging, sport or nursing) can be produced according to the patient's specific breast geometry. The individual anatomical measurements of the 3D surface model can be transferred to specific CAD (Computer Aided Design) software and variable kinds of brassieres could be virtually designed. In the future, as soft tissue research develops, the stiffness of the used brassiere components could be included and bra firmness could be simulated.

Summary Points

- Correlation between breast shape and breast volume for achieving postoperative symmetry is essential.
- Reliable and objective breast volume determination could be helpful in providing pre- and intraoperative assistance to the surgeon to achieve an aesthetically pleasing result, particularly for patients with asymmetric breasts.
- Breast volume determinations are not yet performed as clinical routine because so far no generally recognized method exists.
- Classical breast volume determination techniques exhibit variable reliability, are sometimes difficult to perform because of cumbersome feasibility or even limited practicability, have low patient acceptance and are often cost-intensive.
- There is a need to supplement clinicians with additional evaluation methods to guarantee fast, non-invasive, routine clinical follow-up examinations at close intervals and objective and patient-specific quantification of the breast geometry.
- Three-dimensional surface imaging permits a noninvasive, risk-free, noncontact, nondeformable patient assessment and delivers a high-resolution 3D virtual colored model of the breast region. Precise and accurate pre- and postoperative 3D quantification of shape, volume, surface changes, symmetry, projection, swelling tendency, contour and deformation are enabled.

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Chapter 59
Numerical Modelling of Human Breast Deformation

A. Pérez del Palomar, B. Calvo, and A. Lapuebla-Ferri

Abstract Most surgical procedures in breast plastic surgery are either reconstructive procedures following oncologic interventions (tumorectomy, quadrantectomy, mastectomy…) or aesthetic ones, including both augmentation and reduction. With current techniques, the results of such procedures cannot be fully guaranteed. Usually, surgical planning is based on a photographic and anthropometric study of only the breast. Among others, one of the difficulties that plastic surgeons have is the noticeable change of the breast shape with the position of the patient. Thus, it is more and more necessary to plan a presurgical methodology to help the plastic surgeon and guarantee the patient a successful result of the intervention.

Numerical methods such as finite element simulations can help in predicting the deformations of a specific tissue if a suitable definition of the tissue is introduced. These models take into account the constitutive behaviour of the involved materials, the boundary conditions and the externally applied loads. Thus, numerical modelling can be used as a powerful tool to provide accurate and useful information to the surgeon planning such surgical procedures.

Abbreviations

FEM	Finite element method
CT	Computed tomography
MR	Magnetic resonance

59.1 Introduction

Plastic surgery has suffered a great expansion in the last few decades, with patients demanding accurate and satisfactory outcomes. Medical students and residents who typically learn surgical procedures by performing them on real patients under close supervision, as well as experienced surgeons, may take advantage of virtual simulations of surgery. They can plan and rehearse complex procedures, predict

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_59,

their outcomes and design and evaluate new methods and equipment. However, the majority of the simulation and manipulation systems for surgery have been built using largely phenomenological and heuristic models that have not been validated. This is why modelling the post surgery deformation of human organs for surgery planning systems has turned out to be a very important subject of research, one continuously in development.

With regard to breast morphology, this tissue lies on a mobile and irregular muscular bed and is composed of skin, fat and gland which have different mechanical properties that vary according to genetic factors and age (Pérez del Palomar et al. 2008). One of the difficulties that plastic surgeons have is the noticeable change of the breast shape with the position of the patient. Moreover, the plastic surgeon performs the surgical procedure with the patient in the lying position but needs to move the patient to the standing up position up to 5 times to check the shape of the breast.

Biomechanics is defined as the development, extension and application of mechanics with the purpose of acquiring a better understanding of physiology and pathophysiology and helping in the diagnosis and treatment of disease and injury. That is, the overall goal of biomechanics is, and must remain, the general improvement of the human condition (Humphrey 2002).

Despite the many investigations developed in this field, the exact mechanical behaviour of the different human tissues and organs and the causes of many of their diseases are not completely known yet. This is partially due to the inherent limitations of experimental studies such as their high cost, difficulties associated with the obtaining of accurate measures of strain and stress and, especially, the difficult and sometimes impossible reproduction of certain natural, pathological or degenerative situations. Computational models also provide a standardized framework for parameter studies, such as evaluation of clinical treatments, stress distributions for different geometries and kinematics, evaluation of surgical procedures, injury assessment, surgery planning and the effects of ageing, disease and drugs.

It is important to note that reliability of these models strongly depends on a precise geometrical reconstruction and on an accurate mathematical description of the behaviour of the biological tissues involved, and their interactions with the surrounding environment (Ning et al. 2006).

Biomechanical breast models mainly employing finite element methods have been explored to predict breast deformations in different situations. Applications include guiding clinical biopsy (Azar et al. 2001), modelling compressions similar to X-ray mammography (Ruiter et al. 2002), registering X-ray and MR mammography (Poplack et al. 2004), validating nonrigid registration algorithms (Tanner et al. 2006) and testing reconstruction algorithms for elastography (Washington and Miga 2004; Schnabel et al. 2003). The use of mechanical models in these applications is responsible for providing information about the expected deformations. This prior information helps to constrain possible solutions and thus provides a physical basis for interpolation, reconstruction and prediction for those cases in which there is insufficient information in the image data. These biomechanical breast models have been assessed based on the predicted location of anatomical landmarks selected in breast images acquired before and after *in vivo* compression by visual comparison of the simulated compressed breast image with the uncompressed breast (Azar et al. 2001). However, the small number of landmarks available in a single dataset makes these evaluations limited.

A wide range of values for the material properties of the different tissue types involved has been used in previously cited papers. The constitutive material parameters for fibroglandular and fatty tissues are generally obtained from ex vivo indentation tests (Bakic 2000). Azar et al. (2001, 2002), Wellman (1999) and Krouskop et al. (1998) assumed exponential, Samani et al. (2001) hyperelastic and Bakic (1999) linear elastic stress–strain relationships and used different material parameters. Samani used a hyperelastic material model to approximate Wellman's stress–strain properties. Azar et al. (2001, 2002) applied the same material model as Wellman, but used a corrected stress–strain relationship for fat tissue. All authors considered quasi incompressible materials with a Poisson ratio close to 0.5. Ruiter et al. (2002) concluded that the results do not vary within a significant range of

stiffness ratios of gland and fat regarding the required simulation accuracy. The exponential and Neo-hookean models can be used as approximations, whereas the linear elastic approaches do not perform that well. They argued that the simplest tissue model for breast simulation was the Neo-hookean one, ignoring the differences between the material properties of gland and fat. With regard to the skin, Samani et al. (2001) made the assumption that it can be considered as linear elastic and isotropic for strains lower than 50%. Reishner et al. (1995) examined the two-dimensional mechanical behaviour of human skin samples obtained from different anatomical sites, noting that the skin had varying degrees of anisotropy in different regions of the body. By comparing different biomechanical breast models Tanner et al. (2006) found that, for a compression of 20%, the effect on accuracy caused by the modification of the material properties was however less significant than the application of correct boundary conditions. Using the displacements of the surface of the breast as boundary conditions, they were able to recover the displacement of validation landmarks to a mean error of less than 2.5 mm.

In this chapter a virtual deformable breast model is presented to be used as a tool to predict breast deformations under different conditions.

59.2 Breast Computational Model

To construct a virtual deformable breast model medical data are necessary. The morphology of the patient breast is obtained by means of CT images. This data acquisition allows distinguishing not only the external shape of the breast but also its internal composition (glandular tissue and fat). Here, two datasets corresponding to two women are processed. The first patient (Patient A), a 52-year-old female requiring breast reduction, presents a high proportion of fat with respect to gland tissue; the second one (Patient B), a 36-year-old female requiring breast augmentation, presents a lower proportion of fat with respect to gland tissue. From the CT images, each volumetric model was constructed using the different material density (Fig. 59.1). Then, a surface mesh with triangles (STL) was created for each of the tissues (gland, fat, muscle and bone). Once the models

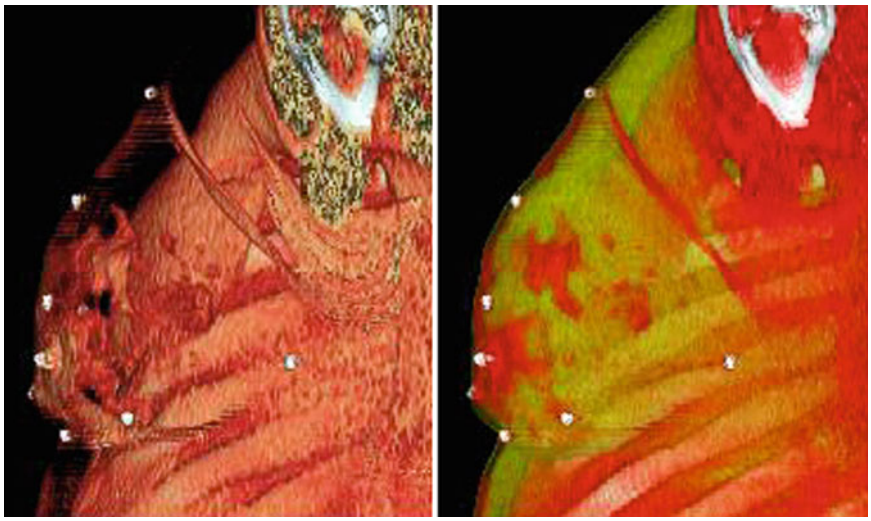

Fig. 59.1 Segmentation of the breast. Segmentation of the breast, distinguishing the different tissues (Patient A). The *white dots* correspond to plumb balls located on the patient to be used as anthropometric measures

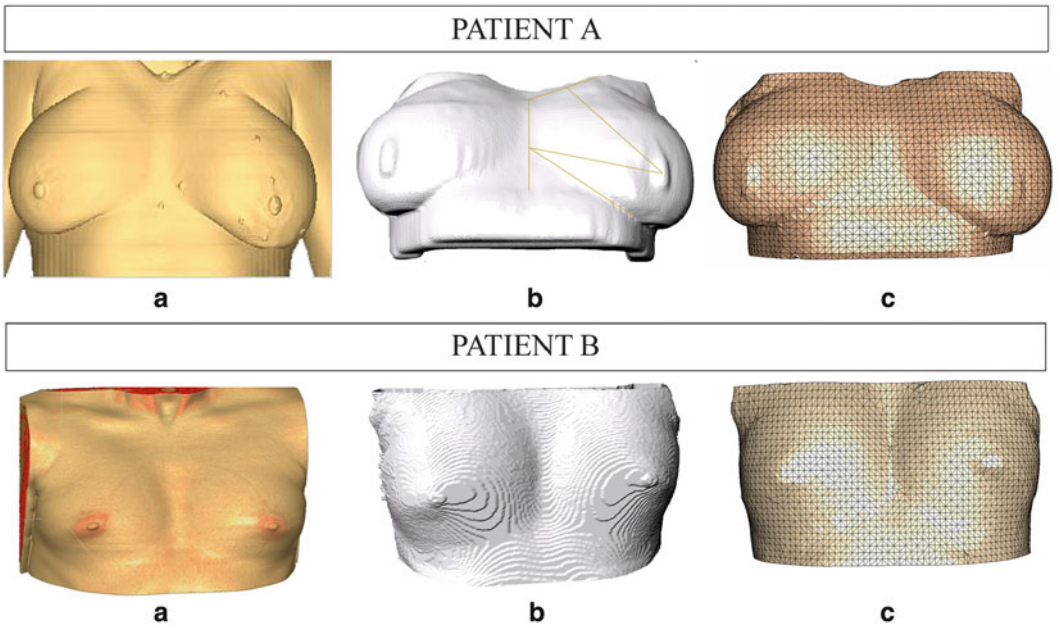

Fig. 59.2 Finite element models of both patients. Geometry reconstruction and finite element mesh of both Patients A and B; (**a**) computed tomography data, (**b**) surface mesh with triangles (STL), (**c**) finite element mesh (FEM)

were constructed, the bones and muscles were removed, obtaining the models shown in Fig. 59.2. These volumes were meshed for their numerical treatment. For further description of this method see Pérez del Palomar et al. (2008).

Once the computational model represents the actual geometry of the breast, a suitable characterization of the tissues involved has to be made. The main constitutive components for breast that are related with its mechanical behaviour are the glandular tissue, the fat and the skin. These tissues can be distinguished using CT images (see Fig. 59.1) and therefore can be separately treated. For the studied cases, Patient A has a similar proportion of glandular tissue and fat (60% glandular tissue/40% fat tissue), while for Patient B this proportion is totally different (90% glandular tissue/10% fat tissue). Therefore, the overall behaviour of the breast will be determined by the mechanical behaviour of each component.

As mentioned before, there is a great dispersion in the material properties used to simulate breast deformation. One thing that is certain is that constitutive models for large deformations have to be used to represent breast behaviour (see Tanner et al. (2006); Azar et al. (2001); Roose et al. (2005); Samani et al. (2001); Pérez del Palomar et al. (2008)). A suitable definition of this material behaviour allows predicting the change of breast shape from a patient lying in a prone position and a patient in a standing position (Figs. 59.3 and 59. 4).

In Fig. 59.3, the positions of different characteristic points drawn by the plastic surgeon are shown. The distances between these points change when the patient moves from the lying to the standing position. These points can be located also in the finite element model by using small titanium balls during the CT acquisition and therefore the new location of these markers in the deformed breast after loading can be compared with the actual locations on the patient. These measures are shown in Fig. 59.4. The comparison of the predicted numerical and the real distances is shown in Table 59.1 for the different reference markers.

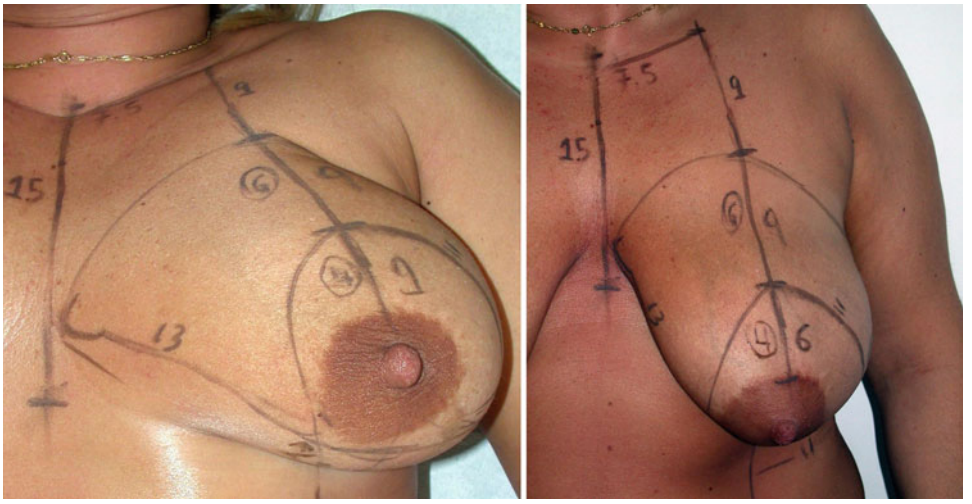

Fig. 59.3 Anthropometric measures of Patient A. Anthropometric measures of Patient A. The distances between the reference points vary with the patient's position

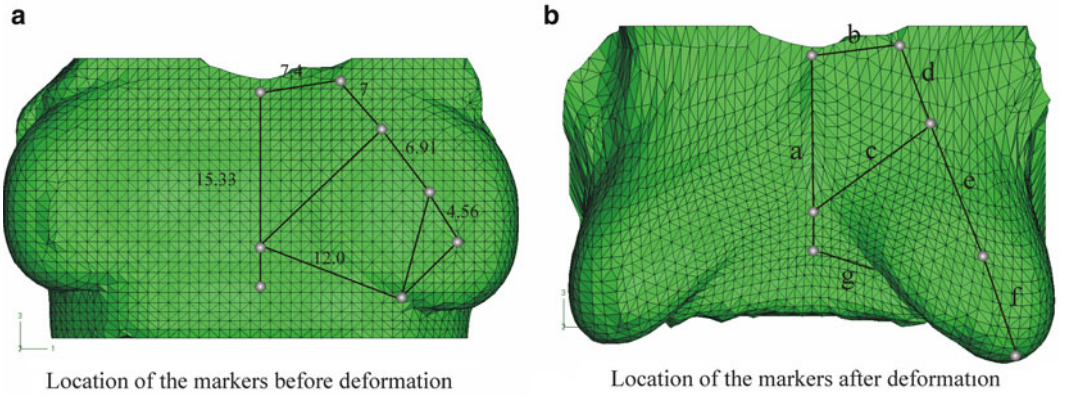

Fig. 59.4 Location of the markers in the finite element model before and after gravity simulation. Location of the markers in the finite element model. The distances between markers between both positions have to coincide with the real measures on the patient. Data corresponding to Patient A

Table 59.1 Comparison of the numerical breast model with real distances on Patient A

	A	b	c	D	e	f	g
Patient (lying)	15	7.5	–	4.6	6	4	13
Patient (standing up)	15	7.5	–	7	9	6	13
Numerical model	15.8	7.6	–	7.5	9.6	6.3	12.2
Error	5.7%	1.5%	–	7.1%	6.7%	5%	6.1%

Distances between the markers in the two positions (lying and standing up). The distances in the finite element model are also shown and the error between the numerical prediction and the real measures has been computed

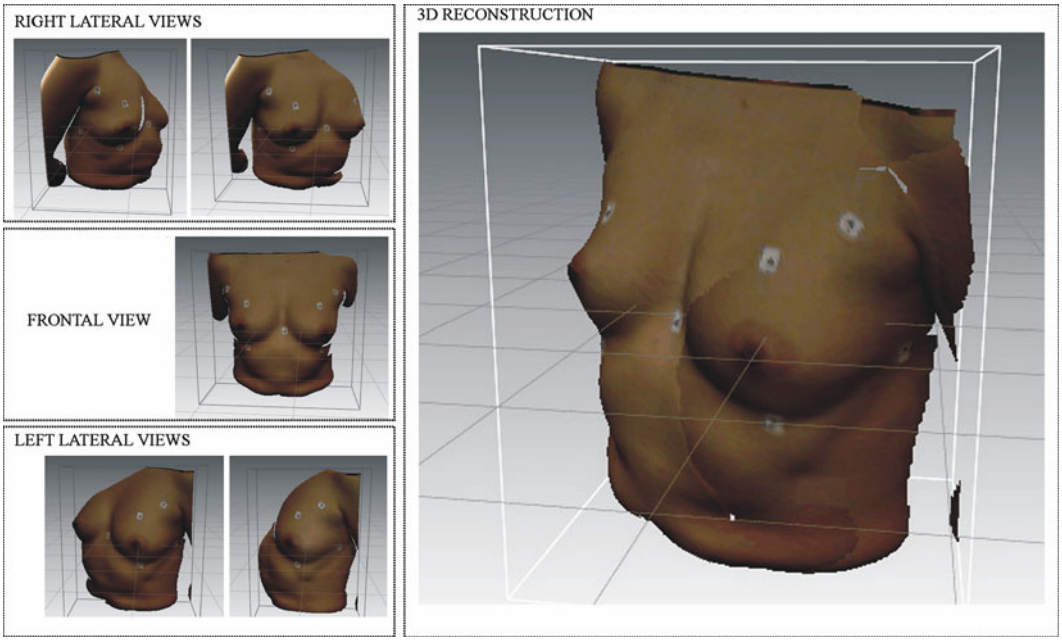

Fig. 59.5 3D scanner data of Patient B. 3D scanner data. On the *left*, sequence of images of the patient from different points of view; on the *right* 3D reconstruction of Patient B in standing up position

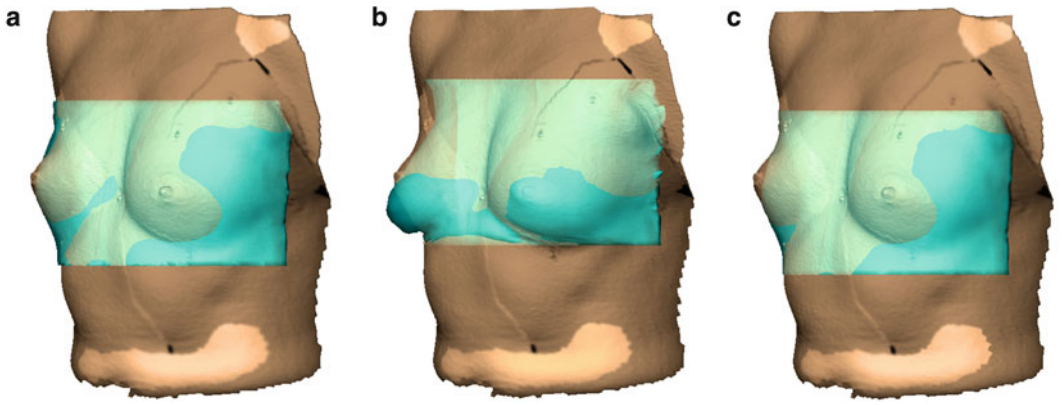

Fig. 59.6 Comparison between finite element simulations and a real patient. Superposition of images. The flesh coloured image corresponds to the reconstruction with the 3D scanner and the blue one with the deformed finite element mesh after different simulations (**a**) 40% fat, 60% gland; (**b**) 80% fat, 20% gland; (**c**) 50% fat, 50% gland

This procedure has proved the ability of the numerical models to predict real deformations of the breast. Finite element deformations represent with high accuracy the real deformations of the patient breast. This method can be improved using digitalized images reconstructed from a 3D scanner. Here, this procedure has been used for Patient B (Fig. 59.5).

The volume ratio of each tissue (gland/fat) can be computed, as has been done for Patient A, using segmentation. The relevance of introducing the correct relation between fat and gland can be seen qualitatively in Fig. 59.6. In this figure the real 3D image of the patient (captured using the

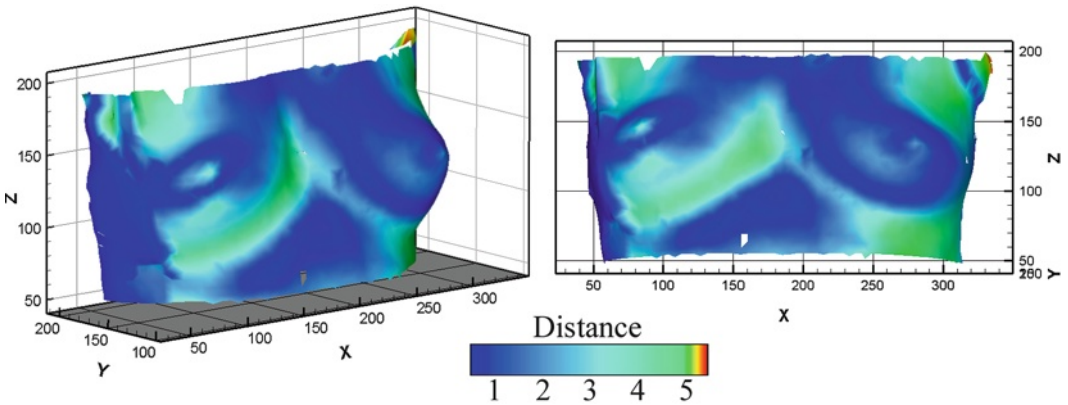

Fig. 59.7 Deviation between the finite element prediction and the real geometry of the patient. The deviation between the prediction of the numerical model and the real shape of Patient B is measured by means of the distance between each geometries. *Blue colour* corresponds to the best fitting between the numerical and the real model. The distance is computed in mm

3D scanner) is superimposed on the deformed mesh of the breast after gravity calculations. This procedure is made modifying the proportion of each tissue, and the qualitative match of the surfaces can be seen. For instance, it can be clearly appreciated that Fig. 59.6a which corresponds to a 40% fat/60% gland breast, fitted much better than Fig. 59.6b in which the fat proportion was increased.

The accuracy of the numerical model can be computed measuring the distance between the finite element solution and the real surface of the woman in the standing position. This can be seen in a colour map of the breast, as shown in Fig. 59.7. In this case, we can see that the mean deviation between both surfaces is 2.4 mm.

59.3 Implications for Breast Simulation

The breast has an inhomogeneous structure containing many layers of different kinds of tissue. However, the two predominant types of tissue within the breast are fat and normal glandular tissue which supports lactation. The proportion of each tissue in a breast depends on the age of the woman, if she is premenopausal or postmenopausal and, in general, on her constitution.

The deformation of soft tissues compromises the accuracy of image-guided surgery based on preoperative images and restricts its applicability. Here, we have presented a numerical model based on biomechanical principles to predict breast tissue deformations, thereby avoiding this limitation. This model can be used as a guideline in numerous clinical applications, such as breast image registration, multimodality data fusion, breast surgery and biopsy. Predicting breast deformations with the reported accuracy will improve the surgical precision for non-palpable lesions and provide plausible breast deformations for validation and teaching purposes. However, the feasibility of the method depends on suitable material characterization.

In this study we propose a method to predict deformations of the breast for presurgical planning. Two different tools are presented to evaluate the accuracy of the models. The first one consists in the validation of the position using landmarks and the second in the registration of the patient in standing

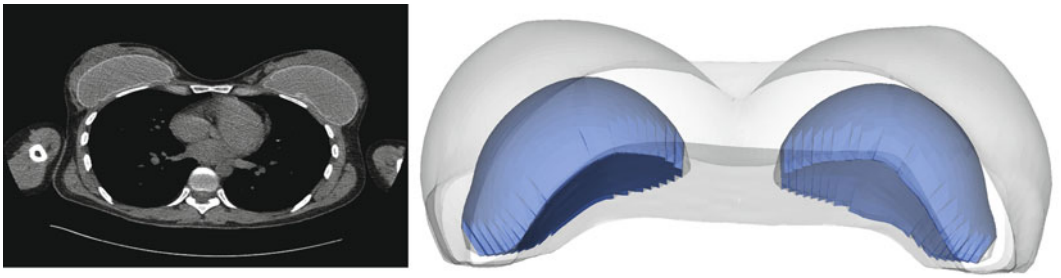

Fig. 59.8 Patient with prostheses and the equivalent finite element model. On the *left*, computed tomography images of a patient after insertion of silicone implants. On the *right*, finite element model of the patient incorporating the meshes of the prostheses

position, comparing the resultant image with the finite element results. These techniques are applied for two different breast models, the first one with a high proportion of fat tissue and the second one with a lower proportion of this tissue. In addition, the reconstruction of the real shape of the breast using a 3D scanner gives more information than using landmarks (Tanner et al. 2006) and can be used as an additional tool for the plastic surgeon to construct an anthropometric study.

Although incorporating other important structures such as the Cooper's ligaments or the effect of the pectoral muscle would also improve the accuracy of the model (Gambarotta et al. 2005), it would involve a loss in simplicity to easily construct breast finite element models.

To conclude, we are interested in finding the best way of presurgically estimating the morphological modifications of the breast depending on a specific intervention (reduction or augmentation). For instance, for augmentation mammoplasties and according to statistical data from American Society of Plastic Surgeons, more than 300,000 augmentation procedures were performed in USA during 2008. Using numerical methods, these surgical techniques can be planned in advance. Thus, a preoperative planning can be traced, including the location, type, size and shape of the implants (Fig. 59.8).

The techniques can also be evaluated by comparing the final deformed shape of the model with the one of the real patient, as shown in Fig. 59.9. The final shape of the FE model should be compared with the one of the real patient in standing position (i.e., with gravity acting on both breasts), as is done in clinical practice to verify the outcomes of surgical interventions.

59.4 Conclusions

Currently, the outcomes of breast surgeries can be predicted within a certain degree of accuracy, but they mostly rely on the surgeon's ability. Many difficulties arise from the intrinsic anatomy of the breast. This organ is heterogeneous, is composed of several tissues (fat, gland and skin) and its mechanical properties vary according to factors such as age or pregnancy. The breast is also an organ that provides support for lactation, and does not sustain external loads in the physiologic situation. Because of this, and because it lies on a mobile myofascial unit over rib cage, breast shape undergoes high changes under applied forces.

For such reasons, plastic surgeons may benefit by virtual surgery simulations. They can provide insight into the mechanical behaviour of the breast and help in surgery planning, to minimize the uncertainty of the results. So a widespread tool in the field of biomechanics such as Finite Element (FE) models is a suitable choice.

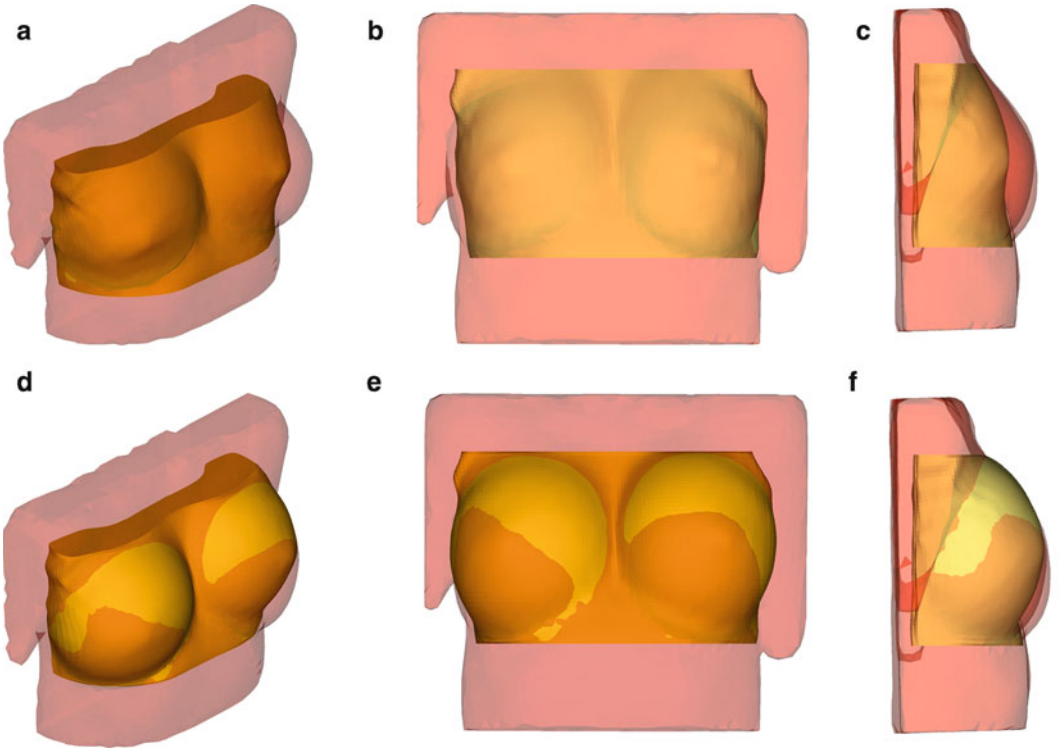

Fig. 59.9 Matching of the deformed shape of the FE model with the one of the real patients after a prosthesis augmentation surgery. Matching of the deformed shape of the FE model with the one of the real patients after a prosthesis augmentation surgery. (**a**–**c**) Before simulation. (**d**–**f**) After simulation

59.5 Applications to Other Areas of Health and Disease

Finite element simulations can be used in the field of biomechanics to be used as a tool to help clinicians in their normal activity. There are many areas in which this tool can be useful. The ability of these numerical techniques to recreate surgical intervention allows the design of prostheses that can minimize damage to the surrounding tissues. Furthermore, the numerical methods can also include not only the mechanical environment of a specific organ but also chemical interactions regarding the use of drugs, for instance.

Summary Points

- Biomechanical breast models mainly employing finite element methods have been explored to predict breast deformations in different situations.
- To construct a reliable finite element model, the morphology of the patient breast has to be constructed using medical data (CT and MR images). Moreover, accurate constitutive properties for the different involved tissues are essential to guarantee the validity of the results.
- The deformation of soft tissues compromises the accuracy of image-guided surgery based on preoperative images and restricts its applicability. Here, we have presented a numerical model,

based on biomechanical principles, to predict breast tissue deformations, thereby avoiding this limitation.
- Predicting breast deformations with the reported accuracy will improve the surgical precision for non-palpable lesions, and provide plausible breast deformations for validation and teaching purposes.
- Plastic surgeons may benefit by virtual surgery simulation. They can provide insight into the mechanical behaviour of the breast and help in surgery planning to minimize the uncertainty of the results.

Key Facts of the Finite Element Method

The finite element method (FEM) (its practical application often known as finite element analysis (FEA)) is a numerical technique for finding approximate solutions of partial differential equations (PDE) as well as of integral equations.

The finite-element method originated from the need to solve complex elasticity and structural analysis problems in civil and aeronautical engineering. Its development can be traced back to the work by Alexander Hrennikoff (1941). Development of the finite element method began in earnest in the middle to late 1950s for airframe and structural analysis and gathered momentum at the University of Stuttgart through the work of John Argyris and at Berkeley through the work of Ray W. Clough in the 1960s for use in civil engineering. A variety of specializations under the umbrella of the mechanical engineering discipline (such as aeronautical, biomechanical, and automotive industries) commonly use integrated FEM in design and development of their products.

Key Facts of Breast Deformities

The breast is a heterogeneous organ, composed of several tissues (fat, gland and skin) and whose mechanical properties vary according to factors such as age or pregnancy. The breast provides support for lactation but does not sustain external loads in the physiologic situation except for the bodyweight. Because of these characteristics, and because it lies on a mobile myofascial unit over the rib cage, its shape undergoes large changes under applied forces. The interaction of the breast implant with the host tissues, the effect of the different prosthetic materials and the surgical procedure itself impose additional difficulties to the surgical procedure, stressing the need for a better understanding and management of the breast reconstruction surgery. Surgeons would greatly benefit from realistic surgical simulations and virtual tools, which could provide insight into the mechanical behaviour of the breast and the implant and, at the same time, help in preoperative planning, thus minimizing the uncertainty of the results.

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Part XI
Anthropometry of Pregnancy: Prenatal and Postnatal Aspects

Chapter 60
Reference Charts for Anthropometric Changes During Pregnancy

Elvira Beatriz Calvo and Laura Beatriz López

Abstract Maternal nutritional status should be viewed as the result of a very long process beginning in the mother's own intrauterine life, and constitutes a critical determinant of pregnancy outcomes for both the mother and her infant.

Strong evidence supports the association between gestational weight gain (GWG) and preterm birth, total birth weight, low birth weight, large and small for gestational age infants, and macrosomia. Moderate evidence relates GWG to cesarean delivery and intermediate-term postpartum weight retention.

In this chapter, the anthropometric indicators used to assess pregnant women nutritional status are reviewed, considering their predictive ability for detrimental pregnancy outcomes.

Criteria for evaluating normality of these indicators and the different instruments used as references in many settings are considered in relation to the epidemiological characteristics and health care facilities of diverse populations.

Evolution of weight gain charts in the last few decades reflects changes in recommendations and better understanding of the role of weight gain in pregnancy management. Nevertheless, there is no standardization across instruments.

Recognizing the importance of adequate weight gain during pregnancy for the mother and newborn health based on prepregnancy nutritional status, as well as the different situation in developed countries – concerned with the increasing prevalence of obesity in women – versus developing countries – where rates of low birth weight in infants are still unacceptable – are among the lessons learned.

Abbreviations

BMI	Body mass index
GWG	Gestational weight gain
IOM	Institute of Medicine
LBW	Low birth weight

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_60,

LGA Large for gestational age
MUAC Mid-upper arm circumference
SGA Small for gestational age
WHO World Health Organization

60.1 Introduction

Maternal nutritional status should be viewed as the result of a very long process beginning in the mother's own intrauterine life, and not only in terms of the comparatively short pregnancy period.

Gestational weight gain (GWG) is a unique and complex biological phenomenon that supports the functions of growth and development of the fetus, influenced by changes in maternal physiology and metabolism, and also by placental metabolism.

The biological mechanism that underlies the relationship between women's nutritional status and reproductive outcomes is not fully understood. The two negative outcomes of principal interest, i.e. intrauterine growth retardation and prematurity, are heterogeneous syndromes, with maternal malnutrition being only one of the causative factors. Improving maternal nutrition has a significant impact on birth weight only in unfavorable conditions.

60.1.1 Gestational Weight Gain Components

Gain components are of two different natures: the products of conception and the maternal tissue accretion (Fig. 60.1). The products of conception comprise the fetus, placenta and amniotic fluid, representing 35% of the total gain on the average. Cross-sectional data indicate that fetal growth follows a sigmoid curve, with growth slowing in the final week of gestation. The rate of placental growth declines toward the end of pregnancy.

Expansion of maternal tissues accounts for approximately two-thirds of the total gain. There are increases in uterine and mammary tissue mass, along with expansion of maternal blood volume, extracellular fluid, and fat stores.

Expansion of the blood volume accounts for 10% of the total gain, and is related to fetal size. Most of the increase in plasma volume occurs before week 34 of gestation; the increase in red blood cell mass is believed to be linear from the end of the first trimester to term. The expansion of the extracellular, extravascular fluid volume accounts for approximately 13% of the total gain in women without generalized edema or with only leg edema. The retention of extracellular fluid can be highly variable; some women accumulate more than 5 L (5 kg).

Several models of body composition have been used to estimate gains in different tissues during pregnancy (Butte et al. 2003, Lederman et al. 1997). Fat tissue is normally accumulated during pregnancy and a great portion of the variance in total weight gain is accounted by this increase in fat mass. It has been estimated that pregnant women who gain 12.5 kg without edema acquire about 3.5 kg of fat. Fat accretion shows a high correlation with total increase in body weight, but no correlation with birth weight. Fat stores have been suggested as a maternal energy reserve for use when the food supply is limited during pregnancy or for further lactation.

Fat free mass can account for up to 58% of total weight gain; protein deposition also occurs predominantly in late pregnancy and it is accrued mostly in the fetus and placenta but also in the uterus, breast and other maternal tissues. Unlike fat stores, increments in total body water, total

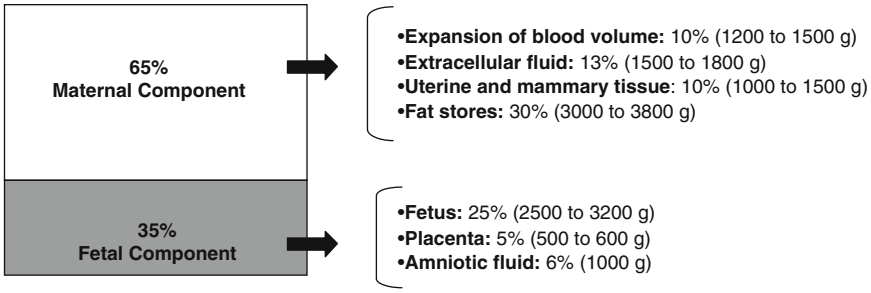

Fig. 60.1 Schematic representation of maternal and fetal components of gestational weight gain (GWG). During normal pregnancy the fetus and placenta account for one-third of total weight gain, while the expansion of blood volume and other maternal tissues for the remaining two-thirds

body potassium, protein and fat-free mass are positively correlated to birth weight across all prepregnancy BMI categories (Butte et al. 2003).

60.1.2 What Measurements Are Appropriate?

60.1.2.1 Height

Maternal height is one of the biologically acceptable predictors of birth weight. Many studies have demonstrated that short maternal stature is associated with low birth weight and stunting in the offspring. A controversial issue is the definition of short stature; the Institute of Medicine (IOM 2009) recommended that women with a height lower than 157 cm should gain weight at the lower range of the proposed standard; studies coming from Africa (Gebremariam 2005) and Asia (Mavalankar et al. 1994) suggest that women shorter than 145 or 150 cm are at higher risk of having a low birth weight (LBW) infant, while data from Latin America (Ferreira et al. 2009) propose a height of less than 152 cm as a risk factor.

There are several kinds of information that height may convey. Height may predict overall maternal body stores and may also reflect socioeconomic conditions. Maternal height is a phenotypic expression of the genetic endowment and the environment during the mother's own childhood.

Finally, maternal height is commonly accepted as a proxy for pelvic size and in turn as a clinical indicator for risk of obstetric complications, particularly cephalopelvic disproportion, prolonged labor, and/or delivery by operative means such as cesarean section. Age is an additional consideration here because pelvic measurements reach final dimensions late in adolescence.

Therefore, use of maternal height as an indicator of nutritional status should take into account the environment in which that woman has grown. A short woman from a developed country may be at risk of obstetric complications because her relatively small pelvis may constraint a vaginal delivery of a normal weight infant.

Measurement of height is best performed in the first weeks in order to avoid errors related to the normal lordosis of pregnancy, which reduces maternal height as pregnancy progresses. In young adolescent mothers, some increase in height may be observed during pregnancy.

Country- or region-specific maternal height cut-off points, which maximize sensitivity and specificity, need to be established for predicting risk of LBW and cephalopelvic disproportion. This range is likely to fall between 140 and 150 cm.

60.1.2.2 Prepregnancy/Early Pregnancy Weight or Body Mass Index (BMI)

Prepregnancy weight or prepregnancy BMI is one of the strongest anthropometric measurements associated with maternal and fetal outcomes.

Measurement of prepregnancy weight is used to assess initial risk of poor pregnancy outcomes, to determine appropriate weight gain goals for women of different nutritional risk status, and to target nutritional interventions for those most in need and those most likely to benefit from them.

The large variation in weight within a specific height category has given rise to various expressions of weight-for-height (referred to tables of desirable weight-for-height) or body mass index (BMI) calculated as weight/height^2. All these measures are primarily weighted for weight (BMI correlates above 0.9 with weight in adult women), and can be substituted.

Unfavorable outcomes of pregnancy demonstrated a U-shaped relationship with prepregnancy weight. Low prepregnancy BMI has been identified as a risk factor of having an infant of LBW or small for gestational age (SGA); on the other hand, a high prepregnancy BMI is linked to a number of fetal and maternal complications, including fetal death, preeclampsia, gestational diabetes, macrosomia, and complicated deliveries.

Prepregnancy weight is also related with the pattern of GWG. Many epidemiological studies around the world suggest that GWG is influenced by maternal weight or BMI. In general, GWG decreases as prepregnancy BMI increases.

In developing countries, many women do not remember their prepregnancy weight. In such cases, weight at gestational ages lower than 12 weeks can be used as an equivalent of prepregnancy weight because during the first trimester weight accretion is minimal.

A low cut-off point of 40 kg is the most cited figure of risk in developing countries' literature for populations with average heights of 150 cm or less.

60.1.2.3 Weight Gain During Pregnancy

Maternal weight gain during pregnancy is a key component of prenatal care, and reflects maternal and fetal health. Both total weight gain and the rate of weight gain are associated with infant and maternal health outcomes.

Many factors determine the total amount of weight gain during pregnancy. Among the physiological factors, the three main components are changes in maternal physiology and metabolism, placenta functions, and fetus growth. Non-physiological factors include psychological, behavioral, family, social, cultural and environmental aspects.

During prenatal care, maternal weight gain at different gestational ages should be used to guide pregnant women in order to achieve an optimal weight which minimizes the risk of adverse fetal and maternal outcomes. For this purpose, charts, curves or guidelines are useful instruments that can be applied at individual level or for epidemiological evaluation.

60.1.2.4 Mid-Upper Arm Circumference (MUAC)

Mid-upper arm circumference is a simple and objective method of assessing nutritional status, widely recognized as an effective tool for screening purposes. Like body weight, it also reflects past and current status, but is less responsive to short-term changes in health and nutrition.

Many studies have evaluated its use as an alternative or complementary measurement during prenatal care. There is a consensus that it has a strong correlation with maternal weight and BMI, and also a positive relationship between MUAC and birth weight has been reported.

In developing countries, pregnant women usually start prenatal control after the first months of pregnancy and thus prepregnancy weight could be unknown; in such cases, total weight gain by gestational age is difficult to determine and MUAC becomes an alternative tool for anthropometric evaluation.

Nevertheless, there is no consensus about the cut-off point that can be associated with an increased risk of LBW, prematurity or insufficient maternal weight gain. The proposed figures vary according to socioeconomic and demographic characteristics of the populations studied. Data from Africa and Asia (Kruger 2005; Ojha and Malla 2007) suggest that, during pregnancy, MUAC below 25 cm can be used as a warning of malnutrition, below 23 cm as a strong indicator of malnutrition, and figures lower than 22 cm are highly associated with an increased risk of adverse pregnancy outcomes, specially LBW. However, there is lack of information about reference figures for MUAC to be applied in pregnant women from other regions of the world.

Different patterns of MUAC change have been described in well-nourished European or U.S. women (with average increments between 0.3 and 0.5 cm), and consistent losses in arm circumference have been reported in studies from developing countries. It seems that subcutaneous fat is used to fulfill fetus requirements when weight gains are in the range of 4–6 kg in thin or normal weight women. With intermediate gains, MUAC could remain unchanged.

Taking into account the abovementioned data, MUAC is not recommended for monitoring, but it is a useful tool for screening purposes.

60.1.2.5 Skinfold Thickness

Skinfold thickness reflects subcutaneous fat stores, which are used to fulfill the fetus and the mother's energy needs during pregnancy and lactation. Bicipital, tricipital and subscapular skinfolds are the most frequently used. Changes in these measurements could also be appropriate to assess maternal nutrition status, but as in the case of MUAC, few studies have evaluated the pattern of their variation at different gestational ages and no cut-off points are available to be applied during prenatal control.

A more extensive description of skinfold use during pregnancy will be addressed by Professor S. Rao in other chapter of this book.

60.1.3 Conditions for a Reference

"A reference is defined as a tool for grouping and analyzing data and provides a common basis for comparing populations; no inferences should be made about the meaning of observed differences. A standard, on the other hand, embraces the notion of a norm or desirable target, and thus involves a value judgment" (WHO 1995a).

Current reference data describe the distribution of anthropometric indices in ostensibly healthy and well-nourished populations with favorable pregnancy outcomes. This is known as the specificity distribution for anthropometric characteristics.

In turn, there are several definitions of what constitutes a healthy population:

- The population lives in a healthy environment.
- The population lives in a healthy environment and contains no overtly sick or very few clinically sick individuals.

- The population lives in a healthy environment and contains only individuals whose present good health will be demonstrated by survival after measurements are taken.
- The population lives in a healthy environment and contains only individuals who live healthily according to present prescriptions.

It should be emphasized that the specificity distribution indicates only the extent to which a particular woman deviates from the median of a healthy population; it does not indicate the probability of suffering an adverse outcome in the future. The latter requires empirical data on the sensitivity distribution, which is the probability of suffering a given adverse outcome, which in turn depends on the prevalence of that outcome in the population. The distance between these two distributions can only be determined empirically.

From the above, it is derived that some conventional cut-off value based on the specificity distribution (e.g. the 3rd centile) has no intrinsic meaning for predicting the risk of adverse outcomes as obstetric complications, LBW, or others. The risk of adverse outcomes increases as distance from the median increases, but the particular point where the risk steps up requires knowledge of the sensitivity distribution and the prevalence of the outcome under study. Most of the empirical evidence of weight gain during pregnancy is not sufficient for constructing reference data based on risk or benefit.

In the case of individual screening, the ability of the standard to appropriately select individuals at risk largely depends on the prevalence and variability of the condition being screened.

When used for categorizing populations, a common reference allows comparison of the nutritional status of populations in different regions of the world.

There is a controversy about the utilization of universal references, even when it could be considered that physiological processes in healthy individuals (growth in the first years of life, gestation) evolve in the same way independently of geography or even ethnicity.

On the other hand, different standards have been proposed for diverse populations, considering variation in genetics, phenotypes or environmental exposures; for example, growth data according to parental size or pregnancy weight gain according to ethnicity, or mean birth weight according to maternal smoking habits.

However, when reference data are used to make decisions about populations, it is better to use statistical methods to control for differences within or across populations than to use different standards.

The relatively lower use of "growth" or nutritional status reference data in prenatal care as compared with pediatric care is noteworthy.

Worldwide, the references accepted and used for monitoring infants' and children's growth are basically normative; that is, they are derived from samples of a "healthy population". Taking the most stringent criteria – such as the WHO multicenter growth reference (de Onis et al. 2004) for children of 0–5 years of age – does not necessarily imply that the sensitivity and specificity of these indicators and their usual cut-offs for predicting several functional outcomes will be optimal. Nonetheless, their usefulness is beyond discussion.

Why, then, are similar criteria not considered sufficiently appropriate to develop references for GWG or other parameters of pregnant women nutritional status?

60.1.4 Relationship Between Reference Data and Functional Outcomes

There is no standard definition of what constitutes a "good pregnancy outcome". The IOM Committee defined a favorable pregnancy outcome as the delivery of a live-born infant with a birth weight

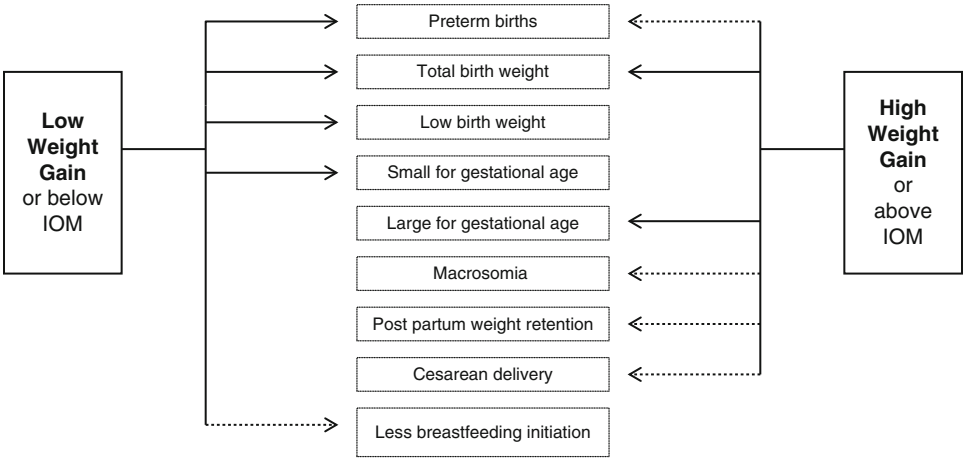

Fig. 60.2 Evidence-based association between GWG and several outcomes. This scheme represents the association between GWG and the most important newborn and maternal outcomes, based on observations from different studies. Strong evidence is shown with *solid arrows* and moderate evidence with *dotted arrows*. IOM = Institute of Medicine recommendations

between 3 and 4 kg at 39–41 weeks of gestation (IOM 1990). Carmichael et al. (1997) defined a good outcome as a vaginal, term delivery of a live infant of average size for gestational age (between the 10th and 90th percentiles of gestation-specific birth weight) from a mother without diabetes or hypertension.

Other outcomes would potentially be included, such as absence of medical complications during labor and delivery, or absence of postpartum weight retention or breast-feeding initiation.

Previous observational research has shown that weight gain monitoring is not highly sensitive when used in isolation to predict pregnancy problems. Because the amount of total weight gain is widely variable among women with good pregnancy outcomes, and as perinatal outcomes of interest are multifactorial in origin, no one should expect that weight gain alone is a perfect diagnostic or screening tool.

On the other hand, there are several consequences for the health of the mother and the child that are potentially causally related to GWG. It is important to consider their incidence, long-term sequelae and baseline risk (concept that can be summarized as the population attributable risk) in order to prioritize its inclusion in the development of a normative instrument or recommendation.

Recently, a systematic review of the literature on outcomes of GWG has been published (Viswanathan et al. 2008). It comprises studies published in English from 1990 through October 2007 and assesses the evidence about five key questions, among which the following are included:

1. Association between total weight gain (or rate of weight gain) during pregnancy and birth outcomes, infant health outcomes, and maternal health outcomes.
2. Evidence that weight gain above or below IOM (1990) recommendations on BMI or weight loss in pregnancy contribute to antepartum or postpartum complications or longer term maternal and fetal complications.
3. Harms or benefits of offering the same weight gain recommendations to all pregnant women, irrespective of age and body weight.

Figure 60.2 summarizes results for major outcomes. Other maternal and infant or children health outcomes had weak or nil evidence of association. The authors also concluded there is inadequate

evidence for the objective assessment of harms and benefits of providing all women (irrespective of age, ethnicity or prepregnancy BMI) with the same recommendations for weight gain in pregnancy.

The majority of studies found an effect of low GWG on preterm birth; high GWG was less consistently associated with this outcome. The association between low GWG and preterm birth was stronger for underweight women than for any other category of pregravid weight status.

Low GWG is significantly associated with lower birthweights across all pregravid weight status groups. High GWG resulting in higher birthweight appears to be limited to underweight and normal-weight women.

The evidence linking low GWG and LBW (<2,500 g) appears to be stronger among women who, before pregnancy, had underweight or normal weight than among women who had overweight or were obese. In general, risks for LBW began to decrease for GWGs above 11.3–13.6 kg.

Several studies evaluated the relationship between continuous total weight gain and birthweight using linear regression techniques, and reported that birthweight increased between 16.7 and 22.6 g for every 1 kg of increase in weight gain.

A large body of literature yielded strong evidence of an association between low GWG and the risk of having an SGA infant. This association is seen whether weight gain is examined in categories or in absolute terms and despite some inconsistencies regarding what variables were controlled for in the analysis.

The increased risk of delivering a large for gestational age (LGA) infant was consistently seen in women with higher absolute weight gains and in women with gains over the IOM 1990 recommendations. The body of evidence is large and strong for this association, despite differences in the definition of LGA and factors that were controlled for confounding.

On the other hand, the evidence suggests that a high gestational weight gain has no effect on macrosomia for underweight women.

The majority of studies suggested an association between high gestational weight gain and cesarean delivery. This association appeared to be stronger for overweight and obese women, and when weight gains were above IOM 1990 recommendations for underweight and normal-weight women.

Gestational weight gain was positively associated with weight retention within 1 year postpartum and with interpregnancy weight gains. In the long term, the effect of GWG on weight retention was less conclusive.

Additionally, weight retention differed across pregravid BMI strata: overweight and obese women retained more weight compared to normal weight women. Postpartum weight retention could be especially problematic for obese women, who may be at risk of increases in fat mass and central adiposity in the postpartum period.

Even when the review found few studies that collected or analyzed data in a manner that allowed compilation and synthesis, the authors concluded that:

Weight loss is not considered appropriate during pregnancy for any weight status.

The review found no evidence for other maternal outcomes such as hyperemesis, abnormal glucose metabolism, hypertensive disorders, gallstones and maternal discomforts of pregnancy.

The Committee of Weight Gain during Pregnancy: Re-examining the Guidelines (IOM 2009) has finally retained measures of birth size (SGA and LGA), preterm birth and childhood obesity as the most important infant health outcomes. In the case of mother health outcomes, only postpartum weight retention and unscheduled primary cesarean delivery were considered, after removing preeclampsia and gestational diabetes mellitus due to lack of sufficient evidence that GWG was a cause.

The Committee based its guidelines "on the presumption that the extensive, consistent observational data that link GWG to fetal growth, as measured by SGA and LGA, as well as those that link GWG to postpartum weight retention are *causal*."

Universality of a reference for clinical use precludes in some way its linkage with a particular outcome. Moreover, indicators and cut-off points for different outcomes in different population settings should be different.

Weight gain during pregnancy should continue to be monitored, given the ease of measuring and due to consistent findings in diverse populations that women who gain above or below the current recommended amounts have worse pregnancy outcomes.

There is enough evidence in the developed countries' literature that pregnancy weight gains within the limits of the IOM 1990 recommendations are related to better outcomes.

60.1.5 Most Used Instruments for Measuring Gestational Weight Gain

60.1.5.1 A Historical Perspective

Gestational weight gain (GWG) charts are useful instruments to monitor GWG in clinical practice. Table 60.1 summarizes some of these curves developed in different geographical areas of the world.

Many approaches have been used for making recommendations about GWG. From the extreme of the National Center for Clinical Excellence in the UK that women should not be weighted at all during pregnancy to avoid anxiety, to a single average weight gain target for all women irrespective of their previous nutritional status, such as the US recommendation in the first half of the twentieth century of ideally no more than 9.1 kg. At that time, a common practice was to restrict weight gain during pregnancy with the aim of preventing toxemia, difficult births and maternal obesity. This policy started to change during the 1970s when experts began to associate LBW with the relatively high rates of infant mortality, disability and mental retardation at that moment. A new target of 10.9 kg with a range of 9.1–11.3 kg was then proposed, based on the amount of obligatory weight gain to meet the physiologic needs of the product of conception, plus the expansion of plasma volume and fat stores during pregnancy (NRC 1970).

The first proposed instruments were developed based on the average GWG observed in samples of healthy pregnant women; many of them have the disadvantage of the small sample size or the theoretical approach in the design. Proposals from the beginning of the twenty-first century are mostly based on longitudinal studies, applying new statistical methods, and/or considering the prepregnancy BMI category for making different recommendations.

60.1.6 Charts Versus Recommendations for Total Weight Gain

Even when GWG charts have been used in clinical practice for many years, there is no standardization across instruments because of lack of appropriate primary data. Different kinds of references have been published, basically those that recommend ranges of weight gain and charts of attained weight or BMI for gestational age.

Table 60.1 Characteristics of main GWG charts and tables

Author and year	Country (*n*)	Study characteristics
Tompkins and Wiehl (1951)	Unites States (*n* = 60)	The mean total GWG in the sample was 10.9 kg, but no ranges, standard deviations or percentiles were reported. The curve developed has been used to generate different charts mostly in the USA
Hytten and Leitch (1971)	England (*n* = 2870)	Average weight gain of healthy, primiparous, normotensive British women with favorable pregnancy outcomes
Gueri et al. (1982)	Dominica (*n* = 340)	A reference table of weight-for-height by week of pregnancy was devised on theoretical grounds, based on the premises that the average weight increase during pregnancy is 20% of the prepregnancy weight and that almost all the increase takes place linearly during the 2nd and 3rd trimesters of pregnancy
Fescina (1983)	Uruguay (*n* = 43)	A chart was developed on the basis of longitudinal follow-up of pregnant women without pathologies. A second chart was proposed to evaluate GWG when prepregnancy weight is unknown
Rosso (1985) Mardones and Rosso (2005)	Chile (*n* = 1745)	The instrument diagnoses, from gestational week 10 onwards, mothers at risk of delivering babies with birth weight under 3,000 g and set weight gain goals for each individual mother based on her nutritional status. For underweight women, weight recommendation was derived from the obtained data, while for overweight and obese women it was based on data extrapolations. The chart has been used in many Latin American countries
WHO Collaborative Study (1995b)	25 population groups throughout the world (*n* = 111,000)	Height, weight, BMI and MUAC in early pregnancy, and weight and BMI attained at 20th, 28th, and 36th weeks were determined. Odds ratios for low birth weight (LBW), preterm delivery, SGA and other outcomes were calculated by each indicator. Weight gain charts for four different country groups were developed
Wong et al. (2000)	China (*n* = 504)	Target weight gains associated with reduced risk of adverse pregnancy outcomes for underweight, average and overweight women were developed
Mahaba et al. (2001)	Egypt (*n* = 830)	A prospective study was conducted to develop weight gain charts for healthy Egyptian pregnant women. The mean total weight gain was 9.3 kg. The velocity growth chart developed for weight gain showed that weight increase was about 1 kg up to the 4th gestational month, then, a steady increase of 0.37 kg/week was observed till the end of pregnancy
Ochsenbein-Kolble et al. (2007)	Switzerland (*n* = 4,034)	Fifth, 50th and 95th centiles of weight and BMI were presented for Caucasian, Asian, and black women. Mean total weight gain was 15.5 ± 5.9 kg
Casanueva et al. (2008)	Mexico (*n* = 438)	Four equations for maternal predicted weight across categories of pregestational BMI (underweight, normal, overweight and obese) and gestational ages were developed and synthesized in a table of reference values
Calvo et al. (2009)	Argentine (*n* = 1,439)	A prospective multi center cohort study was conducted to develop weight gain charts for healthy Argentinean pregnant women. Centile curves of body weight and BMI by gestational age were developed using the LMS method. Mean total weight gain was 11.9 ± 4.4 kg

This table summarizes the authors, year of publication, country, number (*n*) of subjects studied, and the main characteristics of some of the relevant publications which developed charts for evaluate GWG

The evolution of weight gain charts reflects changing recommendations over time and the greater understanding of the role of weight gain in managing pregnancy.

60.1.6.1 Weight Gain Recommendations

The IOM (1990) report recommended different weight gain targets according to prepregnancy BMI groups. The rationale was to achieve birth weights in the range of 3–4 kg for all prepregnant

Table 60.2 IOM recommendations for total gain and rate of weight gain during pregnancy, by prepregnancy BMI (IOM, USA 2009)

Prepregnancy BMI	Total weight gain (range in kg)	Rates of weight gain 2nd and 3rd trimester Mean (range) in kg/week
Underweight (<18.5 kg/m^2)	12.5–18	0.51 (0.44–0.58)
Normal weight (18.5–24.9 kg/m^2)	11.5–16	0.42 (0.35–0.50)
Overweight (25–29.9 kg/m^2)	7–11.5	0.28 (0.23–0.33)
Obese (≥30.0 kg/m^2)	5–9	0.22 (0.17–0.27)

The first column shows the usual classification of prepregnancy BMI; the range of total recommended weight gain for each category and the rate of gain in kilogram per week are shown in the second and third columns, respectively

BMI groups while avoiding LGA infants and other possible risks to the mother and newborn. These recommendations were the first to account for pregravid weight status and to encourage obese women to gain weight during pregnancy in recognition of the needs of the fetus. This report used BMI values of 19.8–26.0 as the definition of normal prepregnancy weight, which corresponds to 90% and 120% of the desirable weight-for-height of the 1959 Metropolitan Life Tables. Since the publication of the IOM report, many studies have intended to determine the optimal GWG that represents a reasonable trade-off between adequate fetal growth and maternal weight retention.

The prepublication copy of IOM (2009) Guidelines, after reviewing main publications during the preceding period, finally modified the previous recommendation by changing the values of prepregnant BMI categories and the recommended weight gain for obese women. BMI values for adults proposed by the World Health Organization (WHO 1995) have been substituted for prepregnant BMI categories.

The Committee formulated the new Guidelines with a range of recommended weight gain for each category of prepregnant BMI. Ranges reflect the imprecision of the estimates, and the reality that good pregnancy outcomes are achieved with different gains and are influenced by many other factors. Ranges were chosen on the basis of values associated with the lowest prevalence of adverse outcomes of greatest interest – cesarean delivery, postpartum weight retention, preterm birth, small or large for gestational age newborn – and according to the quality of available data.

The range of total weight gain was modified only for the obese group and set at 5–9 kg, with respect to the 7 kg of 1990 IOM recommendations. These new guidelines are shown in Table 60.2.

Average pregnancy weight gains in developing countries are much lower than those reported in industrialized countries. Figures in the literature are between 5 and 9 kg for the former ones, compared to 10–15 kg for the latter (Krasovec and Anderson 1991). The extent to which the USA or European standards of pregnancy weight gain are appropriate for undernourished women in developing countries needs to be assessed. These differences in weight gains parallel the differences in the incidence of LBW.

60.1.6.2 Distance and Velocity Curves

Distance is the current value of an anthropometric measurement, and velocity is the rate of change of that measurement.

Height, prepregnant weight, weight at any point during pregnancy, MUAC, and skinfold thickness are distance measurements. Most weight gain charts are actually distance curves, representing attained weight at a given point in pregnancy.

Velocity of weight gain has been described in Tables or Charts in different time intervals: by week, by month or by trimester. It should be adjusted for gestational age, since it is not linear throughout pregnancy.

An alternative to those is a conditional standard, usually regression-adjusted, like the one proposed by Rosso, which takes into consideration the expected weight gain at the end of pregnancy as a function of prepregnant weight.

The chart published by Rosso (1985) and Mardones and Rosso (2005) is based on a single target of weight gain but is expressed in a relative value of standard weight-for-height, from 95% of the standard at the beginning of pregnancy to 120% of the standard at term. This represents different patterns of recommended weight gain for underweight, normal weight and overweight women. The instrument was based on empirical data and intended to increase average birth weight among underweight women. Rosso's chart, like that of Gueri et al. (1982), suggests that underweight women should gain all their weight deficit up to the prepregnancy reference weight as well as the additional weight due to pregnancy needs.

Anderson, in Krasovec and Anderson (1991), pointed out that a 110% increase in weight-for-height could be a more realistic target for developing countries' women, based on her findings in India.

60.1.6.3 Advantages and Disadvantages of Charts

The WHO (1995) recommends that GWG charts should be based on longitudinal studies in selected populations with low prevalences of maternal and fetal complications, with anthropometric measurements being performed before and during the course of pregnancy. Ideally, upper and lower limits around the average curves should be set.

Most recommendations, including those from the IOM, are based on cross-sectional studies and this precludes the analysis of the shape of weight gain curves.

It is sensible to study changes during pregnancy in longitudinal designs in order to develop reference patterns to be used in clinical practice. We have identified only a few cohort studies of prospective nature with an adequate sample size in the literature: Mahaba et al. (2001) in Egypt, Mardones and Rosso (2005) in Chile, Casanueva et al. (2008) in Mexico, and Calvo et al. (2009) in Argentina.

Expressing weight gain in absolute values does not consider proportionality of suggested weight gain for short and tall women. The use of BMI is a practical way to solve this problem, taking into account a woman's height during the whole course of pregnancy, along with keeping to the current recommendations of expressing body size in adults in terms of BMI. Moreover, BMI is not based on the concept of "ideal".

Other aspect to be considered is the reliability of the recalled prepregnancy weight (Brown et al. 2002), which is essential for the calculation of weight gain. When using charts, even if women initiate prenatal care late in pregnancy, their current weight or BMI can be plotted in the appropriate risk area for their gestational age in the chart.

In turn, most charts require accurate estimations of gestational age for proper interpretation of adequacy of achieved weight or BMI. This can be difficult in certain environments.

In the design of weight gain charts, it is necessary to be clear about the outcomes they are intended to predict or prevent: infant outcomes, pregnancy complications, or maternal stores postpartum. Charts need to be interpreted accordingly, and one chart could serve various purposes.

To a certain degree, the curve of average gain in the normative population provides guidance to the health team. However, it is advisable to validate upper and lower limits of the instruments as empirically derived cut-off values to discriminate at least one favorable outcome. Most references (Rosso 1985; Calvo et al. 2009) use birth weight as the outcome.

60.1.6.4 Weight Gain Patterns

Several studies reported on the effects of GWG, by trimester, on infant birthweights. They were consistent in demonstrating that weight gain in the third trimester had the least effect.

One US study (Brown et al. 2002) reported that weight gain during the first trimester was associated with a 31 g increase in birthweight per kilogram of GWG. Comparable gains in infant birthweight for each kilogram of GWG in the second and third trimesters were 26 and 7 g. This study also found that infant birthweight decreased by 211 g among mothers who lost weight during the first trimester.

A Canadian study (Muscati et al. 1996) found similar results: for each 1 kg increase in weight gain up to week 20, birthweight increased by 22 g; increases from week 21 to 30 increased birthweight by 31 g; and weight gain from week 31 to term increased birthweight by 12 g.

Lastly, another US study (Abrams and Selvin 1995) reported an 18 g increase in birthweight for each kilogram gained by the mother in the first trimester. Corresponding increases in the second and third trimesters were 32.8 and 17.0 g, respectively.

Our own study (Calvo et al. 2009) showed differential patterns of weight velocity by trimester in women who gave birth to infants of less than 3 kg and infants of 3 kg or more, particularly between weeks 20 and 24 (0.45 vs. 0.52 kg/week).

60.1.7 Special Pregnancies

60.1.7.1 Multiple Pregnancies

In multiple pregnancies, average weight gain is higher than in singleton pregnancies and it is also positively related to birth weight.

Over the last years, a number of studies have evaluated total weight gain, the rate of weight gain, and their relationship with fetal outcomes in twin pregnancies. One of the most relevant comes from the historical cohort of twin births based on 2,324 pregnancies with non-anomalous, liveborn twins (4,684 infants) from Ann Arbor, Charleston, Baltimore and Miami in the USA (Luke et al. 2003). Data from this cohort have been taken into account by the IOM to set up the cumulative gains and rates of weight gain stratified by maternal prepregnancy BMI (Table 60.3). In mothers with normal prepregnancy BMI, average total weight gain was around 20 kg, with a rate of 0.3 kg/week in the first trimester and around 0.7 kg/week in the second and third trimesters. As in singleton pregnancies, there is an inverse relationship between GWG and pregravid BMI.

In twin pregnancies, maternal weight gain during critical periods of gestation significantly influences twin birth weight, and these critical periods vary by maternal pregravid weight status; birth weight is significantly associated with weight gain before 20 weeks in underweight women, after 28 weeks in overweight women, and during the whole pregnancy in normal-weight women.

According to the IOM (2009), mean GWG for triplet pregnancies varied from 20.5 to 23.5 kg at 32–34 weeks and from 20.8 to 31.0 kg at 32 weeks of gestation for quadruplets.

Table 60.3 Cumulative weight gain and rates of weight gain by prepregnancy BMI status of mothers of twins with average birth weight > 2,500 g (Modified from IOM, USA 2009)

	Prepregnancy BMI		
Weight gain by gestational age	Normal weight (18.5–24.9 kg/m^2)	Overweight (25.0–29.9 kg/m^2)	Obese (≥30.0 kg/m^2)
Up to 13 weeks			
Cumulative weight gain (kg)	3.6 ± 0.3	2.1 ± 0.4	2.0 ± 0.5
Rate of weight gain (kg/week)	0.33 ± 0.02	0.20 ± 0.04	0.18 ± 0.04
Up to 26 weeks			
Cumulative weight gain (kg)	13.1 ± 0.3	11.3 ± 0.4	8.5 ± 0.4
Rate of weight gain (kg/week)	0.77 ± 0.02	0.72 ± 0.03	0.45 ± 0.03
27 weeks to delivery			
Cumulative weight gain (kg)	20.9 ± 0.3	18.9 ± 0.5	15.7 ± 0.5
Rate of weight gain (kg/week)	0.67 ± 0.01	0.61 ± 0.02	0.58 ± 0.03

In this table the figures (mean ± standard error of the mean) refer to the estimated weight gain of mothers of twins with adequate birth weights in different trimesters and according to their prepregnancy BMI. First row refers to total accumulated weight gain, and second row shows the rate of weight gain per week

60.1.8 Adolescent Pregnancy

Pregnant adolescents are at particular risk of both inadequate and excessive GWGs. In addition, there is evidence that adolescents, especially young adolescents (≤16 years old), are more likely to deliver LBW infants and have an increased risk of neonatal and postnatal mortality.

No special charts or patterns have been proposed to monitor pregnancy weight gain in adolescents. According to the 1990 IOM recommendations, young adolescents should gain weight at the upper end of the recommendations, while older adolescents (>16–19 years old) should gain weight similarly to adult women. Nevertheless, there is concern regarding the application of adult criteria to categorize pregnant adolescents into prepregnancy BMI categories and subsequent GWG recommendations.

The misclassification of adolescent prepregnancy BMI could lead to inadequate guidance (Groth 2007).

A recent study (Fernandez et al. 2008) has pointed out that, according to the Center for Disease Control BMI cut-offs points, adolescents with healthy weight and those at risk of overweight are at higher risk of misclassification, and they could be recommended to gain too much weight because they would be assigned the GWG ranges corresponding to the low and average IOM categories, respectively.

In adolescents, an unnecessary higher weight gain during the course of pregnancy can be associated with higher postpartum weight retention and could contribute to higher levels of obesity, with minimal improvement of infant birth weight. For these reasons, the last IOM (2009) document states that young adolescents should be advised to stay within the recommended BMI-specific weight gain range, without either restricting weight or encouraging weight gain at the upper end of the range.

60.1.9 Suggestions for Selecting an Anthropometric Reference in Prenatal Care

Monitoring weight gain has been the most common means of assessing the nutritional status of women and their infants during pregnancy. Maternal weight is sensitive to acute nutritional stresses during pregnancy, and it provides the most general impression of fetal growth as compared to other

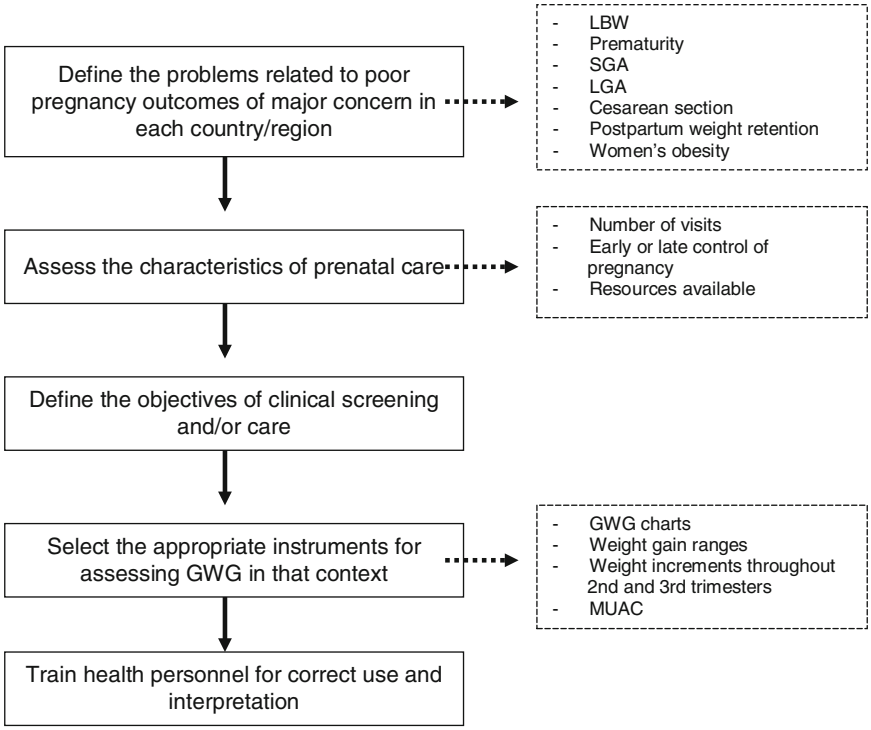

Fig. 60.3 Scheme for selecting the appropriate instruments and processes to evaluate pregnant women nutritional status, according to epidemiology and health care conditions. This figure is thought to guide policy makers and public health agents to select the instruments for maternal nutrition evaluation appropriate for the context

anthropometric measures. Another advantage of weight monitoring for risk assessment is that weight changes are gross enough to detect significant increments during pregnancy.

Figure 60.3 shows a scheme suggested to choose the appropriate instruments and processes to evaluate women's nutritional status during pregnancy, according to the epidemiological and health care conditions for.

Due to the fact that pregnancy is the only common clinical situation where the health provider has at least two patients, the mother and the fetus(es), balancing the amount of weight gain needed to optimize the size of the baby without jeopardizing the health of the mother both in the short and long term is essential. The balance has proven challenging.

While developed countries are concerned about body weight increases in women of childbearing ages combined with a rising trend in weight gain during pregnancy outside the IOM recommendations, in many developing countries prevalence of LBW remains unacceptably high.

Many of the current weight gain charts assume that women initiate prenatal care early in the first trimester and have prenatal visits once a month during pregnancy. The feasibility of this approach is low in developing countries, and it is also matter of debate if such frequency is necessary.

Monitoring weight gain during pregnancy can be difficult in a primary health care setting considering equipment, personnel training, and the need of multiple visits among other obstacles. However, many of these difficulties have been overcome in child growth monitoring, and lessons can be learned from these successful programs.

Define the objectives of care:

- *Adequate resources; mothers seen periodically from early pregnancy*: In countries where more than 60% of women receive regular prenatal care, and equipment as well as trained staff are available,

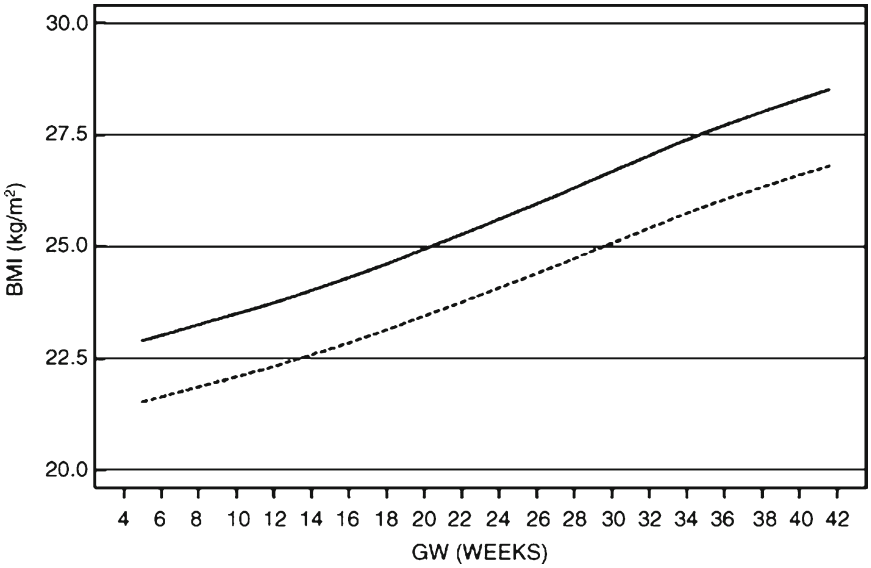

Fig. 60.4 BMI 50th centile curves in European pregnant women. Body mass index (BMI) of European pregnant women along pregnancy. Caucasians and Blacks (*continuous line*) and Asians (*dashed line*). (Reprinted from Ochsenbein-Kölble et al. 2007, Copyright (2007), with permission from Elsevier)

serial weighing during pregnancy should be undertaken (Krasovec and Anderson 1991). Use of charts for individual follow-up is advisable.

- *Adequate resources; at least two measurements from mid-pregnancy*: Assessment of weight increments in the second or third trimester of pregnancy is a simplified means to monitor weight gain. A minimum amount of 1 kg/month throughout the 2nd and 3rd trimesters has been recommended. Taking only two measurements 1 month apart is far more feasible in disadvantaged regions.

  Lack of weight gain or weight loss between two consecutive measurements is very detrimental to the fetus and requires immediate action.

- *Low resources setting*: Where weight gain monitoring is not feasible at all due to limitations in facilities, staff and/or coverage of prenatal care, screening with measurements that require only one contact should still be recommended. Arm circumference or prepregnant weight could be used.

  MUAC can be used as a first screen in order to refer women to facilities for a more complete assessment of nutritional risk.

60.1.10 Select the Instruments

Charts have been developed for screening individuals who may be at risk based on one or more measurements, either for individual treatment or for targeting interventions to groups, and also for monitoring the progress of women between serial visits during pregnancy and for pregnancy management.

Even if women initiate care late in pregnancy, their weight-for-height or BMI can be plotted in the appropriate risk area for their gestational age in a chart. Nevertheless, gestational age must be known.

In Figs. 60.4–60.6 several examples of recently published Charts from different countries are provided.

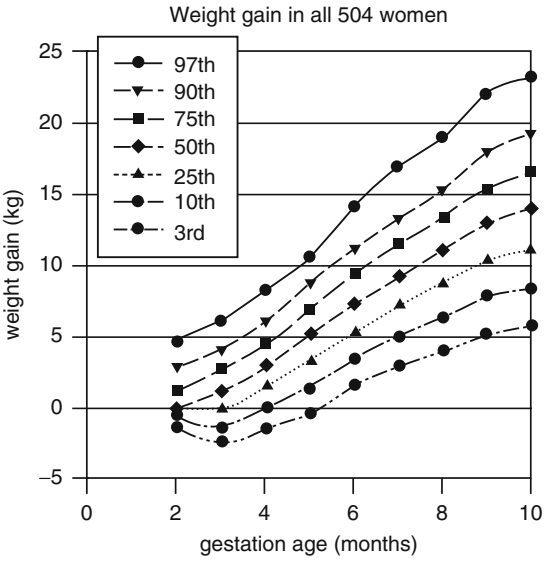

Fig. 60.5 Distribution of weight gain during pregnancy in Chinese women. Percentiles of weight gain during pregnancy in Chinese women with good outcomes. (Reprinted from Wong et al. 2000, Copyright (2000), with permission from Elsevier)

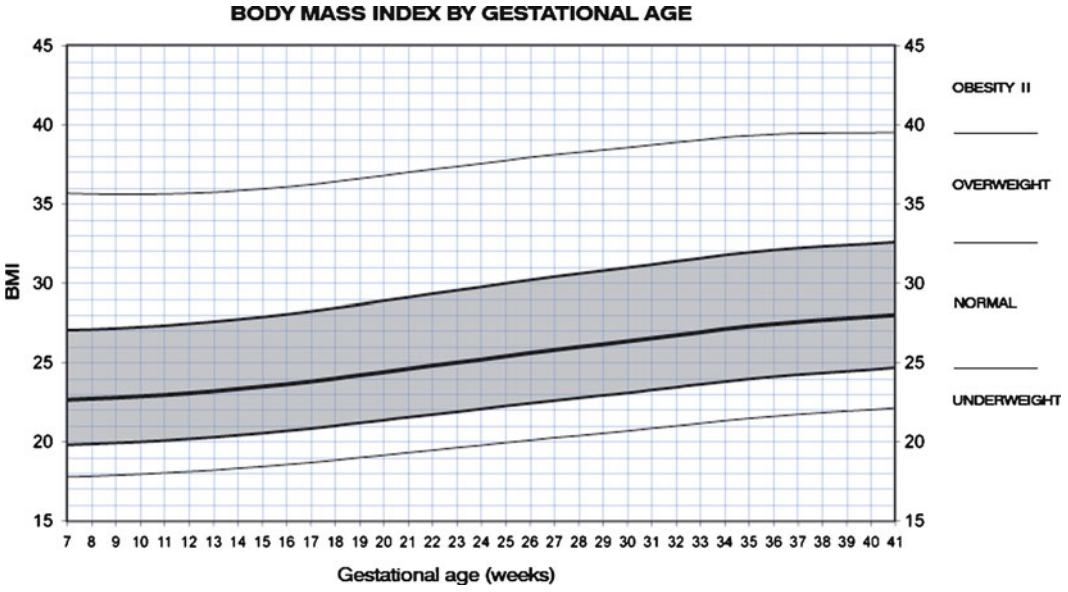

Fig. 60.6 BMI curves by gestational age in Argentine pregnant women with normal weight newborns. The *shadow area* represents the recommended BMI at different gestational ages for women who gave birth to normal weight infants

Anthropometric indicators identify women with nutritional problems, but do not reveal the underlying cause or determinant of the problem, or the best interventions to solve it.

Any guidelines should be used in concert with good clinical judgment as well as discussion between the woman and her prenatal care provider, who should consider other relevant clinical evidence

in addition to the adequacy and consistency of fetal growth, and any available information on the nature of the excess (e.g. fat or edema) or inadequate weight before suggesting that the woman modify her pattern of weight gain.

It is useful to screen reproductive age women either for low or high BMI in order to intervene prior to pregnancy, since prepregnancy weight is highly critical to pregnancy outcome and maternal global health.

The high pregnancy weight gains necessary to ensure favorable pregnancy outcomes for women of low prepregnancy weight may be unrealistic for many women in developing countries. Therefore, equal emphasis should be placed on improving prepregnancy weights.

On the other hand, interventions aimed at treating obesity (modifying dietary habits and physical activity) should be undertaken before pregnancy.

Interventions for undernourished mothers should not be limited to the 9 months of pregnancy or even to the fewer months of acknowledged pregnancy. Supplementation programs can have a greater impact on birth weight in the second pregnancy if intervention is maintained.

Summary Points

Background

- Maternal nutritional status, both prior to and during pregnancy, is a critical determinant of pregnancy outcomes for both the mother and her infant. This is true in industrialized and developing country settings.
- Strong evidence supports the association between GWG and preterm birth, total birthweight, LBW, large and small for gestational age infants, and macrosomia. Moderate evidence relates GWG to cesarean delivery and intermediate-term postpartum weight retention.

Antropometric Indicators

- Maternal height is one of the biologically acceptable predictors of birth weight, along with other indicators. For screening purposes, the range of cut-off points for predicting either LBW or cephalopelvic disproportion is likely to fall between 140 and 150 cm.
- Low prepregnancy BMI has been identified as a risk factor for having an infant of LBW or small for gestational age.
- High prepregnancy BMI is linked to fetal death, macrosomia, preeclampsia, gestational diabetes and complicated deliveries.
- Prepregnancy weight should be interpreted in relation to height to be useful for cross-population comparisons.
- The relationship between prepregnancy weight and pregnancy outcomes is mediated by the amount of weight a woman gains during pregnancy.
- In cases where prepregnancy weight is unknown and total weight gain by gestational age is difficult to determine, MUAC becomes an alternative tool for anthropometric screening.

Reference Charts

- Most reference charts currently available are based on the distribution of weight gains during pregnancy in apparently healthy populations with favorable pregnancy outcomes. Their conventional cut-off values have no intrinsic meaning for predicting the risk of adverse outcomes.
- Weight gain charts' evolution in the last few decades reflects changes in recommendations and a better understanding of the role of weight gain in pregnancy management.

Special Pregnancies

- In twin pregnancies of mothers with normal prepregnancy BMI, average total weight gain is around 20 kg. Mean gestational weight gain (GWG) at the end of pregnancy varies from 20.5 to 23.5 kg for triplet pregnancies and from 20.8 to 31.0 kg for quadruplets.
- No special charts or patterns have been proposed to monitor pregnancy weight gain in adolescents.
- In pregnant adolescents, excessive weight gain can be linked to postpartum weight retention and obesity; thus, they should be advised to gain weight at the same pattern as adult women, without either restricting weight or encouraging weight gain at the upper end of the range.

Prenatal Care

- Anthropometric indicators identify women with nutritional problems, but do not reveal the underlying cause or determinant of the problem, or the best interventions to solve it.
- Monitoring weight gain during pregnancy can be difficult in a primary health care setting considering equipment, personnel training, and the need of multiple visits among other obstacles. However, many of these difficulties have been overcome in child growth monitoring, and lessons can be learned from these successful programs.

Key Features

The criteria commonly used to classify fetal growth are:

Small for gestational age (SGA): birth weight less than the 10th centile for gestational age.
Adequate for gestational age (AGA): birth weight between the 10th and 90th centiles for gestational age.
Large for gestational age (LGA): birth weight greater than the 90th centile for gestational age.
Premature delivery: before 37 weeks of gestation.
Low birth weight: birth weight below 2,500 g. A small infant size at birth is a function of both poor growth and shortened gestation, with most adverse outcomes occurring in the most immature infants.
Macrosomia: is defined as a birth weight higher than 4,000 g.
Cephalopelvic proportion: measurement of fetal head size in relation to maternal pelvic capacity.

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Chapter 61
Prenatal Famine Exposure and Long-Term Consequences for Anthropometry and Adult Health

Tessa Roseboom, Rebecca Painter, and Susanne de Rooij

Abstract This paper describes the findings from a cohort study of 2,414 people born around the time of the Dutch famine. We found more coronary heart disease, a more atherogenic lipid profile, disturbed blood coagulation, and increased stress responsiveness among those exposed to famine in early gestation. Women exposed to famine in early gestation were more obese and had an increased risk of breast cancer. People exposed to famine in mid gestation had more microalbuminuria and obstructive airway disease. Exposure to famine during any stage of gestation was associated with glucose intolerance. Also, women who had been exposed to famine prenatally were more reproductively successful: they started reproducing at an earlier age, had more children, more twins, and were less likely to remain childless. The effects of prenatal famine exposure did not appear to be restricted to those exposed to it prenatally: also, their children appeared to be less healthy.

These findings show that maternal undernutrition during gestation has important effects on health in later life, but that the effects on health depend on its timing during gestation. Early gestation seems to be an especially vulnerable period. Adequate dietary advice to women before and during pregnancy seems a promising strategy in preventing chronic diseases in future generations.

61.1 Introduction

Coronary heart disease remains a major burden on public health in the Western world, and is taking on epidemic proportions in developing countries (Murray and Lopez 1997). Small babies go on to develop more coronary heart disease in adult life (Barker 1995). Restricted intrauterine growth has been identified as an important contributor to later coronary heart disease and its biological risk factors. Developing organ systems adapt in response to the reduced availability of nutrients, particularly during periods of rapid development – so-called critical periods (Hoet and Hanson 1999). These adaptations, while advantageous for short-term survival, can be detrimental for health in later life. Animal experiments indicate that substantial changes in cardiovascular function can result from maternal or fetal undernutrition without necessarily affecting birth weight (Harding 2001). In this chapter, we describe the effects of restricted prenatal nutrition during

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_61,

different periods of gestation on health in later life. In the past 15 years, we have studied the health of people born around the time of the Dutch famine of 1944–1945, this has provided us more insight into fetal origins of adult disease.

61.1.1 Dutch Famine as an Experimental Study Design

While famine is sadly not uncommon in many parts of the world, studying the effects of undernutrition during specific periods of pregnancy is hampered by the fact that undernutrition is usually not restricted to pregnancy alone, and effects of chronic undernutrition and accompanying problems of infection complicate the situation. What is unusual about the Dutch famine is first, that the famine was imposed on a previously well-nourished population; second, that there was a sudden onset and relief from the famine; and third, that despite the adversities of the war, midwives and doctors continued to offer professional obstetric care and kept detailed records of the course of pregnancy, the delivery, and the size and health of the baby at birth. Furthermore, detailed information is available on the weekly rations for the people in Amsterdam, and because birth records were kept we were able to trace those born around the time of the famine allowing us to study the long-term effects of famine. All these characteristics bring about that the Dutch famine is a unique counterpart for animal models that study the effects of restricted maternal nutrition during different stages of gestation.

61.1.2 The Dutch Famine

After weeks of heavy fighting following the invasion on the 6th of June 1944, the Allied forces finally broke through German lines. With lightning speed, the Allied troops took possession of much of France, Luxembourg, and Belgium. By the 4th of September 1944, the Allies had the strategic city of Antwerp in their hands, and on the 14th they entered the Netherlands. Everyone in the Netherlands expected that the German occupation would soon be over. The advance went so quickly that the commanders of the Allied forces too thought it would be only a matter of days before the Germans would surrender. But the advance of the Allies to the north of the Netherlands came to a halt when attempts to get control of the bridge across the river Rhine at Arnhem (operation 'Market Garden') failed.

In order to support the Allied offensive, the Dutch government in exile had called for a strike of the Dutch railways. As a reprisal, the Germans banned all food transports. This embargo on food transports was lifted in early November 1944, when food transport across water was permitted again. By then, it had become impossible to bring in food from the rural east to the urban west of the Netherlands because most canals and waterways were frozen due to the extremely severe winter of 1944–1945, which had started unusually early. Consequently, food stocks in the urban west of the Netherlands ran out rapidly.

As a result, the official daily rations for the general adult population – which had decreased gradually from about 1,800 calories in December 1943 to 1,400 calories in October 1944 – fell abruptly to below 1,000 calories in late November 1944. At the height of the famine from December 1944 to April 1945, the official daily rations varied between 400 and 800 calories. Children younger than 1 year were relatively protected, because their official daily rations never fell below 1,000 calories, and the specific nutrient components were always above the standards used by the Oxford Nutritional Survey (Burger et al. 1948). Pregnant and lactating women were entitled to an extra amount of food, but at the peak of the famine these extra supplies could not be provided anymore.

In addition to the official rations, food came from church organisations, central kitchens, the black market, and foraging trips to the countryside. After the liberation of the Netherlands in early May 1945, the food situation improved swiftly. In June 1945, the rations had risen to more than 2,000 calories (Burger et al. 1948).

There was a serious shortage of fuel during the war which caused a gradual decrease and finally a complete shutting down of the production of gas and electricity, and in several places even the water supply had to be cut off, while the authorities were unable to provide fuel for stoves and furnaces in homes. Throughout the winter of 1944–1945, the population had to live without light, without gas, without heat, laundries ceased operating, soap for personal use was unobtainable, and adequate clothing and shoes were lacking in most families. In hospitals, there was serious overcrowding as well as lack of medicines. Above all, hunger dominated all misery.

The famine had a profound effect on the general health of the population. In Amsterdam, the mortality rate in 1945 had more than doubled compared to 1939, and it is very likely that most of this increase in mortality was attributable to malnutrition (Banning 1946). But, even during this disastrous famine women conceived and gave birth to babies, and it is in these babies that the effects of maternal malnutrition during different periods of gestation on health in adult life can be studied. Because of its unique experimental characteristics, it is not surprising that people born around the time of the Dutch famine have been studied by many investigators.

61.1.3 Dutch Famine Studies

The period of starvation ceased early in May 1945 immediately after the final surrender of the Germans. In addition to the immediate provision of food after the war, medical aid was a top priority for the Netherlands. Doctors from the UK and US were sent to survey medical needs. Clement Smith from Harvard Medical School was among the first to witness the effects of the famine on the health of the Dutch population. He immediately saw the opportunity to obtain information that would help resolve important questions on how poor maternal nutrition affects pregnancy and the development of the fetus before birth. Using obstetric records from Rotterdam and The Hague, he studied effects of prenatal exposure to famine on pregnancy and the fetus (Smith 1947). He found that babies born during the famine (and thus exposed to famine in late gestation) were about 200 g lighter at birth. Later studies focussed on mental performance, following the increasing awareness in the late 1960s that early nutritional deprivation might cause irreversible damage to the brain (Stein et al. 1972). This study among military conscripts did not demonstrate any effect of starvation during pregnancy on the adult mental performance. However, men exposed to famine in early gestation were more likely to be obese, whereas those exposed in late gestation were less likely to be obese (Ravelli et al. 1972). More recently, it has been shown that people conceived during the famine and thus exposed in early gestation had a 2-fold increase in risk of schizophrenia (Hoek et al. 1996) and anti-social personality disorder (Neugebauer et al. 1999). In men, the risk of congenital neural defects was also increased (Stein et al. 1972) which suggests that permanent changes in the central nervous system might be involved. Lumey (1992) studied intergenerational effects of exposure to the Dutch famine and found that women who had spent the first six months of their own fetal life during the famine had slightly smaller babies than women who had not been exposed to famine *in utero*. Later results, however, were inconsistent with these findings and showed that first born babies of women who – as a fetus – had been exposed to the famine in early gestation were somewhat heavier at birth (Lumey et al. 1995).

61.1.4 Methods and Techniques

61.1.4.1 The Dutch Famine Birth Cohort Study

We traced a group of 2,414 term singletons born alive between November 1943 and February 1947 in the Wilhelmina Gasthuis in Amsterdam for whom we had detailed birth records. At ages 50 and 58, we invited the cohort to come to the clinic for detailed investigations. We defined exposure according to the daily official food rations for the general population older than 21 years in Amsterdam. A person was considered to be exposed if the average daily ration during any 13-week period of gestation was below 1,000 calories. The rations for babies never fell below 1,000 calories a day, therefore people born before the famine (as well as those conceived after it) are considered as unexposed.

A person was considered to be prenatally exposed to famine if the average daily ration for adults during any 13-week period of gestation was less than 1,000 calories. Using this definition, all born between January 7th, 1945 and December 8th, 1945 were considered to be exposed *in utero*. All cohort members born between November 1st, 1943 and January 6th, 1945 (born before the famine), and between December 9th, 1945 and February 28th, 1947 (conceived after the famine) were thus unexposed to famine *in utero* and served as the control group. We defined periods of 16 weeks each to differentiate between those who were exposed to famine in late gestation (born between January 7th and April 28th, 1945), mid gestation (born between April 29th and August 18th, 1945) and in early gestation (born between August 19th and December 8th, 1945) (Fig. 5 and Table. 61.1).

61.1.4.2 Results: Long-Term Consequences of Prenatal Exposure to the Dutch Famine

We found that exposure to the Dutch famine in early gestation increased body weight, body mass index, and waist circumference in women but not in men aged 50 years (Table. 61.2a). A poor maternal diet in early gestation which was followed by adequate nutrition during the remaining course of gestation was linked to an increased level of obesity in middle aged women. Exposure to famine in early gestation affected the level of obesity and the distribution of fat differently for men and women. The body mass index and the waist circumference at age 50 were increased in women but not in men (Table. 61.2b). These findings suggest that these women store fat intra-abdominally, because it has been shown that the waist circumference represents intra-abdominal fat mass at least as accurately as the waist-to-hip ratio. Our findings imply that permanent adaptations of central regulatory mechanisms occurred as a result of changes in the mother's body brought about by poor nutrition in early pregnancy followed by rapid improvement later in pregnancy. These adaptations did not restrict linear growth but seemed to have resulted in a disturbed central regulation of the accumulation of body fat in later life.

The Dutch famine study provided the first direct evidence in humans that undernutrition during gestation increases the risk of many diseases that plague our society, such as heart disease, diabetes, airways disease, obesity, renal disease, and cancer (Table. 61.3). The effect size is striking: compared to controls, men and women conceived during the Dutch famine have twice as much cardiovascular disease, and women exposed to famine during gestation even had a 5-fold increase in breast-cancer risk.

The effects of famine appeared to depend on its timing during gestation, and the organs and tissues undergoing critical periods of development at that time. Early gestation appeared to be the most vulnerable period. People who were conceived during the famine – and who had been exposed to famine in early gestation – had a more atherogenic plasma lipid profile (Roseboom et al. 2000a),

Table 61.1 Maternal and infant characteristics according to timing of prenatal exposure to the Dutch famine

	Exposure to famine						
	Born before	Late gestation	Mid gestation	Early gestation	Conceived after	All (SD)	*n*
Number	764	307	297	217	829	2,414	
Proportion of men	53%	49%	49%	50%	53%	52%	2,414
Maternal characteristics							
Age (years)	29	30	28	28	28	28 (6.4)	2,414
Primiparous	40%	30%	37%	39%	39%	38%	2,414
Not married	13.2%	9.8%	20.2%	25.8%	16.3%	15.8%	2,414
Weight at last antenatal visit (kg)	66.7	61.8*	63.5*	67.9	69.1	66.6 (8.7)	2,133
Weight gain 3rd trimester (kg)	3.2	0.0*	4.9*	5.7*	4.3	3.5 (3.2)	1,682
Infant characteristics							
Birth weight (g)	3,373	3,133*	3,217*	3,470*	3,413	3,346 (477)	2,414
Birth length (cm)	50.5	49.4*	49.8*	50.9*	50.5	50.3 (2.2)	2,382
Head circumference (cm)	32.9	32.3*	32.1*	32.8	33.2	32.8 (1.6)	2,397
Ponderal index (kg/m^3)	26.1	25.8*	26.0*	26.2	26.5	26.2 (2.4)	2,382
Placental area (cm^2)	370	339*	346	340*	350	353 (83)	2,056
Gestational age (days)	285	283*	285	287	286	285 (12)	2,044

Mean and standard deviation. * p corrected for gender <0.05 compared to unexposed (born before and conceived after the famine)

Table 61.2a Adult characteristics and body size according to timing of prenatal exposure to the Dutch famine

	Exposure to famine						
	Born before	Late gestation	Mid gestation	Early gestation	Conceived after	All (SD)	*n*
Adult characteristics at age 50							
Weight (kg)	79.0	79.0	76.8	84.2	80.6	79.7 (15.5)	741
Height (cm)	171.0	170.9	168.6	171.0	170.9	170.6 (8.9)	741
Head circumference (cm)	56.9	57.0	56.6	56.8	57.0	56.9 (2.1)	741
BMI (kg/m^2)	26.7	26.7	26.6	28.1	27.2	27.0 (1.2)	741
BMI ≥ 25	65%	63%	64%	75%	67%	66%	741
Waist circumference	91.8	92.4	91.0	95.6	92.5	92.3 (13.0)	741
Waist/hip ratio	87.2	88.0	86.5	88.4	87.5	87.4 (8.8)	741

Mean and standard deviation. geometric mean

Table 61.2b Difference in adult BMI (95% CI) according to timing of prenatal exposure to famine compared to unexposed participants (those born before and those conceived after the famine pooled together)

	Exposure to famine		
	Late gestation	Mid gestation	Early gestation
Men	0.4% (–3.5% to 4.5%)	–1.2% (–5.5% to 3.3%)	0.5% (–4.6% to 6.0%)
Women	–2.1% (–7.0% to 3.1%)	–1.3% (–6.3% to 3.9%)	7.4% (0.7–14.5%)

Mean and standard deviation. geometric mean

altered blood coagulation (Roseboom et al. 2000b), unhealthy lifestyle choices (Lussana et al. 2008), were more responsive to stress in terms of blood pressure (Painter et al. 2006a) and had a doubled risk of coronary heart disease (Roseboom et al. 2000c), Painter et al. 2006b). Women in this group also tended to have the highest body mass index (Ravelli et al. 1999), and had an increased risk of

Table 61.3 Adult characteristics (at the age of 58) according to timing of prenatal exposure to the Dutch famine

	Exposure to famine						
	Born before	Late gestation	Mid gestation	Early gestation	Conceived after	All (SD)	*n*
Adult characteristics							
Proportion of men	48%	43%	39%	43%	51%	46%	783
Plasma glucose 120 min* (mmol/l)	5.8	6.2	6.2	6.2	5.9	6.0 (1.4)	678
Plasma insulin 120 min* (pmol/l)	242	263	254	269	240	249 (2.1)	672
Type 2 diabetes	15.1%	14.2%	13.8%	18.9%	12.6%	14.4%	783
LDL/HDL cholesterol*	2.3	2.5	2.3	2.6*	2.4	2.4 (1.4)	783
Sports	55%	61%	58%	61%	51%	56%	781
BMI (kg/m^2)	28.0	28.0	27.8	27.5	28.7	28.1 (1.2)	783
Coronary heart disease	6.3%	5.7%	3.9%	8.2%	6.9%	6.2%	783
Breast cancer (%)	2.8%	3.7%	3.9%	8.7%	0.8%	3.2%	475

Mean and standard deviation. *geometric mean

breast cancer (Painter et al. 2006c). It is of interest to note that people exposed to famine in early gestation were not small at birth, but did have the most health problems in later life. Although many of these diseases (such as coronary heart disease) were linked to small size at birth, the effects of famine were independent of this. Based on the size of these babies at birth, one would not have predicted these health effects.

We found that undernutrition during any period of gestation was associated with reduced glucose tolerance and raised insulin concentrations at ages 50 and 58. Importantly, this effect was larger than could be explained by the lower birth weights of babies born during the famine and by the low weight gain of their mothers (Ravelli et al. 1998, de Rooij et al. 2006). Also, exposure to famine in mid gestation was linked to a 3.2-fold increase in occurrence of microalbuminuria in adulthood and a 10% increase in creatinine clearance, neither of which can be explained by cardiovascular confounders (Painter et al. 2005). We propose that mid gestational exposure to famine – the period of rapid increase in nephron number – may prevent formation of sufficient glomeruli and thus increase the risk for microalbuminuria and possibly affect renal function in adulthood. This supports the concept that intrauterine conditions during distinct, organ-specific periods of sensitivity may permanently determine health outcome in later life. Another finding in our study also supports this concept: we found that people who had been exposed to famine in mid gestation had an increased prevalence of obstructive airway disease (Lopuhaa et al. 2000). These observations were not paralleled by reduced lung function or increased serum concentrations of IgE. This suggests that the increased prevalence of symptoms and disease may be attributable to increased bronchial reactivity rather than to irreversible airflow obstruction or atopic disease. Because the bronchial tree grows most rapidly in mid gestation, our findings support the hypothesis that fetal undernutrition permanently affects the structure and physiology of the airways during 'critical periods' of development that coincide with periods of rapid growth.

Women – but not men – who were exposed to the Dutch famine of 1944–1945 *in utero* were more reproductively successful than women who were not exposed to famine during their fetal development; they had more offspring, more twins, were less likely to remain childless, and started reproducing at a younger age (Painter et al. 2008a). The increased reproductive success of these women is unlikely to be explained by genes which favor fertility and are passed from mothers to their daughters. *In utero* exposure to famine did not affect the reproductive success of males. These findings suggest that poor nutrition during fetal development, followed by

improved nutrition after birth can give rise to a female phenotype characterized by greater reproductive success.

The constellation of reproductive and metabolic adaptations during fetal development in response to undernutrition *in utero* may be part of a thrifty phenotype which is associated with enhanced reproduction. Post-war Holland provided a postnatal environment of food abundance, which was unlike the conditions anticipated by the environment *in utero*. This disadaptation of a thrifty phenotype may be important in the later occurrence of chronic disease. We have shown that people exposed to famine during gestation have increased risk of cardiovascular disease, metabolic disease, breast cancer, and obesity rates. In conclusion, our findings are consistent with the theory of life history regulation, which proposes that the two traits fertility and body maintenance are mutually balanced, investments in one are traded off by reduction in investment in the other (Stearns 1992). Our findings show that the balance in phenotypic traits underpinning life history regulation may be set by the environmental conditions during fetal development.

We found preliminary evidence that grand-maternal exposure to famine for a brief period during gestation is associated with increased neonatal adiposity and poorer health in the grand-offspring (Painter et al. 2008b). These findings constitute the first direct evidence in humans that the detrimental effects of poor maternal nutrition during gestation on health in later life pass down to subsequent generations. This may imply that improved maternal nutrition during gestation may benefit the health of many generations to come. Also, these findings indicate that the transgenerational effects of famine exposure *in utero* on health in later life differ depending on the exposed parent's sex. Increased neonatal adiposity was only found among the children of prenatally exposed women, whereas poor health was reported among the offspring of both men and women who had been conceived in famine. Importantly, this indicates that effects on health in later life also pass down transgenerationally through the male line. Transgenerational effects of a poor intrauterine environment may thus affect the entire generation parented by exposed individuals.

61.2 Study Limitations

In interpreting our findings, a number of matters need to be considered. Women were less fertile during the famine. The women who did conceive during the famine, whose offspring was exposed to famine in early gestation, may have been of a different constitution. However, correcting for markers of maternal constitution or fertility, such as maternal weight, age and parity and socio economic status did not affect the outcome.

The high rates of infant mortality during the famine affected groups born before the famine and exposed in late gestation most. The two groups with the largest contrast in early mortality (those born before the famine and those conceived after it) are homogeneous in terms of adult health outcomes, indicating that selective survival cannot have a large confounding effect on outcome in later life.

Selective participation of people that were fit enough to attend the clinic, and prior excess mortality among the most seriously affected people may have led to an underestimation of the effect of prenatal famine on subsequent disease.

Finally, there are limitations in pinpointing the exact timing of famine exposure during gestation and associated outcomes in later life, due to the relatively small sample size on the one hand, and partial overlap between the three famine-exposed groups on the other. However, the famine exposure periods do give an estimate of the timing of the focus of effect.

61.3 Interpretation

The findings of the Dutch famine birth cohort study broadly support the fetal origin hypothesis. Chronic diseases originate in the womb through adaptations made by the fetus in response to undernutrition. The effects of undernutrition, however, depend upon its timing during gestation and the organs and systems developing during that critical time window. Furthermore, our findings suggest that maternal malnutrition during gestation may permanently affect adult health without affecting the size of the baby at birth. This gives the fetal origins hypothesis a new dimension. This may imply that adaptations that enable the fetus to continue to grow may nevertheless have adverse consequences for health in later life. Coronary heart disease may be viewed as the price paid for adaptations made to an adverse intrauterine environment. It also implies that the long-term consequences of improved nutrition of pregnant women will be underestimated if these are solely based on the size of the baby at birth.

Little is known about what an adequate diet for pregnant women might be. In general, women are especially receptive to advice about diet and lifestyle before and during a pregnancy. This should be exploited to improve the health of future generations.

61.4 Applications to Other Areas of Health and Disease

The Dutch famine study has highlighted the importance of maternal nutrition during gestation for the health of her offspring in the long term. Although the Dutch famine was a unique situation, the findings of our study may have implications for other situations around the world. Some of these implications will be highlighted below.

We found that people exposed to famine in early gestation were twice as likely to consume a high fat diet and they had a tendency to be less physically active (Lussana et al. 2008). To our knowledge, this is the first report, in humans, that undernutrition during fetal life can influence adult lifestyle choices, such as food preference and sedentary behavior. The combined analysis of our data and animal models suggests that adult lifestyles and metabolic disorders might have a common prenatal background. Therefore, the paradigm that an unhealthy adult lifestyle is the main culprit in the current epidemic of metabolic and cardiovascular diseases may no longer be valid. We must now consider prenatal and perinatal determinants of adverse adult health. Animal models have suggested that the mechanisms underlying the effects of prenatal exposure to undernutrition might be mediated by the induction of leptin resistance and changes in hypothalamic development. At the moment, any pathophysiological consideration in humans is merely speculative, and we need more studies to confirm these intriguing findings.

The Dutch famine study has established the importance of maternal nutrition during early pregnancy for the offspring's cardiovascular risk. The nutritional experience of babies who were exposed to famine in early gestation may resemble not only that of babies in developing countries whose mothers are undernourished in early pregnancy and receive supplementation later on, but also of babies in developed countries whose mothers suffer from severe morning sickness. Morning sickness is common in the first trimester, and severe morning sickness is associated with metabolic changes in the mother which are similar to those seen during starvation. Since the results of our study consistently show that the effects of undernutrition are independent of size at birth, the assumption that the long-term consequences of hyperemesis gravidarum will be limited because of the normal size of the babies at birth no longer holds.

Our findings suggest that maternal nutrition before and during pregnancy play an important role in later disease susceptibility. This suggestion is in line with evidence from animal experiments that identified preconceptional and preimplantation maternal diet as important for the offspring's adult health. Possibly, epigenetic changes, such as imprinting, which takes place before conception and DNA methylation, may be involved. In both animal husbandry and human medicine, the rapid developments in assisted reproduction in the past decades have surpassed the available knowledge about the potential long-term repercussions. These fields could benefit from more knowledge about mechanisms of pathophysiology discussed above. Besides providing insight into the role of prenatal factors in the origins of chronic diseases, this information may also help identify susceptible patient groups and be useful in the development of more appropriate therapies for common chronic diseases in the future. Most importantly, it will contribute to the prevention of chronic disease through the development of adequate dietary advice to women before and during pregnancy.

The issue of generation-spanning effects of poor nutritional conditions during gestation is particularly relevant to populations in transition between traditional and western life styles, because it may shed light on the epidemic of diabetes, obesity, and cardiovascular disease, which is currently rapidly expanding in such countries. In India, currently transitioning to food abundance after generations of poor nutrition, babies are light and small at birth, but have increased neonatal adiposity compared to European babies. Our findings may indicate that increased neonatal adiposity, and possibly increased diabetes risk, is the direct result of poor maternal nutrition which occurred

Fig. 61.1 Pamphlet of famine (Hongersnood) in Holland

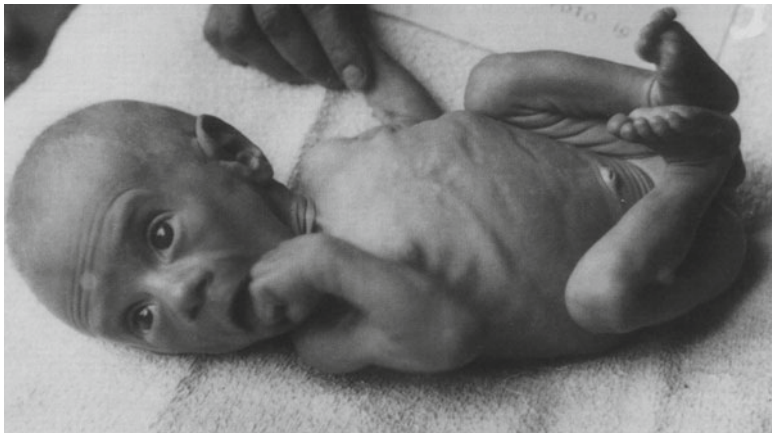

Fig. 61.2 Baby born during the Dutch famine in the Wilhelmina Gasthuis in Amsterdam

Fig. 61.3 Ration (consisting of two slices of bread, two potatoes and half a sugar beet) provided to adults in Amsterdam in April 1945

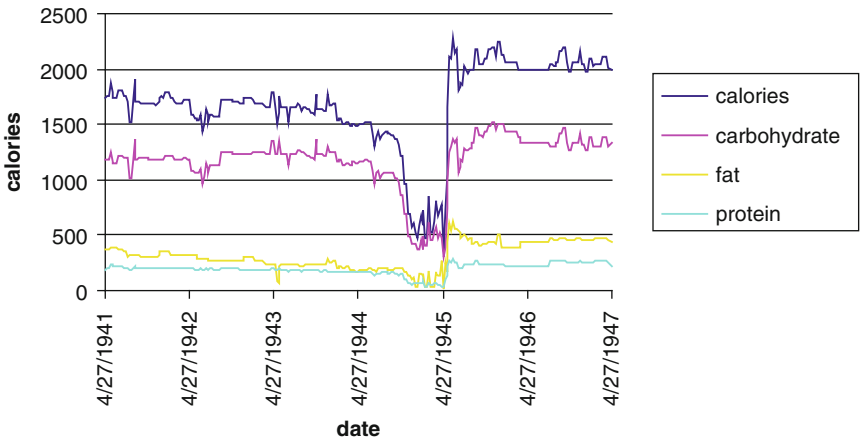

Fig. 61.4 Macro-nutrient content of rations provided to adults in Amsterdam between April 1941 and April 1947

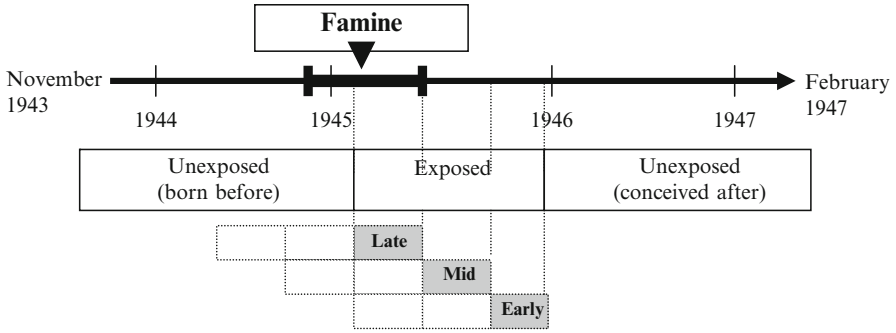

Fig. 61.5 The Dutch famine birth cohort: famine exposure and birth in relation to the timing of the Dutch famine

generations ago. Public health strategies which focus on improved maternal nutrition during gestation may provide a means of promoting cardiovascular and metabolic health which will benefit generations to come.

Summary Points

- Prenatal exposure to the Dutch famine 1944–1945 has lasting consequences for health.
- The effects of famine exposure during gestation depend on its timing during gestation.
- Prenatal exposure to undernutrition of the Dutch famine affects various aspects of health: cardiovascular, and even lifestyle choices.
- The effects of undernutrition are independent of size of the baby at birth.
- The effects of prenatal undernutrition appear to be conveyed to the next generation.

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Chapter 62
Parental Determinants of Neonatal Anthropometry

Gareth Hynes, Cyrus Cooper, and Elaine Dennison

Abstract Evidence is accruing that growth early in life has a profound effect on that individual's risk of many chronic diseases in late adulthood. This chapter attempts to unravel the various ways in which parents influence the anthropometry of their offspring. Much research has been undertaken in this area over the years and there is information linking a myriad of factors with foetal growth. It is the following factors, however, that are the most important and will be discussed here: age, race, parental birth anthropometry, parental height, parental weight, maternal weight gain during pregnancy, maternal activity, diet including calorie, protein and micronutrient intake, parity and interpregnancy interval, socioeconomic status, maternal pathology (hypertension, malaria, anaemia and diabetes) and lastly exposure to toxins (cigarette smoke and alcohol). The literature has been reviewed and a summary is presented to the reader. Where possible, conclusions are drawn as to the relative importance of each factor in determining neonatal anthropometry. The sections also include putative biological mechanisms that may underpin any such link where known, and the potential implications the research has on child health, where this is appropriate. The chapter concludes by briefly examining the debate surrounding the evolutionary origins of the parental determinants of neonatal anthropometry.

Abbreviations

SGA	Small for gestational age
IUGR	Intrauterine growth restriction

62.1 Introduction

Not only is size at birth the strongest determinant of perinatal survival, its influence stretches beyond the perinatal period and far into adult life. Weight at birth for instance is a predictor of heart disease, stroke, diabetes, obesity and osteoporosis in late adulthood. Teasing out which factors are important in determining neonatal anthropometric measures is crucial for two reasons. First, it will help us elucidate the mechanisms by which unborn babies grow: if we know that factor A in the parents

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_62,

causes measure B in the newborn, we can explore the biochemical pathways through which it may be acting, allowing us to advance theories as to why it happens and potentially to develop novel therapeutic targets to aid or hinder the actions of factor A. Secondly, it will help us improve the health of the individuals and the population through targeted clinical and public health measures.

This chapter will attempt to define exactly which parental factors are important in determining neonatal anthropometry. It starts with a note on the term neonatal anthropometry, touches on mechanisms and evolutionary processes underlying any links, and then focuses on the means by which parents exert their influence on the growing child. In each subsection, the posited molecular mechanisms by which these interactions occur are explored, and this is followed where appropriate by reviews of the implications of the research to both individual and public health fields.

62.1.1 Note on Neonatal Anthropometry

There are relatively few anthropometric measures that can be taken from a newborn child. These include birthweight, height, abdominal circumference (measuring primarily the size of the liver), chest circumference, head circumference, ponderal index (paediatric equivalent of BMI) and skinfold thickness (used to measure foetal nutrition). Most studies use birthweight due to the wide availability of relevant data and due to its strong associations with neonatal health.

A small baby may be the result of slow foetal growth, when they would be termed small for gestational age (SGA) due to intrauterine growth restriction (IUGR), or the result of a shortened gestational period, when they would be termed premature. Although premature birth has its own related health problems, this chapter will limit the discussion to factors affecting foetal growth. Where not explicitly mentioned low birthweight can be taken to mean small for gestational age.

62.1.2 Mechanisms and Evolution

Genes and the environment are the ways in which parents influence their unborn child's growth. Genes exert a powerful effect and it could be argued they set the maximal capacity for growth, while it is the surrounding environment that determines whether an individual will reach that maximum potential.

There are several theories in the literature surrounding foetal growth and evolution, and they are generally termed "conflicts." Maternal–offspring conflict emphasises the different needs of mother and baby. Mothers do not wish their child to be too big as this will drain them of needed nutritional resources, so they "constrain" their growth. Unborn babies on the other hand wish to grow bigger to be better able to cope with the outside world. Maternal–paternal conflict is similar, though here while the mother passes on growth-suppression genes, fathers bequeath growth-promoters. These important ideas will be returned to in the conclusion.

62.2 Genetic and Constitutional Factors

62.2.1 Age

Age is undoubtedly associated with neonatal anthropometric measures. Studies consistently show a relationship, which, when examined, would appear to be a U-shape: mothers at the extremes of age tend to have lower birthweight, smaller babies (Karn and Penrose 1951).

Such a link has been discussed in the medical literature since at least the early 1950s, with studies such as that by Karn and Penrose concluding: "Children of the first three parities showed a definite decrease in weight with increasing maternal age, but this effect was not present in higher parities." Most studies to date have replicated such findings, though when the youngest maternal ages have been included they too showed a depressed birthweight (Gage et al. 2009).

There is a multitude of reasons for this, many of which could be described as confounders, and what is less clear is the role age itself plays. Age is clearly associated with parity, and indeed most studies control for this in their analyses. In addition those women at the extreme lower age range tend to be less tall and have a smaller BMI. Cigarette and alcohol consumption may be higher, while educational attainment and socioeconomic status may be lower. By contrast, older mothers tend to have more comorbidities, which may depress the growth of the foetus. In addition, women who become pregnant later in life may do so as a result of ''subfecundity'', or may have accessed infertility therapies that predispose to multiple births.

Another intriguing theory is the weathering hypothesis, proposed by Geronimus in 1992 (Geronimus 1992). It suggests that as women age, the cumulative effect of many years' exposure to adverse events results in irreparable damage that manifests as poor birth outcomes. Geronimus used this to help explain the excess poor birth outcomes experienced by black women in comparison to white women, and in older black women in comparison to younger black women. There has, however, been some criticism that it may be secondary to older white women becoming pregnant after choosing to delay their pregnancies, but older black women becoming pregnant because they have been unable to earlier in life, secondary to the subfecundity mentioned above (Stevens-Simon 2002).

In reality, most studies cannot adequately control for the myriad factors mentioned above, so the role played by age alone remains unclear.

62.2.2 Race

Different population groups have different average birthweights. The mean birthweight in India, for example, is 2,500 g whereas in the UK it is 3,100 g. What is less clear is whether this disparity is the result of true genetic differences between the two populations, or is instead the result of the contrasting cultures of each population. One can easily imagine variation in the average maternal age, height, weight, parity, socioeconomic status, diet, smoking habit, activity and health status between the UK and India. This is of course further complicated by the fact that some of these differences may themselves be due to genetics rather than being true confounders (maternal height or weight for example).

Early studies reported a strong link between race and birthweight, but in retrospect these were often confounded by lack of control for what we now know to be apposite sociodemographic differences. More recent papers have controlled for such factors to a greater or lesser degree, and for the most part find that the link persists. Hulsey, Levkoff and Alexander analysed 10,159 normal spontaneous deliveries, finding that when statistically significant differences in demographic characteristics were controlled, black infants weighed an average of 181 g less than white infants (Hulsey et al. 1991). Around the same time, Goldenberg et al. used a series of regression analyses to determine the effect of black race on various newborn measurements in 1,205 term newborns, adjusting for other known risk factors. "In this model, black race accounted for a mean decrease of 148 g in weight and 0.52 cm in length. There were also significant decreases in mean head (0.44 cm), chest (0.66 cm), and abdominal (0.56 cm) circumferences. Arm and leg lengths were not different, but black arm circumferences (0.14 cm) were significantly larger. Triceps and thigh skin fold measurements were not statistically different… The ponderal index in blacks was significantly less than in whites" (Goldenberg et al. 1991). A recent retrospective study in the US by Tan et al. compared twins' birthweight

in those born to parents of different race. In their study of 121,719 eligible twinsets they controlled for frequency of teenage parents, marriage status, perinatal care service, education, live birth parity, maternal smoking and medical complications. They found infants born to black parents had the lowest average birthweight; white fathers and black mothers had the second lowest means; black fathers and white mothers had the second highest means; and infants born to white parents had the highest mean birthweights. It was concluded both maternal and paternal race were important determinants of birthweight, gestational duration, and foetal growth, that maternal race had larger influence on birthweight than paternal race, and that a proportion of the effect of parents' race on birthweight was the result of its effect on gestational duration rather than foetal growth (Tan et al. 2004). Investigators have argued these findings suggest a genetic basis for the differences.

There is a significant undercurrent of evidence; however, suggesting genetic explanation may be an insufficient interpretation of the link between race and birthweight. Richard David and James Collins Jr have argued for many years that the association can be explained through environmental differences. In their study of Ilinois vital records from 1980 to 1995 involving approximately 80,000 infants, they examined the birthweights of the infants of US-born white mothers, US-born black mothers and African-born black mothers. They realised that the distribution of birthweights among infants of African-born black women approximated that among infants of US-born white women, significantly higher than US-born black women. They state "if genetics played a prominent part in determining black–white differences in birthweight, the infants of the African-born black women should have had lower birthweights than those of the US-born black women. We found the opposite: regardless of socioeconomic status, the infants of black women born in Africa weighed more than the infants of comparable black women born in the United States" (David and Collins 1997). Limitations that they acknowledge include lack of controlling for cigarette-smoking, prepregnancy weight and pregnancy weight gain.

One intriguing phenomenon reported in the literature is known as the epidemiological paradox (also termed the Hispanic paradox or the Mexican paradox). A wealth of data has been advanced that shows South American migrants in the US have babies with greater birthweight than those in similar socioeconomic groups. In fact, according to some measures, they have on average bigger, healthier babies than Caucasians despite the greater wealth and access to healthcare among Caucasian groups. The paradox was first proposed by Markides and Coreil in 1986 (Markides and Coreil 1986). This study found that the mean health status, including infant mortality, of Hispanic individuals in the southwest of the US was broadly comparable to better off white individuals, and far better than the black population with which they share their reduced socioeconomic status. Subsequent studies have questioned this finding. Smith and Bradshaw in 2006, as an example, found that any decrease in mortality was due to the artefact of incorrect identification of Hispanics by the sources used to collect the data for the studies (Smith and Bradshaw 2006).

There are many potential reasons for this paradox, ranging from varying levels of periodontal disease, to an increase in mean height of those migrants that remain in the country in comparison to those that leave. The latter study (Crimmins et al. 2005) was actually using adult height as a marker of poor childhood experiences to suggest that those with worse health and nutrition migrate back to South America, while those who are healthy stay on in their adopted country. This is certainly one potential reason, known as the healthy migrant theory.

62.2.3 Parental Birth Anthropometry

The first evidence that human neonatal birthweight is directly related to maternal birthweight independently of maternal measures such as height and weight emanated from a series of studies by Margaret

Ounsted and colleagues in Oxford. Ounsted used data from the British Perinatal Mortality survery of 1958 to suggest a matrilineal pattern of birthweight inheritance (Ounsted and Ounsted 1968).

Further investigation was undertaken by Klebanoff, who over the following four years published three papers on the subject, concluding in the last that white women with high birthweight (4,000–4,500 g) had a 5.9% risk of having a small for gestational age infant, whereas the rate for white mothers who weighed 2,000–2,499 g at birth was 19.8% (Klebanoff and Yip 1987).

Thoughts that this might have been due to an effect on gestational duration were dismissed by Magnus and others in 1993 (Magnus et al. 1993) – paternal birthweight is inconclusive, with some investigators suggesting it is important, and some reporting it is not. These findings have been corroborated in different populations. In 1999 Ramakrishnan et al. confirmed the maternal link in a developing country. In Guatemala a "child's birthweight increased by 29 g/100 g increase in maternal birthweight which is nearly twice that reported in developed countries. Similarly, child's birth length increased by 0.2 cm for every 1 cm increase in mother's birth length. The effect of maternal birthweight remained significant even after adjusting for maternal adult size" (Ramakrishnan et al. 1999). Agnihotri, in 2008, found for an Indian population: "Both maternal and paternal birthweight are strong determinants of offspring birthweight. The effect of mothers' birthweight on offspring birthweight is weaker than that seen in developed nations" (Agnihotri et al. 2008).

62.2.4 Parental Height

In 1926 Noel Paton and Leonard Findley, professors of physiology and paediatrics respectively at the University of Glasgow, wrote a paper for the Medical Research Council entitled *Poverty, Nutrition and Growth* (Paton and Findlay 1926). Among a number of things they examined they found that parental height was a predictor of a baby's height at two weeks, maternal height more strongly than paternal.

Studies since have put the amount of variation in neonatal birthweight accounted by maternal height at 10% (Magnus et al. 1984), and concluded that approximately for each centimetre increase in maternal height, neonatal weight increases 1.6 g. It has also been shown that a baby born to a shorter mother is symmetrically smaller than a baby born to a taller mother; birthweight and height both decreasing proportionately so that the ponderal index remained the same (Witter and Luke 1991).

Parental height may act through multiple pathways to affect foetal growth. Both genetic inheritance and a shared environment are plausible mechanisms, though the theory of maternal constraint expounded by Margaret Ounsted and discussed elsewhere, may be important in smaller women. The passage through the pelvic canal might be more difficult in smaller women with bigger babies.

62.3 Modifiable Environmental Factors

62.3.1 Parental Weight: Prepregnancy and Pregnancy Weight Gain

There are two aspects to parental weight relevant to this story: one is the mother and father's prepregnancy weight; and the other is maternal weight gain during pregnancy. High pre-pregnancy weight and low pregnancy weight gain generally results in a mean birthweight similar to that of low pre-pregnancy weight and high pregnancy weight gain (Eastman and Jackson 1968). A mother's

prepregnancy weight will influence her baby through genetic inheritance and through the availability of nutritional stores to feed the growing foetus. Her pregnancy weight gain is important in providing nutrients to the unborn baby; and similarly the bigger the baby gets, the more the mother will weigh. So while maternal weight is intuitively linked to neonatal anthropometry, paternal weight is much less so: it can act through genetics alone. And recent studies have confirmed that though paternal height is important, paternal weight is far less so when determining foetal growth (Griffiths et al. 2007).

62.3.2 Maternal Activity

There is some evidence that excess maternal activity is associated with smaller babies. In the Pune maternal nutrition study in India heavy activity levels linked with lower mean birthweight, and smaller neonatal head circumference and mid-arm circumference (Rao et al. 2003). And in a recent study in the UK, maternal self-reported high walking speed was associated with lower birthweight; it increased lean mass but decreased fat mass. This is likely to act via its effect on the amount of nutrition available to the growing baby: activity will burn energy that could otherwise be used by the foetus for growth (Harvey et al. 2007).

62.3.3 Diet

As noted above, prepregnancy weight and weight gain during pregnancy are correlated with the growth of the foetus. In addition to genes and activity levels there is a significant role for calorie intake in determining both these measures. Further to the calorie intake levels, there is a plethora of evidence to support the view that multiple components of the maternal diet are important in determining foetal growth and subsequent neonatal anthropometry, including protein intake and micronutrient levels.

62.4 Caloric Intake

Maternal stores (prepregnancy weight) and intake throughout pregnancy (weight gain during pregnancy) are the sole sources of energy for the growing foetus. The adjudged importance of caloric intake during pregnancy is unsurprisingly similar to pregnancy weight gain: it is important, especially so for mothers with a low weight pre-pregnancy. The reasons for this are outlined in the above section, but it is interesting to note some of the underpinning biological mechanisms. We know that diabetic women have large, macrosomic babies. It is also known that women who are not overtly clinically diabetic but when tested are at a level, we now term subclinical diabetes are at increased risk of having large babies too. The mechanism for this is high levels of circulating maternal glucose, occurring as a result of the diabetes, spill over into the foetal circulation. Here the glucose provokes the release of insulin, insulin-like growth factors and growth hormone, all of which encourage the growth of the foetus. It is logical to suppose that excessive maternal calorie intake would have the same effect on maternal glucose levels and hence foetal growth.

Studies examining the effect of caloric intake have had difficulties in design and in controlling for confounders: caloric intake is hard to measure accurately; it correlates with other nutrient intake,

especially protein; it links with prepreganancy weight; plus there are the potential confounders of race, height, age and socio-economic status. Hence the best studies quantifying the impact caloric intake has tend to be intervention studies where a randomly assigned group of pregnant women are given caloric supplementation and compared with controls who were not given the supplements.

Kramer examined the available literature on this in 1987 and found differences in under-nourished and well-nourished women (Kramer 1987). For the former there was a 99.7 g increase in birthweight per 100 kcal/day supplement. For the latter, the birthweight increase was only 34.6 g, i.e. one-third that of undernourished women. This of course fits with the data above regarding maternal weight gain. It is the position of the American Dietetic Association that most pregnant women need between 2,200 and 2,900 kcal/day "but prepregnancy body mass index, rate of weight gain, maternal age, and appetite must be considered when tailoring this recommendation to the individual."

62.5 Protein

Proteins are essential for growth: their constituent pieces, amino acids, are often termed "the building blocks of life". A recent study by Cuco et al. of 77 healthy women in Italy found protein intake was proportionately related to neonatal birthweight, once adjusted for energy intake, maternal age, prepregnancy BMI, parity, physical activity and smoking. It was reported a 1 g increase in daily protein intake results in 7.8–11.4 g increase in birthweight (Cuco et al. 2006). Although interesting, the number of participants in this study is relatively small. Most studies involving more women; however, have had difficulties with the confounders mentioned above and have used supplementation as a means to measure the effect of protein.

Kramer and Kakuma have recently (re-)examined the subject for the Cochrane Database and found that energy and protein supplements lead to a significant increase in birthweight, but not in height or head circumference (Kramer and Kakuma 2006). High-protein supplements did not result in any change to measured neonatal anthropometry, and though there was a non-significantly decreased risk of stillbirth, there was a similarly non-significant increased risk of neonatal death. Finally isocaloric protein supplements (providing less than 25% of energy intake, and replacing an equivalent amount in the diet) may increase mean birthweight, but may also increase the risk of small-for-gestational-age babies. The data on this are too few, however, to draw definitive conclusions. The authors felt that the increase in birthweight with energy and protein supplements was probably due to the increased energy intake, and that women given high-protein supplements ate less as a result.

Overall, despite protein being important for foetal growth, it would appear that the normal dietary fluctuance between women only accomplishes an increase in the neonatal arthropometric measure of birthweight through the extra energy that the consumption of protein brings.

62.6 Micronutrients

Micronutrients are vitamins and minerals required in small amounts for the normal growth and functioning of the body. There is a paucity of studies for many micronutrients in pregnancy; however, and the current trend of examining multiple micronutrient supplements makes teasing out the valuable from the less useful micronutrients somewhat difficult.

Vitamin A is one such micronutrient that may be a determinant of foetal growth. A study by Wang et al. has found that maternal serum levels of vitamin A are proportionately linked to birth outcomes,

such that a 1 umol/L increase in maternal serum vitamin A (note that absolute levels <0.7 umol/L were considered deficient) was associated with a 250 g increase in birthweight. A 1% increase in serum levels also correlated with a 0.8 cm increase in birth length. A relationship was noted with head circumference but it did not reach significance levels. There was no such relationship for *vitamins C and E*. It was postulated that the positive relationship may be due to the protective anti-oxidative effects of vitamin A, and this may make it especially important in smokers given the toxic oxidative effect of cigarette smoke. However, in these results Wang et al. only adjusted for age and parity. Given the importance of socio-economic factors and their likely relationship to vitamin A intake, however, these results should be interpreted with caution, especially given that previous studies have found no such link (Muslimatun et al. 2002).

Vitamin B9, or folic acid, has well known effects on nervous system development. Evidence has been accruing that it does influence birthweight, and in 2009 Timmermans et al. concluded from their analysis of 6,352 women in the Generation R study in Holland that folic acid supplementation (0.4–0.5 mg) was associated with 68 g higher birthweight (Timmermans et al. 2009). Folate is an important constituent of nucleic acid, a integral part of DNA, and is hence essential during the cell division that directs the growth of the unborn baby.

Vitamin B12 may be associated with birthweight. Past studies, in India and the UK, could find no association, but a more recent Indian study did report a link in a sample of 185 women (Muthayya et al. 2006). The authors felt the lack of a relationship demonstrated previously was due to the women being B12 replete in the case of the UK, and the spread of B12 being too narrow in the previous Indian study, to detect any effect. Vitamin B12 is important in regenerating folate within the body and hence a deficiency, if not compensated for by an increased intake of folate, is liable to have the same deleterious effects that a deficiency of folate will cause.

Vitamin D has been shown to be important in determining bone growth in the unborn baby. Mahon et al. writing in 2009 used high-resolution 3D ultrasound to measure foetal femur length and distal metaphyseal cross-sectional area, together with the ratio of femoral metaphyseal cross sectional area to femur length ("femoral splaying index"). They found: "Lower maternal 25-hydroxyvitamin vitamin D concentration was not related to foetal femur length, but was associated with greater femoral metaphyseal cross-sectional area and a higher femoral splaying index at 19 weeks' gestation" (Mahon et al. 2009). Another recent study, by Scholl and Chen, found "after control for energy, other nutrients, and other potential confounding variables, total intake of Vitamin D was associated with increased infant birthweight; gravidae below the current adequate intake (<5 microg/day or 200 IU) had infants with significantly lower birthweights ($p < 0.05$) (Scholl and Chen 2009). Interestingly a study into *calcium* supplementation in those deficient of calcium did not show any differences between fetuses whose mothers received calcium supplementation during pregnancy and those who received placebo. Vitamin D regulates calcium and phosphate in the blood enabling normal metabolism of bones. It is also an important immune regulator.

Zinc is another micronutrient of controversial importance; with regards pregnancy it is perhaps the most studied of the micronutrients. A review study in 2009 by Hess and King, at the University of California, found three studies, one by Goldenberg and Neggers, concluding supplemental zinc significantly increased birthweight. These studies were performed in those in whom zinc deficiency was likely. Eleven other studies failed to find a relationship but none of these stratified the effects of supplemental zinc on birthweight by maternal weight or zinc status. They concluded thus: "Most studies found no significant impact of maternal zinc supplementation on infant birthweight, but a subset of studies conducted in underweight or zinc-deficient women suggests that there may be a positive effect of zinc supplementation in such women" (Hess and King 2009).

In summary, energy intake, vitamin D, iodine and zinc appear to have significant effects on the growth of the unborn baby. Copper and vitamins A, B9 and B12 may have an impact, but there is

little evidence that normal variations in vitamin B6 and protein intakes at this stage cause changes in neonatal anthropometry. Current work on supplementation suggests that multiple micronutrient supplementation is the most efficacious ways of nutritionally maximising foetal growth in the developed world.

62.6.1 Parity and Interpregnancy Interval

Studies put the odds ratio of having a small for gestational age baby at between 1.3 and 2.1 for nulliparous versus multiparous women. Interpregnancy interval is the amount of time between the end of one pregnancy and the commencement of the next. Interestingly both short and long intervals are associated with low birthweight infants. However, there is still considerable debate as to whether the links are due to confounding effects or true biological pathways. A recent meta-analysis by Conde-Agudelo and colleagues in JAMA on this subject included 67 studies and 11 million births. They found that interpregnancy intervals shorter than 18 months and longer than 59 months are significantly associated with small for gestation age infants (in addition to prematurity). As a result they call on "reproductive clinicians" to advise women to delay subsequent pregnancies for "two to five years" (Conde-Agudelo et al. 2006). Possible biological theories for the link between short interval and low birthweight include the maternal nutrition depletion hypothesis, where a short pregnancy interval does not allow the restoration of maternal stores depleted by pregnancy. Confounders include poorer socioeconomic status, lack of engagement with health services and unplanned pregnancies in those with short intervals. The link between long interval and birthweight may be secondary to the gradual physiological decline in a woman's reproductive capabilities over time, so that a woman many years from her last pregnancy will be in a similar position to a primigravid woman. Confounding this however is the possibility that subfecundity, known to cause unfavourable birth outcomes in itself, is the reason for delayed subsequent pregnancies.

62.6.2 Socioeconomic Status

In the context of pregnancy, socioeconomic status (SES) is a composite measure of maternal or paternal occupation, family income and maternal or paternal education. That it has an effect on neonatal anthropometry is beyond doubt and with an abundance of literature supporting the notion that a considerable proportion of both intra-societal and inter-societal difference in birth outcomes may be secondary to the SES differences. A major limitation of the SES measure is that it has a rather nebulous definition, changing from report to report, not as easily quantifiable as smoking or maternal height.

62.6.3 Pathology

62.6.3.1 Hypertension

The terminology surrounding hypertension in pregnancy can be confusing. In essence there are four permutations, all of which are associated with small-for-gestation age infants in addition to

the potentially catastrophic outcomes for both mother and child. Chronic hypertension is defined as a blood pressure measurement of 140/90 mmHg or more on two occasions before 20 weeks of gestation or persisting beyond 12 weeks postpartum. It is associated with an odds ratio of growth restriction of 4.9 (Gilbert et al. 2007). Gestational hypertension, which has replaced the term pregnancy-induced hypertension, describes women who develop hypertension without proteinuria after 20 weeks of gestation. It is associated with worse outcomes than chronic hypertension, with a three-fold increased risk of small-for-gestational-age babies (Buchbinder et al. 2002). Pre-eclamsia is a multi-organ disease characterised by hypertension and proteinuria after 20 weeks' gestation. Eclampsia is the development of seizures as a result of cerebral oedema secondary to pre-eclampsia. They are associated with more severe forms of foetal compromise. The aetiology of pre-eclampsia is not clear, but abnormal placental implantation and immunological intolerance between fetoplacental and maternal tissue resulting in placental and foetal hypoxia are both candidates.

62.6.3.2 Malaria

Malaria is endemic in large parts of Africa. It is a parasite transferred from its vector, the female anopheles mosquito, to its human host where it infects red blood and liver cells. Pregnant women are more likely to contract malaria, and suffer with it more severely than others. This is related to the transiently impaired immunity associated with pregnancy. Malaria infection is associated with low birthweight babies, mainly due to its effect on disturbing intrauterine growth. It limits growth by sequestering in maternal red blood cells in the intervillous space in the placenta and causing the red blood cell to adhere to specific placental receptors. These receptors – chondroitin sulphate A is an example – transport oxygen and nutrients across the placenta, and hence their disruption limits resources available to the growing baby. It also causes maternal anaemia.

62.6.3.3 Anaemia

Studies of healthy women in developed countries usually fail to show a link between anaemia and birth outcomes. Some even show that mild anaemia is associated with high birthweight. Studies in developing countries, however, tend to show the opposite. Anaemia is a "normal" state for pregnant women: during pregnancy a mother's red cell manufacture increases, but her circulating fluid volume increases more. The result is a "haemodilutional" anaemia. A genuine anaemia of less than 110 g/L (iron-deficient in origin or for other reasons) in addition to this may interfere with oxygen delivery to the unborn baby.

62.6.3.4 Diabetes

Maternal diabetes predisposes to large babies, or macrosomia. In fact, there is a linear association between infant size and maternal blood glucose (from 9 mmol/L upwards) in blood taken two hours after a glucose tolerance test. Reasons are given in the diet section.

62.6.4 Toxins

62.6.4.1 Smoking

Animal studies in 1940 by Essenberg, Scwind and Patras had suggested that smoke exposure in pregnant rats and rabbits leads to lower birthweight babies in comparison with controls (Essenberg and Patras 1940). Winea Simpson published a report linking cigarette use to prematurity, defined at that time as birthweight less than 2,500 g (Simpson 1957). Concluding smokers had twice the risk of having premature babies as non-smokers, she precipitated a "tidal wave of research" in the area. More recent studies have of course confirmed this link and estimated that there are 32,000–61,000 excess low birthweight babies born each year as a direct consequence of maternal smoking (DiFranza and Lew 1995). Paternal smoking may also be related to such changes. Exposure to environmental tobacco smoke leads to a mean 79 g reduction in birthweight, with a dose dependent relationship apparent in the literature.

In utero exposure to tobacco affects the growing foetus, especially during the latter stages of pregnancy, through its effect on foetal oxygenation, skeletal growth plates and growth promoting factors. Although the exact process remains unclear there are several mechanisms that seem likely. The inhibition of growth may be secondary to restricted placental circulation. We now feel that decreased foetal oxygenation rather than nutrition is the exact mechanism. Nicotine in tobacco smoke is metabolised to cotinine, and cotinine has been shown in various animal models to decrease uterine blood flow, umbilical artery flow and foetal oxygenation and acid-base balance. In addition to the effect of nicotine, carbon monoxide is transferred across the placenta and reaches levels in the foetus 15% higher than in the mother. Here carbon monoxide irreversibly binds with haemoglobin to form carboxyhaemoglobin reducing significantly the amount of free haemoglobin available to carry oxygen. The theory that foetal hypoxia is the cause for growth restriction is backed up by findings that cord plasma erythropoietin is significantly higher in smokers, and as EPO is released in response to low oxygen levels, it is likely women who smoke are chronically hypoxic. Nicotine also seems to act directly on growth plate chondrocytes to decrease matrix synthesis and suppress hypertrophic differentiation (via nicotinic acetylcholine receptor type alpha7) leading to delayed skeletal growth. Further studies have linked smoking with decreased maternal placental growth hormone and cord blood insulin-like growth factor 1, both of which are important hormonal regulators of foetal growth (Coutant et al. 2001).

62.6.4.2 Alcohol

The term foetal alcohol syndrome first appeared in the medical literature in a 1973. The first attempts to systematically characterise the problems associated with pregnancy alcohol use; however, came from France in the 1950s and 1960s. In 1984 Mills et al. concluded from their prospective study of 31,604 pregnancies that after adjustment for other risks, a reduction in mean birthweight was seen in drinkers compared with nondrinkers, ranging from 14 g in those drinking less than one drink each day to 165 g in those drinking three to five drinks each day. Consuming less than one drink daily had a minimal effect on intrauterine growth and birthweight.

FAS results from in-utero exposure to alcohol that has been consumed by the mother. The alcohol crosses the placenta and in the developing baby causes cell death via increasing natural apoptosis

and inducing cell necrosis. Alcohol (ethanol) is thought to be directly toxic itself; and acetaldehyde, one of its metabolites, and excess glutamate activity are two more of what is ultimately likely to be a myriad of factors that are implicated in the disease pathogenesis.

62.7 Conclusion

To conclude we return to the debate mentioned in the introduction regarding the various conflict theories surrounding the different evolutionary needs of mothers, fathers and unborn babies. It has been said that pregnancy involves a dialogue between the mother and her fetus, modulating foetal growth from its genetically determined path in relation to her state, environment and history. This was vital to human evolution, and remains important today in the determinations of pregnancy outcome and later health of the offspring.

62.8 Applications to other areas of health and disease

Evidence is accruing that growth early in life has a profound effect on that individual's risk of many chronic diseases in late adulthood. Many factors, including maternal pathology (hypertension, malaria, anaemia and diabetes) and maternal lifestyle (diet, physical activity, cigarette and alcohol consumption) are related to birthweight in the offspring.

Summary Points

- **Age** Extremes of maternal age are linked with smaller babies
- **Race** Controversially linked with neonatal anthropometry
- **Parental birth anthropometry** Maternal birthweight predicts offspring birthweight
- **Parental height** Maternal is more important than paternal height, though paternal height is more important that paternal weight in determining foetal size
- **Parental weight** Maternal prepregnancy weight and pregnancy weight gain are both significant determiners of neonatal size
- **Maternal activity** There is evidence to suggest excessive activity predisposes to smaller babies
- **Diet** Energy intake levels and some micronutrients are important, but protein intake and other micronutrients have accrued fewer positive data
- **Parity and interpregnancy interval** Higher parity is linked to bigger babies, both long and short interpregnancy intervals predispose to smaller babies
- **Socioeconomic status** This nebulous concept seems intransigently linked to birth outcomes
- **Maternal pathology** Hypertension, malaria and anaemia are all associated with smaller babies, but diabetes causes increased foetal growth
- **Exposure to toxins** Tobacco smoke exposure is the single biggest modifiable factor predisposing to intrauterine growth restriction, alcohol causes multiple anthropometric anomalies, and cocaine has also been linked with small babies

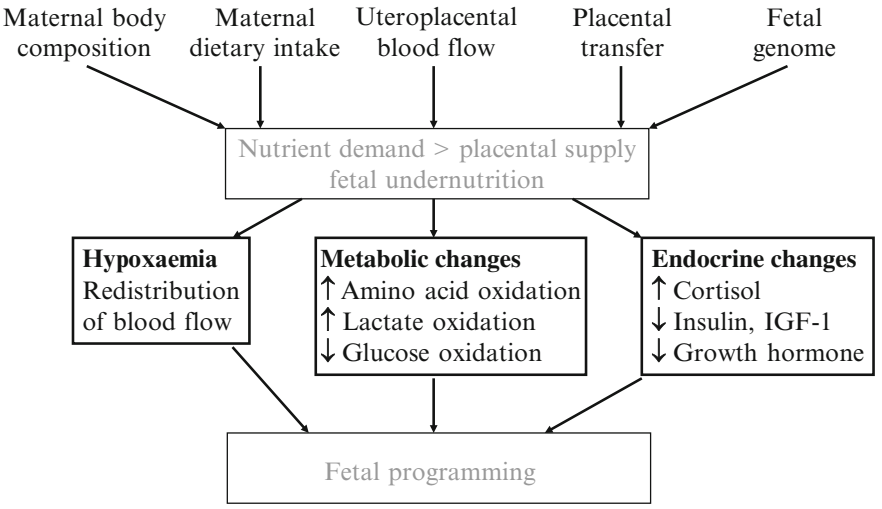

Fig. 62.1 This diagram summarises the way maternal undernutrition may affect foetal growth. Fetal adaptations to undernutrition: a framework

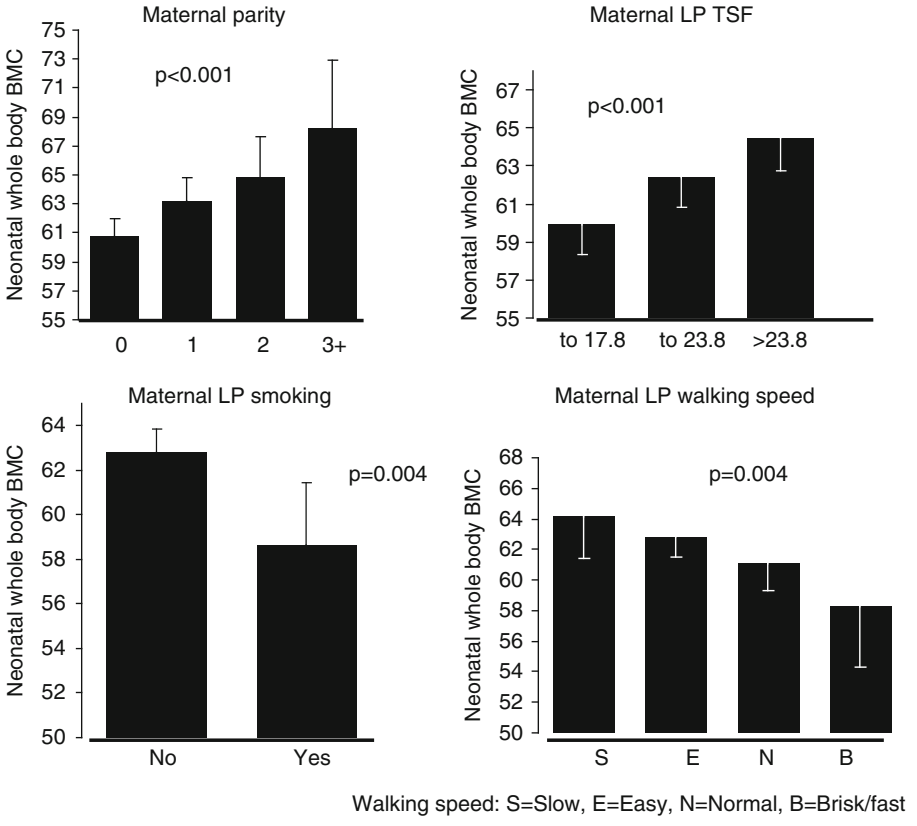

Fig. 62.2 Factors associated with higher bone mineral content in the offspring include higher maternal parity, larger maternal triceps skin fold thickness, abstinence from maternal smoking and slow maternal walking speed. Results are expressed as mean ± SEM, $n = 145$ (Data derived from Godfrey et al. (2001), with permission). Maternal determinants of neonatal whole body bone mineral content (g)

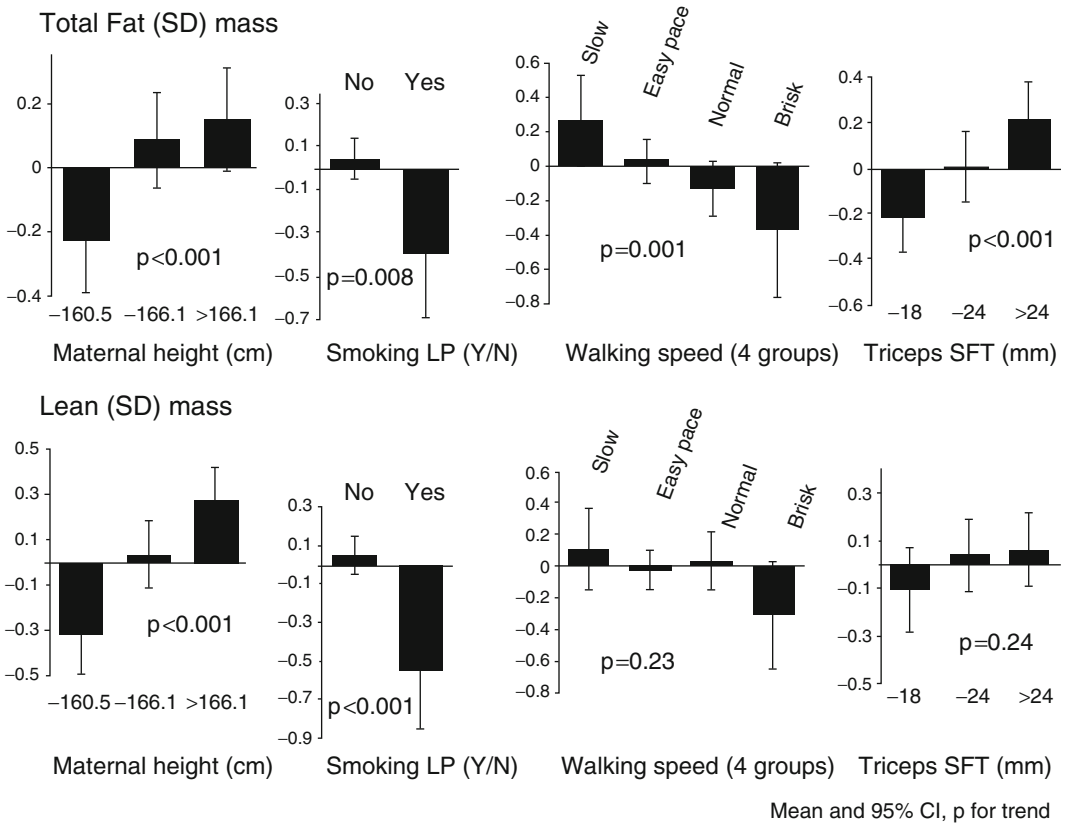

Fig. 62.3 Factors associated with greater fat and lean bone mass in the offspring include higher maternal parity, larger maternal triceps skin fold thickness, abstinence from maternal smoking and slow maternal walking speed. Results are expressed as mean ± SEM, $n = 448$ (Data derived from Harvey et al. (2007), with permission). Maternal determinants of neonatal content body composition

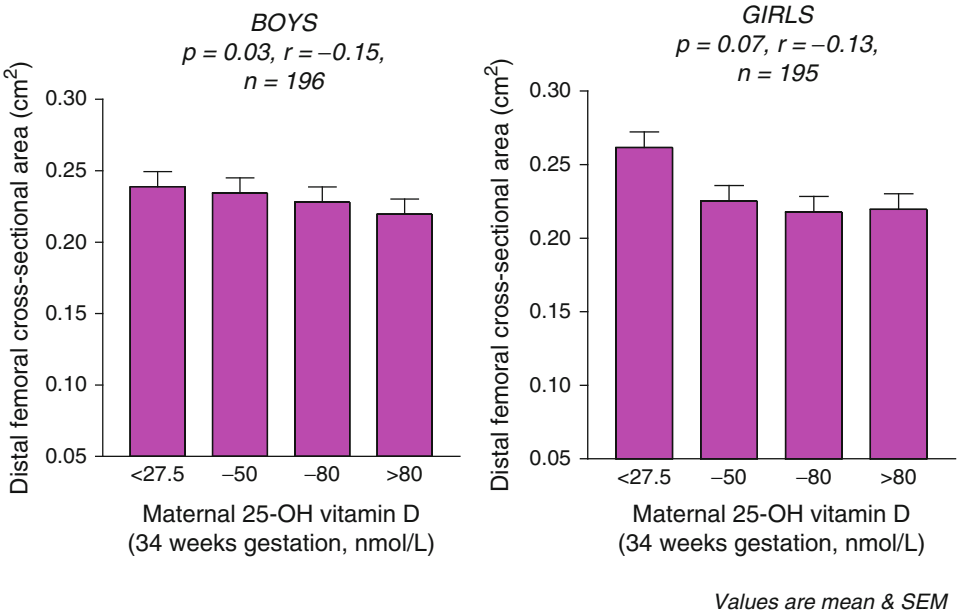

Fig. 62.4 Lower maternal 25(OH) vitamin D concentration at 34 weeks gestation is associated with greater distal femur cross-sectional area in the fetus. Results are expressed as mean ± SEM, $n = 424$ (Data derived from Mahon et al. (2009), with permission). Maternal vitamin D and 19 week distal fetal femur cross-sectional area

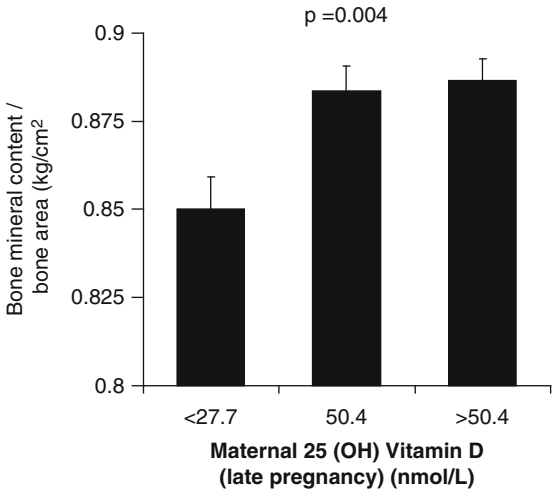

Fig. 62.5 Greater maternal 25(OH) vitamin D concentration in late pregnancy is associated with greater whole body BMC in the offspring at age 9 years. Results are expressed as mean ± SEM, $n = 198$ (Data derived from Javaid et al. (2006), with permission). Nine year whole body BMC by maternal 25(OH)D during late pregnancy and corrected cord blood calcium

Table 62.1 Key features of parity

- Parity may be defined as the state of having given birth to an infant or infants
- An absolute figure may be given to define the number of infants borne

Table 62.2 Key features: which parental factors are associated with neonatal anthropometry and how?

Factors associated with birthweight	Relationship
Age	Lower birthweight at extremes of age
Race	Controversial
Parental birth anthropometry	Larger parents have larger babies
Maternal weight gain in pregnancy	Generally positively associated
Maternal activity	Lower birthweight in very physically active mothers
Maternal diet	Nutrients important
Parity	Larger babies with higher parity
Interpregnancy interval	Lower birthweight if interval very large/small
Socioeconomic status	Controversial due to confounding
Maternal pathology	Many maternal illnesses associated with lower birthweight – diabetes associated with larger babies

This table summarises which parental features are related to anthropometry in the offspring, and describes the effect that feature has

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Chapter 63
Use of Computerized Anthropometry and Morphometrics to Identify Fetal Alcohol Syndrome

Elizabeth S. Moore and Richard E. Ward

Abstract Direct craniofacial anthropometry has changed little in the century and a half since Reitzius used calipers to calculate the first "cranial index." It remains an inexpensive, readily learned technique for objectively measuring facial size and proportion. However, the development of new imaging technologies coupled with powerful computer programs for manipulating data and multivariate analysis for exploring data have opened new frontiers for the clinical application of anthropometry. Computerized anthropometry holds promise for improving our ability to define and recognize craniofacial disorders and for exploring the developmental forces behind variation in facial size and form. Such applications could have a great impact on the diagnosis, treatment, and prevention of fetal alcohol spectrum disorders (FASD), where simple, cost-effective methods for large-scale screening, diagnosis, and surveillance are needed. We review the various methods of indirect or computerized anthropometry that have been used to explore FASD. The vast majority of these studies have focused on creating an objective counterpart to the subjective "gestalt" that dysmorphologists have developed to recognize the phenotypic extreme of FASD known as fetal alcohol syndrome (FAS). Although several studies have demonstrated that computerized anthropometry can successfully recognize individuals previously diagnosed by clinicians as having FAS, no universally accepted "gold standard" has emerged from this work. In addition, only a few of these studies have addressed the potential of computerized anthropometry to recognize a wider range of individuals who have more subtle evidence of damage from gestational exposure to alcohol than is present in the extreme of FAS. However, the wide availability of commercial 3D imaging systems and the convergence of neural imaging studies that allow research to correlate alcohol-induced changes in brain structure to patterns of facial dysmorphology should allow for the collection and analysis of large samples of data, and in the near future may lead to improved recognition of both FAS and FASD individuals as well as greatly improve our understanding of the pathophysiology of alcohol on human development.

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AFR	Automated facial recognition

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_63,

CIFASD	Collaborative Initiative on Fetal Alcohol Spectrum Disorders
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorders

63.1 Introduction

The term fetal alcohol spectrum disorders (FASD) defines the adverse effects of alcohol on the developing fetus and represents a broad spectrum of structural anomalies and behavioral and neurocognitive disabilities (Barr and Streissguth 2001). The more restrictive diagnostic category of fetal alcohol syndrome (FAS) represents only those individuals at one end of the spectrum. Specifically, FAS is used to refer to individuals with intrauterine exposure to alcohol who exhibit growth deficiency and neurodevelopmental abnormalities, as well as a pattern of minor facial anomalies including short palpebral fissures, thin vermilion border of the upper lip, and smooth philtrum (Jones and Smith 1973; Bertrand et al. 2005) (see Fig. 63.1). In ideal situations, when a well-trained, experienced dysmorphologist is present and reliable maternal alcohol exposure information is available, the diagnosis of FAS can be made readily. However, most of the clinical features of prenatal alcohol exposure are not discrete abnormalities; they fall along a spectrum from mild to severe (Aase 1994; Stratton et al. 1996) and may be subject to ethnic differences in the expression of the phenotype (Douglas and Viljoen 2006; Moore et al. 2007; Mutsvangwa and Douglas 2007). Therefore, the diagnosis of even this well known pattern of abnormalities may be difficult. Further, the primary diagnostic features of prenatal alcohol exposure are fairly common, non-specific abnormalities and occasionally many of the features are expressed in individuals not prenatally exposed to alcohol. The diagnosis is also complicated by the fact that each of the features may be affected by multiple environmental and genetic influences unrelated to alcohol exposure. In addition, many individuals exposed prenatally to alcohol do not manifest the facial gestalt that is associated with FAS. For these reasons the clinical diagnosis of individuals with intrauterine damage due to alcohol exposure remains a challenge.

Given the primacy of the facial anomalies (Astley and Clarren 1995), much effort has gone into attempts to refine the degree to which these can be used to improve the diagnosis of FAS and identify other FASD. The goal of this chapter is to review efforts made to date to quantify the facial phenotype associated with FASD through the use of craniofacial anthropometry, specifically computerized craniofacial anthropometry and morphometric analysis. Computerized facial anthropometry and morphometric analysis refers to those techniques that derive measurements, shape assessment, or pattern recognition indirectly from captured images of the face. Although this definition could technically include radiographic images of the head and face (cephalometrics or computerized tomography), we refer here only to those techniques that focus on the surface features of the head and face.

Today, the clinically oriented anthropologist (or the anthropometrically oriented clinician) has an array of options for assessing the human head and face, including direct and indirect anthropometry (see Table 63.1). Indirect methods include two-dimensional (2D) photogrammetry (Clarren et al. 1987; Sokol et al. 1991; Astley et al. 1992, 2002; Farkas 1994; Astley and Clarren 1996, 2001; Hurwitz et al. 1999; Astley 2003; Huang et al. 2005) and three-dimensional (3D) computerized methods such as stereophotogrammetry (e.g., Burke et al. 1983; Burke and Hughes-Lawson 1989; Ras et al. 1996; Shaner et al. 2000; Meintjes et al. 2002; Douglas et al. 2003a, b; Douglas 2004; Douglas and Viljoen 2006; Grobbelaar and Douglas 2007; Mutsvangwa and Douglas 2007;

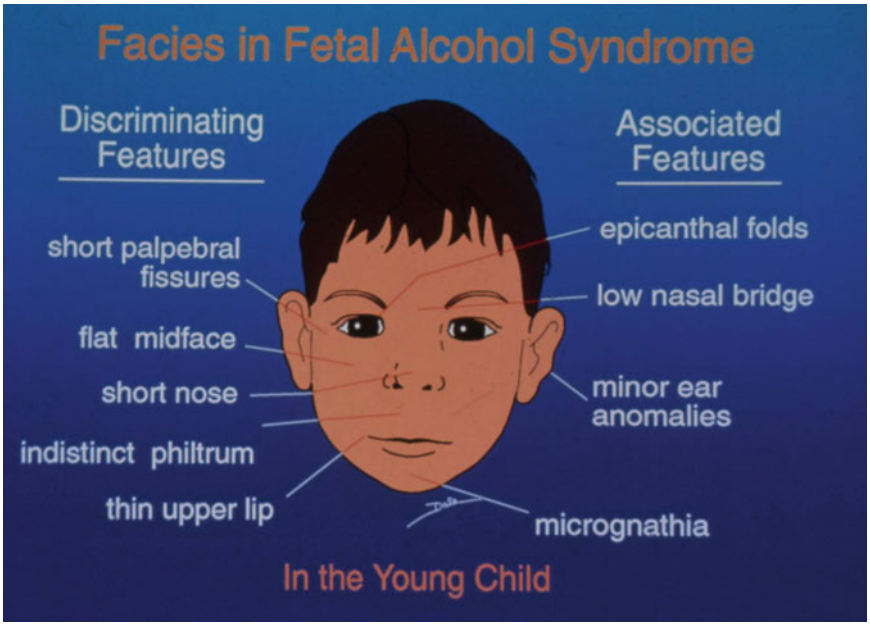

Fig. 63.1 Facial features associated with fetal alcohol syndrome (FAS). The diagram of the face shows both the discriminating and associated features of FAS (Reprinted from Streissguth and Little 1994, with permission)

Mutsvangwa et al. 2009), laser scanning (e.g., Arridge et al. 1985; Moss et al. 1989, 1991; Aung et al. 1995; Bush and Antonyshyn 1996; Aung 1999; Duffy et al. 2000; Da Silveira et al. 2003; Kau et al. 2004, 2005, 2006; Buckley et al. 2005; Hennessy et al. 2006; Moore et al. 2007; Fang et al. 2008), 3D photogrammetry (Hammond et al. 2003, 2004, 2005, 2008; White et al., 2004; Cox-Brinkman et al., 2007; Hammond, 2007), range camera (Strömland et al. 1998, 1999), and infrared photogrammetry (e.g., Ferrario et al. 1996, 1997, 1998a).

From an anthropometric and clinical perspective, indirect (computerized) anthropometry offers many advantages over conventional anthropometry. Computerized anthropometry is less time consuming for the patient and examiner, does not require extensive training, and allows the quantification of angles, surface area features, and volumes plus linear distances. In addition, these techniques provide permanent data that can be used to measure new facial features as knowledge of the craniofacial complex changes (Ferrario et al. 1998b; Hurwitz et al. 1999; Ferrario et al. 2005; Weinberg et al. 2006). These benefits are especially important when working with children and multiple observers, or when attempting to characterize a syndrome or disorder across different ages and ethnically diverse populations. The main weaknesses of computerized anthropometry are the cost of the instrumentation, the lack of reference standards for most populations, and the fact that some technologies are neither portable nor suited for use in the field.

The challenge of choosing the approach most appropriate for a given set of research objectives or of evaluating the results from particular studies requires an understanding of the strengths and weaknesses of each of these forms of computerized anthropometry versus the traditional direct measurement standard. Therefore we will first describe the strengths and weaknesses of the forms of computerized anthropometry that have been used in FASD research, then review their application to the study of FAS/FASD.

Table 63.1 Summary of methods used to capture anthropometric data

Type of anthropometric data capture	Advantages	Disadvantages	Applicability to understanding FAS/FASD	Cost
Direct anthropometry Utilizes calipers, tapes, and rulers to obtain linear, circumferential, and angular measurements directly from the head and face	Inexpensive portable equipment; "gold standard" for measurement accuracy; no limitation presented by hair or other poorly reflective surfaces; no limitation due to poor subject positioning; some population specific normative data available	Time consuming; some technical skill required; no permanent image created; difficult to use on young children; limited applicability for geometric or shape analysis	Widely used in clinical assessment, particularly for obtaining eye, head, and philtrum measurements	$
2D photogrammetry Measurements taken directly from standard or digital photographs	Rapid image capture; equipment cheap and portable; little technical expertise required; useful for young children; creates a permanent record for later analysis; can be easily shared; some geometric or shape analysis possible	Sensitive to subject positioning and lighting conditions; parallax effect can affect accuracy; measurements limited to two dimensions	Useful for assessment of subjective clinical features; measurements possible in two dimensions; collection of key measurements such as head circumference not possible	$
Stereophotogrammetry Measurements are "estimated" from calculations drawn from two or more simultaneously obtained photographs taken from different angles	Rapid image capture; equipment relatively cheap; limited technical expertise required; useful for young children; permanent record; useful for geometric shape analysis	Sensitive to subject positioning, expression, and lighting in original photographs; generally no 3D image produced; no commercially available systems; less portable; circumferential measurements not possible	Useful for large scale data collection; can be used for geometric shape analysis	$$
Computerized 3D Photogrammetry Utilizes full spectrum light, laser, or other energy to create a 3D model of the head and face on which a 2D digital image of the surface of the face is projected.	Rapid image capture; useful for young children; creates a permanent record; 3D data readily manipulated or "morphed" for advanced analysis; readily used for geometric and pattern recognition analysis; widely available commercial systems	The most expensive system; less portable; sensitive to subject facial expression and poorly reflective surfaces such as hair; circumferential measurements not possible	Useful for large scale data collection; reasonable comparability across 3D imaging system; easily manipulated for geometric and other "higher order" analysis	$$$

This table lists the different types of methods used to collect craniofacial anthropometric data, including direct anthropometry, 2D photogrammetry, stereophotogrammetry, and computerized 3D photogrammetry (2D: two-dimensional, 3D: three-dimensional)

63.2 Photogrammetry

Two-dimensional photogrammetry is the process of measuring objects from photographs; it has been used to aid in clinical anthropometry and direct observation (anthroposcopy) for over 50 years (Allanson 1997). The advantages of photogrammetry over direct anthropometry are that photographs can be obtained quickly and they provide a permanent record of the patient that can be retrieved and re-evaluated. In addition, there is no concern about subject movement during the measuring session. Unfortunately, there are also some disadvantages, including that fewer facial measurements may be taken from a photograph than by direct methods, that the quality of the photograph may be adversely affected by lighting and projection distortion (parallax), and that errors may occur in head positioning and in defining bony landmarks. In addition, a measure of scale is required for most data to be compared between subjects (Allanson 1997; Astley 2003; Hammond 2007).

Stereophotogrammetry derives measurements in three dimensions from photographs. This approach was first used clinically to quantify the human face in 1944 by Thalmaan Degen (Burke et al. 1983). Stereophotogrammetry makes it possible to measure soft tissue changes by *estimating* the 3D coordinates of points of an object. This is accomplished by comparing pre-marked points (on the photograph or individual) and then using triangulation from the camera to the common points in different perspectives to estimate distance between the camera and points and between combinations of points on the images. Several clinical studies using stereophotogrammetry have appeared over the last 2 decades (Burke et al. 1983; Burke and Hughes-Lawson 1989; Shaner et al. 2000; Meintjes et al. 2002; Douglas and Viljoen 2006; Mutsvangwa and Douglas 2007; Mutsvangwa et al. 2009). These methods combine the advantages of indirect anthropometry from photographs while avoiding most of the limitations. A major disadvantage of 3D photogrammetry is the lack of a commercially available system of image capture and analysis. This has resulted in the creation of "local" systems, thereby making comparison across studies difficult. In addition, image manipulation is more difficult in this methodology than in those that capture 3D data directly from the subject.

63.3 Computerized 3D Photogrammetry

A variety of indirect means of capturing 3D data from subjects are available. These systems differ from photogrammetric approaches in that the latter estimates 3D data from 2D photographs taken from different angles while the former constructs 3D data directly from light or other energy reflected from the surface of the "imaged" subject. Many of these systems combine photogrammetry data with dense range data from scanners. With these imaging systems 3D surface morphology is captured by recording the x, y, and z coordinates of hundreds of thousands of digital data points on a selected surface (Moss et al. 1989; Aung 1999). This usually requires a light (or alternate energy) source that is directed toward the subject; the reflected light is captured in the form of an individual point location in the x, y, z coordinates. The thousands of digital data points are connected by a triangulation network to render a surface texture (Aung 1999). The image can then be viewed using various computer software programs. A range of data can be collected from the images, including linear distances and the quantification of angles, surface areas, and volumes; in addition, the x, y, and z coordinate data can be extracted for a wide variety of statistical shape analyses (Weinberg et al. 2006).

Three-dimensional photogrammetry systems share the advantages of 2D photographs (speed of capture, permanency, and retrievability) and stereophotogrammetry (allowing for an expanded range of distance, geometric, and angle measurements). However, these systems have the distinct advantage of providing a true 3D model of the subject, which can be manipulated and adjusted ("morphed") to

reflect age-related or treatment-based projection of future appearance. In addition, several widely used commercial systems of both light- and laser-based image capture and analysis are available, thereby facilitating replication across studies. However, these systems remain the most expensive approach to indirect anthropometry.

Laser scanners offer a non-invasive technique that necessitates only a brief period of cooperation from study subjects. The 3D images are obtained by laser triangulation from an optical source projected onto the subject. The light pattern projected on the face is captured and converted into computer-generated images constructed around the projected "cloud" of points in the *x*, *y*, and *z* dimensions. Several studies have reported on the validity and high accuracy of the different laser scanning systems and the evaluated precision and reliability of data generated from the scans (Moss et al. 1988, 1989; Aung et al. 1995; Bush and Antonyshyn 1996; Coward et al. 1997; Kusnoto and Evans 2002; Kau et al. 2004, 2005; Ramieri et al. 2006). The Minolta-Vivid laser scanner is the most widely used, commercially available 3D scanner. It uses an eye-safe class I laser, and comprises a single unit that contains the laser projector as well as optical and digital cameras (the latter is used to capture a surface image that can later be wrapped around the cluster of *x*, *y*, and *z* spatial points). The main disadvantages of this technology include a relatively slow capture speed (compared to 3D light-based cameras), which can result in blurring due to movement of the subject, and sensitivity to non-reflective surfaces (such as hair), which are not well imaged.

Light-based 3D image capture operates in a manner similar to the laser method, except that full spectrum light patterns are projected onto the subject. Some systems project a structured light pattern (e.g., the Genex system) while others use a random light pattern (e.g., the 3dMD system). In addition, some have used a series of light patterns and a video camera to capture the data (the range camera method) (Strömland et al. 1998, 1999). Image capture systems that use light techniques have several advantages over the laser-based system used to capture 3D images. First, the acquisition time is extremely rapid, only 1.5 ms. This is similar to flash photography and eliminates blurred or distorted images from subject movement, which is common in young children (Hammond et al. 2004; Weinberg et al. 2006). In addition, the light-based system has less restrictive lighting conditions, allowing greater flexibility for the site of data acquisition. Several studies have evaluated the precision and error associated with the different 3D photogrammetry systems and found that data collected from these images are highly repeatable and precise (Weinberg et al. 2004, 2006; Aldridge et al. 2005; Gwilliam et al. 2006; Plooij et al. 2009).

63.4 Computerized Anthropometry in FASD

Direct anthropometry, specifically the measurement of eye distances (inner canthal, outer canthal, interpupillary, and palpebral fissure), philtrum length, and head circumference, is still used to assist in the diagnosis of FAS and screening for FASD. Several researchers have concentrated on assessing and measuring craniofacial traits on the actual subjects (Coles et al. 1985; Ernhart et al. 1987; Rostand et al. 1990; Autti-Rämö et al. 1992; Astley and Clarren 1995; Moore et al. 2001, 2002). One study (Astley and Clarren 1995) sought to objectify the FAS facial phenotype using craniofacial anthropometric measurements and a Likert scale on a group of racially mixed children. In addition, several computerized anthropometric methods have been utilized to study the facial features associated with prenatal alcohol exposure (see Table 63.2).

2D Photogrammetry: Digitized photographs have been used in the assessment of the facial phenotype in FAS. In general, their findings support earlier clinical findings of short palpebral fissures, a long midface relative to the length of the nose, a flattened midface in profile, and a somewhat small

Table 63.2 Summary of FAS/FASD studies that utilized computerized craniofacial anthropometry and/or morphometrics

Type of image capture	Authors	Publication date	Type of measurement	Results
2D Photogrammetry				
	Clarren et al. (Clarren et al. 1987)	1987	Shape analysis	They confirmed the FAS facial phenotype in children with heavy prenatal alcohol exposure: short palpebral fissures, relatively long and flat midface, and a retrusive mandible
	Sokol et al. (Sokol et al. 1991)	1991	Anthropometric facial measurements	FAS features were quantified and FAS neonates could be discriminated from non-exposed neonates using measurements obtained from the images. Important features were small nose, long philtrum, then vermilion, scooped bridge of nose, and short palpebral fissures
	Astley et al. (Astley et al. 1992)	1992	Shape analysis	Facial features compatible with FAS are not associated with marijuana exposure. Children with higher alcohol exposure had shorter noses relative to midface height, were retrognathic, and had shorter midface length. Results suggested ethnic differences in the expression of the FAS phenotype
	Astley and Clarren (Astley and Clarren 1996)	1996	Anthropometric facial measurements with other clinical features	FAS diagnosis can be done accurately using objective facial measurements of palpebral fissure length/inner canthal distance ratio, philtrum smoothness, and thinness of the vermilion
	Huang et al. (Huang et al. 2005)	2005	Automated facial recognition (AFR)	Using 2D digital photographs, AFR could moderately differentiate FAS faces from control faces
3D Image				
Range camera	Strömland et al. (Strömland et al. 1999)	1999	Anthropometric facial measurements	Children with FAS consistently had shorter palpebral fissures compared to non-alcohol-exposed children
Stereophotogrammetry	Mutsvangwa and Douglas (Mutsvangwa and Douglas 2007)	2007	Shape analysis	Confirmed FAS facial gestalt with some differences that may be due to ethnic variation
Laser	Moore et al. (Moore et al. 2007)	2007	Anthropometric facial measurements	FAS subjects can be discriminated, eye measurements are important, and ethnic differences are likely
Laser	Fang et al. (Fang et al. 2008)	2008	AFR	AFR techniques automatically detected and differentiated the FAS face from controls

This table lists the key computerized anthropometric studies that have been used to study FAS and/or FASD

mandible (Vitez et al. 1984; Clarren et al. 1987; Vitez 1987; Astley et al. 1992; Astley and Clarren 1996). These researchers concluded that photogrammetry may allow more accurate delineation of the facial phenotype of FAS, which would improve the subjective clinical diagnosis (Clarren et al. 1987; Vitez 1987).

Clarren et al. were the first to report the use of computerized anthropometry coupled with digitized photographs and shape analysis to assess the FAS face. Standard full face and lateral facial photographs were obtained on twenty-one 7-year-old children who had known heavy prenatal alcohol exposure. However, only two of the children had been previously diagnosed with FAS. An additional 21 photographs of 7-year-old children with negligible prenatal alcohol exposure were collected for control purposes. As in stereophotogrammetry, the investigators used a common set of premarked points but then employed geometric analysis (mean triangles) to compare the alcohol-exposed group with the control group. Their results demonstrated that significant differences in form existed between the two groups and that the differences conformed well with the descriptive features identified as characteristic by clinicians (Clarren et al. 1987).

Sokol et al. used measurements from digitized photographs of 97 neonates. To define neonatal facial features of FAS, three reference landmarks were chosen both in the frontal and lateral views (when available) and used to define seven salient frontal and lateral landmarks. The photographs were imaged onto a computer and appropriate reference landmarks were located and calibrated; then the measurement landmarks were digitized for analysis. The authors concluded that FAS-defining features could be quantified in the neonate from photographs as standardized x, y, z coordinates and that FAS could be reliably detected in the neonate with computer assistance (Sokol et al. 1991). Once again, this study appeared to confirm that areas of importance coincided with those previously described by clinicians: small nose with a long philtrum, short palpebral fissures, concave nasal bridge, and thin vermilion.

Following the earlier protocol developed by Clarren et al. (1987), Astley et al. conducted a computerized morphometric assessment of photographs using landmark analysis on marijuana-exposed and unexposed children that were group matched by alcohol exposure. A set of 23 facial landmarks were located and marked on photographs of each child. Landmarks were entered into a database using a computer digitizing table. Analysis of facial shape using geometric analysis was conducted and they found differences in facial traits depending on the type of first-trimester teratogen exposure. Individuals exposed to alcohol exhibited the unique facial features associated with FAS, while those exposed to cocaine and marijuana did not. Astley and coworkers suggested their results reinforce the sensitivity of their diagnostic approach in identifying individuals with FAS (Astley et al. 1992).

Astley and Clarren combined the use of anthropometric measurements of photographs with multivariate analysis to develop an FAS screening, diagnostic, and surveillance tool. Using stepwise discriminant analysis of three facial features (reduced palpebral fissure length/inner canthal distance ratio, smooth philtrum, and thin upper lip), they were able to differentiate individuals with and without FAS with 100% accuracy. The sensitivity and specificity were unaffected by age, sex, and race (Astley and Clarren 1996). The facial features used in this study were taken from an earlier study completed by the same researchers in which the measurements were taken on subjects and not on photographs (Astley and Clarren 1995). Astley and Clarren's work ultimately led to the development of the widely adopted 4-Digit Diagnostic Code (Astley and Clarren 2000) and the *FAS Facial Photographic Analysis Software* (Astley 2003), described in the Discussion section below.

Stereophotogrammetry: Mutsvangwa and Douglas used stereophotogrammetry to compare facial landmark data of FAS and normal subjects (see Fig. 63.2). In looking at only landmarks representing palpebral fissure length, upper lip thinness, and philtrum smoothness, they did not find any significant difference in shape between the two groups. However, when landmarks affected by mid-face hypoplasia were added, they found significant differences in shape between the two groups, broadly

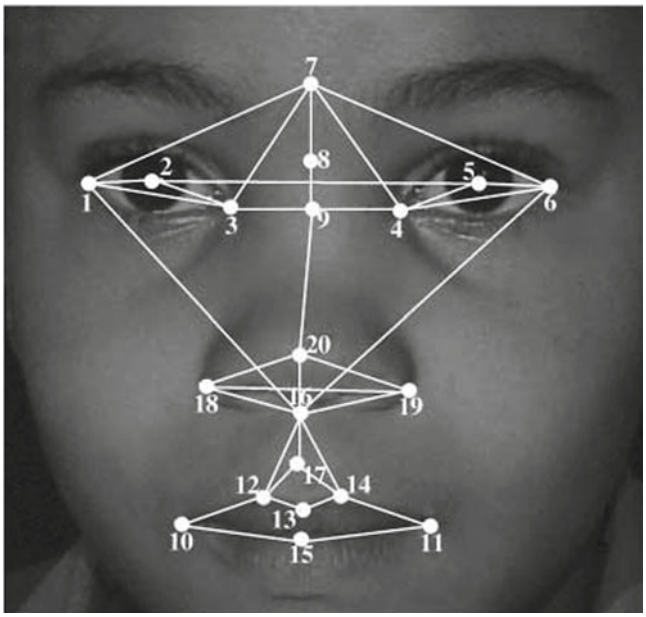

Fig. 63.2 Photographs and landmarks obtained using photogrammetry tools. The landmarks are: (*1*) left outer canthion; (*2*) left pupil centre; (*3*) left inner canthus; (*4*) right inner canthus; (*5*) right pupil centre; (*6*) right outer canthus; (*7*) glabella; (*8*) nasion; (*9*) sellion; (*10*) left cheilion; (*11*) right cheilion; (*12*) left crista philtre; (*13*) labiale superius; (*14*) right crista philtre; (*15*) stomion; (*16*) subnasale; (*17*) midpoint of philtrum furrow; (*18*) left alare; (*19*) right alare; (*20*) pronasale. The photograph shows the landmarks obtained using photogrammetry tools by Mutsvangwa and Douglas in their 2007 study. The landmarks are: (*1*) left outer canthion; (*2*) left pupil centre; (*3*) left inner canthus; (*4*) right inner canthus; (*5*) right pupil centre; (*6*) right outer canthus; (*7*) glabella; (*8*) nasion; (*9*) sellion; (*10*) left cheilion; (*11*) right cheilion; (*12*) left crista philtre; (*13*) labiale superius; (*14*) right crista philtre; (*15*) stomion; (*16*) subnasale; (*17*) midpoint of philtrum furrow; (*18*) left alare; (*19*) right alare; (*20*) pronasale. (Reprinted from Mutsvangwa and Douglas 2007, with permission)

confirming the FAS gestalt reported in the literature. In their study population, thinness of the upper lip was not a significant discriminator of FAS. They suggest that the disagreement in characteristic FAS facial shape between their results and that reported in the literature may be due to ethnic variation (Mutsvangwa and Douglas 2007).

Laser scanning: Moore et al. used a 3D laser scanner (Minolta Vivid 700 Series Non-Contact 3D) to assess linear measurements across four ethnic populations (North American whites, African Americans, Finnish whites, and "Cape Coloureds" from South Africa) (see Table 63.3 and Fig. 63.3). Measurements that reflected reduced size of the eye orbit were the most consistent feature discriminating FAS and controls across each study population. However, each population had a unique, though often overlapping, set of facial measurements that discriminated the two groups, suggesting important ethnic differences in the presentation of FAS. It is possible that these differences were accentuated by the wide age distribution between the study populations (Moore et al. 2007).

Light-based 3D image capture: In spite of its potential and the availability of commercial systems, few studies to date have employed this technology to study FAS/FASD. Strömland et al. used a range camera system to compare nine children with FAS to study controls. All children with FAS had shorter palpebral fissures, and in six of them the outer canthal distance was shorter than that in the reference group (Strömland et al. 1999). Ongoing work by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) is utilizing the 3dMD system to assess the FAS/FASD face in as many as 600 subjects from six different study sites.

Table 63.3 Craniofacial measurements and landmarks. Numbers keyed to Fig. 63.3

Type	Number	Measurement	Abbreviation
Width	1	Minimal frontal width	ft-ft
	2	Bizygomatic width	zy-zy
	3	Bitragal width	t-t
	4	Bigonial width	go-go
	5	Inner Canthal width	en-en
	6	Outer Canthal width	ex-ex
	7	Palpebral fissure length	en-ex
Depth	8	Upper facial depth	n-t
	9	Midfacial depth	sn-t
	10	Lower facial depth	gn-t
Length	11	Nasal length	n-sn
	12	Nasal bridge length	n-prn
	13	Philtrum length	sn-ls
	14	Lower facial height	sn-gn
	15	Total facial height	n-gn
	16	Ear length	sa-sba

This table lists the anthropometric measurements used by Moore et al. (2007) in their 3D laser scanner study that compared facial measurements of children with FAS across four different ethnic groups

Automatic facial recognition: Though not an image capture technique, automated facial recognition (AFR) uses machine training and higher order surface features to analyze 3D data generated from laser- or light-based systems. Automated facial recognition is utilized in several different application domains, such as forensics, biometrics, telecommunications, HDTV, and medicine, and it has shown promise for identifying individuals with FAS. It has many advantages over other techniques, including the fact that analysis is not dependent on linear measurements or geometric structures. The approach requires little expertise on the part of the observer, and it may more easily handle differences due to age, ethnicity, and gender compared to other forms of analysis (Huang et al. 2005). Huang et al. used AFR methods on 2D digital photographs of 31 FAS and 32 non-FAS facial images. The performance of the classifier for FAS prediction used 25 "components" and resulted in 70.0% correct classification of individuals previously identified by a trained dysmorphologist as having FAS (Huang et al. 2005). Fang et al. also used AFR techniques to demonstrate that computer algorithms can be used to automatically detect facial features that can discriminate FAS and control faces in 3D images (Fang et al. 2008). Thus, pattern recognition analysis may eventually lead to computerized diagnosis of individuals with FAS.

63.5 Discussion

It is remarkable that in spite of the multiple technologies applied and three decades in pursuit of a quantitative phenotype for the effects of intrauterine alcohol exposure, no "gold standard" has emerged. In fact, almost all previous research has done no better than an 80–90% correct classification of individuals already known to have FAS (by clinical diagnosis) compared to unaffected controls. It could be argued that prior studies have been limited in performance by the lack of a consistent standard for determining prenatal alcohol exposure. It could also be argued that progress has been slowed by the lack of agreement on critical diagnostic criteria for FAS and FASD. This has led to difficulties in

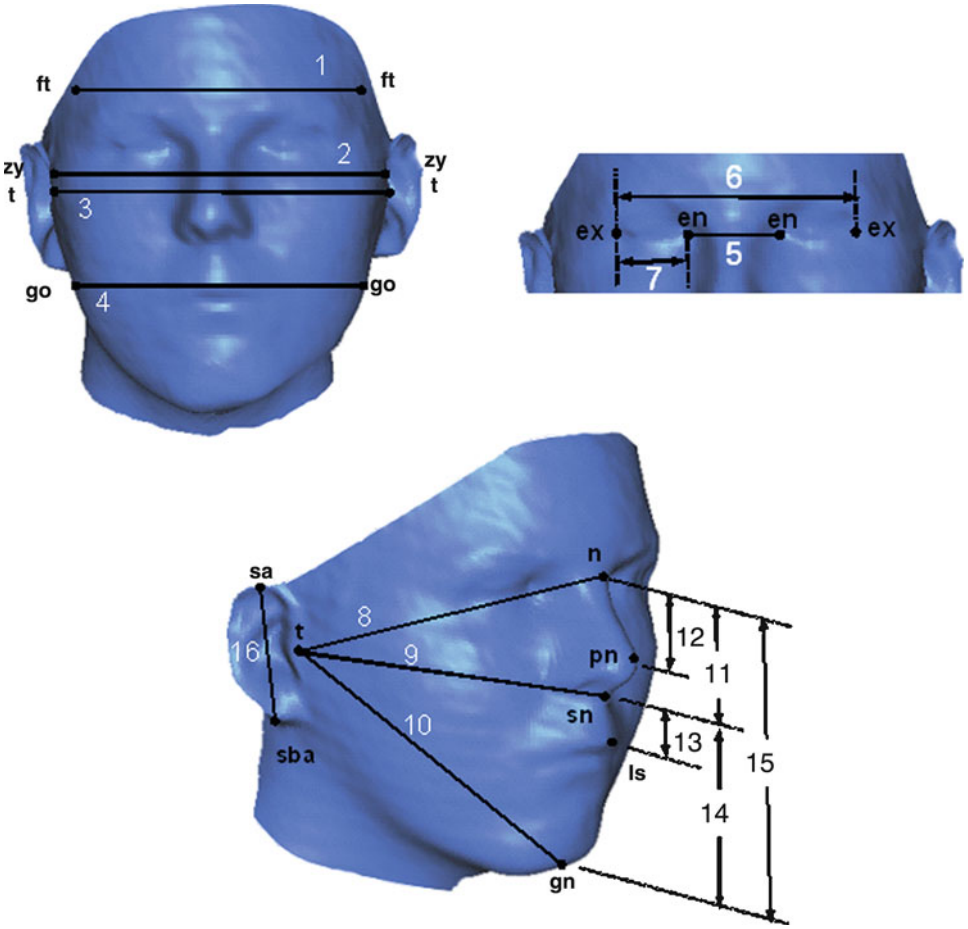

Fig. 63.3 Anthropometric measurements obtained using a 3D laser scanner (Minolta Vivid 910fw; KonicaMinolta Sensing Americas, Inc., Boulder, CO). Measurement names are listed in Table 63.3. Anthropometric measurements obtained by Moore and colleagues using a 3D laser scanner (Minolta Vivid 910fw; KonicaMinolta Sensing Americas, Inc., Boulder, CO). Measurement names are listed in Table 63.3. (Figure 63.3 and Table 63.3 are reprinted from Moore et al. 2007. With permission)

comparing results across studies and in consistently defining the target groups. More to the point, with one or two notable exceptions, none of these technologies has proven useful in (or been applied to) improving our ability to identify individuals who do not have clinically recognized facial gestalt associated with FAS. Thus, the sometimes bewildering array of studies and results reflect in part a lack of convergence of the research goals and objectives of the studies. However, we can assess the effectiveness of existing and previously used technologies in relation to three questions. The first would be, "Does it improve our ability to recognize individuals who fit the clinical diagnosis of FAS?" The second question would be, "To what degree can computerized anthropometry be used to expand the diagnostic phenotype for FASD?" The third question is, "To what degree can computerized anthropometry be used to improve our understanding of the pathophysiology of intrauterine alcohol exposure?"

Improving the phenotypic definition of the FAS face: Traditionally FAS is diagnosed using the gestalt method. The gestalt method, when used by an experienced, well-trained professional, can be highly accurate and reproducible (Clarren et al. 1987). However, its validity wanes when it is conducted by

untrained or inexperienced clinicians in the diagnoses of a condition like FAS that represents just part of the full spectrum (Astley and Clarren 1996). Astley and Clarren used anthropometry (and computerized anthropometry) in conjunction with other clinical tools to improve the accuracy and reliability of FAS diagnosis and to advance the identification of the full continuum of FASD (Astley et al. 1992; Astley and Clarren 1995, 1996, 2001; Astley 2003). They created the 4-Digit Diagnostic Code to provide a common standard for the diagnosis of FAS, one that correlates with structural, neurological, and functional measures of brain damage that are associated with prenatal alcohol exposure (Astley and Clarren 2000; Astley 2006). Their research has demonstrated a strong correlation between their 4-Digit Diagnostic Code classification and neuropsychological outcomes and brain structure anomalies (Astley et al. 2009a, b, c, d).

The 4-Digit Diagnostic Code was created to improve diagnostic accuracy. The four digits in the code reflect the magnitude of expression of the four key diagnostic features of FAS: (1) growth deficiency; (2) the FAS facial phenotype; (3) central nervous system damage/dysfunction; and (4) gestational alcohol exposure. The magnitude of expression of each feature is ranked independently on a four-point Likert scale with 1 representing complete absence of the FAS feature and 4 "classic" presence of the FAS feature. The 4-Digit Diagnostic Code is used for diagnosis, screening, and surveillance in several locations throughout the world. Computerized anthropometry is used to assess the magnitude of expression of two of the three facial features associated with the FAS facial phenotype. Three facial variables are assessed: palpebral fissure, upper lip, and philtrum. Palpebral fissure lengths are measured in standard deviations from the norm. These are adjusted for age, and when possible race, using published palpebral length standards. The upper lip and philtrum are measured on five-point photographic Likert scales using lip and philtrum guides (available for Caucasians and African Americans) (Astley and Clarren 1996, 2000; Astley 2006).

The *FAS Facial Photographic Analysis Software* developed by Astley and Kinzel measures the magnitude of expression of the key features of FAS by analyzing an imported digital photograph. According to Astley, the computerized image analysis program is very effective in measuring and ranking the magnitude of expression of the FAS facial phenotype (Astley 2003). The program requires standardized facial photographs (frontal, three-quarter view, and lateral) to be taken. In addition, an internal measure of scale is place on the patient's forehead. Digital photographs are scanned or downloaded into the software program. As in their direct assessment, three facial features (palpebral fissure length, upper lip thinness, and philtrum smoothness) are used in the analysis. The standards and guides used in the program are the same as used in the 4-Digit Diagnostic Code. Right and left palpebral fissure lengths and inner canthal distance are measured with a distance measurement tool. The user clicks the mouse pointer on the landmarks (endocanthion and exocanthion) and the program computes the distance between the landmarks. The program adjusts for the foreshortening of the length due the use of a 2D image. The phenotypic expressions of philtrum smoothness and upper lip thinness are recorded on a five-point Likert scale. The user selects the lip and philtrum (ranked 1–5) that best matches the patient's lip. Upper lip thinness is also recorded on a continuous scale with an objective measure of shape called circularity (or perimeter^2/area). Using the "circularity tool," the user outlines the upper lip and the program calculates the circularity and assigns a rank of 1–5. Once all three facial features have been evaluated, the software program assigns an A-B-C score to each feature based on the measurement or rank assigned. It then combines these results to assign an overall score (1–4) for the severity of the facial phenotype. Based on the 4-Digit Diagnostic Code, a rank of 4 represents a severe level of expression of the FAS facial phenotype and a rank of 1 is the absence of the expression of the facial phenotype (Astley 2003).

The 4-Digit Diagnostic Code creates homogeneous categories that are useful for clinical and research purposes; however, difficulties remain with the applicability of this tool due to the subjectivity in assessing the three cardinal facial features of FAS. Jones et al. noted that even after extensive

training, pediatricians were inconsistent in identifying a thin upper lip and smooth philtrum. Thus, despite the use of the Astley-Clarren lip-philtrum guides as a visual aid, only fair agreement was achieved in their assessment of small palpebral fissures (Jones et al. 2006). Cranston and colleagues evaluated consistency among the different methods used to measure palpebral fissure length (ruler, calipers, and Astley's photometric technique). Despite receiving training on the photometric method, the measurer obtained concordance between the ruler and photometric measures on only 42% of the subjects. The concordance was even lower between caliper measurements and those obtained with the ruler (24%) and photometric technique (18%) (Cranston et al. 2009).

Expanding the recognition of the FASD face: Moore et al. demonstrated that direct anthropometry could be used to identify individuals who lacked the full expression of clinical traits necessary to be classified as FAS, but who had known intrauterine alcohol exposure and at least one other clinical manifestation of the syndrome (Moore et al. 2001, 2002). These "partial FAS" individuals in fact were correctly discriminated (classified) from both the full FAS and the control population with an accuracy rate of 88%, a sensitivity of 86% (three FAS classified as PFAS), and a specificity of 94% (two members of the control group classified as PFAS) with just five variables (Moore et al. 2002). Moreover, Moore et al. demonstrated a distinct pattern of facial measurements in the partial FAS group that correlated strongly with that seen in the full-blown FAS cases, though it was less extreme (Moore et al. 2001, 2002). This finding supports viewing FASD as a continuum, though one that can be effectively identified through a wider range than is currently practiced.

Given the success of direct anthropometry in discriminating beyond the standard FAS phenotype, it is reasonable to expect the computerized anthropometric approaches and associated advanced analytical techniques to have similar or greater success in expanding our ability to identify a wider range of individuals with FASD. However, it is critical that such studies incorporate a design that is not dependent on the a priori definition of clinical FAS. Thus, a more efficient design would be one that grouped alcohol-exposed and non-alcohol-exposed samples matched for age, sex, and ethnicity. Results from such designs would not be tied to previously recognized "gestalt" features but rather would reflect the ability to detect the range of size and shape differences as a consequence of the effects of intrauterine alcohol exposure.

There is a clear need to develop an approach that combines the objective assessment of facial size and form made possible by computerized anthropometry with a clearly defined and widely accepted classification of the various clinical manifestations of FASD, as outlined by Astley and colleagues (Astley and Clarren 2000, 2001; Astley 2006; Astley et al. 2009a, b, d). In addition, the application of any variety of geometric shape analysis, such as that practiced by Hammond and colleagues (Hammond et al. 2003, 2004, 2005, 2008; Hammond 2007) and Klingenberg and colleagues (Klingenberg 2002; Klingenberg et al. 2002, 2004; Klingenberg and Monteiro 2005) could help move the anthropometric description of FAS/FASD beyond linear or proportional measures.

Improving the understanding of the pathophysiology of gestational alcohol exposure: Ultimately, computerized anthropometry analysis may have a larger impact on improving our understanding of the pathophysiology of alcohol exposure as neural imaging, craniofacial imaging, and data from animal models converge. Correlations between the magnitude of expression of the FAS facial phenotype and brain structure and function have been reported in both MRI and neuropsychological and behavioral studies (Astley and Clarren 1996, 2000, 2001; Astley et al. 2002, 2009a, b, d). As Astley and colleagues (Astley et al. 1999; Astley and Clarren 2001) point out, these results support the often cited reflection that "the face predicts the brain" (DeMyer et al. 1964); specifically, midline facial anomalies correlate with underlying developmental problems in the brain. These results are consistent with mice studies that found a similar parallel between in utero alcohol exposure, disruptions in the face, and structural deficits in the brain. Thus, studies consistently demonstrate that subtle midline facial

anomalies, such as those seen in FASD, appear to be pathognomonic of underlying structural brain deficiencies and malformations (Astley et al. 1999, 2009b; Astley and Clarren 2001).

63.6 Conclusion

The convergence of sophisticated imaging technologies (both facial and neural) coupled with higher level analytical approaches, including geometric and pattern recognition analysis, should lead to improvements in our ability to recognize and diagnose cases of FAS as well as a larger range of individuals with more subtle expressions of FASD. Simultaneously these applications should create new insight into the underlying pathophysiology of gestational exposure to alcohol. Of course, this added insight will only have meaning if it leads to a reduction in the occurrence and prevalence of this serious and ultimately preventable public health problem.

63.7 Applications to Other Areas of Health and Disease

Clearly, computerized anthropometry has wide applicability for the study of an array of craniofacial syndromes. In addition, these techniques have applicability in plastic and reconstructive surgery as well as in forensic science, such as predicting how a missing child's face would change with age. Perhaps most importantly, advances in computerized anthropometry and morphometrics may lead to advances in telemedicine, wherein computerized facial analysis can be applied to images obtained from isolated or remote locations and shared with physicians and other specialists who can use the remotely obtained data to assist in diagnosis, treatment planning, and outcome assessment.

63.8 Practical Methods and Techniques

Computerized anthropometry allows for the remote collection of data and it has been argued that it requires little expertise. This may be true for the original image processing, but for most of the methodologies outlined in this chapter, subsequent treatment of the data requires knowledge of human anatomy and of the craniofacial landmarks used in traditional anthropometric analysis. Future applications that involve automated analysis and categorization of facial patterns (facial recognition techniques) may obviate the need for anthropometric expertise. On the other hand, applications of these methodologies to exploring the link between facial form and the effects of alcohol on development will always require a deep understanding of craniofacial anatomy, growth, and development.

Summary Points

- Craniofacial anthropometry has a long association with clinical applications in the recognition, diagnosis, treatment, and understanding of craniofacial disorders.
- Craniofacial anthropometry is perceived as time consuming, difficult to use with young children, and necessitating a level of skill and experience that make it difficult to use in large-scale studies.
- Computerized craniofacial anthropometry offers a variety of options that overcome some of the

problems evident with direct anthropometry.
- Computerized anthropometry includes both 2D and 3D options.
- Computerized anthropometry offers the advantage of creating a permanent record of the face for continued analysis.
- Computerized anthropometry creates data that is easily utilized in geometric and other forms of morphometric analysis beyond size and proportion.
- 2D and 3D computerized anthropometry have been applied to the study of fetal alcohol spectrum disorders (FASD).
- Several studies have demonstrated that computerized craniofacial anthropometry can accurately identify individuals with previously diagnosed FAS, one end of the FASD continuum.

Key Points

Potentially improves the phenotypic definition of the FAS face
Expands the recognition of FASD
May improve the understanding of the pathophysiology of gestational alcohol exposure

- 3D studies offer the best hope of establishing objective criteria for identifying individuals within a wide range of FASD expressions.
- Computerized craniofacial anthropometry, coupled with information from other domains, such as neural imaging, should help generate improved understanding of the causes of the FASD phenotype.

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Chapter 64
Correlating Maternal and Infant Anthropometric Variables and Micronutrients at Birth in the Pakistani Population

Shahzad K. Akram and Christine Carlsson-Skwirut

Children can be ensured a healthy start in life if women start pregnancy healthy and well nourished, and go through pregnancy and childbirth safely.

UNICEF/WHO, December 2004

Abstract Foetal growth restriction is a large scale global problem affecting millions of pregnancies annually. It is dependent on both environmental and genetic factors. The consequences of babies being born small for their gestational ages or with low birth weights are substantial with increase in both immediate mortality and morbidity among neonates and their mothers, as well as increased morbidity in later childhood and adult life. Environmental constraints are, in large part, preventable and are further sub-classified into physical and nutritional factors. Maternal size and poor nutritional states increase both morbidity and mortality risks. These problems are most prevalent in sub-Saharan Africa and south-central Asia, where poverty is rampant and diets are deficient in key nutrients. We looked at the correlation of maternal anthropometry and micronutrients with birth weight in the Pakistani population, where the prevalence of growth restriction and LBW is 17%. Correlations were seen between both maternal physical and micronutrient measurements and birth weight. This suggests the potential use of maternal anthropometrical measurements as an initial measure to identify pregnancies at a high risk of growth restriction. Furthermore, multi-micronutrient supplementation may also prove to be beneficial to both short- and long-term outcomes of maternal and foetal growth, and health.

Abbreviations

BMI	Body Mass Index
DNA	Deoxyribonucleic Acid
FGR	Foetal Growth Restriction
GDM	Gestational Diabetes Mellitus
IU	International Units

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_64,

IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
RDA	Recommended Daily Allowance
SGA	Small for Gestational Age
SI	Système International d'unités
TCA	Tricarboxcylic Acid
UNICEF	United Nations Children's Fund
USDA	United States Department of Agriculture
WHO	World Health Organisation

64.1 Introduction: Causes and Measures of Maternal and Neonatal Health and Disease

Adequate nutrition is quintessential for normal growth, development and function, both pre-natally and following delivery, through to later life. Poor nutrition in the mother can lead to deficiencies in pregnancy, with profoundly devastating effects on both the child and the mother. Anaemia at the time of delivery, for example, is correlated with an increased risk of maternal mortality. Thus, we see that maternal and child nutrition exhibit a truly complex and sensitive relationship. This is more readily seen in under-nutrition in lower-income countries, particularly in sub-Saharan Africa and south-central Asia. The consequences of under-nutrition are vast and devastating, contributing to an estimated 3.5 million deaths per annum globally (Black et al. 2008). Furthermore, certain metabolic disorders in the mother may significantly affect birth size and weight. The most prevalent metabolic disorder is that of diabetes mellitus, which, in the gestational period, results in abnormal glucose metabolism in the placenta and foetus. This gestational diabetes mellitus (GDM) contributes to infant birth weights significantly greater than those of the normal population percentiles. The fine balances of foetal growth and birth weight are therefore crucial for both short- and long-term health outcomes in the child, with a tip of this balance in either direction contributing to increased morbidity and mortality in newborns and infants.

For the purposes of this chapter we chose to focus on a particular population group, that of rural Pakistan. This population represents the majority lower socio-economic class prevalent in south-central Asia, namely Pakistan, India, Sri Lanka and Bangladesh. In these countries, an estimated 70% of inhabitants live in poorer rural settings (WHO 2009). In terms of the population, this amounts to an astounding figure of approximately one billion people. It is in these settings that the greatest poverty and thus the vast problems associated with maternal and child under-nutrition exist. The topographical representation of Pakistan can be seen in Fig. 64.1, along with key population facts (Table 64.1).

Though the exact prevalence of low birth weight (LBW) is unknown, it is estimated between 10% and 25%, depending on the region. This can be seen more clearly in Table 64.2, where six independent studies have calculated the incidences of LBW in different cities across Pakistan (n = 2625, mean incidence 17%). These figures represent the documented cases of growth restriction and LBW and must therefore be seen as such, as the actual incidences may in fact be much higher. Infant and maternal morbidity and mortality statistics, given as population health figures, for the Pakistani population are represented in Table 64.3. The national figures are compared with regional averages, as shown in the World Health Statistics report, 2009 (WHO 2009). In the table, one can see that the percentage of 5 year olds who are underweight is a substantial 31.3%. This leads to increased morbidity with a corresponding increase in mortality rate in this population group, as can be seen in the table (92 per 1,000 live births).

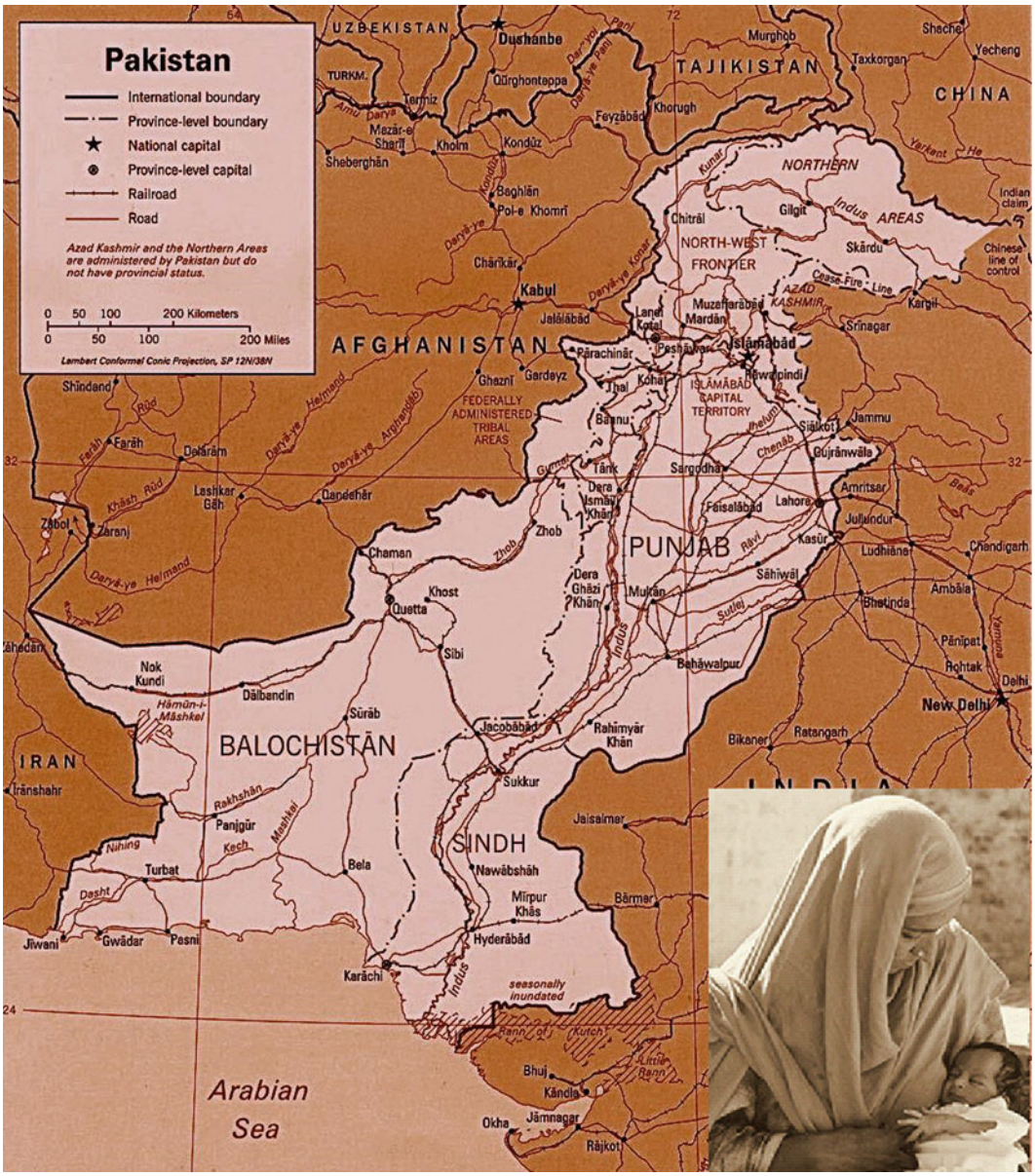

Fig. 64.1 Topographical map of Pakistan. A topographical map of Pakistan, showing bordering countries. The bottom right corner depicts a mother and child in the rural setting, as the majority of the population is based in rural areas

64.2 Maternal Anthropometry and Growth Outcomes

We began by briefly discussing the highly complex relationship between maternal and infant parameters, where maternal size not only factors in, but, directly correlates to foetal size. In simpler terms, the size of the mother is believed to affect the birth size of the infant. Physically, this can be described more appropriately as "Maternal Constraint". The physical size of the mother, along with her physiological state, "constrains" gestational growth, based on environmental factors. These physical constraints can

Table 64.1 Key facts of Pakistan

1. The total rural and urban population of Pakistan is estimated to be *147,100,000* (based on the most recent population census, 2006).
2. The rural population is estimated to be *95,000,000*.
3. The urban population is estimated to be *52,100,000*.
4. The total numbers of live births per year are estimated to be *3,800,000*.
5. The number of live births per year in rural areas is estimated to be *2,600,000*.
6. The number of live births per year in urban areas is estimated to be *1,200,000*.
7. The prevalence of growth restriction is an estimated 17% per annum, which amounts to *646,000* babies being born small for their gestational ages (SGA) per annum with the majority in rural areas.

This table lists key population statistics, including total population, number of live births and the estimated numbers of babies born small for their gestational ages (SGA), per annum. The statistics further describe the differences between rural and urban populations, as the greatest prevalence of SGA is in rural areas. All statistics are based on the Government of Pakistan population statistics (FBS 2006)

Table 64.2 Literature review on the incidence of low birth weight (LBW) babies in the Pakistani population

Author	Population included in study (*n*)	Incidence of LBW (%)
1. Janjua 2009	540	18.5
2. Akram 2008	89	13.4
3. Badshah 2008	1,039	9.9
4. Jalil 2008	695	16
5. UNDP 2005	N/A	19
6. Shamim 1999	262	25
	Total: 2625	***Mean: 17***

This table lists the incidence of low birth weight (LBW) in the Pakistani population. The mean incidence of LBW was seen to be 17% (6 studies, $n = 2625$) (Akram et al. 2008; Shamim et al. 1999; Janjua et al. 2009; Jalil et al. 2008; UNDP 2005; Badshah et al. 2008)

Table 64.3 Morbidity and mortality rates in Pakistan and South-East Asia

Morbidity/mortality parameter	Population statistics (Pakistan)	Regional averages (South-East Asia)
Neonatal mortality rate (per 1,000 live births)[a]	53	38
Infant mortality rate (per 1,000 live births)[b]	73	60
Children under 5 years underweight for age (%)	31.3	N/A[c]
Under 5 mortality rate (per 1,000 live births)	90	82
Maternal mortality ratio (per 100,000 live births)	320	420

The table summarises the morbidity and mortality statistics as a measure of population health for the Pakistani population, comparing the Pakistani population with regional averages (South-East Asia)
[a]Neonatal mortality rate = probability of dying between birth and the first 30 days of life
[b]Infant mortality rate = probability of dying between birth and 1 year of age
[c]N/A = not available) (WHO 2009)

only be taken in to consideration once other metabolic and genetic causes of disease have been excluded (Price and Coe 2000). These trends of growth restriction follow an inter-generational pattern, whereby daughters born with a LBW to small mothers are likely to be small themselves and thus perpetuate this cycle of growth restriction from generation to generation (Ounsted et al. 1988). This is clearly seen in the Pakistani population, where average maternal and subsequent birth- weights are significantly lower than those of higher-income countries.

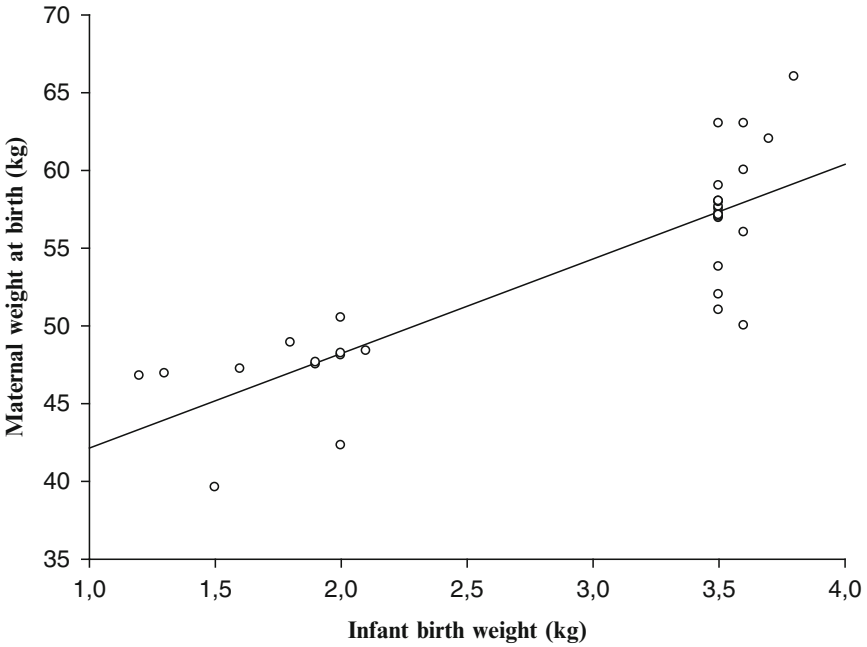

Fig. 64.2 Correlation of maternal and infant weight at birth. A correlation of infant birth weight (kg) and maternal weight at birth (kg) in the Pakistani population. The positive correlation emphasises the significance of maternal size influencing birth weight outcomes (Akram et al. 2008)

In keeping with the idea of maternal constraint, physical measurements of the mother should therefore correspond to foetal growth and birth weight outcomes. Akram et al., have shown these correlations in their study in rural Karachi, Pakistan (Akram et al. 2008). Figure 64.2 shows the positive correlation of maternal weight at birth and birth weight in the Pakistani population. Additional anthropometric measurements taken include maternal height, upper mid-arm circumference and mid-triceps skin fold thickness. These measurements represent body-fat composition and thus the nutritional status of the mother. Figure 64.3 depicts the use of callipers to measure the mid-triceps skin fold thickness.

64.3 Infant Anthropometry as a Reflection of Growth

Foetal growth is largely dependent on the foetal genome and the foetal environment. Abnormalities in either of these two variables may lead to foetal growth restriction (FGR). More specifically, genetic abnormalities, or environmental/nutritional changes, can alter the normal cycles of growth, thereby leading to inadequate growth. Prenatal, this growth restriction is better known as "intrauterine growth restriction" (IUGR), subsequently leading to children being born small for their gestational ages (SGA). FGR, or IUGR, is further classified as "symmetrical" and "asymmetrical", depending on the causes and onset of insult to the foetus resulting in poor growth outcomes. Nutritional deprivation in the early gestational period has been seen to symmetrically restrict foetal growth, as all developing cells are equally affected. In comparison, nutritional deficiencies seen in the latter half of gestation account for a more asymmetrical growth restriction, whereby the

Fig. 64.3 Callipers measuring skin-fold thickness. The use of skin fold callipers to measure the mid-triceps skin fold thickness as a measurement of body fat. Skin fold thickness is a key anthropometric variable.

basic organs have already developed. This results in shunting of the available nutrition away from the rest of the body to maintain nutrient supply to the brain, resulting in asymmetrically large heads in babies born with LBW. Though there are little data on the Pakistani population, the majority of growth restricted babies are seen to be symmetrical, implying that their nutritional deficiency is a chronic problem. This goes hand in hand with maternal constraint, where small mothers are more likely to give birth to babies with LBW. This is most likely the result of poor underlying maternal nutrition restricting foetal growth in an attempt to "save" the pregnancy (Gluckman and Hanson 2004).

64.4 Micronutrients and Their Correlations with Maternal and Foetal Anthropometry

Looking beyond the problems associated with anthropometry and metabolic disorders, nutritional and dietary intake of the mother also significantly contributes to pregnancy and foetal outcomes. Micronutrients, simply vitamins and minerals, are crucial for growth and development at both the cellular and systemic levels. Deficiencies of key micronutrients may lead to maternal anaemia, hypertension, diabetes, complications of labour and even death (Ramakrishnan 2002). Micronutrients,

Table 64.4 Vitamins and minerals, RDA and correlations with anthropometry

Vitamins	RDA	Correlation with maternal and infant anthropometry	Minerals	RDA	Correlation with maternal and infant anthropometry
A	770 μg	Yes (Dancheck et al. 2005)	Calcium	1,000 mg	Yes (Atallah et al. 2002)
D	5 μg	Yes (Scholl and Chen 2009)	Copper	1,000 μg	Yes (Zadrozna et al. 2009)
E	15 mg	Yes (Dancheck et al. 2005)	Chromium	30 μg	No available data
K	90 μg	No available data	Iodine	220 μg	Yes (Alvarez-Pedrerol et al. 2009)
B1	1.4 mg	Yes (Fawzi et al. 2007)	Iron	27 mg	Yes (Scholl and Hediger 1994)
B2	1.4 mg	Yes (Fawzi et al. 2007)	Magnesium	350–400 mg	Yes (Makrides and Crowther 2001)
B3	18 mg	Yes (Fawzi et al. 2007)	Manganese	2 mg	No available data
B5	6 mg	Yes (Baker et al. 1977)	Molybdenum	50 μg	No available data
B6	1.9 mg	No (Thaver et al. 2006)	Phosphorus	700 mg	No available data
B12	2.6 μg	Yes (Baker et al. 1977)	Selenium	60 μg	Yes (Zadrozna et al. 2009)
Folate	400–600 μg	Yes (Tamura and Picciano 2006)	Zinc	11 mg	Yes (Akram et al. 2008)
Biotin	30 μg	No (Baker et al. 1977)			
C	85 mg	Yes (Fawzi et al. 2007)			

An overview of key vitamins and minerals and their recommended daily allowances (RDAs) for women in the pregnancy age group (15–40 years), along with their correlation with maternal and infant anthropometry. The RDAs are based on North American recommendations (USDA 2009). All measures are given in SI units

therefore, play a significant role in pregnancy outcomes and maternal health. Recommended daily allowances (RDA) of all the vitamins and minerals during pregnancy can be seen in Table 64.4. Additionally, correlations with maternal and new born anthropometry can also be seen in the table, along with supporting references. The RDAs for all micronutrients, based on North American statistics, are higher during pregnancy (USDA 2009).

64.5 Fat-Soluble Vitamins

64.5.1 Vitamin A

Vitamin A deficiency is an extremely common form of micronutrient malnutrition. An estimated 5.6% of pregnant women worldwide are affected, and 20% of all maternal mortality is attributed to its deficiency. The most common clinical manifestations, however, are that of decreased immunity and poor vision, leading to blindness due to corneal scarring. Not much data are available on the affects of its supplementation during pregnancy in the Pakistani population. The RDA is 4,000 international units (IU), though in deficiency prone areas, WHO and UNICEF have recommended two supplemental injections of 200,000–400,000 IU. Though there is no direct correlation with maternal or foetal anthropometry in the Pakistani population, positive correlation trends have been seen in other parts of the world (Table 64.4). Furthermore, it is well known that adequate supplementation decreases maternal and infant mortality rates.

64.5.2 Vitamin D

Vitamin D is essential for the normal physiological balance of calcium and phosphate, both in blood and in skeletal tissue, as well as maintaining general cellular function, muscle contractions and nerve conduction. Unfortunately no data are available on vitamin D supplementation or correlations with maternal or infant size in the Pakistani population. Scholl et al., have shown that serum levels do in fact correlate with maternal body mass index (BMI) and infant birth weight, as can be seen in Table 64.4 (Scholl and Chen 2009).

64.5.3 Vitamin E

This vitamin plays a key role as an "anti-oxidant", helping the body dispose of potentially harmful free-radicals. If left unhindered, free-radicals are believed to adversely affect reproductive cells, as well as to potentiate erroneous cell reproduction. Deficiencies of this vitamin have, therefore, been shown to increase rates of infertility and frequent miscarriages, as well as an increased incidence of premature deliveries. However, not much data are available on the correlations with maternal or foetal anthropometry. Though deficiencies are suspected in the Pakistani population, there are no available data.

64.5.4 Vitamin K

Vitamin K is fundamental for the regulation of certain proteins, collectively known as vitamin K proteins. So far, the only known role of this vitamin in health is in the maintenance of normal coagulation. There is no evidence of its correlation with maternal or foetal anthropometry.

64.6 Water-Soluble Vitamins

64.6.1 Vitamin B-Complex

This family of vitamins, known as the B-complex, consists of several clinically significant vitamins, namely, B1, B2, B3, B5, B6, B12, folate and biotin. These are discussed in brief as follows:

Thiamin (vitamin B1), riboflavin (vitamin B2) and niacin (vitamin B3) are all essential cofactors for glucose and energy metabolism. As one can imagine, deficiencies present as marked metabolic effects in the mother, and, more significantly, may lead to impaired foetal growth. Thus, levels of these vitamins indirectly correlate to foetal anthropometry and birth weight outcomes.

Pantothenate (vitamin B5) is structurally part of the carrier protein co-enzyme A, which is an essential part of glucose metabolism. More specifically, co-enzyme A is integral in the tricarboxcylic acid (TCA) cycle. Deficiencies of this vitamin thereby also lead to impaired glucose metabolism and the corresponding growth restriction. Though there are no available data on the Pakistani population, Baker et al., have shown a significant positive correlation of levels with infant birth weight (Baker et al. 1977).

Pyridoxine (vitamin B6) deficiency has not been shown to alter pregnancy outcomes, nor correlate to maternal and infant anthropometry. Its principal function is that of amino acid metabolism. Interestingly, excesses of this vitamin may, in turn, be harmful to both the mother and foetus.

Folic acid and cobalamin (vitamin B12) are essential for normal cell reproduction, neural cell function and for the production of erythrocytes, amongst other functions. There have been no isolated trials on vitamin B12 supplementation, or correlations with maternal anthropometry. Deficiencies are, however, believed to cause growth stunting. Folate deficiencies, on the other hand, have clearly been shown to increase the risk of IUGR, thereby resulting in babies being born with lower birth weights (Tamura and Picciano 2006). Unfortunately, no data on the correlations of folate levels and anthropometry are available in the Pakistani population.

Biotin is essential for the production of fatty acids, fat metabolism and cell growth. There is little evidence for the role of supplementation of this vitamin in pregnancy and no evidence of correlations with maternal anthropometry or birth weight.

64.6.2 Vitamin C

This water-soluble vitamin plays a key role in the maintenance of collagen structure in the intracellular matrices. Deficiency of vitamin C results in poor wound healing and "scurvy". Mot much data are available, suggesting the possible beneficial effects of supplementation of this vitamin in pregnancy in decreasing the incidence of babies being born SGA.

64.7 Minerals

Details of key minerals can be seen in Table 64.4. Clinically, the most significant of these deficiencies are calcium, iodine, iron and zinc. These shall be discussed in more detail. There is limited evidence to conclude correlations with anthropometry and the minerals, copper, chromium, magnesium, manganese, molybdenum, phosphorus and selenium.

64.7.1 Calcium

Calcium plays an important role in bone metabolism, muscle contraction and neuronal cell signalling, where calcium-gated channels are present in certain synapses. Additionally, it is present in teeth, soft tissues and other processes of metabolism. An estimated 1–2% of adult weight consists of calcium. Low levels have been associated with osteoporosis and, in severe cases, muscle and nerve dysfunction. Though there are no data on its correlation with maternal and foetal anthropometry in Pakistan, Atallah et al., have correlated low calcium levels with LBW (Atallah et al. 2002).

64.7.2 Iodine

This mineral is important in the normal functioning of the thyroid gland and thyroid hormones. Deficiencies in pregnancy have been seen to positively correlate with LBW, though there is little evidence on correlations with maternal anthropometry.

64.7.3 Iron

Clinically, the most common micronutrient deficiency globally is that of iron. Iron deficiency anaemia increases the risks of maternal mortality, particularly towards the latter part of pregnancy. Furthermore, serum levels of iron have been correlated with foetal size and birth weight outcomes, suggesting the importance of supplementation during pregnancy (Scholl and Hediger 1994).

64.7.4 Zinc

Zinc is quintessential for normal DNA binding and function and thus for nuclear reproduction and cellular growth and development. Deficiencies have been well correlated with IUGR and birth weight. Similar trends have been seen in the Pakistani population, where serum zinc levels correlate positively to both maternal and new born anthropometry (Akram et al. 2008).

64.8 Other Trace Elements

The trace elements are key functional components in normal cell and tissue functioning. There are no data available on the correlation of these minerals with anthropometry in the Pakistani population. However, recent studies on copper and magnesium have shown strong positive correlation with both IUGR and babies being born small for their gestational ages. Furthermore, selenium levels inversely correlate with IUGR and birth weight, indicating the potential toxicity of this trace mineral in pregnancy. The roles of chromium, manganese, molybdenum and phosphorus are still unclear in pregnancy and birth weight outcomes.

64.9 Applications to Other Areas of Health and Disease

Based on current trials there is insufficient evidence to suggest, or negate, a multiple micronutrient supplementation programme, particularly in the Pakistani population, though a reduction of the number of "low birth weight" babies has been seen with multiple micronutrient supplementation in other countries. This may potentially help reduce the vicious cycle of under-nutrition. One would thus expect to see a reduction in the corresponding associated health problems of poor nutrition, thereby decreasing the health burden on already burdened low-income countries. Furthermore, timely nutritional supplementation has been shown to aid in positive maternal outcomes in pregnancy, with decreased incidences of preterm labour and pregnancy complications. As stated in a WHO report on LBW, "*children can be ensured a healthy start in life if women start pregnancy healthy and well nourished, and go through pregnancy and childbirth safely*" (WHO 2004).

64.10 Practical Methods and Techniques

Measurements of maternal and new born anthropometry include height, weight, BMI, mid-triceps/mid-calf skin fold thickness, mid-arm/mid-calf circumference, as well as abdominal wall thickness and head circumferences in new born infants (Table 64.5). With the correct instruments and training

Table 64.5 Key maternal and infant factors contributing to growth outcomes

Maternal factors	Infant factors
• Maternal size correlates with infant size (Maternal Constraint).	• Genetic and environmental factors affect birth weight outcomes.
• Adequate nutrition is important throughout pregnancy.	• Foetal and infant nutrition are important for adequate growth.
• Maternal glucose metabolism is an important regulator of birth weight outcomes.	• Thyroid hormone levels are essential for both growth stature and neurological development.
• Correct thyroid hormone levels are essential for normal foetal growth and development.	

This table emphasises the key maternal and infant factors contributing to foetal and infant growth outcomes and development

of personnel, these measurements can be made fairly accurately in even the most remote of rural settings. Simple training of health care workers in rural Pakistan may be a relatively cheap and effective way of identifying currently affected pregnancies and those at higher risks of developing growth restriction. The implications are potentially tremendous, as high risk pregnancies can be identified in a timely manner and referred to specialist facilities for further assessment and appropriate management. The current data, however, are rather limited, suggesting the need for further trials.

Summary Points

- Maternal anthropometry positively correlates with infant birth weight and anthropometry, emphasising the importance of maternal constraint. Maternal anthropometry can therefore be used to screen for pregnancies at a higher risk of developing growth restriction.
- The mean incidence of LBW in the Pakistani population is 17% (10–25%), based on several population-based studies.
- Foetal growth is dependent on both genetic and environmental factors. Environmental factors are based on both maternal size (maternal constraint) and nutritional state. Genetic factors include genetic malformations and disorders.
- Adequate maternal and foetal nutrition is paramount to normal growth and development. This can be more clearly seen with the vitamins A, C, D, E, B1, B2, B3, B5, B12, folate and pantothenate, as these vitamins positively correlate with birth weight outcomes.
- Adequate mineral consumption is also essential for normal growth. The minerals and trace elements calcium, copper, iodine, iron, magnesium and zinc, are of particular importance, as these have been shown to positively correlate with birth weight outcomes.
- Excessive consumption of certain nutrients may cause toxicity. Higher levels of the mineral selenium have been seen to negatively correlate with birth weight.
- Clinical measures of maternal anthropometry, namely BMI, limb circumference and skin-fold thickness, may be used to identify for growth restricted pregnancies. Timely identification of higher risk pregnancies can thus allow for the appropriate referral to specialised centres for further diagnosis and intervention.

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Chapter 65
Neonatal Anthropometry: A Tool to Evaluate the Nutritional Status and Predict Early and Late Risks

Luis Pereira-da-Silva

Abstract Neonatal anthropometry is an inexpensive, noninvasive and convenient tool for bedside evaluation, especially in sick and fragile neonates. Anthropometry can be used in neonates as a tool for several purposes: diagnosis of foetal malnutrition and prediction of early postnatal complications; postnatal assessment of growth, body composition and nutritional status; prediction of long-term complications including metabolic syndrome; assessment of dysmorphology; and estimation of body surface. However, in this age group anthropometry has been notorious for its inaccuracy and the main concern is to make validated indices available.

Direct measurements, such as body weight, length and body circumferences are the most commonly used measurements for nutritional assessment in clinical practice and in field studies. Body weight is the most reliable anthropometric measurement and therefore is often used alone in the assessment of the nutritional status, despite not reflecting body composition.

Derived indices from direct measurements have been proposed to improve the accuracy of anthropometry. Equations based on body weight and length, mid-arm circumference/head circumference ratio, and upper-arm cross-sectional areas are among the most used derived indices to assess nutritional status and body proportionality, even though these indices require further validation for the estimation of body composition in neonates.

Abbreviations

AA	Arm area
AFA	Arm fat area
AGA	Appropriate-for-gestational age
AMA	Arm muscle area
BS	Biceps skinfold
BSF	Body surface
BW	Birth weight
CHL	Crown-heel length
CI	Cephalic index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_65,

CTS	Central to total skinfold ratio
DEXA	Dual X-ray absorptiometry
HC	Head circumference
IUGR	Intrauterine growth restriction
LBW	Low birth weight
LGA	large-for-gestational age
MAC	Mid-arm circumference
MAC/HC	Mid-arm circumference/head circumference ratio
PI	Ponderal index
SBS	Subscapular skinfold
SGA	Small-for-gestational age
SPS	Suprailiac skinfold
TBF	Total body fat
TS	Tricipital skinfold
VLBW	Very low birth weight
WAA	Water arm area
W/L	Weight-for-length ratio

65.1 Introduction

In newborn infants, anthropometry has the advantages of being easy to perform and convenient for bedside measurements. Unfortunately, in this age group, anthropometry has been notorious for its inaccuracy in untrained hands and for its inter-observer variation (De Bruin et al. 1995; Prins 1995).

Direct measurements, such as body weight, length, and body circumferences are the most commonly used measurements for nutritional assessment in clinical practice and field studies (Pereira-da-Silva et al. 2007).

Some indices and equations derived from direct measurements have been proposed and used in newborn infants for improving the accuracy of the anthropometry (De Bruin et al. 1995; Prins 1995).

Most of the measurements are widely regarded as being too inaccurate to be recommended in everyday practice. Although such assumptions are superficially correct, it is possible to train health care professionals to perform accurate measurements. Furthermore, accurate sequential measurements are possible and provide more information than single measurements alone (Prins 1995; Pereira-da-Silva et al. 2007).

65.2 Neonatal Anthropometry as a Tool

65.2.1 Diagnosis of Foetal Malnutrition and Prediction of Early Postnatal Complications

Newborn infants with intrauterine growth restriction (IUGR) are usually small-for gestational-age (SGA), defined as body weight < 3rd centile (Olsen et al., 2010).

Most IUGR infants are the consequence of uteroplacental insufficiency occurring in the third trimester, affecting mainly the weight, so that the neonate appears wasted, presenting as an

asymmetric SGA. An early and prolonged insult during gestation causes chronic under-nutrition with impairment in both skeletal and soft tissue growth, resulting in a stunted neonate with reduction of both weight and length, a symmetrical SGA (Beattie 1994).

While the definition of SGA is based exclusively on the birth weight (BW), the classification of asymmetric or symmetric SGA is based on the ponderal index (PI) which includes the length (Patterson and Pouliot 1987).

SGA and IUGR are not synonyms. Some SGA infants are constitutional and not undernourished. Conversely, some appropriate-for-gestational age (AGA) infants are undernourished but cannot be defined as IUGR based on BW criteria (Beattie and Johnson 1994). In this case, mid-arm circumference/head circumference index (MAC/HC) or reduced skinfold thickness may identify foetal growth restriction regardless of BW (Owen 1997; Pereira-da-Silva et al. 2007). Reduced weight-for-length (W/L) ratio (Yau and Chang 1993) and individualized BW ratio (Wilcox et al. 1993) are other complimentary measurements capable of identifying IUGR.

Identifying IUGR at birth facilitates the anticipation of therapeutic measures for early metabolic and other complications, like poor gut function, hypothermia, hypoglycemia, hypocalcemia and polycythemia (Beattie and Johnson 1994). Asymmetrical IUGR neonates are more prone to these complications (Patterson and Pouliot 1987) and preterm infants with IUGR additionally are at higher risk of respiratory distress syndrome, sepsis, and necrotizing enterocolitis, as compared with AGA neonates of equivalent gestational age (Pereira-da-Silva et al. 2007).

At the other extreme, macrosomic and large-for-gestational age (LGA) neonates have a higher risk of vaginal birth trauma. When excessive growth is due to endocrine-metabolic disturbances, as in infants of diabetic mothers, increased risk of hypoglycemia, hypocalcemia, polycythemia and hyperbilirubinemia is present (Pereira-da-Silva et al. 2007). Nevertheless, most cases of macrosomic and LGA neonates are constitutional (Beattie and Johnson 1994).

65.2.2 Postnatal Assessment of Growth, Body Composition and Nutritional Status

In preterm infants, the changes in body compartments are greatly influenced by hydro-electrolytic management and energy-protein support. In these patients, direct and derived anthropometric measurements may estimate body composition, assess quality of growth and guide nutritional management. The fat compartment is more variable and sensitive to changes in nutritional status. Fat-free mass reflects the skeletal and body growth, assessed by crown-heel length (CHL) and length of body segments (Gibson et al. 2003).

A recent investigation using magnetic resonance imaging has shown that preterm infants born within 32 weeks have decreased subcutaneous adipose tissue and increased intra-abdominal adipose tissue. Their accelerated weight gain is accompanied by increased total and subcutaneous adiposity, while severity of illness is the principal determinant of increased intra-abdominal adiposity (Uthaya et al. 2005).

Skinfold measurements, MAC and derived measurements like muscle and fat upper-arm areas may estimate body fat and fat-free compartments. However, anthropometric techniques have limitations in estimating body composition in neonates and small infants; therefore, routine nutritional assessment in this age group is still mainly based on the body weight (De Bruin et al. 1995; Prins 1995).

65.2.3 Prediction of Long-Term Complications, Including Metabolic Syndrome

Neonatal morphometry may predict long-term complications.

Low BW, SGA and particularly asymmetrical SGA are predictors of high blood pressure, central obesity, dyslipidemia, diabetes type 2 and coronary heart disease in adulthood (Jaquet et al. 2005; Uhing and Das 2009). This is explained by multifactorial mechanisms which relate foetal undernutrition to insulin resistance and metabolic syndrome later in life (Jaquet et al. 2005).

Cognitive and neurodevelopment deficits have been associated with symmetrical SGA (Pereira-da-Silva et al. 2007).

In the other extreme, foetal macrosomia and LGA neonates, especially those related to maternal diabetes are associated with future obesity and metabolic syndrome (Pereira-da-Silva et al. 2007).

Morphometry at birth associated with the anthropometric outcome may predict late complications more accurately than the isolated morphometry at birth. For instance, greater postnatal catch-up growth in infants with IUGR predisposes to high blood pressure and metabolic syndrome (Jaquet et al. 2005; Uhing and Das 2009).

65.2.4 Dysmorphology Assessment

Anthropomorphic measurements provide more accurate assessment in infants with dysmorphic features. Appropriate techniques and standards are recommended for several anthropomorphic measurements (Fletcher 1998). This kind of assessment is facilitated by specialized computer programs (Zankl 2004).

For evaluating disproportionate growth disorders, measurements of trunk and limbs should be obtained, as well as arm span, crown-rump length, crown-rump length/crown-rump length (CHL) ratio, upper and lower limb lengths, hands and feet lengths, thoracic index, and inter-nipple distance (Dangerfield and Taylor 1983; Fletcher 1998).

For measuring the arm span, the arms should be extended at right angles to the body with open hands; the tip of each middle finger should be marked and the distance between the marks measured; the span should approximate the CHL, and a shorter span may indicate short upper limbs (Fletcher 1998).

For measuring the crown-rump length, the infant should be lying on the side with the hips flexed to 90° and the distance between the top of the head to the posterior distal part of the thighs should be taken (Fletcher 1998). The mean value of crown-rump length/CHL ratio varies from 0.653 at 27 weeks to 0.673 at 40 weeks, and an increased value may indicate short lower limbs (Fletcher 1998).

Perineal measurements such as anal placement, penile length, and testicular volume may be useful in particular conditions (Fletcher 1998).

For accurate assessment of craniofacial dysmorphisms some measurements should be taken: head length (maximal dimension of the sagital axis); head width (maximal biparietal diameter); ear width, protrusion and rotation measurements; in relation to the eyes, the outer and inner canthal distances, inter-pupillary distance, palpebral fissure length, and slant of the palpebral fissure; in relation to nose and mouth, the nasal length and width, length of colunella, philtrum length, and mouth width (Fletcher 1998). Cephalic index (CI) should be determined: CI = head width ×100/head length; the CI is 76–80.9 in a normal head, <75.9 in dolicocephaly and >81 in brachycephaly (Fletcher 1998). Standards for 15 angular and 11 linear craniofacial parameters measured on lateral head radiograph in term and preterm neonates, have been recently published (Paulsson and Bondemark 2009). Key points of CI see Table 65.1.

Table 65.1 Key points of cephalic index (CI)

1. CI is useful to define more precisely disproportionally long or narrow heads (dolicocephaly) and disproportionately wide heads (brachycephaly), present in some syndromal abnormalities.
2. For the head length measure the maximal dimension of the sagital axis and for the head width measure the maximal biparietal diameter. Then, calculate the CI = head width × 100/head length.
3. Normal head CI = 76–80.9; dolicocephaly CI < 75.9; and brachycephaly CI > 81

65.2.5 Estimate of Body Surface (BSF)

The BSF estimate is necessary for calculating the doses of some drugs, glomerular filtration rate and fluid balance in burns cases (Current 1998). BSF may be estimated by direct visualization of normograms based on weight and CHL (Meban 1983). In alternative, a simplified equation has been proposed for proportionate neonates: BSF = (weight + 4)/30, in which BS is expressed in m^2 and weight in kg (Current 1998).

65.3 Standards

To determine if an infant's measurements fall within normal ranges, an appropriate standard should be used. When comparing with population-based standards, the population should have similar backgrounds and potential, including gender, race, gestational age, genetic potential, altitude and type of feeding (Fletcher 1998). For example, measures of adiposity, such as skinfolds, are usually greater in female infants (Rodriguez et al. 2004). The growth pattern in infants with specific syndromes and conditions should be interpreted with specific charts, if available, as for Down's syndrome, Silver-Russell syndrome, cleft lip or palate and symptomatic congenital heart disease (Pereira-da-Silva et al. 2007). Specific intrauterine growth charts for twin infants are also available (Ananth et al. 1998). To evaluate intrauterine growth, the pregnancy should be accurately dated. The growth pattern of healthy breastfed infants differs to a significant extent from the NCHS/WHO international reference which is based on predominantly formula-fed infants. The new international growth references developed by the WHO multicentre growth reference study (www.who.int/childgrowth/en) describe how infants should grow rather than describing how infants grow. These growth references were constructed based on scientifically robust tools and an international sample of healthy breastfed infants living in health-promoting conditions.

Another issue concerns the consensus as to the limits for definition of normality. Depending on the epidemiologic power of the studies that produced the standards, their limits may be <10th and >90th centile, <5th and >95th centile, <3rd and >97th centile, <2.5th and >97.5th, or 2SD around the mean (Fletcher 1998). In fact, these are pure statistical definitions of normality, which should be confirmed by clinical risk assessments of the main adverse outcomes for each standard.

65.4 Direct Measurements

65.4.1 Weight

Since measurement of body weight is simple and reliable, it has been the most used isolated parameter for monitoring growth and nutritional status in neonates in clinical practice (Johnson et al. 1997; Gibson et al. 2003). It is has been reported that body weight is an independent predictor of body

Table 65.2 Classification of infants according to the birth weight (BW) and BW related with gestational age

- Normosomic: BW ≥ 2,500 g and ≤ 4,000 g
- Microsomic or LBW: BW < 2,500 g
- VLBW: BW < 1,500 g
- ELBW: BW < 1,000 g
- Macrosomic: BW > 4,000 g
- AGA: BW ≥10th and ≤90th centile, or ≥5th and ≤95th centile, or ≥3rd and ≤97th centile, ≥2.5th and ≤97.5th centile, or ≥–2SD and ≤+2SD of the mean, according to the standards used
- SGA: BW <10th centile, or <5th centile, or <3rd centile, or <–2SD below the mean, according to the standards used
- LGA: BW >90th centile, or >95th centile, or >97th centile, >97.5th centile, or >+2SD above the mean, according to the standards used
- Asymmetrical IUGR: PI <2.5th centile
- Symmetrical IUGR: PI >97.5th centile
- IUGR: commonly SGA. A small proportion of SGA infants are constitutional, and a small proportion of AGA infants suffered IUGR who should be diagnosed based on other anthropometric indices

AGA appropriate-for-gestational age; *ELBW* extremely low birth weight; *IUGR* intrauterine growth restriction; *LBW* low birth weight; *LGA* large-for-gestational age; *PI* ponderal index; *SGA* small-for-gestational age; *VLBW* very low birth weight

composition in preterm and term infants (Koo et al. 2000). However, it does not give any information on body compartments and quality of growth. For instance, in preterm infants the weight gain may result from positive balance of water and sodium rather than accumulation of fat or muscle mass (Prins 1995).

Based on the BW, neonates are classified as macrosomic if >4,000 g, microsomic or LBW if <2,500 g, very low birth weight (VLBW) if <1,500 g, and extremely low birth weight (ELBW) if <1,000 g. Classification of infants based on gestational age and birth weight see Table 65.2.

Technique and instrumentation: Patients are weighed naked, ideally to the nearest gram.

The digital electronic weighing scales have excellent precision and reproducibility and reduce dramatically the observer bias and reading errors as compared with beam-scales (Prins 1995; Gibson et al. 2003). With the aim of minimizing the handling of sick and fragile preterm infants, recent incubators are fitted with weighing scales, but their precision has not been validated. The weighing procedure is difficult because drips and inserted tubes should not touch the mattress, and errors may also be caused by the infant's movements (Prins 1995).

Standards: Appropriate charts and standards relate body weight with infant's age.

- Intrauterine growth is assessed by curves relating BW with gestational age. The old Lubchenco's curves (1966) (Fig. 65.1) have been widely used for many years (Fenton 2003), but their current use in preterm infants is fraught with several methodological problems that include the small sample of extremely preterm infants, errors in estimating gestational age and combined-gender curves (Rubin 2009). Contemporary charts should be preferred, such as the large gender-specific, racially diverse, population-based surveys of BW for various gestational ages published by Olsen et al. (2010); these provide 3rd and 97th percentiles cutoffs for defining SGA and LGA births and plausible mean and standard deviations as well (Tables 65.3 and 65.4); validated smoothed percentile curves are also available (3rd–97th) (Fig. 65.1). SGA and LGA classifications using Lubchenco's standards (1966) differ significantly from the Olsen's standards (2010). Specific BW standards stratified by placental chorionicity are available for monochorionic (Fig. 65.2) and dichorionic (Fig. 65.3) twins (Ananth et al. 1998).
- Ehrenkranz's postnatal growth chart (Ehrenkranz et al. 1999) has a longitudinal growth grid for 100-g BW intervals from 500 to 1,500 g (Fig. 65.4). This chart has the advantage of being based

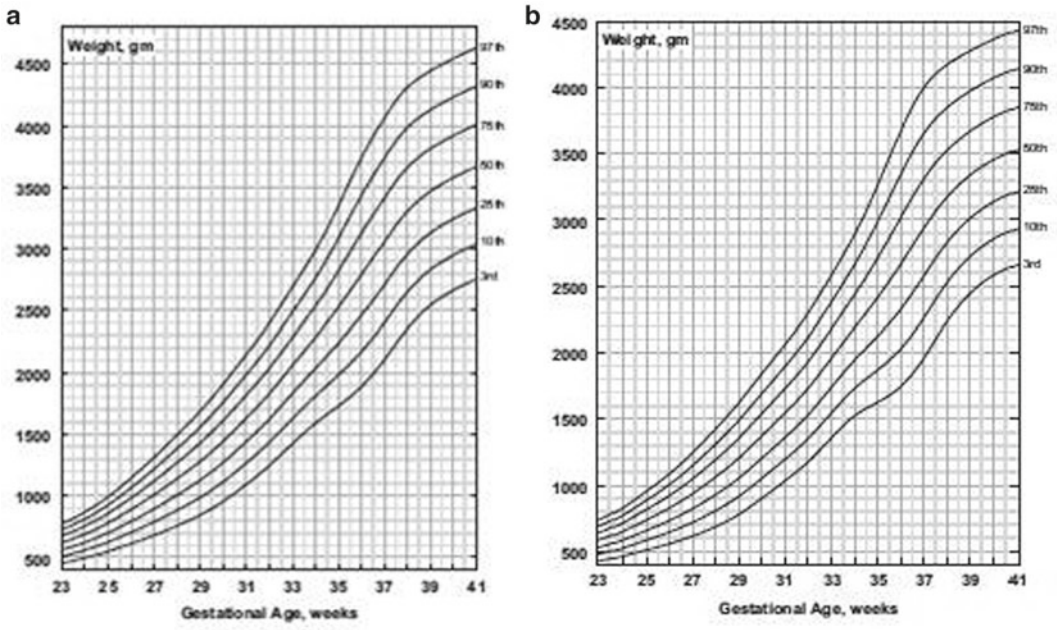

Fig. 65.1 Olsen's intrauterine gender-specific curves for birth weight. Intrauterine growth weight curves for males (**a**) and females (**b**) as estimated from live birth at gestational ages from 23 to 41 weeks (Olsen IE et al. 2010. With permission by © American Academy of Pediatrics)

Table 65.3 Male birth weight (g) charts in relation to gestational age (GA), expressed in centiles, means and standard deviations (Adapted from Olsen et al. 2010, Copyright © American Academy of Pediatrics, 2010)

	Centile								
GA (weeks)	3	10	25	50	75	90	97	Mean	SD
23	NA[a]	509	563	621	677	727	NA[a]	622	74
24	497	561	623	690	756	813	869	689	96
25	550	626	700	780	857	926	992	777	116
26	613	704	794	890	983	1,065	1,145	888	145
27	680	789	895	1,009	1,120	1,218	1,312	1,001	170
28	758	884	1,007	1,141	1,271	1,385	1,496	1,138	203
29	845	988	1,128	1,280	1,429	1,560	1,688	1,277	218
30	955	1,114	1,272	1,443	1,612	1,761	1,906	1,435	261
31	1,093	1,267	1,441	1,631	1,818	1,984	2,147	1,633	275
32	1,246	1,433	1,622	1,829	2,034	2,218	2,398	1,823	306
33	1,422	1,625	1,830	2,057	2,284	2,488	2,688	2,058	341
34	1,589	1,810	2,035	2,285	2,536	2,763	2,987	2,288	364
35	1,728	1,980	2,238	2,527	2,819	3,084	3,348	2,529	433
36	1,886	2,170	2,462	2,792	3,127	3,432	3,737	2,798	498
37	2,103	2,401	2,708	3,056	3,411	3,736	4,060	3,058	518
38	2,356	2,652	2,959	3,306	3,661	3,986	4,312	3,319	527
39	2,545	2,833	3,131	3,469	3,813	4,129	4,446	3,476	498
40	2,666	2,950	3,245	3,579	3,919	4,232	4,545	3,582	493
41	2,755	3,039	3,333	3,666	4,007	4,319	4,633	3,691	518

[a]Not available because of small sample size

Table 65.4 Female birth weight (g) charts in relation to gestational age (GA), expressed in centiles, means and standard deviations (Adapted from Olsen et al. 2010, Copyright © American Academy of Pediatrics, 2010)

	Centile								
GA (weeks)	3	10	25	50	75	90	97	Mean	SD
23	NA[a]	477	528	584	639	687	NA[a]	587	80
24	464	524	585	651	715	772	828	649	89
25	511	584	657	737	816	885	953	738	121
26	558	645	732	827	921	1,004	1,085	822	143
27	615	719	822	936	1,047	1,147	1,244	934	168
28	686	807	928	1,061	1,193	1,310	1,425	1,058	203
29	778	915	1,052	1,204	1,354	1,489	1,621	1,199	226
30	902	1,052	1,204	1,373	1,542	1,693	1,842	1,376	246
31	1,033	1,196	1,361	1,546	1,731	1,897	2,062	1,548	271
32	1,177	1,352	1,530	1,731	1,933	2,116	2,297	1,730	300
33	1,356	1,545	1,738	1,956	2,178	2,379	2,580	1,960	328
34	1,523	1,730	1,944	2,187	2,434	2,661	2,888	2,194	357
35	1,626	1,869	2,123	2,413	2,711	2,985	3,261	2,420	440
36	1,745	2,028	2,324	2,664	3,015	3,339	3,667	2,675	514
37	1,958	2,260	2,575	2,937	3,308	3,651	3,997	2,946	551
38	2,235	2,526	2,829	3,173	3,525	3,847	4,172	3,184	512
39	2,445	2,724	3,012	3,338	3,670	3,973	4,276	3,342	489
40	2,581	2,855	3,136	3,454	3,776	4,070	4,363	3,461	465
41	2,660	2,933	3,214	3,530	3,851	4,142	4,433	3,546	477

[a]Not available because of small sample size

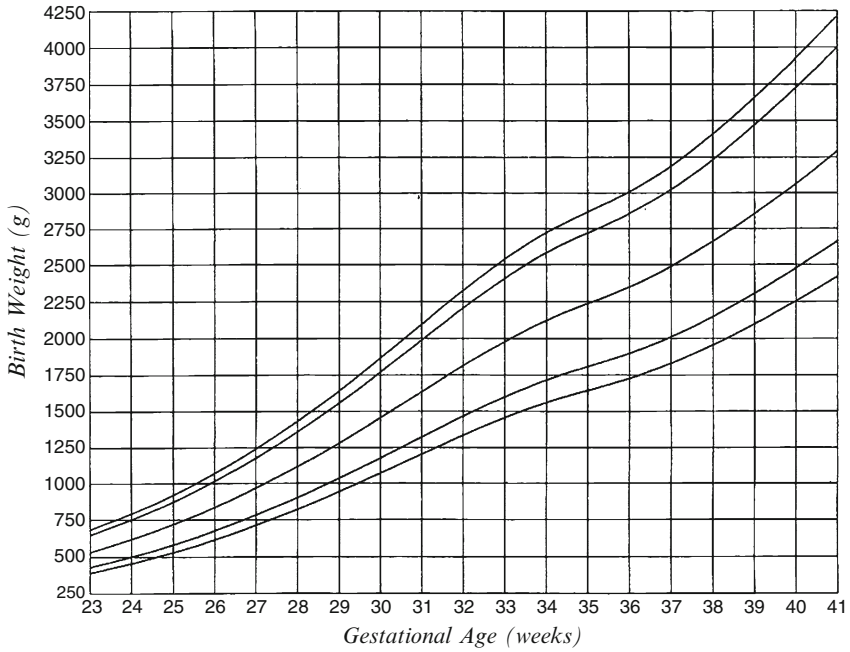

Fig. 65.2 Ananth's BW grid for monochorionic twins. Birth weight centiles (5th, 10th, 50th, 75th, and 95th) for twins with monochorionic placentation (Ananth 1998. With permission by © Lippincott Williams & Wilkins)

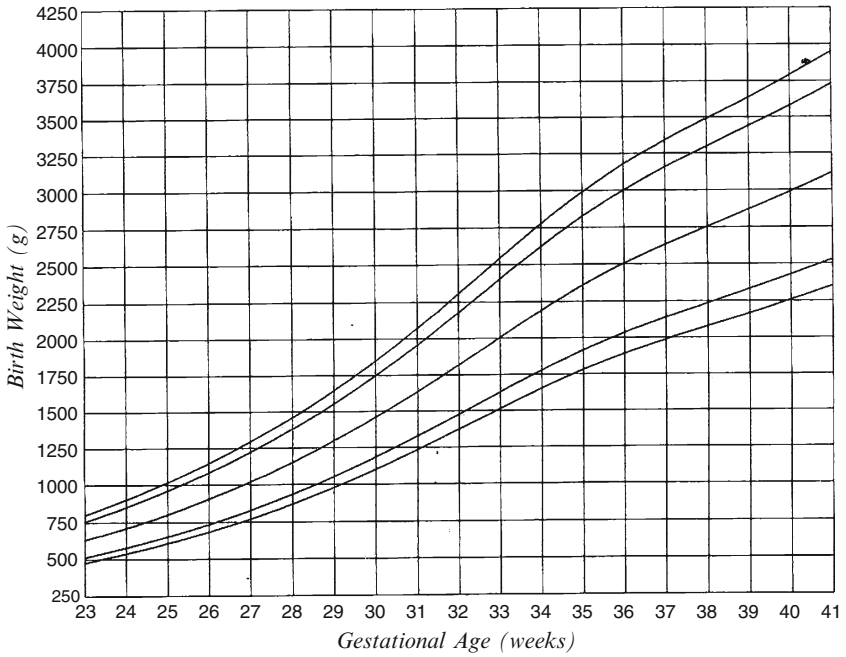

Fig. 65.3 Ananth's BW grid for dichorionic twins. Birth weight centiles (5th, 10th, 50th, 75th, and 95th) for twins with dichorionic placentation (Ananth 1998. With permission by © Lippincott Williams & Wilkins)

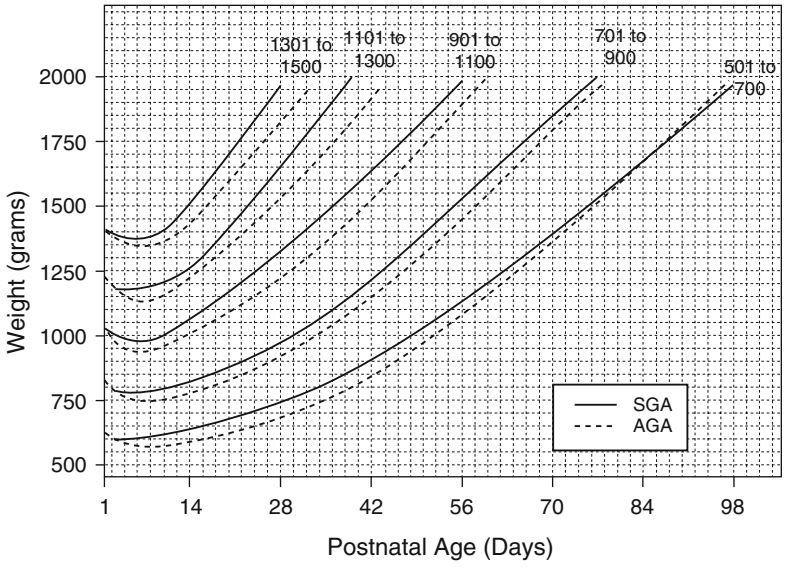

Fig. 65.4 Ehrenkranz's postnatal weight grid for very low BW infants. Postnatal longitudinal weight grid for very low BW infants (Adapted from Ehrenkranz et al. 1999. With permission by © *American Academy of Pediatrics*). This chart is useful for monitoring weight from birth up to circa 100 postnatal days, with specific curves for appropriate-for-gestational age (AGA) infants (*dashed lines*) and small-for-gestational age (SGA) infants (*solid lines*). Available at http://pediatrics.aappublications.org/cgi/content/full/104/2/280

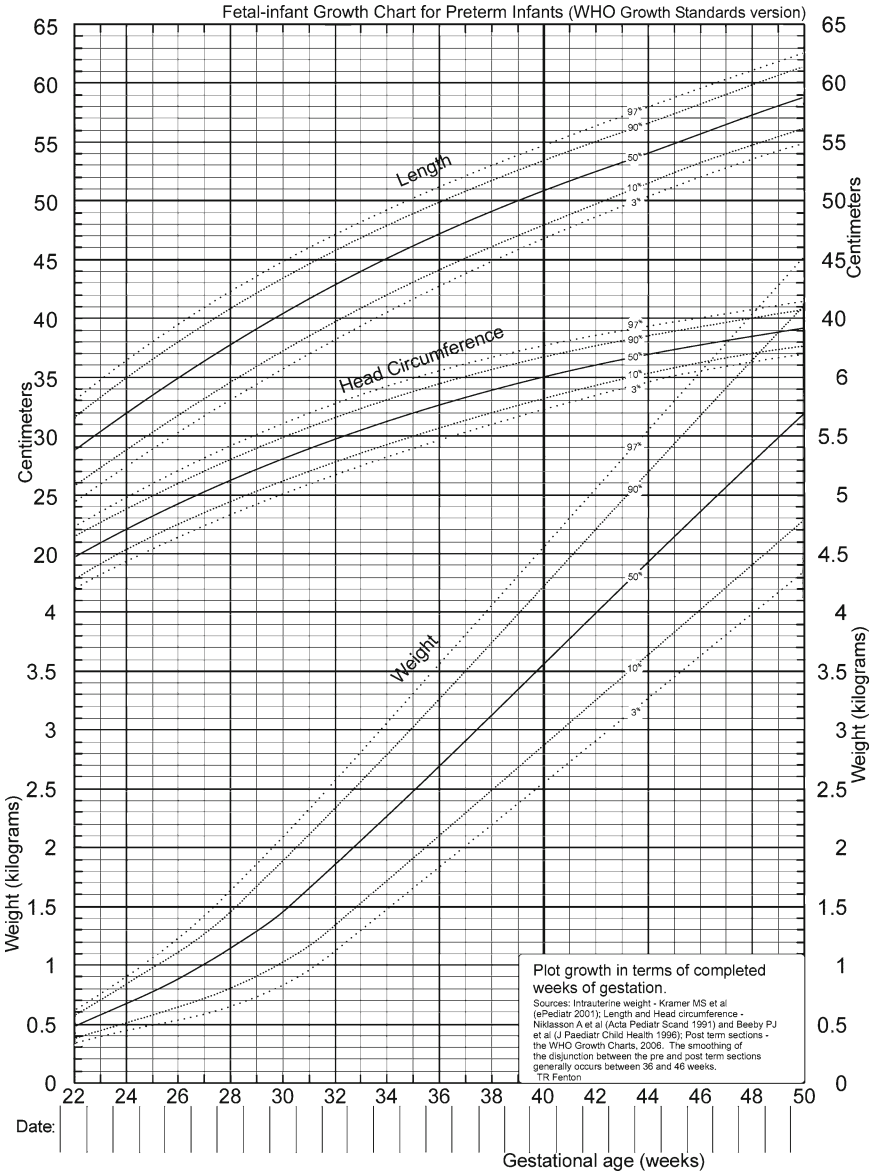

Fig. 65.5 Fenton's growth chart for very low birth weight (VLBW) infants up to 50 postnatal weeks Chart for monitoring weight, length and head circumference of VLBW (updated with recent data and a new format: Fenton 2003, courtesy of © BioMed Central).The Fenton's chart is useful for monitoring the growth of preterm infants from birth up to 50 postnatal weeks, including after discharge. Available at http://members.shaw.ca/growthchart/

on a large multicentric prospective cohort of VLBW infants. Reflecting imperfect and disparate nutritional practices, in fact it represents "things as they are" on current nutritional practices and not a guide for "ideal growth" (Rubin 2009). Using the Ehrenkranz's weight chart it is possible to monitor the weight up to circa 100 postnatal days (about 14 postnatal weeks). Furthermore, specific charts for SGA and AGA and for major morbidities are provided.

- Fenton's chart 2003 (updated in 2008) (Fig. 65.5) allows monitoring the growth of preterm infants up to 50 postnatal weeks. Fenton has updated the Babson and Benda's chart (1976) with

a meta-analysis of several recent data sets. In spite of the more recent update in 2008, this chart is not based solely on longitudinal data, it may not represent the actual growth of preterm infants, and its validity is limited by the heterogeneity of data sources.

- A more accurate assessment of growth in VLBW infants may be provided by the weight growth velocity i.e., measuring the body weight gain in g^{-1} kg^{-1} day (Olsen et al. 2002). Standards for neonatal growth velocity are available (Olsen et al. 2002), but as rule of thumb approximately 16 g^{-1} kg^{-1} day is the average weight gain for the entire period from 23 to 37 weeks' gestation (Uhing and Das 2009).

65.4.2 Crown-Heel Length

Length is considered a rough indicator of lean mass, reflecting the skeletal growth (Koo et al. 2000; Gibson et al. 2003). Since linear growth continues after birth despite acute loss of body weight, linear measurements may better reflect actual growth than body weight (Prins 1995).

Monitoring of linear growth has been neglected in preterm infants. This is probably due to the difficulty in obtaining accurate measurements of CHL in neonates (Prins 1995). Some factors influence the accuracy and reliability of crown-heel measurement in this age group (Johnson et al. 1997; Shinwell and Shlomo 2003). A major factor is the reluctance of the observer to extend the lower limbs forcefully, especially in full-term infants who are more comfortable in flexion (Fletcher 1998). Shinwell and Shlomo (2003) found that the CHL significantly increases over the first 2 days after birth, probably due to a gradual decrease of the intrauterine state of flexion. The accuracy of measured CHL is of utmost importance when CHL is included squared or cubed in indices, since a small error in CHL measurement causes an exponential distortion in the final results of the equations (Prins 1995).

Technique and instrumentation: Recumbent CHL is measured with the infant in supine position. Two participants should collaborate in the measurement, and the mother may be one of them. One participant positions the infant's head crown against the headboard of the length board according to the Frankfort plane: the eyes facing upwards and the lower margin of the orbit in the same vertical line as the upper margin of the auditory meatus. The second participant extends the lower limbs completely by gently pressing the infant's knees down, holds the feet vertically, at a right angle to the length board, move the footboard up against the heels firmly and registers the length (Prins 1995; Fletcher 1998). An alternative method with similar accuracy but causing significantly less discomfort has been proposed. It consists of measuring with only one lower limb extended. Using this method, trunk and limb axes should be parallel and the line between the ileac crests at a right angle with the trunk axis (Pereira-da-Silva et al. 2006).

Tape measurements are less expensive and easy to use but of doubtful reliability. More reliable measurements are obtained using recumbent infant boards to the nearest 1 mm, such as the neonatometer (Prins 1995). The prematurometer has been designed for measuring preterm infants inside the incubators (Gibson et al. 2003).

Standards: For assessment of intrauterine linear growth, contemporary Olsen et al. charts (2010) are available. These are large gender-specific, racially diverse, population-based surveys of birth length for various gestational ages (Tables 65.5 and 65.6); validated smoothed percentile curves are also available (3rd–97th) (Fig. 65.6). In spite of being old combined-gender curves and including small numbers of extremely preterm infants, the Lubchenco's chart (1966) has the advantage of permitting the assessment at birth of both length and PI which includes the length.

Table 65.5 Male birth length (cm) charts in relation to gestational age (GA), expressed in centiles, means and standard deviations (Adapted from Olsen et al. 2010, Copyright © American Academy of Pediatrics, 2010)

	Centile								
GA (weeks)	3	10	25	50	75	90	97	Mean	SD
23	NA[a]	28.0	29.1	30.3	31.4	32.4	NA[a]	30.5	1.6
24	27.9	29.1	30.3	31.5	32.8	33.9	34.9	31.5	1.8
25	28.8	30.2	31.5	32.9	34.2	35.4	36.5	32.7	2.1
26	29.9	31.3	32.8	34.3	35.7	37.0	38.2	34.2	2.2
27	31.0	32.6	34.1	35.7	37.3	38.6	39.8	35.6	2.4
28	32.2	33.9	35.5	37.2	38.8	40.2	41.5	37.2	2.5
29	33.5	35.2	36.9	38.7	40.3	41.7	43.1	38.6	2.5
30	34.8	36.6	38.3	40.1	41.8	43.2	44.6	39.9	2.8
31	36.2	38.0	39.8	41.6	43.3	44.7	46.1	41.5	2.5
32	37.7	39.5	41.2	43.0	44.7	46.1	47.5	42.8	2.7
33	39.1	40.9	42.6	44.4	46.1	47.5	48.9	44.3	2.6
34	40.4	42.2	43.9	45.7	47.4	48.9	50.3	45.6	2.6
35	41.5	43.3	45.0	46.9	48.6	50.2	51.6	46.8	2.7
36	42.7	44.5	46.2	48.1	49.9	51.5	53.0	48.0	2.8
37	44.0	45.7	47.4	49.3	51.1	52.6	54.1	49.2	2.7
38	45.2	46.8	48.5	50.2	52.0	53.5	55.0	50.2	2.7
39	46.1	47.7	49.3	51.0	52.7	54.2	55.6	51.0	2.4
40	46.9	48.4	49.9	51.6	53.2	54.7	56.1	51.6	2.4
41	47.5	49.0	50.5	52.1	53.7	55.1	56.5	52.1	2.4

[a]Not available because of small sample size

Table 65.6 Female birth length (cm) charts in relation to gestational age (GA), expressed in centiles, means and standard deviations (Adapted from: Olsen et al. 2010, Copyright © American Academy of Pediatrics, 2010)

	Centile								
GA (weeks)	3	10	25	50	75	90	97	Mean	SD
23	NA[a]	27.7	28.7	29.9	31.0	31.9	NA[a]	29.9	1.8
24	27.5	28.7	29.8	31.1	32.3	33.3	34.3	31.0	1.7
25	28.3	29.7	31.0	32.3	33.6	34.8	35.9	32.3	2.0
26	29.2	30.7	32.1	33.6	35.1	36.3	37.4	33.4	2.2
27	30.2	31.9	33.4	35.0	36.6	37.9	39.1	35.0	2.3
28	31.4	33.1	34.8	36.5	38.1	39.5	40.8	36.4	2.5
29	32.8	34.6	36.3	38.0	39.7	41.2	42.5	37.8	2.7
30	34.3	36.0	37.7	39.5	41.3	42.7	44.1	39.6	2.6
31	35.7	37.5	39.2	41.0	42.7	44.1	45.5	40.9	2.6
32	37.1	38.9	40.6	42.3	44.0	45.5	46.9	42.1	2.6
33	38.6	40.3	41.9	43.7	45.4	46.9	48.3	43.7	2.6
34	39.8	41.5	43.2	45.0	46.7	48.2	49.7	45.0	2.6
35	40.9	42.6	44.3	46.2	48.0	49.5	51.0	46.0	2.7
36	42.0	43.7	45.5	47.4	49.2	50.8	52.3	47.2	2.8
37	43.2	44.9	46.6	48.5	50.3	51.9	53.4	48.4	2.8
38	44.4	46.1	47.7	49.5	51.2	52.7	54.2	49.5	2.6
39	45.3	46.9	48.5	50.2	51.9	53.3	54.7	50.1	2.5
40	46.1	47.6	49.1	50.8	52.4	53.8	55.1	50.7	2.4
41	46.7	48.2	49.7	51.3	52.8	54.2	55.5	51.3	2.4

[a]Not available because of small sample size

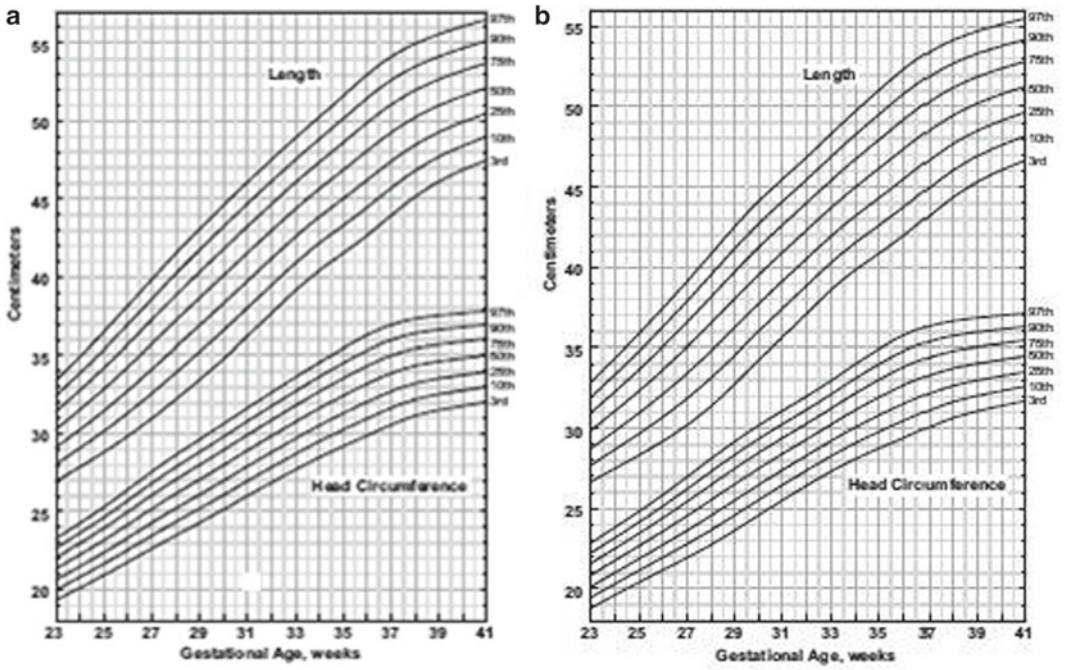

Fig. 65.6 Olsen's intrauterine gender-specific curves for birth length and head circumference. Intrauterine growth length curves for males (**a**) and females (**b**) as estimated from live birth at gestational ages from 23 to 41 weeks (Olsen IE et al. 2010. With permission by © American Academy of Pediatrics)

For monitoring the postnatal linear growth of premature infants, the Ehrenkranz's longitudinal growth grid (1999) provides the average weekly length versus postnatal age in weeks, stratified by 100-g BW interval (Fig. 65.7). Fenton's chart 2003 (updated in 2008), based on longitudinal data and meta-analysis of several recent data sets, provides the average weekly length versus postnatal age in weeks up to 50 postnatal weeks (Fig. 65.5). As a rule of thumb the linear growth rate in preterm infants should average 0.9 cm/week (Uhing and Das 2009). For key points of CHL see Table 65.7.

65.4.3 Length and Diameter of Body Segments

Assuming that the growth of body segments is proportionate to CHL, an alternative approach to quantifying linear growth is the measurement of short distances. This determines minimal daily variations in growth, especially in tiny and sick neonates who do not tolerate manipulations well (Prins 1995). Lengths and breadths are interpreted as skeletal dimensions because they are made between bony landmarks. The most used body segment measurements are the knee-heel length, foot length, and elbow-wrist length (Prins 1995).

Technique and instrumentation: Total upper limb length is measured between the acromion and the tip of the middle finger; the upper arm length: from the acromion along the posterior lateral aspect of the arm to the distal medial border of the olecraneon; the forearm: with the forearm pronated, from the most prominent point of the olecraneon to the distal process of the radius along the lateral surface of the forearm; the hand length: from the distal crease at the wrist to the tip of the middle finger; the

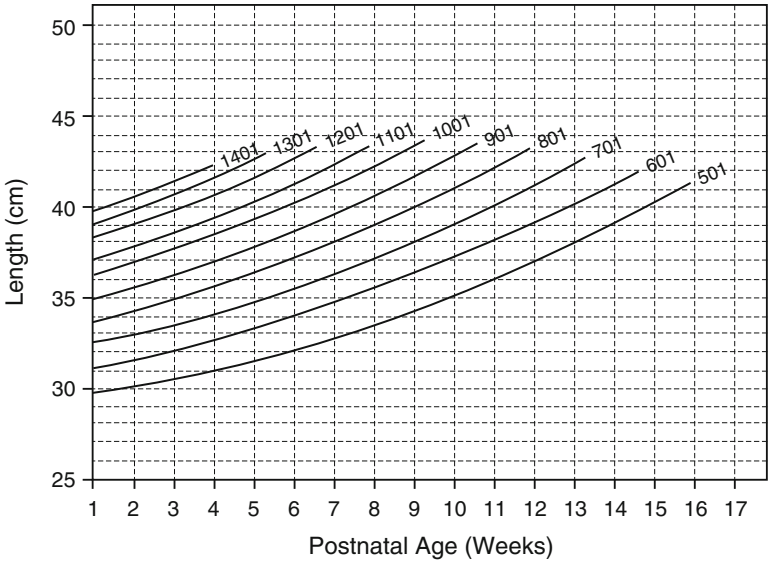

Fig. 65.7 Ehrenkranz's postnatal length grid for very low BW infants Postnatal longitudinal length grid for 100-g BW intervals, for VLBW infants (adapted from: Ehrenkranz et al. 1999. With permission by © *American Academy of Pediatrics*). Linear growth should regularly be measured in preterm infants to assess the skeletal growth. VLBW: very low birth weight. Available at http://pediatrics.aappublications.org/cgi/content/full/104/2/280

Table 65.7 Key points of crown-heel length

1. CHL measurement at birth is especially important for diagnosing stunted-born infants.
2. Forceful extension of lower limbs necessary for accurate CHL measurement causes discomfort, especially in full-term infants. Measurements with only one lower limb extended may be preferable, provided trunk and limb axes are parallel and the line between the ileac crests at a right angle with the trunk axis.
3. To define accurately symmetrical intrauterine growth restricted neonates, standards including both CHL and PI standards at birth are necessary.
4. Postnatal CHL measurements reflect the skeletal growth and should be included in the routine nutritional assessment.
5. Linear growth rate in preterm infants should average 0.9 cm/week

total lower limb length: from the greater trochanter of the femur to the lateral malleolus of the ankle along the lateral aspect of the leg; the foot length: from the posterior prominence of the heel to the tip of the longest toe (Fletcher 1998).

Measurements are more accurately performed if the chosen sites are marked (washable marker) before the measurements.

Tape measurements are easier and simple. The effects of soft tissues can be reduced and made less variable using recommended calipers which apply firm pressure (Fletcher 1998).

The knenometer is a hand-held device, resembling a pair of calipers, for a more reliable measurement of the knee-heel length. The measuring system, suitable for use inside an incubator, is based on a magnetic encoder which automatically records the knee-heel length when the pressure applied on the heel reaches a preset pressure. The measurements should be taken with the knee at 90° and the foot at a right angle. A less expensive electronic model has been described (Engstrom et al. 2003), and a simple perspex gauge has been proposed with satisfactory accuracy in skilled hands (Prins 1995).

Metal foot gauge allows a more accurate measurement of the foot length (Dangerfield and Taylor 1983).

Standards: There are neonatal references for several body segments, including: lengths of upper and lower limbs, arm, forearm, hand, foot, and bi-acromial and bi-iliac diameters. Some of these references are gender-specific and presented as mean and standard deviations (Dangerfield and Taylor 1983).

65.4.4 Body Circumferences

Most of the body circumferences are difficult to interpret, since they include the skin, subcutaneous tissue, muscle, bone, blood vessels and nerves. Trunk circumference and especially the abdomen circumference additionally include organs and deep fat tissue (Pereira-da-Silva et al. 2007).

65.4.4.1 Head Circumference

The increase in HC (synonym of occipito-frontal circumference) reflects brain growth, even though HC gives only an approximation of skull volume as a linear dimension and not a volumetric one (Prins 1995). The occipito-frontal circumference is one of the most reliable measurements in neonates (Johnson et al. 1997). When interpreting HC measurements, some factors should be taken into account. In the presence of head molding or scalp oedema, HC should be measured 48–72 h after birth, after their reduction or resolution (Prins 1995; Fletcher 1998). HC above or below the reference limits may represent a variant of normal, being constitutional or familial; therefore, the parents' HC should also be measured (Fletcher 1998).

In the neonatal period HC measurement is important for detection of cerebral pathology and as a guide to the need for an ultrasound scan. A macrocephaly may indicate hydrocephaly. Small HC at birth is associated with suboptimal cognitive and neurodevelopment outcome, especially in SGA infants (Pereira-da-Silva et al. 2007).

Technique and instrumentation: For measuring HC, the tape encircles the most prominent parts of the forehead and occiput, i.e., supraorbital ridge and occipital protuberance. The largest occipito-frontal circumference of three consecutive measurements is considered (Sasanow et al. 1986; Prins 1995). A flexible non-stretchable tape with precision to the nearest 1 mm is recommended. Disposable paper tapes may be more reliable and preferable to plastic or cloth tapes (Prins 1995).

Standards: Intrauterine head growth may be assessed using the contemporary Olsen et al. charts (2010). These are large gender-specific, racially diverse, population-based surveys of birth head circumference for various gestational ages (Tables 65.8 and 65.9); validated smoothed percentile curves are also available (3rd–97th) (Fig. 65.6).

For monitoring the postnatal head growth of premature infants, the Ehrenkranz's longitudinal grid (1999) provides the average weekly HC versus postnatal age in weeks for infants stratified by 100-g BW interval (Fig. 65.8). Fenton's chart 2003 (updated in 2008), based on longitudinal data and meta-analysis of several recent data sets, provides the average weekly HC versus postnatal age in weeks up to 50 postnatal weeks (Fig. 65.5). As a rule of thumb the HC growth rate in preterm infants should average 1 cm/week (Uhing and Das 2009).

65.4.4.2 Mid-Arm Circumference

The mid-arm circumference (MAC) reflects the combined arm muscle and fat. Since MAC is relatively unaffected by fluid shifts, it may be used in assessing loss or gain of muscle plus fat.

Table 65.8 Male birth head circumference (cm) charts in relation to gestational age (GA), expressed in centiles, means and standard deviations (Adapted from Olsen et al. 2010, Copyright © American Academy of Pediatrics, 2010) HC at birth should be measured, reflecting the intrauterine brain growth

	Centile								
GA (weeks)	3	10	25	50	75	90	97	Mean	SD
23	NA[a]	20.0	20.6	21.3	22.0	22.7	NA[a]	21.3	1.0
24	20.1	20.8	21.5	22.2	23.0	23.6	24.3	22.2	1.1
25	20.9	21.7	22.4	23.2	23.9	24.6	25.3	23.1	1.1
26	21.8	22.5	23.3	24.2	25.0	25.7	26.4	24.1	1.3
27	22.6	23.5	24.3	25.2	26.0	26.8	27.6	25.2	1.3
28	23.5	24.3	25.2	26.1	27.1	27.9	28.6	26.1	1.4
29	24.3	25.2	26.1	27.1	28.0	28.8	29.6	27.0	1.4
30	25.1	26.1	27.0	28.0	29.0	29.8	30.6	27.9	1.5
31	26.0	27.0	27.9	28.9	29.9	30.8	31.6	28.9	1.5
32	26.9	27.8	28.8	29.9	30.9	31.8	32.6	29.8	1.5
33	27.7	28.7	29.7	30.8	31.8	32.7	33.6	30.7	1.6
34	28.5	29.5	30.5	31.6	32.7	33.6	34.6	31.6	1.6
35	29.2	30.3	31.3	32.4	33.6	34.5	35.5	32.4	1.6
36	29.9	31.0	32.1	33.2	34.3	35.3	36.3	33.2	1.7
37	30.6	31.7	32.7	33.9	35.0	36.0	36.9	33.8	1.7
38	31.2	32.2	33.2	34.4	35.5	36.4	37.3	34.4	1.7
39	31.5	32.5	33.5	34.6	35.7	36.6	37.6	34.6	1.6
40	31.8	32.8	33.8	34.8	35.9	36.8	37.7	34.8	1.5
41	32.0	33.0	34.0	35.0	36.1	37.0	37.8	35.1	1.5

[a]Not available because of small sample size

Table 65.9 Female birth head circumference (cm) charts in relation to gestational age (GA), expressed in centiles, means and standard deviations (Adapted from: Olsen IE et al. 2010, Copyright © American Academy of Pediatrics, 2010). HC at birth should be measured, reflecting the intrauterine brain growth

	Centile								
GA (weeks)	3	10	25	50	75	90	97	Mean	SD
23	NA[a]	19.5	19.5	19.9	21.6	22.2	NA[a]	20.8	1.2
24	19.6	20.3	21.0	21.8	22.5	23.2	23.8	21.7	1.1
25	20.4	21.1	21.9	22.7	23.4	24.1	24.8	22.7	1.2
26	21.2	22.0	22.7	23.6	24.4	25.1	25.9	23.5	1.2
27	21.9	22.8	23.6	24.5	25.4	26.2	27.0	24.5	1.3
28	22.7	23.7	24.6	25.5	26.5	27.3	28.1	25.5	1.5
29	23.6	24.6	25.5	26.5	27.5	28.4	29.2	26.5	1.5
30	24.6	25.6	26.5	27.5	28.5	29.4	30.2	27.5	1.5
31	25.5	26.5	27.4	28.4	29.4	30.3	31.1	28.4	1.5
32	26.5	27.4	28.3	29.3	30.3	31.2	32.0	29.3	1.5
33	27.3	28.3	29.2	30.2	31.2	32.1	33.0	30.2	1.5
34	28.1	29.1	30.1	31.1	32.2	33.1	34.0	31.1	1.6
35	28.8	29.8	30.8	31.9	33.0	34.0	34.9	31.9	1.6
36	29.4	30.5	31.5	32.7	33.8	34.8	35.8	32.6	1.7
37	30.1	31.1	32.2	33.3	34.4	35.4	36.3	33.3	1.7
38	30.7	31.7	32.7	33.7	34.8	35.7	36.7	33.8	1.6
39	31.1	32.0	33.0	34.0	35.1	36.0	36.9	34.0	1.5
40	31.4	32.3	33.3	34.3	35.3	36.1	37.0	34.2	1.5
41	1.5	32.6	33.5	34.5	35.5	36.3	37.1	34.5	1.5

[a]Not available because of small sample size

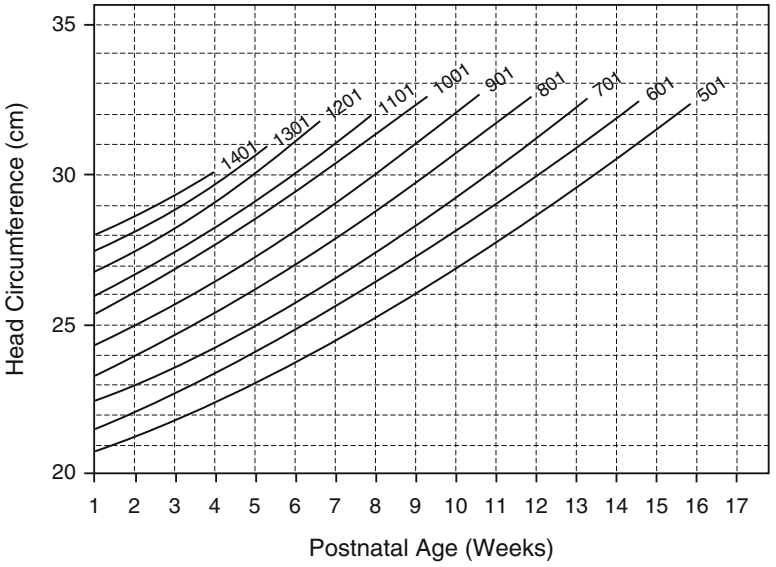

Fig. 65.8 Ehrenkranz's postnatal head circumference grid for VLBW infants. Postnatal longitudinal head circumference grid for 100-g BW intervals, in VLBW infants (Adapted from Ehrenkranz et al. 1999. With permission by © *American Academy of Pediatrics*). Head circumference should be regularly measured in preterm infants to estimate the brain growth. Available at http://pediatrics.aappublications.org/cgi/content/full/104/2/280

In conjunction with changes in weight, the quality of growth in preterm infants may be more accurately determined (Sasanow et al. 1986).

Low inter-examiner and intra-examiner reliability has been reported for MAC measurements in neonates (Johnson et al. 1997).

When compared to dual X-ray absorptiometry (DEXA) measurements, MAC reasonably correlates with lean and fat mass soon after birth (Koo et al. 2004). The discriminatory ability in detecting disturbances in body composition increases in derived anthromopetric measures including MAC, such as MAC/HC ratio and the mid-arm muscle area (Koo et al. 2004).

Technique and instrumentation: A flexible non-extendible tape is appropriate for MAC measurement. Measurements are taken with the arm extended in a horizontal position, at mid distance between the tip of acromion and the olecraneon process, where a typical crease may help indicating the site in preterm infants (Sasanow et al. 1986). In very premature infants, a poor reliability in MAC measurements has been reported (Prins 1985), which may result from compression of the skin when attempting to adjust the tape perfectly around the arm with very loose tissues, or by small spaces left between the wrinkled skins when avoiding compression (Prins 1985; Pereira-da-Silva et al. 2009). For tiny infants measurements may be easier using a flexible tape with approximately 1 cm width (Fig. 65.9).

Standards: For intrauterine nutritional assessment, the Sasanow's (1986) combined-gender MAC references are available for infants soon after birth, from 25 to 42 weeks of gestational age (Table 65.10), although a small number of ELBW infants has been included.

For monitoring the postnatal nutritional status of preterm infants, the Ehrenkranz's longitudinal grid (1999) may be used, which provides the average weekly MAC versus postnatal age in weeks for infants stratified by 100-g BW interval (Fig. 65.10).

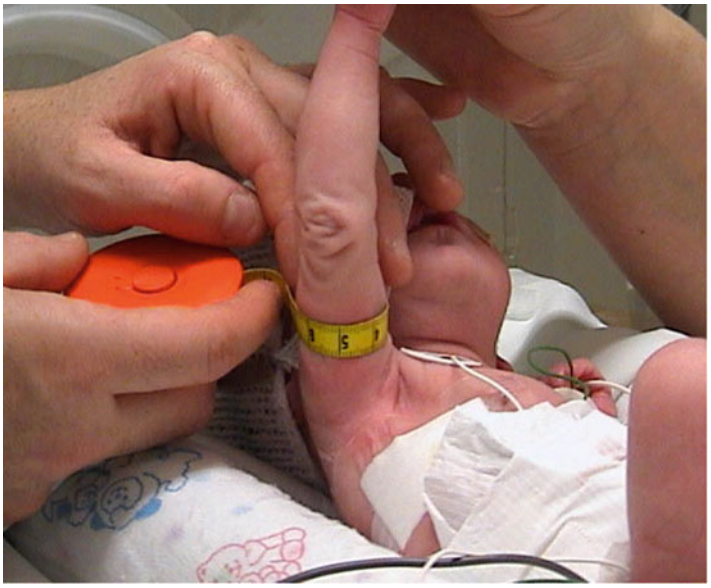

Fig. 65.9 Measurement of mid-arm circumference. Mid-arm circumference (MAC) measurement. MAC reflects the combined arm muscle and fat. Measurements should be taken with the arm extended, at mid distance between the tip of acromion and the olecraneon process. A flexible tape with approximately 1cm width may be easier to use for tiny infants

Table 65.10 References for mid-arm circumference (MAC) and for mid-arm circumference/ head circumference ratio (MAC/HC) from 25 to 42 weeks of gestational age (GA) (Adapted from Sasanow et al. 1986, © Elsevier). Low MAC/HC at birth indicates foetal malnutrition and is especially useful in diagnosing malnourished AGA neonates not identified by the criterion exclusively based on birth weight, and has predictive value of early symptomatic metabolic abnormalities

	MAC (cm)		MAC/HC ratio	
GA (weeks)	Mean	SD	Mean	SD
25–26	4.9	0.7	0.22	0.02
27	5.25	0.3	0.22	0.01
28	5.5	0.5	0.23	0.02
29	5.7	0.4	0.23	0.02
30	6.0	0.7	0.23	0.02
31	6.4	1.0	0.23	0.03
32	7.0	0.5	0.24	0.02
33	7.0	0.8	0.24	0.02
34	8.3	0.5	0.27	0.01
35	8.1	0.6	0.26	0.01
36	8.3	0.6	0.26	0.02
37	9.5	0.7	0.28	0.02
38	9.5	0.7	0.28	0.01
39	9.7	0.9	0.28	0.02
40	10.1	0.6	0.29	0.02
41	10.2	0.6	0.29	0.02
42	10.6	0.5	0.30	0.01

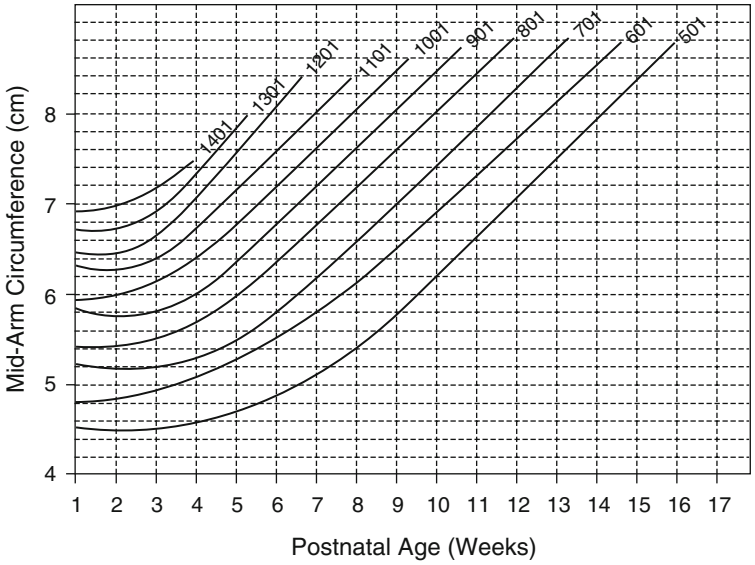

Fig. 65.10 Ehrenkranz's postnatal mid-arm circumference grid for VLBW infants. Postnatal longitudinal mid-arm circumference (MAC) grid for 100-g BW intervals, in VLBW infants (Adapted from Ehrenkranz et al. 1999. With permission by © *American Academy of Pediatrics*). MAC is simple to measure and may assess loss or gain of muscle plus fat. Used in conjunction with changes in weight, MAC may give a better insight on the quality of growth in preterm infants. Available at http://pediatrics.aappublications.org/cgi/content/full/104/2/280

65.4.4.3 Other Circumferences

Mid-thigh circumference (like MAC) is frequently used in developing countries to assess nutritional status of infants, when scales are not available (Prins 1995). Mid-thigh circumference is measured in supine position, in at mid distance between the proximal border of the patella and the anterior superior iliac spine, with the lower limb gently extended (Fletcher 1998). The average values in full-term neonates are 15.59 cm in Blacks and 15.48 cm in Caucasians (Pereira-da-Silva et al. 2007).

Neonatal references for other body circumferences like chest circumference and abdominal circumference have been published (Dangerfield and Taylor 1983), but these measurements, as mid-thigh circumference, have not been validated as indicators of body composition in this age group (Pereira-da-Silva et al. 2007).

65.4.5 Skinfolds

Skinfold thickness measurement is an inexpensive method for neonatal nutritional assessment, convenient for bedside measurements. The routine use of this method in neonates is limited due to a low reliability when the skill and practice of the observer is insufficient (Prins 1995).

When skinfold thickness is measured to estimate total body fat (TBF) it is assumed that thickness of subcutaneous fat reflects a constant proportion of TBF, and that the sites used for the measurements reflect the average thickness of the subcutaneous fat layer (Prins 1995). The most commonly used sites for measurements are the tricipital skinfold (TS) and the subscapular skinfold (SBS) (Prins 1995). Other sites used are the biceps (BS) and the suprailiac (SPS).

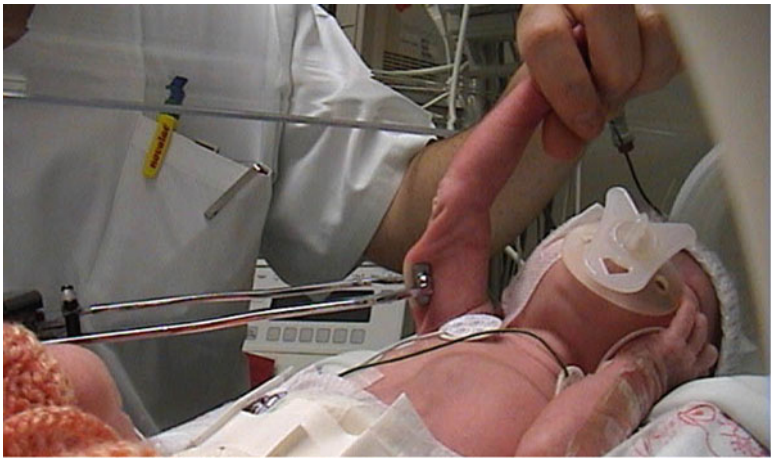

Fig. 65.11 Measurement of triceps skinfold. Triceps skinfold (TS) measurement. TS is the most commonly used skinfold to estimate peripheral subcutaneous fat. TS is measured on the posterior surface of the arm with the elbow extended, at the mid distance between the acromion and olecraneon

Although not yet validated, an equation has been proposed to estimate the central to total skinfold ratio (CTS) in neonates: CTS = (SPS + SBS)/(TS + BS + SPS + SBS) (Rodriguez et al. 2004).

Skinfolds as indicators of fat mass have been validated in neonates as compared with gold standard methods. The predictive value of regional and whole body anthropometry, for whole body composition, was validated by DEXA measurements. Good correlation was found between the skinfold measurements and fat mass (Schmelzle and Fusch 2002; Koo et al. 2004). In contrast, others found poor correlation between skinfold measurements and both total and regional body fat assessed by magnetic resonance imaging (Olhager and Forsum 2006; Pereira-da-Silva et al. 2009). This discrepancy may be explained by several factors, the most important being the influence of hydration on the skinfold compressibility (Olhager and Forsum 2006) and fact that skinfold measurements do not reflect non-subcutaneous fat, especially in preterm infants (Uthaya et al. 2005). Furthermore, low reproducibility and high inter-observer coefficient of variation have been reported for skinfold measurements in term and preterm infants (De Bruin et al. 1995).

Technique and instrumentation: The procedure for measurement consists of lifting a skinfold with the index or middle finger and thumb, while pulling away the subcutaneous tissue from the underlying muscle fascia. In the first minute after the application of the caliper there is a steady decrease followed by a relative stabilization of the registered thickness. Some authors suggest that reading may be taken 15 s after the application of the caliper (Schmelzle and Fusch 2002), but more reliable measurement is reached with 60 s readings, especially in preterm infants in whom the presence of edema may give a spuriously high estimate of subcutaneous fat (Prins 1995). The decrease of skinfold measurement from 15 to 60 s is called dynamic skinfold thickness measurement which correlates with the extracellular water (Thornton et al. 1982).

The TS is measured on the posterior surface of the arm with the elbow extended and the arm held by the side of the body, at the mid distance between the acromion and olecraneon (Fig. 65.11). The BS is measured on the anterior surface of the arm at the same level of TS measurement. The SBS is measured at the lower angle of the scapula with the arm relaxed (Fig. 65.12). The SPS is measured immediately above the iliac crest, along the axis of the anterior mamilary line with the infant lying supine (Prins 1995; Schmelzle and Fusch 2002).

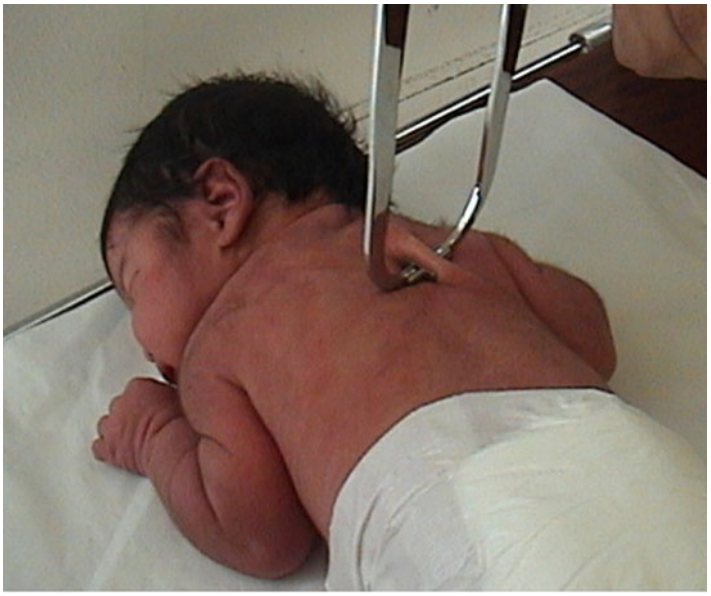

Fig. 65.12 Measurement of subscapular skinfold (SBS). Subscapular skinfold (SBS) measurement. SBS is the most commonly used skinfold to estimate central subcutaneous fat. The SBS is measured at the lower angle of the scapula

Table 65.11 Triceps (TS), biceps (BS), subscapular (SBS) and suprailiac (SPS) skinfold thickness in male neonates, in relation to gestational age (GA) (Adapted from Rodriguez et al. 2004. With permission of © Springer Verlag, 2004)

	TS (mm)		BS (mm)		SBS (mm)		SPS (mm)	
GA (weeks)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
32–33	2.59	0.58	2.31	0.63	2.49	0.56	1.73	0.52
34	3.07	0.70	2.42	0.69	2.89	0.80	2.20	0.67
35	3.25	0.61	2.61	0.62	3.03	0.64	2.30	0.63
36	3.44	0.84	2.77	0.79	3.25	0.78	2.53	0.75
37	4.05	0.98	3.46	0.91	3.77	1.01	3.15	0.85
38	4.03	0.85	3.47	0.83	3.69	0.80	3.17	0.76
39	4.21	0.84	3.61	0.89	3.92	0.90	3.32	0.76
40	4.23	0.83	3.63	0.83	3.95	0.85	3.35	0.74
41	4.26	0.88	3.68	0.77	3.94	0.79	3.43	0.78

Skinfolds are estimators of fat mass. TS and BS estimate peripheral subcutaneous fat and SBS and SPS estimate central subcutaneous fat. TS and SBS are the most commonly used sites for measurements. Skinfolds usually are thinner in male neonates

Appropriate calipers should be used, exerting a constant pressure of 10 g/mm^2 of contact surface area whatever the overture of the jaws of the calipers; the most commonly used are the Holtain (Holtain Ltd, Croswell, Crymych, UK) and the Harpenden (CMS Instruments, London, UK), respectively with resolutions of 0.1 and 0.2 mm (Prins 1995).

Standards: Gender-specific references for TS, BS, SBS, SPS and CTS at birth have been published for neonates from 32 to 41 weeks of gestational age. Female neonates not only had greater ST measurements but also larger CTS values (Tables 65.11–65.13) (Rodriguez et al. 2004).

Formulae and standards for dynamic skinfold thickness measurements in neonates were proposed to estimate the extracellular water content (Thornton et al. 1982).

Table 65.12 Triceps (TS), biceps (BS), subscapular (SBS) and suprailiac (SPS) skinfold thickness in female neonates, in relation to gestational age (GA) (Adapted from Rodriguez et al. 2004, with permission of © Springer Verlag, 2004)

	TS (mm)		BS (mm)		SBS (mm)		SPS (mm)	
GA (weeks)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
32–33	2.72	0.62	2.32	0.63	2.81	0.76	2.04	0.72
34	3.17	0.72	2.53	0.78	3.17	0.94	2.34	0.87
35	3.25	0.61	2.52	0.58	3.17	0.72	2.43	0.65
36	3.44	0.84	2.83	0.87	3.37	0.88	2.69	0.83
37	4.05	0.98	3.22	0.70	3.78	0.93	3.16	0.79
38	4.03	0.85	3.59	0.88	4.03	0.99	3.37	0.83
39	4.21	0.84	3.61	0.84	4.09	0.88	3.40	0.76
40	4.23	0.83	3.61	0.88	4.19	0.91	3.47	0.83
41	4.26	0.88	3.74	0.80	4.25	1.00	3.69	0.82

Skinfolds as estimators of fat mass. TS and BS estimate peripheral subcutaneous fat and SBS and SPS estimate central subcutaneous fat. TS and SBS are the most commonly used sites for measurements. Skinfolds usually are thicker in female neonates

Table 65.13 Central to total skinfold (CTS) ratio from 32 to 41 weeks of gestational age (GA): mean ± standard deviation (Adapted from Rodriguez et al. 2004. With permission of © Springer Verlag, 2004)

	Males Mean ± SD	Females Mean ± SD
32–33	47.24 ± 3.93	48.70 ± 4.14
34	47.87 ± 3.73	48.80 ± 4.16
35	47.55 ± 3.18	49.17 ± 3.02
36	48.28 ± 3.24	49.03 ± 3.08
37	47.87 ± 3.01	49.48 ± 3.05
38	47.64 ± 3.12	48.71 ± 3.09
39	48.04 ± 3.25	48.76 ± 3.30
40	48.17 ± 3.06	49.15 ± 3.47
41	48.13 ± 3.19	49.06 ± 3.52

A central accumulation of fat may be estimated by an increased CTS, calculated by the equation CTS = (SPS + SBS)/(TS + BS + SPS + SBS)

BS biceps skinfold; *CTS* central to total skinfold ratio; *SBS* subscapular skinfold; *SPS* suprailiac skinfold; *TS* tricipital skinfold

65.5 Derived Measurements

The derived anthropometric measurements are based on formulae which use direct measurements, assuming that the association of various direct measurements may predict body composition better than each value on its own (De Bruin et al. 1995).

65.5.1 Weight and Length Based Equations

Birth weight-for-length ratios allow the assessment of body proportionality. Assuming that length is affected to a relatively lesser extent than weight except in severe cases, these indices are used to predict symptomatic metabolic abnormalities in neonates with abnormal intrauterine growth due to under- and over-nutrition (Koo et al. 2004; Olsen et al. 2009).

65.5.1.1 Ponderal Index (PI)

[Weight (in g)/Length^3 (in cm)] × 100. Rohrer's PI is an index of thinness at birth, and is the appropriate criterion for defining SGA or IUGR of symmetrical or asymmetrical type (Tamim et al. 2004). The old Lubchenco's chart (1966) (Fig. 65.1) is one of the rare large population-based charts including a grid for PI at birth, and it is still used when this tool is needed (Olsen et al. 2009). It includes 0.1-PI intervals from circa 1.8 to 3.1 and from 26 to 42 weeks of gestation; it has the disadvantages of being combined-gender. More recently, gender-specific reference values for PI at birth from 32 to 42 weeks of gestation, including smoothed percentile curves (2.5th to 97.5th), estimated from 100,716 children, have been published (Lehingue et al. 1998) (Table 65.14). As a general rule of thumb, the SGA infant is classified as asymmetric if PI is <2 or <2.3 in preterm and term infants, respectively (Beattie and Johnson 1994; Pereira-da-Silva et al. 2007). Asymmetrical SGA at birth is a predictor of adverse early metabolic outcome and increased risk of mortality (Patterson and Pouliot 1987; Wilcox et al. 1993). From birth to discharge, the percentage of preterm infants with low PI seems to decrease, in spite of an increase in the percentage of those with weight deficit (Olsen et al. 2009).

65.5.1.2 Body Mass Index (BMI)

[Weight (in Kg)/Length^2 (in m)] × 100. BMI is synonym of both adiposity index and Quetelet's index. BMI has been proposed as an index of adiposity during the neonatal period, but it seems to be a weak measure of intrauterine malnutrition and a poor predictor of postnatal short-term outcome (Pereira-da-Silva et al. 2007). Gender-specific reference values for BMI at birth from 32 to 42 weeks of gestation, including smoothed percentile curves (2.5th to 97.5th), estimated from 100,716 children, have been published (Lehingue et al. 1998) (Table 65.15).

65.5.1.3 Weight-for-Length (W/L) Ratio

[Weight (in g)/Length (in cm)]. W/L ratio at birth, rather than PI or BMI, is reported as a good predictor of subcutaneous fat (Yau and Chang 1993; Rodriguez et al. 2004), and a complimentary tool in predicting early postnatal metabolic abnormalities (Owen 1997).

65.5.1.4 Benn Index

[Weight (in g)/Length^n (in cm)]. In the Benn index, the relative weight is calculated as the ratio of actual to predicted weight, where the length power n varies with gestation and is estimated by log–log regression. It is not a practical and simple mathematical formula, and like other weight-for-length indices it may not be appropriate for estimating intrauterine malnutrition, as different gestations require different indices (Pereira-da-Silva et al. 2007).

65.5.1.5 Individualized Birth Weight Ratio

This ratio is derived from the actual BW divided by predicted BW expressed as a percentage, for each individual infant (Wilcox et al. 1993). This is a good method for differentiating constitutional SGA and LGA from abnormal intrauterine growth (Pereira-da-Silva et al. 2007). This ratio is considered a more accurate, even though not a practical method for characterizing BW (Fletcher 1998).

65.5.2 Mid-Arm Circumference/Head Circumference Ratio

Assuming that in acute protein-energy malnutrition the brain is relatively spared compared to muscle and fat wasting, MAC/HC at birth has been proposed to identify intrauterine malnutrition and standards have been published (Sasanow et al. 1986) (Table 65.10). MAC/HC is especially useful in diagnosing malnourished AGA neonates who would be not identified as IUGR by the criterion exclusively based on BW (Patterson and Pouliot 1987). It has independent predictive value of body composition in infants with abnormal intrauterine growth (Koo et al. 2004), and a predictive value of symptomatic metabolic abnormalities as well (Patterson and Pouliot 1987).

65.5.3 Upper-Arm Cross-Sectional Areas

Equations have been proposed to calculate the upper-arm cross-sectional areas derived from MAC and TS: arm area (AA), arm muscle area (AMA) and arm fat area (AFA). Calculation of these areas is based on theoretical assumptions: the mid-arm is cylindrical, the subcutaneous fat is a concentric ring evenly distributed around a circular core of muscle, the fat thickness is half the TS, and the muscle includes the humeral diameter (Jellifee and Jellifee 1969). Using the Jellifee and Jellifee method (1969): $AA = MAC^2/4\pi$; $AMA = (MAC - \pi TS)/4\pi$; $AFA = AA - AMA$.

Based on dynamic skinfold measurement specific equations have been proposed (Thornton et al. 1982) to estimate the extracellular water content in neonates by calculating the water arm area (WAA), assuming that the 15 s (TS_{15}) reading reflects subcutaneous water *plus* fat, and the 60 s (TS_{60}) reading reflects only the fat, therefore WAA: $AMA_{15} = (MAC - \pi\ TS_{15})^2/4\pi$; $AFA_{60} = AA - (MAC - \pi\ TS_{60})^2/4\pi$; $WAA = AA - (AMA_{15} - AFA_{60})$.

Hypothesizing that Jellifee and Jellifee method (1969) might underestimate adiposity, Rolland-Cachera et al. (1997) proposed different equations for calculating the upper-arm cross-sectional areas, assuming that the AMA constitutes a circle surrounded by a rim (fat), the unrolled rim is a rectangle, and the outer circumference of the rim is equal to the inner circumference: $AFA = MAC \times TS/2$; $AMA = AA - AFA$.

Based on the Jellifee and Jellifee method (1969), standards for upper-arm cross-sectional areas have been published for neonates (Sann et al. 1988), and their validation for estimating body composition only recently has been published. Upper-arm muscle and fat areas are among the derived anthropometry that better predict whole-body composition, in comparison with with DEXA measurements (Koo et al. 2004). To be consistent with these results, the upper-arm anthropometry should also be a reliable predictor of regional body composition at the level where the anthropometric measurements were taken. However, a poor correlation was found between upper-arm anthropometry and both upper-arm ultrasound measurements in full-term infants (Pereira-da-Silva et al. 1999) and upper-arm magnetic resonance imaging measurements in preterm infants (Pereira-da-Silva et al. 2009). The discrepancy between the results may be explained by an oversimplification in the geometrical assumptions for calculation of upper-arm cross-sectional areas, and by the low reliability of MAC (Johnson et al. 1997) and of TS (De Bruin et al. 1995) measurements on which the equations are based. Therefore, upper-arm cross-sectional areas values in neonates should be interpreted with caution.

65.5.4 Formulae Derived from Multiple Measurements

Dauncey's formula, associating skinfolds measured in two sites (TS and SBS) and further nine anthropometric measurements, has been proposed to estimate TBF in neonates and older children. This method assumes that the body is a sum of a sphere (head) and several hollow cylinders of fat (trunk and limbs) (Pereira-da-Silva et al. 2007).

The Weststrate's method, based on equations including whole-body density and skinfolds measured in four sites, has been proposed to estimate the percentage of fat from the neonatal period up to 18 years (Pereira-da-Silva et al. 2007).

The Catalano's model includes the weight, CHL, HC and skinfolds, for predicting TBF in neonates with >2,000g (Pereira-da-Silva et al. 2007).

The reliability of the above-mentioned methods to predict body composition in neonates has been questioned, after being revalidated by total-body electrical conductivity and DEXA measurements (De Bruin et al. 1995; Schmelzle and Fusch 2002).

65.6 Applications to Other Areas of Health and Disease

Neonatal anthropometry may be a tool to predict long-term complications. Low BW and IUGR infants, especially if associated with rapid postnatal catch-up growth, are more susceptible to future insulin resistance and metabolic syndrome. Asymmetrical IUGR is especially prone to this outcome, while an increased risk of poor neurodevelopmental outcome is associated with symmetrical IUGR.

Summary Points

- **Morphometry at birth**: Identify small-for-gestational age infants, which may indicate intrauterine growth restriction (IUGR). For a more accurate diagnosis also check for reduced MAC/head circumference ratio, which can be used to diagnose foetal malnutrition regardless of BW. Use the PI to classify IUGR as asymmetric or symmetric. Identify macrosomic and large-for-gestational age infants as well. Anticipate therapeutic measures for the early complications expected in large-for-gestational age and IUGR infants.
- **Postnatal growth and nutrition**: In preterm infants measure body weight daily, since this is the most reliable measurement in neonates. Measure the crown-heel length (CHL) and length of body segments weekly to assess skeleton and body growth. For assessing the quality of growth, estimate body composition on the basis of weekly measurements of MAC, tricipital and SBS, and the cross-sectional muscle and fat areas. Interpret these measurements with caution, since they require further validation in neonates.
- **Long-term complications**: Identify low BW and IUGR infants (using the above-mentioned criteria), and avoid rapid postnatal catch-up growth which predisposes to future insulin resistance and metabolic syndrome. Using PI classify IUGR as asymmetric or symmetric type. Asymmetrical IUGR is especially prone to the referred outcome. Symmetrical IUGR is at increased risk of poor neurodevelopmental outcome.
- **Dysmorphies**: Measure arm span and crown-rump length/CHL ratio if a disproportional growth disorder is suspected. Use appropriate craniofacial measurements and standards for the diagnosis of craniofacial dysmorphies.
- **Body surface (BSF)**: When required, estimate BSF by direct visualization of normograms based on weight and CHL. As an alternative, use the simplified equation proposed for proportionate neonates: BSF = (weight + 4)/30, where BSF is in m^2 and weight in kg.

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Chapter 66
Anthropometric Measurements in Sudanese Newborns: Value in Measuring Weight at Birth and Its Relationship with Maternal Characteristics

Eltahir M. Elshibly and Gerd Schmalisch

Abstract In developing countries, low birth weight (LBW) (<2,500 g) is the strongest determinant of infant morbidity and mortality. In this chapter we describe a method to measure birth weight (BW) using anthropometric measurements and investigate the effect of maternal age, anthropometry, education and socio-economic status on determining the risk for LBW and preterm birth.

Anthropometric measurements were performed in 1,000 singleton Sudanese newborns and their mothers. Maternal measurements (including weight, height and mid-upper-arm circumference) and 11 newborn anthropometric measurements were taken within 24 h of delivery. In addition, maternal age, education and socio-economic status were recorded. Correlation analysis and multivariate regression analysis with backward selection were used to investigate the value of newborn anthropometric measurements in measuring birth weight and the effect of maternal variables on gestational age and birth weight.

A simple formula utilizing chest (CC), mid thigh (MT) and head (HC) circumferences measured in cm was obtained to predict BW as follows: BW(g) = 97*CC + 74*MT + 85*HC – 4,000, with a standard error of 285 g. For birth weights <2,000 g the specificity of the formula was near 100% and the sensitivity was >80%. Applying a cut-off point of 2,500 g, all infants (100%) with birth weight <2,000 g were correctly identified.

Among maternal characteristics birth order was the strongest determinant of birth weight. Firstborn babies were nearly twice likely to be LBW than infants of multiparous mothers. All maternal anthropometric measurements and age were positively correlated ($p < 0.001$) with birth weight to a variable extent; however, maternal anthropometry explained less than 6% of the variability of the newborn anthropometry. The postpartum maternal lean body mass (LBM) was found to be the major associate of newborn size (birth weight, body lengths and body circumferences), while skin fold thicknesses were mainly associated with maternal age and maternal BMI. Maternal education was significantly associated with birth weight and body circumferences (except the abdominal) and the ponderal index increased significantly with increasing number of years of education. No association between social class and newborn anthropometry was obtained.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_66,

Our formula combining chest, mid thigh and head circumferences was found to predict birth weight. Birth order and the postpartum maternal LBM were found to be the most important maternal parameters which influence birth weight and the risk for LBW. The duration of maternal education, and not social class, was found to significantly affect the risk for LBW.

Abbreviations

BMI	Body Mass Index
BW	Birth Weight
CC	Chest Circumference
CI	Confidence Interval,
ELBW	Extremely Low Birth Weight
GA	Gestational Age
HC	Head Circumference
LBM	Lean Body Mass
LBW	Low Birth Weight
MANOVA	Multivariate Analysis of Variance
MH	Maternal Height
MT	Mid Thigh circumference
MUAC	Mid Upper Arm Circumference of the mother
MW	Maternal Weight
NGO	Non Governmental Organization
PI	Ponderal index
ROC	Receiver Operating Characteristic curve
SD	Standard Deviation
SL	Supine Length of the newborn
VLBW	Very Low Birth Weight
WHO	World Health Organization

66.1 Introduction

It is well recognized that infants weighing <2,500 g (LBW) contribute the lion's share to infant mortality and morbidity worldwide. Advances in modern obstetric and neonatal care (Grimmer et al. 2002) in industrialized countries greatly improved their outcome; however, the outcome of LBW infants is much less favorable in developing countries due to the lack of proper medical, perinatal and antenatal care and follow up (Simiyu 2005; Elshibly and Schmalisch 2008a).

According to a study by the World Health Organization (WHO) (WHO Report 1996) it is estimated that 98% of perinatal deaths worldwide occur in developing countries with Africa having the highest rate of almost 33%. Within Africa the highest rates occur in western, central and eastern parts with an average perinatal mortality around 80/1,000. The WHO report also showed that regions with the lowest coverage of trained birth attendants at delivery have the highest perinatal mortality rates.

In Africa the proportion of LBW infants is higher than in developed countries (Milabyo 2006; Mokhachane et al. 2006) and most deliveries occur at home in the absence of skilled personnel (Onayade et al. 2006). In Lesotho over 40% of women prefer to deliver at home under

the care of traditional midwives (Anonymus 1993). Scales to measure the birth weight in order to identify LBW babies are often not available. Consequently, only about half of the newborns are weighed at birth and for a smaller proportion of them gestational age is known (Blanc and Wardlaw 2005). Even when a community health worker or relative may be present to help, she or he cannot identify LBW babies and thus refer them to receive appropriate medical care. This situation calls for a method of identifying LBW babies that can be used where measuring scales are not available. Identifying LBW babies at home and referring them to a health facility will considerably improve their chances of survival and will lead to great reduction in infant mortality rates in Africa.

Beside biological factors like gestational age (GA), maternal weight and height (Voigt et al. 2004), life style factors such as tobacco, alcohol or caffeine consumption and dietary habits (Nordentoft et al. 1996) can affect birth weight. Socio-demographic and socio-economic factors are also known to affect birth weight. Wasunna and Mohammed (2002), for example, pointed out that maternal education and household income can influence birth weight considerably.

Despite the large body of literature there is no consensus as to which maternal characteristics are associated with newborn anthropometric measurements. The study of maternal-neonatal associations is of particular relevance and importance, especially in Africa where there are much higher percentages of women with low education, poverty and poor nutritional status who are therefore at increased risk of adverse reproductive outcomes including LBW and preterm birth. The identification of such women is therefore important in order to determine the level of care and priorities for referral to better equipped centers where reasonable obstetric and neonatal care can be provided.

Anthropometric measurements are non invasive, inexpensive, and rapid methods to assess nutritional status of newborns, detect growth abnormalities and monitor growth (Moyer-Mileur 2007). This is of special importance in developing countries where expensive measuring equipment is commonly not available. Personnel for measurements can be trained easily in using inelastic tapes which are readily available.

In this chapter we describe anthropometric measurements in a sample of mothers and infants from an inner urban area of Khartoum (Sudan) who delivered in the Soba University Hospital with an average of 4,000 births a year. We introduce a simple method of weighing infants where scales are not available and report the relationships between maternal age, anthropometry, education and socio-economic status and the features of the newborns.

66.2 Anthropometric Measurements in Mothers and Their Newborns

66.2.1 Techniques Used in the Assessment of Maternal and Newborn Anthropometry

As described recently (Elshibly and Schmalisch 2008b, 2009) anthropometric measurements were taken from 1,000 mothers and their newborns in the Soba University Hospital in Khartoum, Sudan. The mothers were recruited from a large inner urban area of Khartoum with wide differences in socio-economic status. The three social classes (low, middle, high) were determined by the area of residence.

In this study only healthy mothers with live born infants who were sure of the last date of their menstrual period were included. Mothers who were not sure of their dates or who had multiple pregnancy or diabetes mellitus or whose infants had anomalies were not included in the study.

The measurements were taken within 24 h of birth in the postnatal wards of the Soba University Hospital in Khartoum by one investigator (ELS) in order to avoid interobserver-variability. The newborn measurements included birth weight, head, chest, mid arm, mid thigh and abdominal circumferences. Furthermore, baby's supine (crown heel), crown rump and upper limb lengths were measured as well as triceps and sub scapular skin fold thicknesses. The ponderal index (PI) was calculated as follows:

$$\mathrm{PI} = 100 \cdot \frac{\mathrm{BW}}{\mathrm{SL}^3}$$

where BW is the birth weight in g and SL is the supine length in cm.

The maternal anthropometry included mother's weight, height and mid upper arm circumferences (MUAC). Using maternal weight and height the body mass index (BMI) was calculated as follows:

$$\mathrm{BMI} = \frac{\mathrm{MW}}{\mathrm{MH}^2}$$

where MW is the maternal weight in kg and MH is the maternal height in m. The lean body mass (LBM) was calculated as follows:

$$\mathrm{LBM} = 1.07 \cdot \mathrm{MW} - 148 \cdot \frac{\mathrm{MW}^2}{\mathrm{MH}^2}$$

where MW is the maternal weight in kg and MH is the maternal height in cm.

The baby's weight was measured by a scale (Atom Medical, Tokyo, Japan) to the nearest 10 g while the mother's weight was measured by a scale to the nearest 100 g. The mother's height was measured with a scale to the nearest millimeter. The baby's supine and crown rump lengths were measured by an infantometer (Atom Medical, Tokyo, Japan) to the nearest millimeter. Upper limb length was measured from the tip of the acromion process of the humerous bone to the most distal skin crease close to the hand. In order to minimize intra-observer variability all circumferences were measured by an inelastic tape to the nearest millimeter. The skin fold thicknesses were measured with a skin fold Caliper (Holtain, Dyfed, UK) to the nearest millimeter.

66.2.2 Education, Social Status and Anthropometric Measures of the Mothers

Of 1,000 mothers 71 (7.1%) had less than 3 years of education and 309 (30.9%) mothers had an education between 3 and 8 years. A considerable number of women had high school education (48.7%) and 13.3% had university education.

Most mothers (64.4%) belonged to a lower social class, 31.3% to the middle social class while only 4.3% were from a high social class. Between social classes and the education was a significant ($p < 0.001$) relationship, as shown in Fig. 66.1. Nevertheless of the 644 mothers from the lower social class, 354 (55%) had a high school education or more.

Six hundred and thirty (63%) mothers were multiparous with parity ranging between 2 and 14. The distribution of the parity of the mothers is shown in Fig. 66.2. Table 66.1 shows the descriptive statistics of the maternal anthropometric measurements. The maternal BMI shown in Table 66.1 is the postpartum BMI and not the commonly used BMI taken before pregnancy. This is because, in Africa it is seldom possible to obtain BMI before pregnancy as women commonly present to health facilities only when they are in the advanced stages of pregnancy.

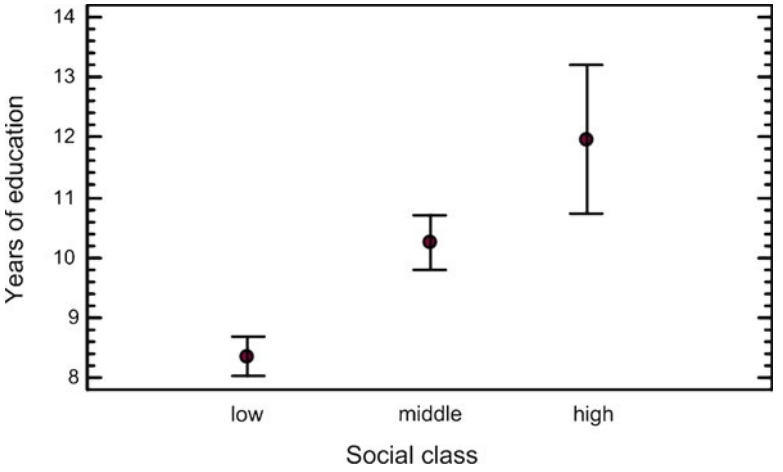

Fig. 66.1 Relationship between social class and years of education of the mothers. The figure shows a significant increase in the mean number (with 95% CI) of years of education with higher social class

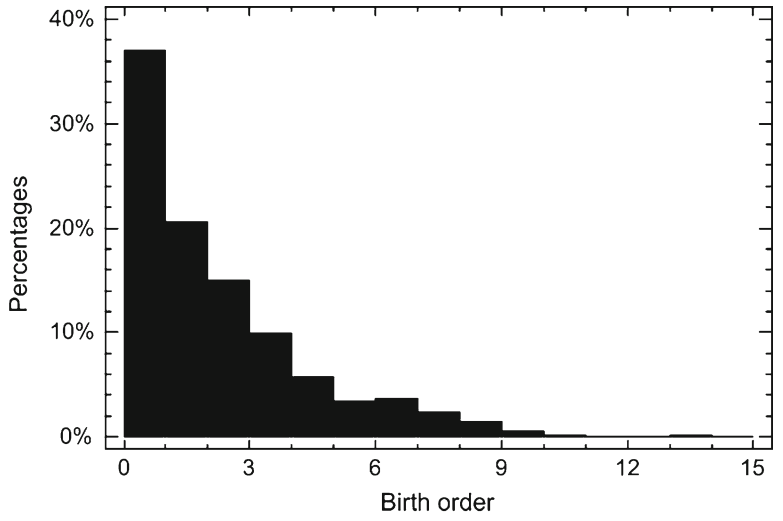

Fig. 66.2 Distribution of the birth order. The figure shows the relative frequency distribution of the birth order of the 1,000 investigated mothers

66.2.3 Anthropometric Measures of the Newborns

Of 1,000 singleton infants with complete anthropometric measurements, 514 were male (51.4%) and 486 were female (48.6%). Taking the mean, boys were 34.9 g heavier than girls; however, as shown in Table 66.2 there was no statistically significant difference between boys and girls in gestational age, birth weight, incidence of preterm birth, LBW, VLBW, ELBW and SGA. The descriptive statistics of the anthropometric measurements of all babies are shown in Table 66.3:

The relationship between anthropometric measurements and gestational age was investigated by a correlation analysis. As shown in Table 66.3, with the exception of PI there was a statistically

Table 66.1 Characteristics of the investigated mothers

	Mean (SD)	Range
Age (years)	27.0 (5.4)	16–52
Number of years of education	9.1 (4.3)	0–19
Birth order	2.8 (2.1)	1–14
Measured parameters		
Body weight (kg)	65.2 (13.0)	33.5–109.9
Body height (cm)	159.6 (6.2)	139.5–195.5
Mid arm circumference (cm)	26.9 (3.9)	17.0–40.9
Calculated parameters		
Body mass index (kg/m^2)	25.5 (4.8)	13.5–47.1
Lean body mass	44.2 (4.9)	27.6–57.5

This table describes the measured and calculated maternal anthropometric parameters

Table 66.2 Comparison between boys and girls

	Boys $N = 514$	Girls $N = 486$	P-value
Gestational age (weeks)	39.1 (1.75)	39.1 (1.09)	**0.993**
Preterm birth (<37 weeks)	28 (5.5%))	29 (6.0%)	**0.723**
Birth weight (g)	3148.7 (545.1)	3113.8 (532.4)	**0.306**
LBW (<2,500 g)	47 (9.1%)	36 (7.4%)	0.320
VLBW (<1,500 g)	5 (1.0%)	6 (1.2%)	0.768
ELBW (<1,000 g)	2 (0.4%)	2 (0.4%)	1.000
SGA (<10th percentile)	83 (16.1%)	80 (16.5%)	0.962

This table shows a comparison of anthropometric measurements between boys and girls. No statistically significant differences were observed because all *p*-values were >0.05

Table 66.3 Anthropometric measurements of the newborns

	Mean (SD)	Range	Correlation with gestational age (*R*-squared)
Gestational age (weeks))	39.1 (1.8)	28–42	
Measured parameters			
Birth weight (g)	3131.7 (538.9)	800–5,100	**11%*****
Supine length (cm)	49.3 (2.9)	28.0–60.2	**10.4%*****
Crown rump length (cm)	33.6 (2.2)	21.0–46.4	**11.2%*****
Limb length (cm)	15.0 (1.0)	10.3–21.2	**9.7%*****
Head circumference (cm)	34.4 (1.7)	25.0–40.0	**13.7%*****
Chest circumference (cm)	31.7 (2.4)	19.4–39.5	**13.3%*****
Abdominal circumference (cm)	28.2 (2.7)	15.3–37.5	**6.3%*****
Mid arm circumference (cm)	10.0 (1.1)	5.0–16.0	**9.4%**
Mid thigh circumference (cm)	15.0 (1.7)	6.5–21.5	**6.9%**
Triceps skin fold thickness (mm)	0.81 (0.21)	0.32–1.96	**1.4%****
Sub scapular skin fold thickness (mm)	0.83 (0.24)	0.18–3.4	**0.6%***
Calculated parameters			
Ponderal index (g/cm^3)	2.61 (0.45)	1.31–6.11	0.4%

This table describes mean, standard deviation (SD) and the range of the gestational age and the measured and calculated anthropometric parameters of the newborns. Their relationship with the gestational age was described by the square of the Pearson correlation coefficient in percentages. Statistically significant correlations are printed in bold: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

significant positive correlation with all investigated parameters. The highest correlations were seen for head circumference, chest circumference and crown rump length, whereas the influence of gestational age on skinfold thicknesses was distinctly lower.

66.3 Applications to Other Areas of Health and Disease: Weighing Newborns Without Using Scales

66.3.1 Prediction of Low Birth Weight by Anthropometric Measurements

Due to the high LBW rate and LBW mortality in Africa (WHO Report 1996) there is an urgent need to identify these babies and refer them to receive specialized medical care (Table 66.4). However, the measurement of birth weight in developing countries has always been a problem due to the unavailability of scales. Several aids have been suggested earlier. Mullany et al. (2006) suggested the use of a spring calibrated hand held scale to measure birth weight in order to overcome the difficulty and Mohanty et al. (2006) described the use of color-coded weighing machines, height rods and tapes for use by peripheral health workers and traditional birth attendants. Because these custom-made devices are not widely available, several studies were conducted to predict LBW using anthropometric parameters which can be easily measured.

The results of these studies are quite variable and there is no consensus as to which anthropometric parameter is the best predictor of LBW. A study in Turkey has shown that chest and mid arm circumferences were found as a good predictor (Arisoy and Sarman 1995), while in Nigeria (Ezeaka et al. 2003) occipitofrontal, midarm, and midthigh circumferences and length were found to be good predictors of both birth weight <2,500 and <2,000 g. Other studies (Gozal et al. 1991; Ramaiya et al. 1994) found midarm circumference to be useful for this purpose. Subscapular skin fold thickness was also found to be of value in this respect and together with mid arm circumference, they were found to be useful tools for determining the degree of maturity of a newborn, independent of birth weight (Excler et al. 1985). In a recent study in Nepal (Sreeramareddy et al. 2008) head and chest circumferences were the best anthropometric surrogates of LBW.

It is well recognized that all of these parameters are strongly correlated with the birth weight and a cut-off point may be of value to identify LBW infants – however, each parameter by itself is distinctly less accurate than measuring birth weight in g by a scale. Furthermore, predicting a category of birth weight using only one anthropometric measurement may be less accurate than using a number of measurements for that purpose. Therefore, we have developed a simple formula to determine birth weight using different anthropometric measurements.

Table 66.4 Key features of low birth weight

1. Low birth weight (LBW) is defined as birth weight <2,500 g
2. LBW is the strongest determinant of infant morbidity and mortality
3. In Africa the LBW rate is distinctly higher than in developed countries and contributes greatly to the high perinatal death rate
4. The identification of LBW infants is important in order to arrange for specialized medical care
5. However, in Africa the identification of LBW is often not possible due to unavailability of scales
6. An alternative could be the measurement of body circumferences in order to identify LBW newborns.
7. In addition to life style factors maternal characteristics such as parity, height, lean body mass index and education affect the LBW rate

This table lists the key facts of low birth weights and the problems of their identification in developing countries

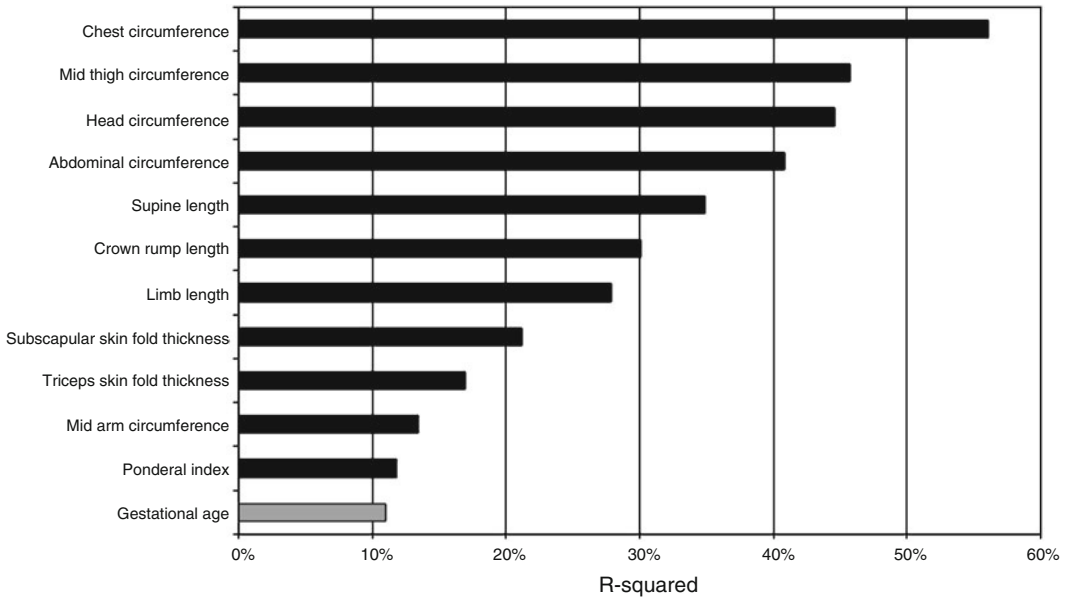

Fig. 66.3 Correlation of birth weight with anthropometric measures. The figure shows correlation of birth weight, measured as Pearson correlation coefficient (*R*-squared), with anthropometric parameters of the newborn (*black*) in comparison with correlation of birth weight with gestational age (*grey*). The anthropometric parameters are ordered according to decreasing *R*-squared

66.3.2 Prediction of Birth Weight Using a Regression Model

To investigate the relationship between birth weight and anthropometric measures, a correlation analysis was performed. As shown in Fig. 66.3, the birth weight is considerably better correlated with anthropometric measures than with gestational age. The highest coefficients of correlation (*R*-squared > 45%) were found between birth weight and chest, mid thigh and head circumferences. However, newborn anthropometric parameters were strongly correlated with each other (e.g. chest circumference and mid thigh circumference with *R*-squared =53%) which may hamper the interpretation of the correlations matrix shown in Fig. 66.3. For this reason a multivariate regression analysis considering all newborn characteristics together with a backward selection was performed to identify the most important correlation as shown previously (Elshibly and Schmalisch 2008a).

The backward selection showed that the three variables that predict birth weight best were chest, mid thigh and head circumferences. The resulting regression model was as follows:

$$\text{Birth weight}\,(\text{g}) = 96.8 * \text{CC} + 74.4 * \text{MT} + 84.5 * \text{HC} - 3{,}960$$

where CC is the chest circumference (cm), MT is the mid thigh circumference (cm) and HC is the head circumference (cm). The standard error of the mean was 285.2 g and *R*-squared was 71% and hence higher than any one parameter shown in Fig. 66.3. The scatter plot of the predicted and measured values of birth weights is shown in Fig. 66.4. The calculated regression line is nearly identical with the line of identity. For practical usage the formula was simplified by rounding off the figures, so that it can be used by health workers in the field as follows.

$$\text{Birth weight}\,(\text{g}) = 97 * \text{CC} + 74 * \text{MT} + 85 * \text{HC} - 4{,}000$$

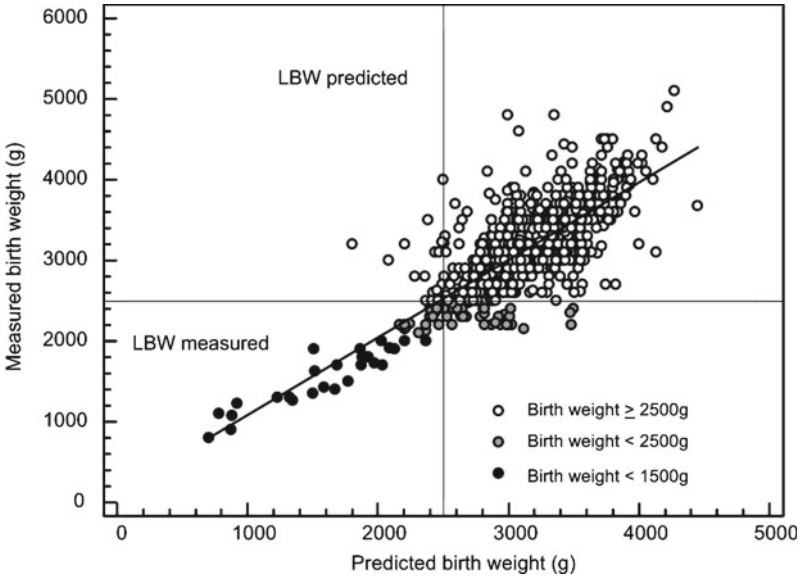

Fig. 66.4 Predicted and measured birth weight. This scatter plot shows the predicted and measured birth weight values of all newborns with the regression line. All infants <2,000 g (*bold dots*) are correctly identified when using a cut off value of 2,500 g

The mean difference in the estimated birth weight between the two equations is 22.5 g (0.7%) and is practically negligible.

This simplified formula may be a powerful tool to asses the BW and allow the health worker in the field to identify LBW infants and consequently determine the immediate management, including initiating breastfeeding, keeping the baby warm and isolated and adopting behaviors that minimize the risk of infection till transport is available to the nearest equipped health facility.

The weight can be calculated with a small pocket or cell phone calculator or manually. These measurements are recommended to be taken by a health professional like a midwife or a nurse who should have special training in taking these measurements. The health worker in remote areas may also obtain additional clinician support per telecommunication.

As far as birth weight measurement is concerned nothing can parallel measurement by a standard scale performed by a trained health professional, but our formula represents a reasonable and practical alternative method to be used in the developing world where scales to measure birth weight are not always available.

66.3.3 Sensitivity and Specificity of the Regression Model

To assess the predictive value of a regression model several statistical measures can be used (see Table 66.5). Sensitivity and specificity of the regression model were calculated by reclassification of the data. Youden's index (= Sensitivity/100 + Specificity/100 – 1) which estimates the probability of correct BW classification was then calculated (Youden 1950). Youden's index ranges between 0 which denotes no diagnostic value and 1 which denotes maximum accuracy.

As shown in Table 66.6, for birth weights <2,000 g specificity is near 100% and the sensitivity is >80%. For this birth weight category the regression model shows the highest Youden's index and thus

Table 66.5 Key features of specificity and sensitivity of regression models

1. Linear regression models can be used to predict birth weight by using one or more anthropometric parameters
2. By defining a cut-off value for birth weight allows every newborn to be assigned into one of the two weight classes (e.g. low birth weight and normal birth weight)
3. Sensitivity and specificity are statistical measures for assessing the correct prediction of weight classes by the regression model
4. Sensitivity represents the proportion of truly predicted low birth weight infants
5. Specificity represents the proportion of truly predicted normal infants.
6. The sensitivity and specificity are dependent on the cut-off value. In general, the higher the sensitivity, the lower the specificity, and vice versa.
7. This relationship can be represented graphically using a receiver operating characteristic (ROC), or simply ROC curve. This curve is a graphical plot of the sensitivity vs. (1 – specificity) for each cut-off point.
8. Youden's index is defined as sensitivity + specificity – 1. This is one way to attempt summarizing the performance of a predictive model. The higher the Youden's index the higher is the predictive value of a model.

This table lists the commonly used statistical measures to describe the accuracy of a predictive model

Table 66.6 Specificity and sensitivity of the predicted birth weight

	Birth weight <1,500 g	Birth weight <2,000 g	Birth weight <2,500 g
Specificity	99.8%	100%	98.3%
Sensitivity	81.8%	87.5%	66.7%
Youden's index	0.82	0.88	0.65

This table shows the specificity and sensitivity of the developed regression model to predict several weight classes. For birth weight <2,000 g the Youden's index has the highest values which means that for this weight category we have the highest number of correct predictions

the highest accuracy in the correct classification of birth weights. For birth weights about 2,500 g the sensitivity is lower; however, as shown in Fig. 66.4 if we use a cut-off point of 2,500 g, all infants (100%) with a birth weight <2,000 g are correctly identified. This means that newborns with the highest risk, e.g., very low birth weight infants (VLBW) with birth weight <1,500 g or extremely low birth weight infants (ELBW) with birth weight <1,000 g can be reliably identified.

66.4 Relationship Between Maternal Factors and Newborn Anthropometric Measures

66.4.1 Effect of Parity on Birth Weight

The association between maternal characteristics and newborn size at birth has been widely studied. Beside antenatal care and woman's health status, birth order was found to be one of the major factors affecting birth weight (Celik and Younis 2007), and several studies have shown that birth weight increases with increase in birth order (Maruoka et al. 1998; Peters et al. 1983; Seidman et al. 1988).

As shown in Table 66.7 an increasing birth order was associated with increasing maternal age, bodyweight and mid arm circumference but not with maternal height. There was no statistically significant association between birth order and social class but the number of years of education of mothers with three and more births was significantly lower when compared to mothers with one or two births.

Table 66.7 Effect of birth order on maternal and newborn characteristics

	First birth ($N = 370$)	Second birth ($N = 206$)	≥ Third birth ($N = 424$)	p-value
Maternal characteristics				
Maternal age	23.8 (4.6)	26.0 (4.4)	30.0 (4.8)	***p < 0.001***
Body weight (kg)	62.8 (12.6)	63.9 (13.1)	67.4 (13.0)	***p < 0.001***
Body Height (cm)	159.3 (6.4)	159.8(6.2)	159.9 (6.6)	$p = 0.401$
Mid arm circumference (cm)	26.2 (3.9)	26.8 (4.0)	27.6 (3.7)	***p = 0.002***
Years of education	9.94 (4.1)	9.92 (3.8)	7.98 (4.4)	***p < 0.001***
Newborn characteristics				
Gestational age (weeks)	39.1 (1.8)	39.1 (1.7)	39.0 (1.8)	$p = 0.573$
Birth weight (g)	3021.6 (527.2)	3156.9 (497.1)	3215.7 (553.0)	***p < 0.001***
LBW-rate (%)	12.2%	5.3%	6.4%	***p = 0.003***

This table shows that birth order was strongly associated with maternal characteristics except body height (statistically significant p-values are printed in bold). Birth order did not affect the length of gestation; however, it was the strongest determinant of birth weight and LBW rate

Table 66.8 Effect of social class on gestational age and newborn anthropometry

	High social class ($N = 43$)	Middle social class ($N = 313$)	Low social class ($N = 644$)	p-value
Gestational age (weeks)	39.1 (1.2)	39.1 (1.9)	39.0 (1.7)	$p = 0.777$
Birth weight (g)	3208.1 (590.7)	3164.9 (541.9)	3110.5 (533.5)	$p = 0.218$
Supine length (cm)	49.4 (2.8)	49.6 (2.8)	49.2 (3.0)	$p = 0.232$
Head circumference (cm)	34.4 (1.4)	34.3 (1.7)	34.4 (1.7)	$p = 0.944$

This table shows that the social class had no statistically significant effect on the length of gestation, birth weight supine length and head circumference.

Table 66.9 Effect of the number of years of education on newborn anthropometry

	0–8 years ($N = 380$)	9–12 years ($N = 487$)	>12 years ($N = 133$)	p-value
Gestational age (weeks)	39.1 (1.9)	39.0 (1.8)	39.2 (1.3)	$p = 0.505$
Birth weight (g)	3078.2 (552.0)	3139.3 (520.1)	3257.1 (550.8)	***p = 0.004***
Supine length (cm)	49.1 (2.9)	49.4 (2.9)	49.7 (2.8)	***p = 0.066***
Head circumference (cm)	34.2 (1.7)	34.4 (1.6)	34.8 (1.7)	***p = 0.006***

This table shows that birth weight and head circumference increase with increasing number of years of education, (statistically significant p-values are printed in bold)

In our study population birth order was the strongest determinant of birth weight (Elshibly and Schmalisch 2008b). With increasing birth order (parity) birth weight increased significantly ($p < 0.0001$) as shown in Table 66.7. However, increasing birth order did not seem to affect gestational age at all. The LBW rate of first-born babies of 12.2% was nearly twice that of infants of multiparous mothers.

66.4.2 Effect of Education and Social Status on Birth Weight

Despite the wide variation in the social status of the investigated mothers we did not see any effect of social class on newborn anthropometry (Table 66.8), while the number of years of education had a statistically significant effect on birth weight and head circumference but not on gestational age, as shown in Table 66.9. The fact that the duration of maternal education and not maternal social class

Table 66.10 Correlation between maternal and newborn characteristics

	Mothers					
Newborn	Age	Weight	Height	MUAC	BMI	LBM
Gestational age	–	–	1.02%$^{++}$	–	–	0.73%$^{++}$
Birth weight	1.16%$^{+++}$	2,74%$^{+++}$	2.22%$^{+++}$	2.92%$^{+++}$	1.26%$^{+++}$	4.31%$^{++}$
Supine length	–	1.16%$^{++}$	3.49%$^{+++}$	1.42%$^{++}$	–	3.49%$^{+++}$
Crown rump length	–	2.08%$^{+++}$	1.89%$^{+++}$	2.58%$^{+++}$	0.89%$^{++}$	3.56%$^{+++}$
Limb length	–	0.58%$^{+}$	3.80%$^{+++}$	–	–	2.25%$^{+++}$
Head circumference	–	0.78%$^{++}$	1.47%$^{+++}$	1.15%$^{++}$	–	1.80%$^{+++}$
Chest circumference	–	1.97%$^{+++}$	2.71%$^{+++}$	1.41%$^{+++}$	0.63%$^{+}$	3.89%$^{+++}$
Abdominal circumference	–	1.35%$^{+++}$	0.98%$^{++}$	1.05%$^{++}$	0.66%$^{+}$	2.23%$^{+++}$
Mid arm circumference	0.80%$^{++}$	3.98%$^{+++}$	2.63%$^{+++}$	4.82%$^{+++}$	2.14%$^{+++}$	5.60%$^{+++}$
Mid thigh circumference	0.53%$^{+}$	2.48%$^{+++}$	2.44%$^{+++}$	2.88%$^{+++}$	1.09%$^{+++}$	4.29%$^{+++}$
Triceps skin fold thickness	2.74%$^{+++}$	2.84%$^{+++}$	0.47%$^{+}$	5.01%$^{+++}$	2.50%$^{+++}$	2.56%$^{+++}$
Sub scapular skin fold thickness	1.41%$^{+++}$	2.55%$^{+++}$	–	3.75%$^{+++}$	2.79%$^{+++}$	1.72%$^{++}$
Ponderal index	–	–	–	–	0.50%$^{+}$	–

This table describes the correlation matrix of characteristics of mothers and newborns
– no statistically significant correlation, $^{+}p < 0.05$, $^{++}p < 0.01$, $^{+++}p < 0.001$

was found to significantly affect newborn anthropometry agrees well with the literature. Karim and Mascie-Taylor (1997) found that birth weight increases with higher maternal education while Raum et al. (2001) and Voigt et al. (2004) showed in Germany that better educated mothers give birth to heavier babies and income plays a minor role.

However, as shown in Fig. 66.1 social class and education were not independent ($p < 0.001$). To overcome this difficulty, a multivariate analysis of variance (MANOVA) considering the interaction of both items and using maternal characteristics (including birth order, age, weight, height, MUAC, BMI, LBM) as covariates was recently performed (Elshibly and Schmalisch 2009). The MANOVA confirmed the results of the univariate analysis and showed that there was no statistically significant effect of social class on birth weight. However, a significant effect of maternal education was obtained on birth weight ($p = 0.004$), head ($p = 0.007$), chest ($p = 0.022$), mid arm ($p < 0.001$), and mid thigh ($p = 0.015$) circumferences as well as on ponderal index ($p = 0.008$). All measurements increased with increasing number of years of education.

The increasing ponderal index (which describes the relationship between body weight and length) with increasing number of years of education indicates that the nutritional status at birth is improved with increasing number of years of education. Thus, if better education in the mother leads to better weight, height and head circumference measurements in their newborns, female education should receive the highest priority in policy making, especially in developing countries where there is a high percentage of less educated mothers.

66.4.3 Correlation Between Maternal and Newborn Anthropometric Measurements

As the mother provides the environment in which the infant grows, maternal characteristics are expected to be associated with newborn anthropometry. The correlation matrix of all maternal anthropometric measurements with those of their newborns is shown in Table 66.10. There was a wide variation in the correlation between maternal characteristics including (age, weight, height, MUAC, BMI, and LBM) and newborn anthropometric measurements. The strongest correlations

were seen for LBM with mid arm circumference (*R*-squared = 5.6%) and for maternal MUAC with triceps skin fold thickness (5.01%). Maternal characteristics showed only a weak association with gestational age and PI.

However, the interpretation of the correlation matrix is impaired by the fact that most maternal anthropometric parameters were strongly associated with each other (namely, maternal weight and BMI with $r = 0.921$, maternal weight and MUAC with $r = 0.812$, maternal height and LBM with $r = 0.685$). Therefore, in a recently described (Elshibly and Schmalisch 2009) multivariate regression analysis all maternal characteristics were considered and a backward selection was used to identify the most important associations between maternal and newborn anthropometry. The strongest effect of maternal characteristics on newborn anthropometry (*R*-squared = 5.6%) was seen on mid arm circumference, supine length and birth weight of the newborn. Maternal LBM showed the strongest association with newborn anthropometric profile except for the skin fold thicknesses which were mainly associated with maternal age and BMI. This agrees well with the results of Kulkarni et al. (2006) who found postpartum LBM to be the most important determinant of birth weight and consequently highlighted the importance of increasing lean body mass in young women.

It seems that maternal fat stores measured by maternal age and BMI are more associated with skin fold thicknesses while the fat free maternal mass is more associated with the size of the newborn. As maternal age advances, maternal BMI and weight increase significantly ($p<0.001$) and it may be that older more obese mothers give birth to infants with increased fat stores. Support to this assumption is provided in the Austrian study (Kirchengast and Hartmann 2003) which showed that offspring of younger mothers were lighter than offspring of older ones.

Summary Points

- Africa has the highest perinatal mortality rates accounting for almost 33% of perinatal deaths worldwide, most deaths are due to LBW.
- The identification of LBW infants is therefore important in order to institute immediate care and arrange for urgent referral.
- In Africa most deliveries occur at home in the absence of skilled personnel and scales to measure birth weight.
- In order to help health workers we developed a simple formula to estimate birth weight.
- This formula utilizes three newborn body circumferences (chest, mid thigh and head) which can readily be obtained by using an inelastic tape measure.
- The birth weight can then be calculated with a small pocket or cell phone calculator or manually.
- LBW infants can then receive immediate management and can urgently be transported to an equipped health facility.
- Maternal age and anthropometry were significantly associated with newborn anthropometric measures; however, maternal anthropometry explained less than 6% of the variability in newborn anthropometry.
- The postpartum maternal LBM was found to be the major associate of newborn size (birth weight, body lengths and body circumferences).
- Birth order and postpartum maternal LBM were the most important parameters that influenced birth weight and the risk for LBW.
- Skin fold thicknesses were mainly associated with maternal age and maternal BMI.
- The duration of maternal education and not maternal social class was found to significantly affect newborn anthropometry.

- The influence of maternal education is also shown by the increase in the ponderal index with increasing years of education.
- The high impact of education calls for better education for females, especially in developing countries.
- Improving female education should receive very high priority in United Nations, government and Non-Governmental Organisation (NGOs) projects.

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Chapter 67
Total Body Water in Newborns

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Abstract In this chapter, the modifications that occur in water distribution from the fetus to the newborn, focusing on the neonatal period, are reviewed. This is a critical period in life as the newborn infant has to adapt itself to a new environment. The main water compartments, intra- and extracellular, undergo changes throughout infancy, with an increase in intracellular space and a decrease in extracellular space as the child grows. The mechanisms of water dynamics behind these modifications are discussed. The flow of water through the cell membranes occurs through the cells (i.e., transcellular) or between the cells (i.e., paracellular). Water crosses the cell membranes through the lipid bilayer or through membrane pores (aquaporins). In paracellular flow, the flux occurs through wide spaces between the cells. Water molecules can also cross the membrane through diffusion in response to osmotic or hydrostatic pressure differences. Motionally distinct water fractions have been described: free bulky water and bound water, where bound water can be tightly bound or loosely bound water. Water can be liberated according to the need of the organism from the bound water fraction irrespective of its location, in the intra- or extracellular compartments.

Healthy newborn infants lose approximately 5–10% of their body weight during the first week of life. This loss in birth weight is attributed to fluctuation of total body water. After birth, the extracellular water compartment undergoes a contraction, followed by natriuresis, diuresis, and weight loss; the infant is oliguric during the first 24–48 h of life. Gestational age is a strong determinant of water loss in newborn, mainly preterm, infants. Insensible water loss through the skin plays a major role in water depletion, as newborns possess a greater surface area, and it has been shown that preterm infants have greater transepidermal water loss than term infants, and this is more pronounced in appropriate-for-gestational-age infants compared to small-for-gestational-age infants. Small-for-gestational-age newborn infants have been shown to possess greater total body water than is appropriate for gestational age infants.

The knowledge of water distribution in neonates and the differences between the two major groups of newborns (appropriate and small-for-gestational-age infants) is fundamental for administering fluids for those infants in the intensive care units without challenging their homeostasis.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_67,

Abbreviations

AVP	Arginine-vasopressin
AQP2	Aquaporin 2
AQP3	Aquaporin 3
AQP4	Aquaporin 4
ANP	Atrial natriuretic peptide
AGA	Appropriate for gestational age
cAMP	Cyclic adenosine monophosphate
PGE2	Prostaglandin E2
RDS	Respiratory distress syndrome
SGA	Small for gestational age
V2	Vasopressin receptor

67.1 Total Body Water in Newborns

The human body is a complex organism that changes as the body develops, matures, and ages. The impressive changes in water distribution from the fetus to the newborn and thereafter from infancy to adulthood are now known. Although knowledge of the main body compartments and body composition has increased, some aspects of the flow of water between these spaces remain poorly understood. Research is being conducted to understand how changes in body composition are associated with renal functioning, insensible water losses, the distribution of water in the different organs, and the physiology of water flow.

The neonatal period is critical to development; it is during this period that the most striking changes in human body composition occur since the newborn has to adapt itself to a new environment while it is growing and developing. In premature babies, these physiological events occur in a body in which the organs are not yet fully developed. Technology has improved the survival of very tiny newborns, some of which have suffered a severe intrauterine growth restriction. In this chapter, data on water distribution, mechanisms of water flow, and differences in water distribution between appropriate and small-for-gestational-age newborns will be reviewed.

67.2 Body Water Compartments

Body water is distributed in two compartments: intracellular and extracellular spaces (interstitial and vascular spaces). Both compartments lose water as the fetus grows, and the extracellular compartment corresponds to approximately 40% of the newborn body at birth. Proportions of 46.3% (males) and 47.0% (females) of body weight for extracellular water and of 27.6% (males) and 26.2% (females) of body water have been reported for intracellular water (Butte et al. 2000). The decrease in water content during gestation is not uniform, and a decrease in extracellular water and an increase in intracellular water toward the end of gestation have been described (Friis-Hansen 1983). The modifications in the proportions of extracellular to intracellular water that occur in the human body from intrauterine life to adulthood as a consequence of the modifications in the content of body fat, proteins, and minerals are shown in Fig. 67.1 (Friis-Hansen 1983).

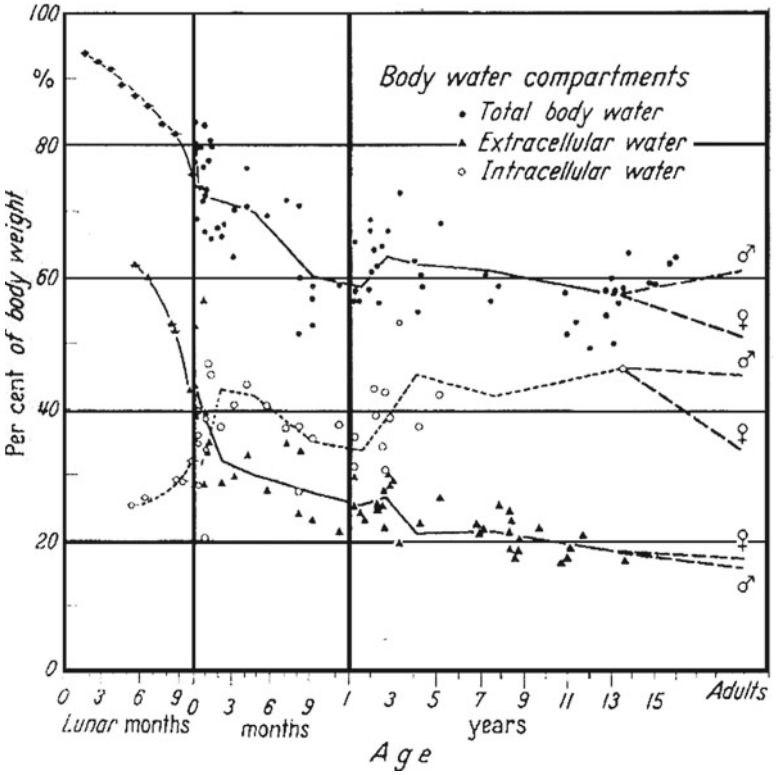

Fig. 67.1 Modifications in the proportions of extracellular to intracellular water in human body from intrauterine life to adulthood. Modifications in body water compartments from early fetal life to adult life: ●, total body water; ▲, extracellular water; ○, intracellular water (From Friis-Hansen (1983), reprinted by permission of the publisher)

During intrauterine life, the growing embryo and fetus possess a predominance of water in their bodies, ranging from 80% to 85% between 26 and 31 weeks of gestation to approximately 75% of body weight at full term (Yssing and Friis-Hansen 1965; Friis-Hansen 1983). This alteration in water content of the fetus corresponds to the great velocity of growth and cell division during intrauterine life; as the cells increase in number and become bigger, the intracellular substance diminishes and the proportion of body water decreases. The acquirement of solid mass, mainly protein, fat, and minerals, as the fetal body is being built accounts for this impressive modification in body composition during intrauterine life until the end of gestation. Although there is a reduction in growth velocity after birth, it is still very fast and up to 2 years of age there are important changes in body composition due to the acquisition of solid mass (Fomon and Nelson 2002).

Newborn infants have a high proportion of water, which diminishes as they get older. The reduction in the proportion of total body water is rapid during the first 130 days of life, and extracellular water decreases more rapidly than total body water during the same period. Furthermore, both total body water and extracellular water are greater in males compared to females (Fomon and Nelson 2002). Body composition in children up to 2 years of age has been analyzed, and the proportions of body water found were 73.9% of body weight for males and 73.2% of body weight for females in neonatal period (Butte et al. 2000). Although not striking, differences in the values reported by the different authors exist (Yssing and Friis-Hansen 1965; Butte et al. 2000; Fomon and Nelson 2002; Olhager and Forsum 2003; Ferreira and Souza 2004; Ellis et al. 2007) and are presented in Table 67.1. These differences are probably due to the measurement techniques used, as well as small

Table 67.1 Body composition: proportions of total body water in full-term newborn infants or preterm newborn infants

Author (year)	Gestational age and age at analyze (*n*)	TBW[a]	ECW[a]	ICW[a]	Technique
Yssing and Friis-Hansen (1965)	Full term	76.6 (boys) 74.3 (girls)	39.6 (boys) 39.3 (girls)	36.0 (boys) 31.8 (girls)	Not given
Butte et al. (2000)	Full term at 0.5 m (age) (76)	73.9 ± 6.8 (boys) 73.2 ± 5.2 (girls)	46.3 ± (6.8) 47.0 ± (6.3)	27.6 ± 2.4 26.2 ± 2.7	Deuterium dilution
Fomon and Nelson (2002)	Birth	69.6 (boys) 68.6 (girls)	42.5 42.0	27.0 26.7	Deuterium dilution (data from 1982)
Olhager and Forsum (2003)	30–33 w at term age (8) Full term (9)	67.4 ± 2.5 (64.0 – 71.3) 68.1 ± 4.1 (57.9 – 72.2)			Doubly labeled water
Ferreira and Souza (2004)	Full term 24 h (age) (30)	68 ± 4	39 ± 6	29 ± 6	Bioelectrical impedance
Ellis et al. (2007)	Full term 1.7–23 w (age) (49)	81.7 ± 1.7 (77.6 – 85.8)			Deuterium dilution

Proportions of total body water in full-term newborn infants or preterm newborn infants related by different authors
[a]% of body weight

differences in the ages of the children at the time of measurement. Regardless, both Butte et al. (2000) and Fomon and Nelson (2002) found slightly greater values for boys compared to girls (Butte et al. 2000; Fomon and Nelson 2002).

67.3 Mechanisms of Water Flow

During gestation, water volume is divided between the fetus, the placenta, and the amniotic fluid. Modifications of the proportion of water from the fetus to the term baby are equal to the alterations in the volume and composition of the amniotic fluid. These dynamic changes depend on fetal urine production, which starts as early as 7–8 weeks of gestation, with fetal glomerular filtration rates increasing during the last trimester of gestation; on fluid actively secreted by the fetal lungs; on fetal swallowing, which begins as embryogenesis is complete, and is functional by the end of gestation; and on intramembranous flux across the amnion between the fetus and the amniotic cavity (Beall et al. 2008).

The flux of water is regulated in part by biological membranes either transcellularly (i.e., through the cells) or paracellularly. The composition of the fluid that crosses the membranes is dependent on the type of flow. There are two routes for the transcellular flow: through the lipid bilayer (low) or through the pores or channels (aquaporins) of the membranes. The aquaporins allow the passage of free water and some small molecules. In paracellular flow, the flux occurs through wide spaces between the cells and both water and solutes cross the membranes, although large molecules are excluded.

Water molecules can also cross the membrane without net water flow via diffusion in response to osmotic or hydrostatic pressure differences (Beall et al. 2008). Osmotic differences are determined by the solute concentration on both sides of the membranes, which are dependent on renal function

and the active transport of solutes and ions (mainly sodium) across the membrane. Hydrostatic pressure differences are related to cardiac output and hormones, such as adrenergic hormones from the adrenal and renin–angiotensin systems.

67.3.1 Aquaporins

Aquaporins are cell membrane proteins that function as water channels. Their function is dependent on their location in the cell membrane. Their position on opposite sites of the cell membrane is important for the regulation of water transfer across the cell. Some aquaporins permit the transfer of other molecules, such as glycerol, urea, and other small molecules, and are called aquaglyceroporins (Beall et al. 2008). In the kidney, these are located in the collecting ducts. The binding of arginine-vasopressin (AVP) to the vasopressin receptor (V2) activates the adenylyl cyclase, increasing intracellular cAMP and thereby phosphorylating the aquaporin 2 (AQP2) localized in intracellular vesicles of the epithelial duct cell. The phosphorylated AQP2 reaches the apical plasma membrane of the collecting duct cell, forming channels in the membrane. Water flows through the channels inside the cell and exits the cell through aquaporins 3 (AQP3) and 4 (AQP4) localized in the basolateral membrane of the cell. AQP3 is the main channel in the cortical collecting duct and AQP4 is located primarily in the medullary collecting duct. However, in newborn infants, the capacity of the immature kidneys to respond to this physiologic pathway is low, and water absorption, and thus urinary concentration capacity, is limited during the first weeks after birth (Bonilla-Felix 2004; Sulyok and Nyúl 2005).

Water transport via AQPs occurs in both directions and is related to osmotic gradients created by the energy-dependent Na–K pump. Although there are other mechanisms for water transport, such as passive diffusion across the membrane lipid bilayer, cellular membrane co-transporters, and paracellular junctions, the AQPs allow a more specific regulation of water movement (Zelenina et al. 2005).

67.3.2 Physical Water Compartments

The distribution of water between the two major water compartments in the human body is related to the concept that the mobility of tissue water is important to understand the body fluid redistribution that occurs in the newborn infant more than the compartmentalization per se. Motionally distinct water fractions have been described: free bulky water and bound water, where bound water can be tightly bound or loosely bound water. Water can be liberated according to the need of the organism from the bound water fraction in the intra- or extracellular compartments, irrespective of its location (Sulyok 2006).

The term *physical water compartments* indicates a physical state of tissue water, with water molecules interactions between dipole water molecules and tissue biopolymers, including proteins and glycosaminoglycans, forming polarized water layers. Multiple layers of polarized water are arranged in parallel with alternating positive and negative sites, which enhance the degree of polarization and motional restriction, increasing the stability of the multilayer (Sulyok 2006). Bioexponential analysis revealed that the bound water fraction in proportion to total tissue water corresponds to 42–47% in the skin, 50–57% in the muscle, and 34–40% in the liver, and that this pattern of distribution does not vary with age or fluid intake. Moreover, in response to complete fluid deprivation, the reduction of the bound water fraction accelerates (Sulyok 2006). This is an interesting concept to understand the mechanisms of water flow control.

Table 67.2 Key facts about stimulus for secretion of arginine-vasopressin

- Changes in plasma osmolality.
- Changes in blood pressure.
- Arginine-vasopressin is secreted under stress conditions.
- The response of the immature neonatal kidney to arginine-vasopressin is limited.

This table lists the principal mechanisms for stimulation of arginine-vasopressin hormone, emphasizing the limitation in neonatal period

67.3.3 Arginine-Vasopressin

Arginine-vasopressin (AVP) is the principal antidiuretic hormone that regulates free water excretion by the kidneys. It is synthesized in the neurohypophysis and stored in nerve terminals of neurons originating primarily from the supraoptic and paraventricular nuclei of the hypothalamus. The two principal stimuli responsible for the secretion of AVP are changes in plasma osmolality and changes in blood pressure. Osmoreceptors located near the supraoptic nuclei detect changes in plasma osmolality and trigger or inhibit the release of AVP as needed. Whether the sensitivity of the osmoreceptors is fully mature at birth has not been established. Hemodynamic alterations are detected by baroreceptors localized in cells of the cardiac atria, carotid sinus, and aorta, and stimulate AVP secretion for blood pressure control (Zaffanello et al. 2008).

The ability to concentrate urine in children at birth is not well documented; it develops progressively during the first 18 months of life, at which point it reaches full maturity. The immature neonatal kidney is incapable of responding adequately to AVP. In newborn infants, many factors contribute to the inadequacy of neonatal kidney responses to control water reabsorption: transducer pathways for AVP are limited by PGE-2-mediated inhibition of cAMP synthesis; water movement across collecting ducts is limited by the low medullary tonicity; low protein intake results in low urea production and there is decreased salt reabsorption, both contributing to the low medullary osmolarity; and the physical length of the loop of Henle in the developing kidney is short, increasing progressively with renal growth after birth (Zaffanello et al. 2008).

Arginine-vasopressin is secreted under stress conditions. It has been demonstrated that preterm newborn infants with respiratory distress syndrome (RDS) requiring mechanical ventilation possess high levels of urine and plasma AVP (Ronconi et al. 1995). The renal osmotic response, as shown by urinary osmolality, to endogenous AVP in preterm infants becomes blunted with advancing age after birth (Table 67.2) (Kovács et al. 1986).

67.3.4 Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP), part of the family of natriuretics peptides, is produced chiefly in the heart and stored in the secretory granules of the atrial and ventricular myocites. Its liberation into the circulation is triggered by increased cardiac wall stretch and increased blood pressure. ANP acts primarily on the cardiovascular and renal systems through receptors localized in target tissues, and is a potent natriuretic, diuretic, and vasodilator hormone. The interaction and modulation of ANP actions by other hormones, such as arginine-vasopressin, glucocorticoids, and catecholamines, creates a dynamic equilibrium among different hormonal pathways and contributes to the preservation of total body water and blood pressure control (Zaffanello et al. 2008).

After birth, with the increase in pulmonary blood flow as a consequence of lung expansion and the elevation of systemic vascular resistance, substantial and very rapid changes in the circulation of the newborn infant occur in order for it to adapt itself to the new environment. Pulmonary circulation

Table 67.3 Key facts about atrial natriuretic peptide

• ANP is a potent natriuretic, diuretic, and vasodilator hormone.
• ANP is produced in the heart and it is stored in the secretory granules of atrial and ventricular myocites.
• ANP liberation is triggered by increased cardiac wall stretch and increased blood pressure.
• ANP acts in conjunction with other hormones contributing for the preservation of total body water.

This table lists the main physiological functions of atrial natriuretic peptide
ANP atrial natriuretic peptide

Table 67.4 Key facts about total body water in newborns

• As the human body changes from intrauterine life to adulthood, an increase in intracellular water and a decrease in extracellular water occur as a consequence of the modifications in the content of body fat, proteins, and minerals.
• The flux of water is regulated by biological membranes, aquaporins, and hormones such as arginine-vasopressin and atrial natriuretic peptide.
• Motionally distinct water fractions have been described: free bulky water and bound water. Water can be liberated according to the need of the organism from the bound water fraction irrespective of its location, in the intra- or extracellular compartments.
• Healthy newborn infants lose approximately 5–10% of their body weight during the first week of life as a consequence of water loss mainly from the skin and kidneys.
• Transepidermal water loss is inversely related to gestational age during the first 4 weeks of life.
• Small-for-gestational-age newborn infants possess greater total body water than appropriate-for-gestational-age newborn infants.
• Transepidermal water loss is higher in appropriate-for-gestational-age newborn infants than in small-for-gestational-age newborn infants during the first days of life.

This table lists the main facts of body water distribution and body water turnover during the neonatal period

and pressure changes occur, and the cardiac cavities increase in size and pressure, which stretches the atrial wall and thus releases ANP. Although the ANP concentration is similar in umbilical venous cord blood and peripheral venous blood on the day of delivery in full-term newborn infants, it increases after birth and reaches a peak level around the second day of life, and then diminishes and maintains a plateau after 1 week of life (Mir et al. 2003).

Preterm newborn infants with respiratory distress syndrome have high ANP plasma levels before the onset of respiratory recovery, and more severe lung disease is correlated with a later onset of diuresis (Ronconi et al. 1995). The ANP concentration gradually diminishes during the post-diuretic phase, returning to pre-diuretic levels after 1 week of age (Kojima et al. 1987). ANP is an important hormone in newborn infants for the control of water volume and blood pressure (Table 67.3)

67.3.5 Hyaluronan

Hyaluronan, with its polyanionic nature and gel-like properties, is implicated in the control of water mobility in lungs; as the major macromolecular compound involved in water balance, it is also found in the kidneys (Sedin et al. 2000; Sulyok 2005). Hyaluronan or hyaluronic acid is one of the glycosaminoglycans, which are unbranched polysaccharide chains composed of repeating disaccharide units. It is produced on the cytoplasmic side of the plasma membrane and transported across the plasma membrane to the extracellular space. Hyaluronan has been shown to be abundant in the interstitium of the renal inner medulla (Dwyer et al. 2000). It has been also shown to be present in the renal medullary interstitium, and its content in the papilla increases during water diuresis and modestly diminishes during water deprivation, thereby demonstrating a role for hyaluronan in water control (Hansell et al. 2000).

In the renal outer medulla, the concentration process results from the high medullary interstitial osmolality, which provides a driving force for osmotic water flow across the collecting ducts. However, controversies remain regarding the mechanism responsible for the concentration process in the renal inner medulla. A theory has been proposed in which the inner medulla, consisting of a hyaluronan matrix, functions as a mechanico-osmotic transducer produced by the renal pelvic wall contractions (Knepper et al. 2003). The renal inner medulla is surrounded by the renal pelvocalyceal wall, which undergoes intermittent contractions, compressing the renal medullary parenchyma and thus altering the flow rates in tubule and vascular structures of the inner medulla. Knepper et al. (2003) hypothesized that these peristaltic contractions would compress the hyaluronan matrix, producing osmotic changes in the renal inner medulla and hydrostatic pressures that would draw water out of the descending limb (Knepper et al. 2003). This hypothesis still needs to be tested. It has been argued that this mechanism would be unlikely to occur in the perinatal period because of the characteristics of the structure and functioning of the kidney in newborn infants. Another explanation has been postulated in which the incapacity to concentrate urine in the immature kidney results not only from the decreased cortico-papillary osmotic gradient and the diminished renal tubular response to arginine-vasopressin, but also due to the elevated hyaluronan encountered in the neonatal renal papilla (Sulyok and Nyúl 2005). Another argument against the mechano-osmotic theory has been proposed recently, suggesting that extravasated plasma albumin exerts a role in the process of concentrating urine in the renal inner medulla (Pinter and Shohet 2006). The mechanisms responsible for the concentration of urine in renal inner medulla remain unknown, necessitating further research.

67.4 Postnatal Adaptations of Body Water

Healthy newborn infants lose approximately 5–10% of their body weight during the first week of life. This loss in birth weight is attributed to the fluctuation of total body water. After birth, the extracellular water compartment contracts, followed by natriuresis, diuresis, and weight loss; the infant is oliguric during the first 24–48 h of life. Modifications in body composition in extreme preterm, appropriate-for- gestational-age, newborn infants during the first days of life have been studied (Bauer et al. 1991). It was found that weight loss was not accompanied by a reduction in body solids; instead, there was a significant decrease in total body water with a reduction in extracellular water related to a decrease in interstitial volume, while the plasma volume and intracellular volume remained unchanged. After regaining birth weight, these babies did not show any significant increases in body solids or total body water, but interstitial volume returned to birth values and there was no evidence of catabolism. These alterations in the dynamics of body fluid compartments were related to high extrarenal water loss on the first day of life, followed by marked diuresis on subsequent days. These data confirm the assumption that water loss occurs after birth, with a contraction of extracellular volume (Bauer et al. 1991).

Full-term infants possess significantly more total body water than do preterm infants when they achieve term age, but when the proportion of water for body weight was compared, the values were found to be similar and not significantly different (Olhager and Forsum 2003). The adipose tissue volume was higher for term than for preterm babies, but this difference was also not significant. When the proportion of total adipose tissue volume for body weight was compared, non-significantly higher levels were found for preterm babies, and a non-significantly smaller volume of subcutaneous total adipose tissue was demonstrated (Olhager and Forsum 2003). Furthermore, loss of body water after birth occurs to the same extent in healthy preterm neonates as in babies with respiratory distress syndrome and is unrelated to the volume of fluid administered (Tang et al. 1997).

67.4.1 Initial Weight Loss

Initial weight loss in newborn infants is a consequence of water loss, mainly from the skin and kidneys. Post-natal weight loss is a good estimate of extracellular volume depletion, and maximum weight loss in extremely low birth weight infants is correlated with maternal hypertension, fluid intake, urinary output, total days on oxygen, and gestational age (Verma et al. 2009). Post-natal weight loss is related to maturation; a multivariate analysis revealed that gestational age is a strong determinant of maximum weight loss in these babies (Verma et al. 2009). Transepidermal water loss is inversely related to gestational age during the first 4 weeks of life and is higher in preterm than in term babies, gradually decreasing after birth. Insensible water loss through the skin plays a major role in water depletion, as newborns have a greater surface area. It was also shown that insensible water loss through the skin is more pronounced in preterm babies than in term babies and, during the first days of life, its volume exceeds that of urine output (Hammarlund et al. 1983). Therefore, it has been hypothesized that the skin may serve as an important route of water depletion and extracellular volume decreases after birth in very preterm newborn infants. This epidermal water loss is a consequence of the lack of keratin in the skin of preterm babies, which poses an epidermal barrier; in extremely low birth weight newborn infants, the skin keratinizes after the first week of life, between weeks 2 and 3, explaining the vulnerability of these babies to water depletion (Sridhar and Baumgart 2006).

The loss of weight during the first days after birth in preterm newborn infants is a consequence of loss of water. The body composition of very low birth weight preterm babies (appropriate-for-gestational-age) has been studied, and the weight loss that occurs during the first 5 days of life was found to be due to the loss of water and diminished extracellular water. Furthermore and importantly, urine output significantly increased from day 1 to day 5 without significant changes in creatinine clearance, fractional excretion of sodium, and urine osmolality (Bauer and Versmold 1989).

In spite of the loss of water after birth as a consequence of the adaptation to extrauterine life, the efficiency of the control of water distribution in the body of the newborn is remarkable. Measurements of total body water in nine preterm newborn infants revealed that despite a wide variation in the water supply during postnatal days 3, 10, and 17, the percentage of body water remains constant, as shown in Fig. 67.2 (Micheli et al. 1994).

67.5 Differences in Water Distribution Between Appropriate- and Small-for-Gestational-Age Newborns

Appropriate- and small-for-gestational-age newborn infants differ in relation to transepidermal water loss. In both groups, an important water loss from the skin occurs during the first 4 weeks of life, primarily within the first 2 weeks. However, this loss of water is more intense in the appropriate-for-gestational-age (AGA) group compared to the small-for-gestational-age (SGA) group, as can be seen in Figs. 67.3 and 67.4. On the first day of life, the transepidermal water loss in AGA infants is higher than in SGA infants of corresponding gestational age, although in preterm infants born after 31–36 weeks of gestation the difference in transepidermal water loss between AGA and SGA is very small after the first 3 days of life (Hammarlund et al. 1983).

In SGA preterm newborn infants one to 2 weeks after birth, the insensible water loss is higher than in AGA of corresponding post-conceptional age, as shown in Fig. 67.4, possibly indicating that the metabolic rate and/or the activity of the SGA preterm babies increases after birth, influencing water loss (Hammarlund et al. 1983). In fact, the total energy expenditure resulting from the oxidative

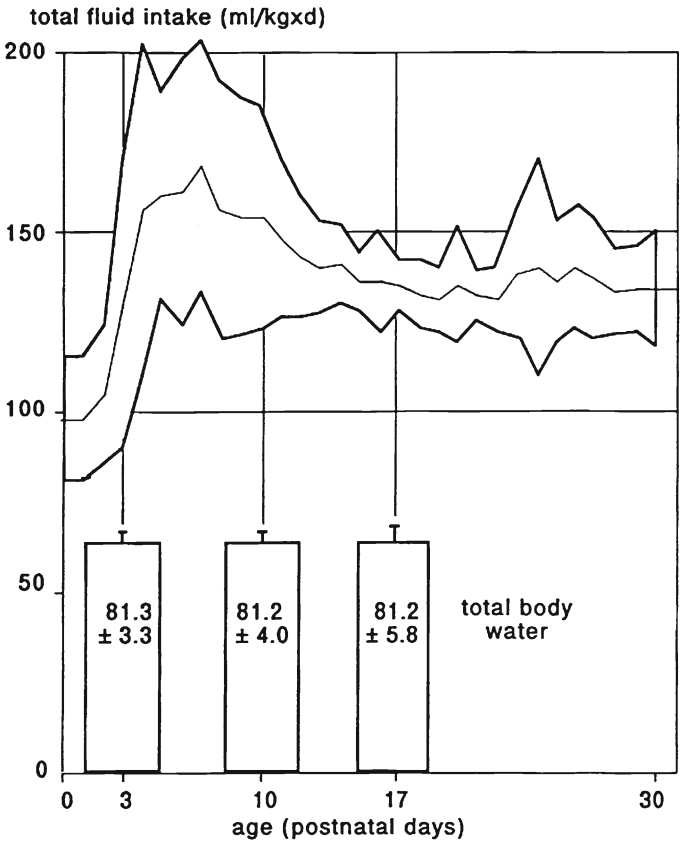

Fig. 67.2 Efficiency of the control of body water distribution in newborn infants. The upper part shows the mean (range) value of total fluid intake in nine healthy premature infants. It is striking how efficiently the concentration of water in the body is regulated; no change in the percentage of total body water over a very wide range of fluid intakes (From Micheli et al. (1994), reprinted by permission of the publisher)

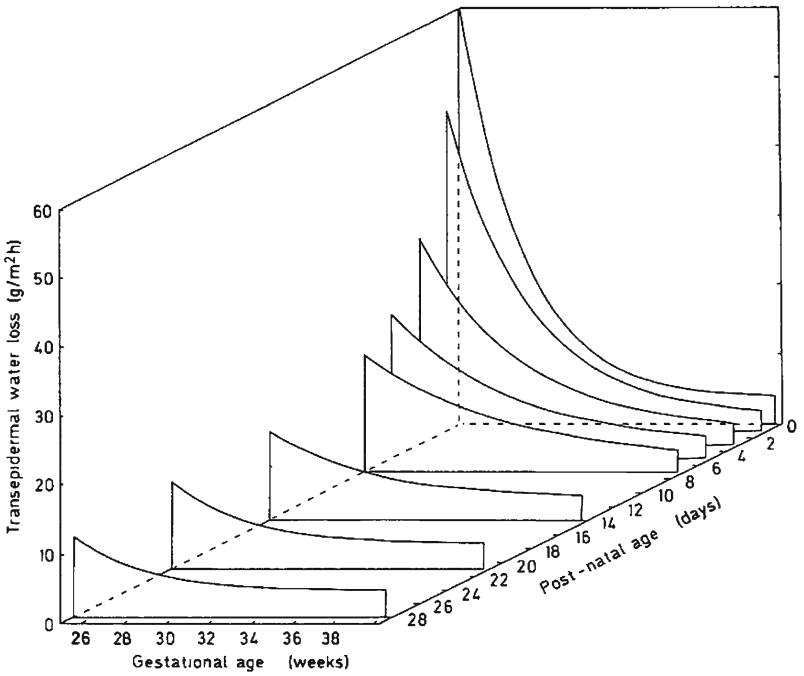

Fig. 67.3 Transepidermal water loss in appropriate-for-gestation-age newborn infants during neonatal period. The regression of transepidermal water loss (g/m^{2}h) on gestational age at birth at different post-natal ages in appropriate-for-gestational-age infants. This figure shows the differences in transepidermal water loss from birth to 28 days of life in relation to the gestational age at birth (From Hammarlund et al. (1983), reprinted by permission of the publisher)

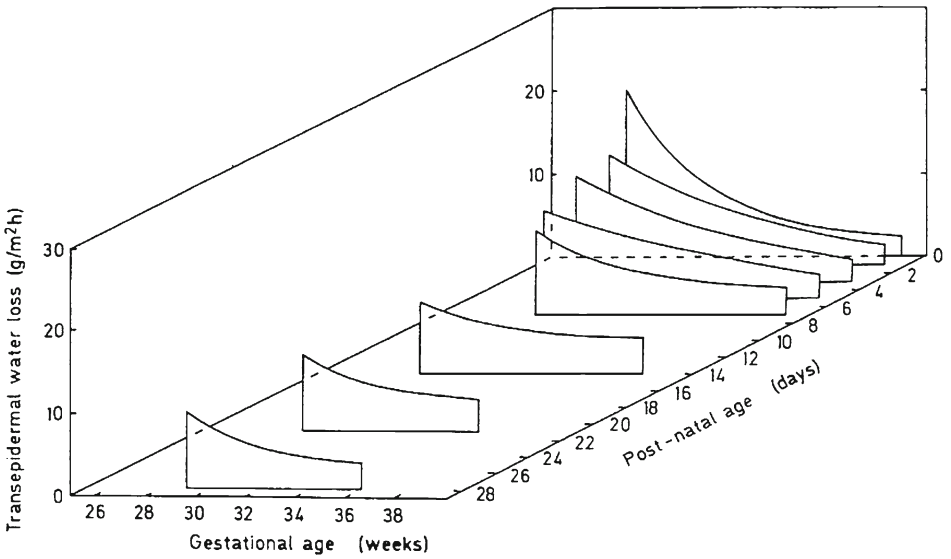

Fig. 67.4 Transepidermal water loss in small-for-gestation-age newborn infants during neonatal period. The regression of transepidermal water loss (g/m²h) on gestational age at birth at different post-natal ages in small-for-gestational-age infants. This figure shows the differences in transepidermal water loss from birth to 28 days of life in relation to the gestational age at birth (From Hammarlund et al. (1983), reprinted by permission of the publisher)

metabolism of carbohydrates, fat, and protein is greater in preterm infants at term age than in term babies, and it has been hypothesized that preterm infants are more active than their counterparts; this study did not compare SGA and AGA (Olhager and Forsum 2003). Neonatal body water turnover is greater in SGA babies; the loss of water via the urine is faster and greater in this group of babies compared to preterm and term AGA newborn infants (MacLennan et al. 1983).

SGA newborn infants possess greater total body water than their AGA counterparts (MacLennan et al. 1983; Hartnoll et al. 2000; Méio et al. 2008). The concern with the distribution of body water and nutritional gain among AGA and SGA infants after birth is important when dealing with these two groups of infants in the neonatal period. The provision of adequate nutritional support in the neonatal period is fundamental for the survival and outcome of newborn infants, as evidence points to long-term consequences of malnutrition, both during intrauterine life, in intrauterine growth restriction, and after birth, in post-natal growth failure (Finken et al. 2006). The distribution of water in the body is well known to be related to the nutritional status of the newborn infants.

In addition to possessing a greater proportion of water after birth, SGA preterm infants maintain this difference toward term age in relation to their AGA correspondents; term SGA also have more water than term AGA infants. Although SGA preterm newborn infants catch up in growth after birth, this increase in growth is not sufficient for them to outgrow their growth deficiency. Comparison of two groups of AGA and SGA babies, matched according to gender and gestational age, revealed that total body water in SGA preterm infants is greater than in AGA preterm infants both at 7 days of age and at term age. Although a decrease was detected in total body water and the weight *Z*-score from birth to term age (Fig. 67.5), and an increase was observed in measures that reflect gain in body mass, such as the triceps skinfold and Rohrer ponderal index (Fig. 67.6), in both groups, the change from birth to term age was quite similar in both AGA and SGA, as the differences between the groups were not significant (Méio et al. 2008). It appears that two components comprise the modifications in total body water between the groups: a greater water loss in AGA infants and an insufficient increase in solid mass in both groups, with a comparable growth velocity in both groups after birth.

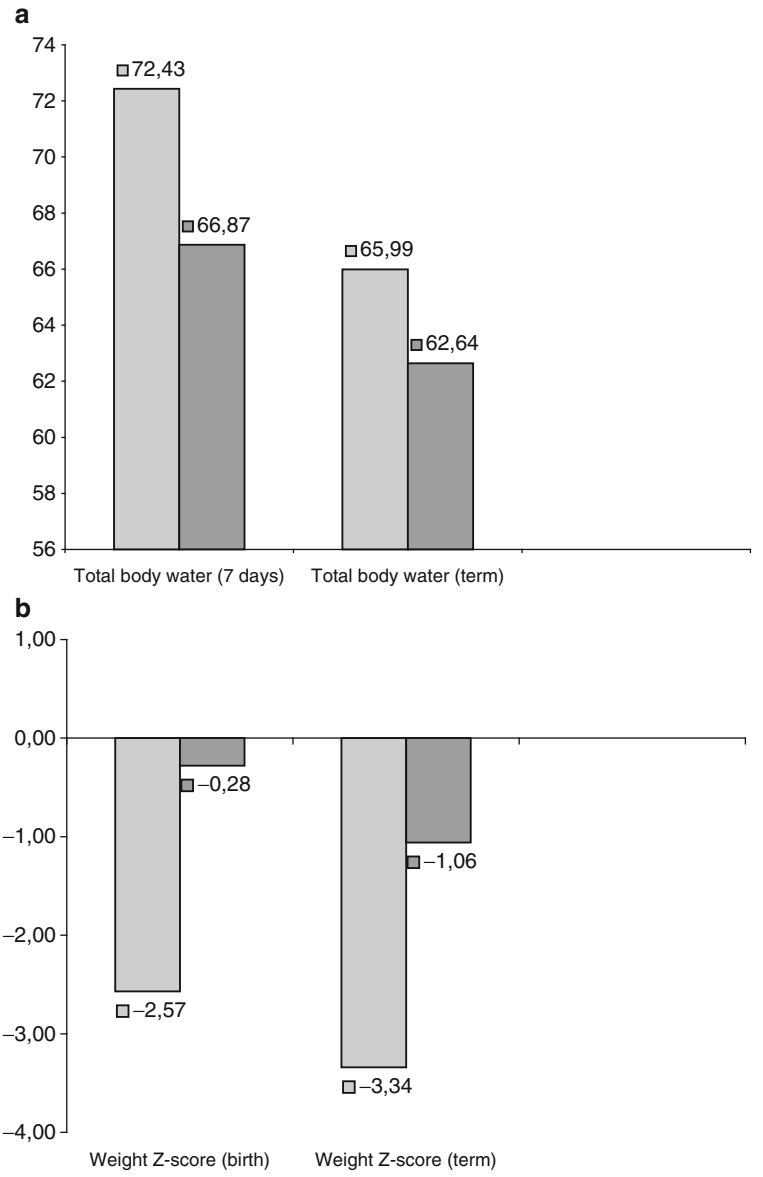

Fig. 67.5 Differences in total body water and weight *Z*-score between appropriate-for-gestational-age and small-for-gestational-age newborn infants. Comparison of the proportion of total body water (7 days of life and term age) and weight *Z*-score (birth and term age) in small-for-gestational-age and appropriate-for-gestational-age newborn infants matched by gender and gestational age, showing the decrease toward term age. (**a**) Total body water; (**b**) weight *Z*-score. First column (*light gray*) – small-for-gestational-age newborns, second column (*dark gray*) – appropriate-for-gestational-age newborns

In conclusion, knowledge regarding the water distribution in neonates and the differences between the two major groups of newborns (appropriate- and small-for-gestational-age infants) is fundamental for the appropriate administration of fluids to infants in intensive care units without challenging their homeostasis.

67.6 Applications to Other Areas of Health and Disease

In clinical practice, the management of fluid administration in critically ill newborn infants is critical. Assessments of body water, electrolyte concentrations, blood pressure, and renal function are important tools for controlling homeostasis in the neonatal period. In addition, knowledge of the mechanisms

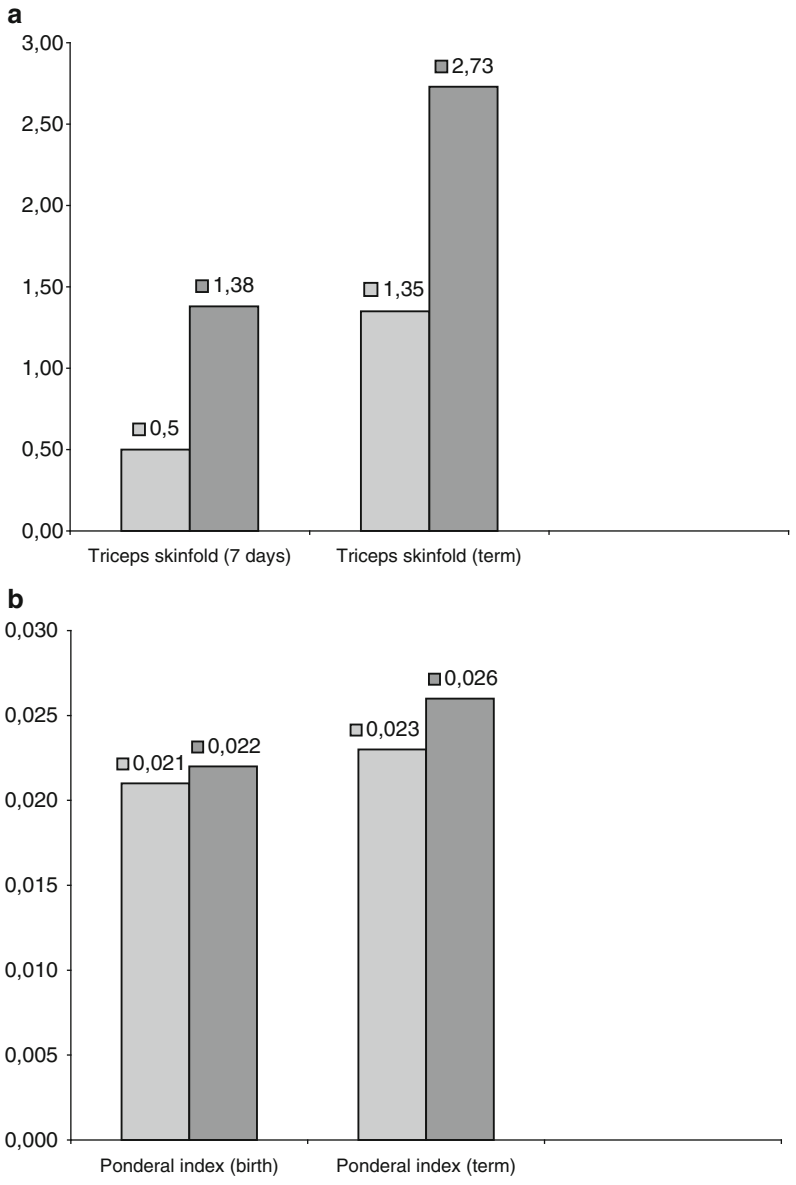

Fig. 67.6 Differences in triceps skinfold and ponderal index values between appropriate-for-gestational-age and small-for-gestational-age newborn infants. Comparison of the proportion of ponderal index (birth and term age) and triceps skinfold (7 days of life and term age) in small-for-gestational-age and appropriate-for-gestational-age newborn infants matched by gender and gestational age showing the increase toward term age. (**a**) Triceps skinfold; (**b**) ponderal index. First column (*light gray*) – small-for-gestational-age newborns, second column (*dark gray*) – appropriate-for-gestational-age newborns

of water loss after birth, chiefly in preterm newborn infants, is of great importance in caring for these babies. The goal of fluid and electrolyte equilibrium is not to maintain body water status after birth, but to allow the physiological changes to occur appropriately. Inappropriate fluid management has important clinical implications in the incidence and severity of diseases, such as respiratory distress syndrome, patent ductus arteriosus, and bronchopulmonary dysplasia.

New equipment to measure body composition that can be used at the bedside can facilitate decisions that must be made during the first weeks after birth. Moreover, an understanding of the changes that occur during this period, mainly in preterm newborn infants, is crucial for the clinician.

Knowledge of the distribution of water between the body compartments, the mechanisms responsible for the regulation of water flow, and neonate kidney functioning in newborn infants and later throughout childhood is fundamental to understand the mechanisms of drug distribution and turnover. In clinical practice, pharmacological dosages of medicine are estimated based on body weight, total body water, or surface area. Knowledge of the body composition is an important issue for the pharmaceutical industry, as new drugs targeted at children are being developed and manufactured.

Summary Points

- From intrauterine life to adulthood, the content and distribution of body water changes as a result of growth. The two main compartments, extracellular and intracellular, exhibit dynamic changes, with a decrease in extracellular volume and an increase in the intracellular volume, as the child grows.
- The changes in the distribution of water in the human body, chiefly in the neonatal period, are characterized by a decrease in total body water. The initial water loss in newborn infants is reflected by the well-recognized weight loss during the first days of life. Moreover, this water loss is more evident in preterm than in term infants.
- Transepidermal water loss and insensible water loss are important mechanisms related to the initial water loss, chiefly in preterm infants. Moreover, this loss is more accentuated in appropriate-for-gestational-age than in small-for-gestational-age infants. Knowledge of how this water loss occurs is crucial for the management of small preterm newborn infants in intensive care units.
- The water balance in the neonate body results from the integration of hormones pathways and the target organs, mainly the cardiovascular system and the kidneys. Hormones such as arginine-vasopressin and atrial natriuretic peptide are important in the control of water and electrolytes homeostasis and in blood pressure control. Biological cell membranes are also involved in regulating water flux.
- Differences in appropriate- and small-for-gestational-age newborn infants are currently being studied, and the repercussions of intrauterine growth restriction in adulthood, with ongoing evidence of its role in adult metabolic disease, highlight the importance of a better understanding of the dynamic changes that occur during this period of life.
- Small-for-gestational-age newborn infants possess a greater proportion of body water than appropriate-for-gestational-age newborn infants. Although they demonstrate a catch-up growth after birth, they maintain the difference in the proportion of body water when compared with appropriate-for-gestational-age infants.

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Part XII
Anthropometry of Infants and Children

Chapter 68
Failure to Thrive in Infancy: Anthropometric Definitions

Else Marie Olsen and Charlotte M. Wright

Abstract The term Failure to Thrive (FTT) has been widely used during the last century to describe poor growth in early childhood. The condition has traditionally been classified on the basis of the presence or absence of somatic illness, with most cases being of non-organic or mixed origin. In early literature definitions of FTT included emotional and behavioural symptoms, which strongly linked the condition to maternal deprivation and psychosocial adversity. However, a consensus in 1985 concluded that the primary identification of FTT must be based solely on anthropometric parameters. Albeit, there is no consensus about a specific anthropometric definition, and a broad range of different anthropometric indicators and cut-off points have been used to identify FTT. Most criteria have been based on weight measures, equalling FTT with slow weight gain, and FTT have thus for example been defined as weight falling below the 3rd percentile, downward crossing of weight over two or more main percentile lines, and weight gain below the 5th percentile conditioned on birth weight taking into account the normal phenomenon of regression towards the mean. The concurrence between different criteria of FTT, however, is low, and different criteria are likely to identify different child populations with different risks of adverse outcome. Thus, during the last decade it has been suggested that this rather vague term should be abolished in favour of more valid anthropometrical descriptions based on explicit measures of growth or nutritional status.

Abbreviations

BMI	Body mass index (kg/m^2)
CDC	Centres for Disease Control and Prevention
DSM	Diagnostic and Statistical Manual of Mental Disorders
FTT	Failure to thrive
ICD	International Classification of Diseases
NCHS	National Centre for Health Statistics
NOFTT	Non-organic failure to thrive

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_68,

PEM	Protein and energy malnutrition
SD	Standard deviation
SDS	Standard deviation score
WHO	The World Health Organisation

68.1 Introduction

The concept of FTT has been recognised for more than a century, and was first described in 1899 by Holt as a condition of malnutrition in infants with weight faltering and wasting in connection to weaning (Kessler and Dawson 1999). Since the mid-nineteenth century the term 'failure to thrive' has been widely used to describe various kinds of inadequate growth in childhood, with or without obvious organic disease. Early studies also included a variety of emotional and behavioural symptoms within the 'diagnosis' of FTT (Kessler and Dawson 1999). However, a consensus in 1985 concluded that the primary identification of FTT needs to be based solely on anthropometric parameters (Drotar 1985). However, no consensus exists concerning a specific anthropometric definition of FTT, and the term has been used to cover a broad range of different anthropometric indicators not necessarily identifying the same populations of children at risk (Wilcox et al. 1989; Olsen 2006). This has hampered comparisons between studies and research results and the utility of the term concerning prevention and treatment.

Within the last couple of decades, there has been a growing recognition that the concept of FTT is unclear, and several clinicians and researchers have suggested that the term should be abolished, in favour of, for example 'pediatric undernutrition', or a more specific use of the different growth parameters (Kessler and Dawson 1999).

In this chapter we describe different conceptions of FTT used during the last century with special focus on the use of different anthropometric definitions and its consequences concerning the identification of children at risk.

68.2 Approaching the Concept of FTT

Neither the WHO International Classification of Diseases, ICD-10, nor the American Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) includes FTT as a specific diagnosis, and no anthropometric definition is mentioned in either. In the ICD-10 FTT is included within the diagnostic entity "Other lack of expected normal physiological development", with the diagnostic code 'R628', also including 'Infantilism not otherwise specified', 'lack of growth', and 'physical retardation', are placed in the main section 'General symptoms and signs'. Thus, although the term FTT has often been used as a specific diagnostic entity or syndrome, it is in fact a symptom with multifactural causality. In both the DSM-IV and the ICD-10, FTT is included in the description of reactive attachment disorder, while the ICD-10 also includes it in the description of feeding/eating disorders of childhood. It has thus long been recognised that a common characteristic in FTT is relative undernutrition (Kessler and Dawson 1999; Wright 2000), which relates FTT to the concept of malnutrition in general, and especially to 'protein-energy malnutrition' (PEM/Kwashiorkor), with the ICD-10 code E45. The term PEM, however, has primarily been used to describe nutritional deprivation among children in developing countries, while the term FTT has mainly comprised children in more

affluent societies. FTT and malnutrition/PEM are thus described in different literatures, and also, somewhat different anthropometric criteria have been used to define both.

Early childhood is characterised by rapid growth, including rapid changes in weight and height,[1] and deviations of growth parameters from the normal pattern may be the first or most prominent symptom of disease in a small child. At the individual level, FTT is thus an important indicator of physical and/or psychosocial problems in infancy, while at the population level it may constitute a significant problem involving a large number of children. Its prevalence, however, varies greatly with the definition used and the population investigated. In early clinical studies from the US, 1–5% of hospitalised children and 10–30% of children seen in out-patient clinics were reported to have FTT (Kessler and Dawson 1999). Likewise, in a Danish registry-study from 2002, done by one of the authors (EMO), 4% of 0–2-year-old hospitalised children were diagnosed with FTT, using the ICD-10 diagnosis R628. Population studies, defining FTT as conditional weight gain below the 5th percentile (see Sect. 68.5 anthropometric parameters for an explanation of this) or as weight dropping below the 3rd percentile on a weight-for-age chart have, not surprisingly, identified 3–5% (Skuse et al. 1994; Wilensky et al. 1996; Wright and Birks 2000; Blair et al. 2004; Olsen et al. 2007b), while population studies using downward crossing of two or more major weight-for-age percentiles have identified around 20% of an infant population as failing to thrive (Edwards et al. 1990; Olsen et al. 2007b). Thus, the anthropometric criteria used for defining FTT obviously influence the prevalence found and, as we shall see, also the characteristics of the children identified.

68.3 Applications to Other Areas of Health and Disease

Traditionally, FTT has been seen as either organic, or non-organic, based on the presence or absence of serious or persistent somatic illness (Kessler and Dawson 1999). Almost any kind of disease in the major organs can cause weight loss, or impede growth and weight gain in a child, but organic disease in fact primarily explains only a minority of cases (Sills 1978). Thus, in population-based studies, it has been a consistent finding that less than 10% of children identified with FTT seem to have a pure organic origin, while approximately 15% have a mixed causation. In the remaining majority of children, no organic disease is found (Wright et al. 1997; Drewett et al. 1999). Until the mid-1980s, FTT was almost entirely described in institutionalised or psychosocially disadvantaged children, and especially 'non-organic FTT' (NOFTT) was considered as being primarily caused by the absence of the mother or psychosocial deprivation (Kessler and Dawson 1999). Also, psychosocial dwarfism, a condition with retarded height growth and depressed growth hormones – primarily seen in toddlers – was sometimes used interchangeably with NOFTT. In addition to anthropometrical indices, criteria involving behavioural characteristics of the child, or the quality of the mother–child-relationship were thus proposed in early clinical studies, which strongly linked the condition to emotional deprivation. Later population studies, however, found no evidence of such an association in general (Kessler and Dawson 1999). Instead, FTT, defined solely by anthropometrical criteria (and the absence of an obvious somatic explanation), has been found to be associated with early neurodevelopmental problems, including oral motor dysfunction and early feeding problems. It has thus been recognised that a clear distinction between organic FTT and NOFTT can rarely be made, and it has been recommended that FTT should be regarded as a continuum of multifactural causality (Drotar 1985; Kessler and Dawson 1999).

[1] In children under the age of approximately 2 years, height is in principal the supine height, that is length, and height and length are used interchangeable in this chapter.

68.4 What Is the Ideal Definition of FTT?

First of all, if this is a measure of poor growth or 'thriving' the definition should identify children with exceptionally slow growth or weight gain, as opposed to children who are constitutionally small. What is ideally required therefore is a definition based on two or more anthropometrical measurements over time. Secondly, it should identify children whose slow growth relates to undernutrition and/or disease processes, and places them at a greater risk of adverse outcome. Testing the validity of the different definitions that have been used is particularly handicapped by the absence of any gold standard measure of undernutrition or abnormal growth. In practice, therefore, the only measure that can usually be applied is the proportion of normal children who fall below any particular threshold. However, a further test can be the extent to which different definitions identify children with other anthropometric criteria that suggest poor (or good) growth in combination with results from longitudinal population studies indicating reasonable anthropometrical thresholds concerning long-term risk.

68.5 Anthropometrical Parameters Used in Previous Research

Many different anthropometrical parameters and cut-off values have been used in connection with FTT, and the most frequently used anthropometrical criteria during the last couple of decades are listed in Tables 68.1 and 68.2. Table 68.3 shows some classic criteria of moderate and severe malnutrition, sometimes used interchangeably with FTT (Wright et al. 1994).

68.5.1 Attained Measures

The criteria for FTT have mainly been based on static criteria which are in turn based on the attained low size: such as single measurements of weight and/or height, usually using weight-for-age or height-for-age. In contrast, fewer have used weight-for-height or body mass index (BMI), which equates to the anthropometric classifications of malnutrition in children. The classic definition of protein-energy malnutrition (PEM) by Gomez is thus based on low weight-for-age, while WHO has long recommended height-for-age and weight-for-height as the primary indicators of nutritional status in children. When low length or height has been used as the only anthropometric parameter in connection with FTT, this has predominantly been done to identify older children with chronic FTT; this condition now resembles 'Stunting' as in chronic undernutrition. Failure to thrive in infancy may be regarded an acute or semi-acute condition resembling 'Wasting', which involves some degree of thinness as a result of loss of body tissues and poor weight gain prior to the reduced gain in height seen in chronic undernutrition or stunting. However, although the WHO still recommend low weight-for-height as the primary anthropometrical parameter of acute undernutrition (wasting), neither weight-for-height nor BMI has been used much to diagnose FTT in affluent countries (WHO 1995).

Most early studies of FTT used criteria based on attained measures of low weight or, sometimes, low length with a cut-off around the 3rd or 5th percentile, but a cut-off as high as the 10th percentile has been used in some cases. Others have based the definition on Standard Deviations (SD) and used cut-offs as low as minus 2 SD, corresponding to an attained value just above the 2nd percentile (2.28th) (Drotar 1985; Wilcox et al. 1989; Olsen 2006).

Although both weight and height measures have been used separately as the defining parameter of FTT in infancy, the term has primarily been used to clinically describe poor height or

Table 68.1 Static criteria of failure to thrive most commonly used during the last two decades

Attained growth parameter	Cut-off value	Additional requires
Weight-for-age	<3rd percentile <5th percentile <10th percentile <-2 SD-scores[a]	*Some require the criterion to be fulfiled for several months or persistently.*
Height-for-age	<3rd percentile <5th percentile ≤20th percentile <-2 SD-scores[a]	
Height as percentage of the median height-for-age	≤90%	
Weight-for-height	<3rd percentile <5th percentile ≤10th percentile <-1 SD-scores[a] <-2 SD-scores[a]	*Some require the criterion to be fulfiled for several months or persistently. And some corrects for gestational age.*
Discrepancy between height (*H*) and weight (*W*)	*H* > *W* with more than 2 SD	

Many different growth parameters and a broad range of cut-off points have been used as defining criterion of failure to thrive. This table shows examples of commonly used criteria based on attained measurements
[a]SD = standard deviation using a standard growth reference (for example the WHO/NCHS/CDC references)

Table 68.2 Dynamic criteria of FTT used during the last two decades

Attained growth parameter	Cut-off value	Additional requires
Downward crossing of weight-for-age	≥1 major percentile lines ≥2 major percentile lines ≥2 SD	
Conditional weight gain:	Identifying the slowest gaining 5% of children after adjusting for regression to the mean conditioned on a previous weight, often birthweight.	
Fall in weight-for-age From either:		
• Normal/appropriate/ >2,500 g at birth,	<3rd percentile	*Some require the criterion to be fulfiled for several months or persistently.*
• Above the cut-off value at birth	<5th percentile	
• From an earlier established curve	<10th percentile	
Persistent decline/lack of weight gain	No specification	
Documented weight loss		
Fall in height-for-age or weight-for-height	<10th percentile	
Growth failure		*Some require the presence of psychosocial/ cognitive problems*

Failure to thrive is currently most often described as weight faltering, but still, many different criteria are being used. This table shows some examples, with the most commonly used in bold

weight gain. The use of such static criteria may be convenient or necessary when follow up measures are not available, but static criteria based solely on a low weight or height will inevitably over-include constitutionally small, but otherwise normally growing children, while initially under-including larger children with slow postnatal weight gain who have not yet crossed the given low percentile cut-off.

Table 68.3 Classical criteria of Malnutrition sometimes used interchangeable with FTT

Type of malnutrition	Definition	Algorithm	Cut-off		
			Mild	Moderate	Severe
Gomez	Weight as percentage of median weight-for-age	$\frac{\text{Actual } W \cdot 100}{\text{Median } W \text{ for age}}$	75–90%	60–74%	<60%
Waterlow (Wasting)	Weight as percentage of median weight-for-height	$\frac{\text{Actual } W \cdot 100}{\text{Median } W \text{ for the actual height}}$	80–90%	70–80%	<70%
McLaren and Read	Ratio between weight and height as percentage of the ratio between the median weight and median height for age	$\frac{\text{Actual } W / H \cdot 100}{\text{Median } W \text{ for age/Median H for age}}$	85–90%	75–84%	<75%
Waterlow (Stunting)	Height as percentage of median height-for-age	$\frac{\text{Actual } H \cdot 100}{\text{Median } H \text{ for age}}$	90–95%	85–89%	<85%

This table shows some traditional definitions of malnutrition (FTT), widely used in developing countries, using an international standard growth curve; for example the NCHS/CDC/WHO curves
W = weight, H = height

68.5.2 Dynamic Measures

Dynamic measures of growth and weight gain are thus greatly to be preferred in principle, and more recent studies have attempted to using change-based (dynamic) measures (Wilcox et al. 1989; Olsen 2006).

Early population-based studies often used semi-dynamic criteria by excluding children with birthweights at or below the cut-off value (usually the 3rd percentile), resulting in identifying children with a fall from a birthweight above the cut-off value. The required birthweight differed, however, from a weight just above the 3rd till above the 25th percentile, leading again to the identification of presumably very different risk populations (Skuse et al. 1994; Wilensky et al. 1996; Drewett et al. 2001), but this impedes the monitoring of children with lower birthweights and will still under-include larger children. An attempt to solve this uses a definition of dropping through two or more major percentile lines/spaces (e.g. crossing both the 25th and 10th centile) on an ordinary weight chart. This definition seems reasonable and is widely used in both clinical practice and research, especially in the US. However, this criterion also hampers the identification of FTT in constitutionally small children because the conventional chart 'runs out' of major percentile lines to cross. Furthermore, criteria based on a simple fall on an ordinary growth chart do not allow for the phenomenon of regression towards the mean, where large children tend to cross downwards towards the mean, while small children, on average, tend to move upwards. This therefore has the effect of over-identifying over-large children regressing downwards. A further complication is that the spacing of centiles varies in some countries (notably the US) from 0.4 to 0.7 SD.

Within the last couple of decades, the use of conditional weight gain has emerged, identifying the slowest weight gaining children after allowing for the expected regression to the mean (Wright et al. 1994; Cole 1995; Olsen 2006). This is predominantly a research-based method as most conditional methods require the use of SD scores (also called Z scores). SD scores adjust for both age and gender and on average children will maintain the same SD score over time. Thus a fall in weight centile can be detected by observing a negative change in SD score and the effect of baseline SD score can be allowed for by using the method of residuals.

$$\text{Conditional change} = \text{late SDS} - \text{early SDS} * R$$

where *R* is the regression coefficient of early on late SD scores for the whole (or a reference) population. The normal range of conditional change can be predicted theoretically on the basis of *R* and this has been shown to be valid empirically (Wright et al. 1994; Cole 1995). Most commonly, weight faltering would be defined as the lower 5% or 1% threshold for conditional weight gain.

68.6 How Do Different Criteria of FTT Concur?

The basic problem concerning definitions of FTT is that the many different criteria in use can be expected, on theoretical grounds, to identify different populations of children exhibiting different risk of adverse outcomes and we cannot assess which is the best as there is no gold standard method of diagnosing FTT. However, if failure really is a condition characterised by undernutrition, you might expect that the different definitions would nonetheless to substantially overlap.

Only a few studies have compared different definitions of FTT in affluent child populations. The early studies were performed in selected clinical cohorts of referred children (Wright 1994; Raynor and Rudolf 2000). Thus, Wright and colleagues compared the degree of malnutrition according to the three criteria of Gomez, Waterlow, and McLaren and Read (see Table 68.3) in a group of 258 children under the age of 48 months (average age 17.8) referred to an infant/toddler growth clinic for evaluation of FTT. Only children with weight less than the 5th percentile or deceleration of weight crossing two major percentile-lines (defined as 95th, 90th, 75th, 50th, 25th, 10th, and 5th) were included. In addition, Raynor and Rudolf also included BMI and the Thrive index method with slow weight gain conditioned on birthweight, and compared these five criteria in a group of 83 children between 4 and 30 months of age referred to a FTT clinic with weight below the 3rd percentile or deceleration in weight gain over two percentile channels. In the latter study, children were only included in the absence of organic disease. Both studies found large differences regarding the prevalence of FTT and degree of undernutrition as identified by the different criteria. However, these two studies are prone to major selection bias since children were all identified for referral on the basis of a growth abnormality of some kind.

To our knowledge ours is the only population study to compare different definitions within a whole unselected population (Olsen et al. 2007b). In this study, seven commonly used anthropometric criteria of FTT/PEM were applied to an affluent birth cohort of Danish infants born in the year 2000, and the prevalence and concurrence were investigated in two age periods: 2–6 months and 6–11 months of age. In Table 68.4 the crude prevalence of the seven different criteria when applied to this cohort are shown. As can be seen, the prevalence greatly varied among criteria. As many as, 27% of this non-selected infant population met one or more criteria in at least one of the two age groups, and 10% met at least one criteria at both ages. Thus, according to the criteria of Gomez and Waterlow less than 2% of the children were failing to thrive in one or both of the age periods, and next to none at both ages, while more than 20% crossed two or more percentile lines from birth till at least one of the two age periods. If conditional weight gain is a reflection of undernutrition you would expect a substantial overlap with low BMI (wasting) and to some extent with low height (stunting), but in fact the concordance between them is poor, and arguably no more than chance; although many thin children were also among those with the slowest conditional weight gain and vice versa, most children with slow conditional weight gain were not wasted, and most wasted children did not have slow weight gain. Also, wasting was on the whole associated with tall stature rather than low stature.

Table 68.4 The prevalence of moderate failure to thrive when applying seven different anthropometric definitions to a normal infant population from an affluent society

	Anthropometric criterion of failure to thrive						
Age at which failure to thrive is identified	Weight fallen ≥ 2 major percentile lines from birth	Weight gain conditioned on birth weight ≤ 5%	BMI < 5th percentile	Weight < 5th percentile	Length < 5th percentile	Weight < 75% of median weight for age (Gomez)	Weight < 80% of median weight for length (Waterlow)
Age 2–6 months	14.7	5.0	4.8	3.7	3.3	1.8	1.3
Age 6–11 months	20.6	5.0	4.3	4.7	3.3	0.6	0.5
At least one of the two age groups	22.2	7.3	6.5	5.8	5.0	1.8	1.3
Both age groups	11.4	1.8	1.5	2.0	1.2	0.3	0.0

This table gives the crude prevalence of seven commonly used anthropometric criteria when applied to the Copenhagen Child Cohort 2000 (CCC 2000), in percentage of children screened by each specific criterion. The CCC 2000 consists of 6,090 children born during the year 2000 in Denmark and follow prospectively (references 22 + 11).

68.7 The Use of Growth Curves When Identifying FTT

Usually the identification of FTT has been based on age- and sex-specific percentile charts for weight or height, so valid diagnosis depends on valid growth charts. In the mid-1990s, the adequacy of older growth references was questioned, including the American NCHS reference, used since 1978 by WHO as the international standard (De Onis et al. 1997). The concerns included low frequency of measurements during the first year of life, outdated curve-smoothing techniques, and evidence of secular changes in the body size. Also, evidence of a different growth pattern in breastfed children had been found. New updated growth references from affluent societies have been published in recent years, including the UK 1990 reference (Freeman et al. 1995), the new American CDC charts based on national surveys (Kuczmarski et al. 2000), and a European growth reference (Euro Growth) based on the data from 11 European countries (Haschke et al. 2000). Also, new age-specific BMI charts covering childhood have been published recently making this method more feasible (Cole et al. 2000; WHO 2006).

However, all of these updated growth charts are growth references, showing how children in a certain population grew at a particular time, whereas a growth standard would show the optimal growth pattern for all children. Since a standard defines how children should grow, deviations are evidence of abnormal growth, and does not provide as sound a basis for such value judgements. The new growth standard from WHO provides a worldwide international standard of child growth up to age 5, using data from 6 optimally nourished cohorts worldwide (WHO 2006). The WHO have shown that infants in all six centres showed very similar linear growth, thus justifying the construction of a single world standard. When this standard is applied to UK children it shows an excellent fit for length at all ages, as expected, but also shows UK infants to be considerably heavier by the age of a year, with only around 0.5% of infants below the 2nd percentile, and similarly lowered rates of centile falls (Wright et al. 2006). This therefore suggests that the lower thresholds in use, based on local reference data, may have been set too high up till now.

68.8 Does Failure to Thrive Matter in the Long Term?

Failure to thrive, on the whole, has been found to be associated with subsequent growth delay and cognitive deficiencies in later childhood (Kessler and Dawson 1999). Furthermore, FTT has long been regarded an indicator of physical and/or psychosocial problems in early childhood with expected adverse prognoses as a result of the primary cause. However, risk factors associated with FTT have been shown to vary according to the anthropometric definition used (Olsen et al. 2007a). Thus, being among the slowest weight gaining 5% of children (from birth till around 9 months) in an affluent infant population was associated with lower size at birth, birth complications, and abnormal overall development as assessed by public health nurses. When adding the criterion of thinness (BMI below the 5th percentile) to the above criterion, FTT was associated with being small for gestational age, being thinner at birth, having poor eye-contact around 9 months of age as perceived by the parents, and again with abnormal overall development. However, when defining FTT as downward crossing of weight with two or more main percentiles (from birth till around 9 months), it was found to be associated with larger size at birth, being fully breastfed the first four living months, higher maternal age and social status of parents and with parents living together, but not with abnormal development. This strongly indicates that the validity of different anthropometric definitions of FTT greatly varies concerning identification of infants truly at risk. The commonly used criterion of downward crossing of weight with two or more main percentiles thus clearly seems to be far too over-inclusive, including children at presumably lower risk.

Only testing criteria against subsequent outcomes can truly determine whether a growth pattern is pathological. In developing countries with high child mortality rates, attained weight-for-age has been found to be a good discriminator of long-term mortality, while slow weight gain indicates short-term mortality (Bairagi et al. 1985). However, child mortality is a rare outcome in affluent societies, though poor conditional weight gain has been found to be associated with "sudden infant death syndrome" (Blair et al. 2000). Alternatively, cognitive delay and behavioural difficulties are possible outcomes of FTT in affluent populations, and, in a meta-analysis, including controlled population-based studies, Corbett SS and Drewett RF found evidence of minor cognitive delays in the children with early FTT independently of the anthropometric criteria used (Corbett and Drewett 2004). Only three of the eight population studies, however, showed a significant difference, and of these one was performed in a population of preterm children, while the other two studies, as the only ones, included both weight and height in their criterion of FTT, with Dowdney et al. defining cases as children with both weight and height below the 10th percentile at 4 years when the height of the parents were allowed for, while Wilensky et al. defined FTT as weight-for-age below the 3rd percentile for at least 3 months within the first year of living combined with a weight-for-length at or below the 10th percentile.

68.9 Conclusions

We argue that FTT as a concept defies definition simply because it does not represent an identifiable syndrome. The concurrence between different criteria of FTT is low and no single measurement seems adequate on its own for identifying undernutrition or growth delay in the general child population. Rather than using this inevitably vague and often confusing term, clinicians and researchers should be encouraged to characterize their patients on the basis of explicit and well validated measures of growth or nutritional status. For example, a combination of slow weight gain and thinness could be a valid definition of weight faltering related to undernutrition in infancy.

Table 68.5 Key features of percentiles in ordinary growth charts

1. Growth charts constitute a visual description of the expected size of children at different ages in a given population.
2. At each age point an ordinary growth chart represents the percentage distribution of ranked growth measurements at that age in the given reference population and percentile lines join given percentiles for each age.
3. In paper versions of growth charts (used in everyday clinical work) only certain main-percentiles are shown.
4. In American charts the main-percentiles are usually the 5th, 10th, 25th, 50th, 75th, 90th, 95th, while most European charts include the 3rd and 97th percentile instead of the 5th and 95th.
5. Percentiles should be interpreted as follows: if a child has an attained weight at a given age corresponding to, for example, the 25th percentile then 25% of children in the given reference-population have a weight at or below that weight at that age.
6. In some cases standard deviation (SD) lines are used instead of percentiles and these can then be used to describe more extreme parts of the distributions (e.g. -3SD).
7. UK growth charts use selected main centiles all spaced 2/3SD apart (98th, 91st, 25th, 50th, etc.) and include as extreme centiles the 0.4th (-2.67 SD) to the 99.6th (+2.67 SD).
8. As most growth charts are based on cross-sectional data, percentiles do *not* describe the growth pattern (although they are often used that way), but only whether a given child is average (or extreme) at a given point in time.
9. In computerised growth programmes, data can be expressed as Standard Deviation Scores (*Z*-scores), making description of extreme percentiles and direct comparison between different measurements, gender and ages possible.

This table gives a short description of the interpretation and use of percentiles.

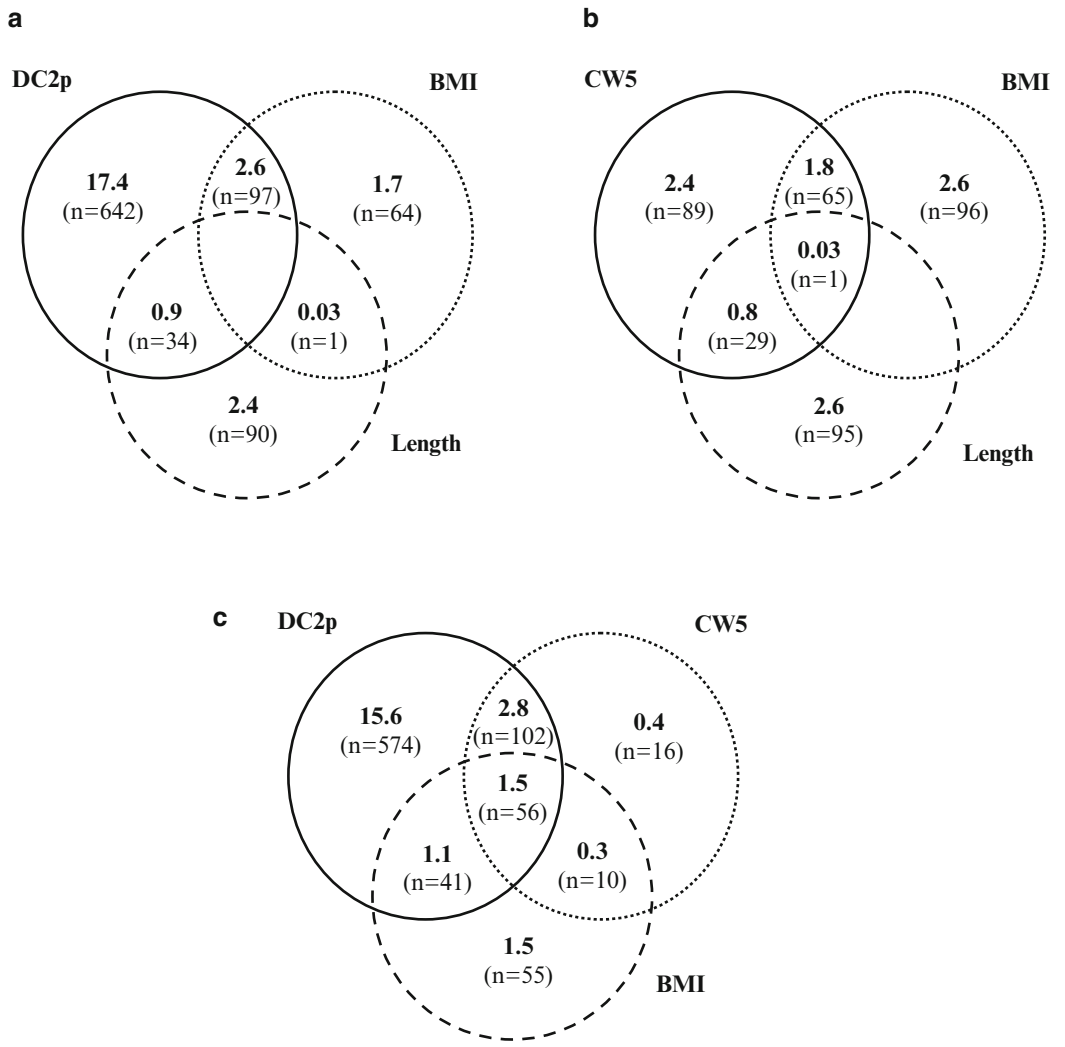

Fig. 68.1 (**a**–**c**) The concurrence between different anthropometrical criteria of weight faltering in a Danish population sample of 3,692 infants at the age of approximately 8 months (Olsen et al 2007b). (**a**) The figure shows the concurrence between 'weight downward crossing from birth ≥2 main percentile lines' (DC2p), 'BMI < 5th percentile', and 'Length < 5th percentile' in percentage of the total 3,692 children (*n*). Among the 3,692 children, 928 (25.1%) fulfiled one of these three criteria at the age of approximately 8 months. (**b**) The figure shows the concurrence between 'weight downward crossing from birth ≥2 main centile lines'(DC2p), 'weight gain < 5th percentile conditioned on birthweight'(CW5), and 'length < 5th percentile' in percentage of the total 3,692 children (*n*). Among the 3,692 children, 375 (10.2%) fulfiled one of these three criteria at the age of approximately 8 months. (**c**) The figure shows the concurrence between 'weight downward crossing from birth ≥ 2 main centile lines' (DC2p), 'weight gain < 5th percentile conditioned on birthweight' (CW5), and 'BMI < 5th percentile' in percentage of the total 3,692 children (*n*). Among the 3,692 children, 854 (23.1%) fulfiled one of these three criteria at the age of approximately 8 months

Summary Points

- Failure to thrive is a symptom, not a specific condition or syndrome.
- Various different anthropometric parameters and cut-off values have been used to define it, resulting in widely varying prevalences.
- Concordance between commonly used criteria is low

- The correlates of FTT are largely determined by the criteria used to define it, but undernutrition seems to be the commonest underlying cause.
- Definitions that involve a fall down the centile chart should always allow for the phenomenon of regression to the mean.
- The new WHO growth standards suggest that the lower threshold for weight and weight gain may have been set too high.
- It has been suggested that the term FTT is both pejorative and too vague to be clinically valid and should be replaced with more explicit descriptors such as 'weight faltering' or 'slow growth'.
- A combination of slow weight gain and thinness seems to be the most valid way of identifying weight faltering related to undernutrition.

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Chapter 69
Estimation of Children's Weight in Medical Emergencies

Anne-Maree Kelly

Abstract In medical emergencies drug dosage, equipment sizing and electrical countershock dose are based on a child's weight. Severity of illness and urgency of treatment usually preclude formal measurement of weight on scales. Incorrect weight estimation could result in drug toxicity or sub-therapeutic treatment, both of which may carry serious adverse outcomes. Methods for estimating weight rely on age–length–weight relationships and include age-based formulae and length-based methods. An alternative is visual estimation of weight by a parent or clinician. Available evidence suggests that parental estimation is the most accurate [where the parent is prepared to give an estimate], followed by length-based methods such as the Broselow Tape with age-based formulae being least accurate. Among the age-based formulae, the Best Guess formulae appear to perform best. Challenges to the age- and length-based methods are significant inter-ethnic variation in the age–height–weight relationship, the trend towards increasing weight across the world and how to factor body habitus into estimation methods in a way which is easily applied.

Abbreviations

CI	Confidence interval
cm	Centimeter
ED	Emergency department
kg	Kilograms
RMSE	Root mean square error
SD	Standard deviation

69.1 Introduction

In emergency departments, it is often necessary to know a child's weight for assessment of clinical status, to enable accurate drug and intravenous fluid dose calculation, to aid selection of correctly sized equipment [such as endotracheal and nasogastric tubes] and to determine the strength of

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_69,

electrical cardiac counter shock for paediatric resuscitation. Overestimation of weight could lead to drug overdosing and underestimation could result in sub-therapeutic treatment. Measuring a child's weight on a set of calibrated scales is the gold standard, but is not always possible due to the severity of illness and the urgency of treatment.

Without again going into the details of child growth, it is clear that age, height [length] and weight are inter-related. These relationships have formed the basis for methods devised to estimate children's weight in emergency situations. In the past, age-weight and length-weight charts derived from population data were used. In recent years, such charts have fallen out of use, being replaced by age-based formulae and length-based weight estimation methods. An alternative with some support is the use of weight estimation made by parents or clinicians. This chapter summarizes the basis and evidence for the more commonly used techniques, their limitations and feasibility in critical care practice.

69.2 Definitions and Statistical Considerations

For consistency and ease of understanding, agreement with actual weight will, wherever possible, be reported as an average difference, 95% limits of agreement and/or root mean square error [RMSE]. The 95% limits of agreement indicate the range within which 95% of the difference between measured and estimated would fall. Wide limits of agreement indicate poor agreement between methods, even when the average difference is small. This is based on the methodology for comparing test outcomes promoted by Bland and Altman (1986). RMSE combines an assessment of both average difference and spread of data. Where the above were not reported, standard deviation [SD] or mean percent difference is used. Where a negative difference is reported, this implies that the formula or method underestimated actual weight (Table 69.1).

69.3 Age-Based Formulae

Age-based weight estimation formulae are summarized in Table 69.2. Only some have been validated. This section will focus on formulae that have undergone validation and are in common use.

Table 69.1 Key features of estimation of children's weight in medical emergencies

1. With respect to age-based formulae, the most accurate are the Best Guess formulae, with the caveat that they have not been validated outside Australia.
2. The Broselow Tape is more accurate than age-based formulae and has the added advantage that drug doses and equipment sizes can be read directly off the tape.
3. Clinician estimation of children's weight has unacceptable error for use in clinical practice.
4. Where they are prepared to give an estimate of weight, parents are more accurate than other weight estimation methods.

This table lists the key facts relating to estimation of children's weight in medical emergencies including the relative accuracy of age-based formulae, length-based approaches and estimation by parent or clinician

Table 69.2 Summary of age-based formulae

Formula name	Ages of application (years)	Formula
Age-plus-four (also known as APLS)	1–10	Weight (kg) = 2 × [age in years + 4]
Argall	1–10	Weight (kg) = [age + 2] × 3
Best Guess Formulae	<12 months	Weight (kg) = [age in months + 9]/2
	1–5 years	Weight (kg) = [2 × age in years [rounded to the half]] + 10
	5–14 years	Weight (kg) = 4 × age in years.
Luscombe	1–10 years	Weight (kg) = [3 × age in years] + 7
Leffler	1–10 years	Weight (kg) = [2 × age in years] + 10
Theron	1–10 years	Weight (kg) = exp[0.175571 × age in years + 2.197099]
Shann	1–9 years	Weight (kg) = [2 × age in years] + 9

This table provides information regarding age of application and the formulae for calculation of more commonly used age-based weight estimation formulae

69.3.1 Age-Plus-Four Formula (Also Known as Advanced Paediatric Life Support Formula)

The age-plus-four formula, as it is called, has gained popularity through the Advanced Paediatric Life Support course and manual (Mackway-Jones 2001). The formula is expressed as weight (kg) = 2 × [age in years + 4] and applies to children aged 1–10 years.

In validation sets, mean differences between estimated and measured weight have been reported of –3.52 kg [95% CI –2.95–4.09] in a sample of UK children (Argall et al. 2003), –2.84 kg [95% CI –7.66 to +13.43 kg] in a sample of New Zealand and Pacific Island children (Theron et al. 2005), –4.2 kg [RMSE 7.5] in a sample of Australian children (Krieser et al. 2007) and 2.3 kg [95% CI 0–5.90 kg] in a sample of Indian children (Varghese et al. 2006). Thompson et al. (2007) report mean differences of –2.0 kg [SD 2.3 kg] in preschool children and –9.5 kg [SD 11.2 kg] in school aged children.

Sandell and Charman (2009) took a different approach to analysing agreement between this formula and measured weight, preferring to report the average ratio of estimated to observed weight. They found the age-plus-four formula had an average ratio of 0.88 (i.e. underestimated by an average of 12%), with 95% limits of agreement for the ratio of 0.54–1.22. Average difference was found to increase with increasing weight. Similar results were reported by Luscombe and Owens (2007) who reported a mean underestimate of weight by this formula of 18.8% [95% CI 18.42–19.21%].

When compared to other methods, the age-plus-four formula has been reported to perform less well than the best guess formulae (Krieser et al. 2007; Thompson et al. 2007), the Argall formula (Krieser et al. 2007), length-based methods (Sandell and Charman 2009), the Broselow Tape (Krieser et al. 2007; Theron et al. 2005; Varghese et al. 2006) and parental estimate (Krieser et al. 2007).

Importantly, Theron et al. (2005) elegantly demonstrated that ethnicity and related body size significantly impacts this formula. They report that the mean percent error difference [(actual weight – estimated weight × 100)/actual weight] varied from +11.13% in Pacific Island children to –5.12% for Asian/Indian children.

69.3.2 Argall Formula

This formula was derived by Argall et al (2003) from a 300-patient dataset that they collected to test the agreement between actual weight and estimated weight using the age-plus-four formula and the Broselow Tape. The formula they derived is weight (kg) = [age in years + 2] × 3. In their derivation set, they reported a mean difference between actual weight and estimated weight of –0.52 kg, but did not report 95% limits of agreement or range of differences by age.

Two validation studies have been reported. Nguyen et al. (2007) investigated it in a multiethnic sample of 410 children attending an Australian ED. They reported a mean difference between measured and estimated weight of –1.66 kg, with wide 95% limits of agreement (–12.3 to +8.9 kg). RMSE was 5.65. Overall, only 37% of Argall estimates were within 10% of measured weight. The formula underestimated weight in heavier children, especially those weighing more than 35 kg. It performed better in Asian children than in Caucasians (mean bias –0.86 vs. –1.66 kg, RMSE 4.66 vs. 5.71). In a sample of Indian children (Varghese et al. 2006), the Argall formula was found to overestimate weight. Mean difference was 2.38 kg [95% CI –0.80 to +8.70] for the <15 kg group and 7.0 kg [95% CI –0.21 to +14.32] for the >15 kg group. Black et al. (2002) report a mean percent difference from actual weight of –13.8%, with percent difference increasing with age.

When compared to other methods, the Argall formula has been reported to better estimate children's weight than the age-plus-four formula (Krieser et al. 2007). It has been reported to be less accurate than parental estimate, the Best Guess formulae and the Broselow Tape (Krieser et al. 2007; Varghese et al. 2006).

69.3.3 Best Guess Formulae

This set of three formulae, each for a different age group, was developed by Tinning and Acworth (2007) by applying regression analysis to data on 70,181 presentations of children to a tertiary ED in Brisbane, Australia. Two validation studies have been reported: one in the population from which the formulae were derived and the other in a different Australian ED with a multiethnic population.

Thompson et al. (2007), in a retrospective study of high acuity patients, found a mean difference between estimated and actual weight of –0.1 kg [SD = not reported] for infants, 0 kg [SD 2.3 kg] for preschool children and 0.6 kg [SD 9.6 kg] for school age children. The Best Guess formulae were considerably more accurate than the age-plus-four formula.

In a multiethnic sample from another hospital, Kelly et al. (2007) reported a mean difference for the preschool age group of 0.9 kg [95% CI –0.5 to 5.3 kg]. However, for 24% of the sample the estimated weight was more than 20% different from the measured weight. Almost all of these were overestimations of weight. For the school-age group, the average difference between estimated and measured weight was 0.4 kg, but with very wide 95% limits of agreement, –14.4 to +15.2 kg. In 36% of cases, estimated weight was more than 20% different from the measured weight, with approximately two-thirds of these being overestimations of weight. In ten children, the formula overestimated weight by more than 50%. Further analysis showed that overestimation occurred in the lower body mass index children in this multiethnic sample.

When the Best Guess formulae have been compared to other weight estimation methods, they have been reported to be more accurate than the Argall and age-plus-four formulae, have a similar accuracy to the Broselow Tape, and be less accurate than parental estimation (Krieser et al. 2007). It should be noted that the Best Guess formulae have not been tested outside Australia.

Table 69.3 Summary of agreement between age-based formulae and actual weight

Formula		No. studies	No. subjects	Weighted mean difference [estimated – actual weight, kg]	Range of mean differences (kg)
Age-plus-four		4	1,786	–2.79	–4.2 to +2.24 kg
Argall		2	577	–0.22	–1.7 to +3.43
Best	Infant	1	272	–0.1	*
Guess	Preschool	2	1,025	0.35	0 to 0.9
	School	2	957	0.56	0.4 to 0.6

This table summarizes agreement between age-based formulae and actual weight for formulae where this data is available

69.3.4 Weaknesses of Age-Based Formulae

While age-based formulae are, in the main, easy to calculate, the evidence suggests that ethnicity and body habitus pose serious challenges to them. Unless they have been satisfactorily validated in the population to which they are being applied, there is considerable risk of a clinically relevant difference between estimated and actual weight. This risk is less for younger children and increases with increasing weight. Additionally, as age–weight relationships may change with time, the accuracy of these formulae may diminish unless the formulae are re-validated at intervals.

69.3.5 Summary

The relative weighted performance of the age-based formulae is summarized in Table 69.3. Available evidence suggests that the most accurate are the Best Guess formulae, with the caveat that they have not been validated outside Australia.

69.4 Length–Weight Relationship-Based Methods

69.4.1 The Broselow Tape

While length–weight charts have been available for some decades, in the 1980s, James Broselow, a North Carolina-based emergency physician, extended this concept by developing a simple tool to improve weight estimation using height–weight data from the National Center for Health Statistics [USA]. Based on the 50th centile of weights for height, the Broselow Pediatric Emergency Tape® provides emergency personnel with standardized, precalculated medication doses, fluid resuscitation volumes and equipment sizes using color-coded zones based on similar height–weight correlations. The tape is used by laying it alongside the patient and reading the color zone that matches the child's height (Table 69.4). It is important to note that it can be used only for children between 46 and 145 cm in length and between 3 and 36 kg. It has undergone several revisions over the years, the last in 2007.

The predictive accuracy of the Broselow Tape has been tested in a number of studies. Reported mean differences between estimated and actual weight range from –2.4 to +0.3 kg, with a weighted mean difference of –1.07 kg (Table 69.5). Several studies have reported that agreement is better for

Table 69.4 Key features of the Broselow Tape

1. The tape can only be applied to children between 46 and 145 cm in length and between 3 and 36 kg.
2. It is used by laying it alongside the patient and reading the color zone that matches the child's height.
3. The length–weight relationships used to calculate the Broselow Pediatric Emergency Tape® are based on the 50th centile of weights for height of US children.
4. The tape classifies children, based on length, into color-coded weight zones.
5. Zones on the tape list precalculated medication doses, fluid resuscitation volumes and equipment sizes based on length–weight correlations.

This table lists the key features of the Broselow Tape

Table 69.5 Summary of agreement between estimated weight using Broselow Tape and actual weight

Authors	Year	Sample size	Mean difference between estimated and actual weight (kg)
Argall et al.	2003	300	–2.74
Hofer et al.	2002	904	–0.52
Jang et al.	2007	665	–1.54
Krieser et al.	2007	410	–1.80
Nieman et al.	2006	7,813	–1.01
Theron et al.	2005	909	–1.89
Varghese et al.	2006	500	0.03
Weighted mean difference			–1.10

This table summarizes agreement between estimated weight using Broselow Tape and actual weight along with a calculation of weighted mean difference

smaller children but that this method increasingly underestimates weight for older children, especially above 15–20 kg (Hofer et al. 2002; Jang et al. 2007; Krieser et al. 2007; Lubitz et al. 1988; Nieman et al. 2006; So et al. 2009; Varghese et al. 2006). Overall the Broselow Tape has been shown to predict weight within 10% in 60% of cases (Hofer et al. 2002; Lubitz et al. 1988; Nieman et al. 2006).

Where the Broselow Tape has been compared to other methods, it has been found to be more accurate than the age-plus-four and Argall formulae (Krieser et al. 2007; Varghese et al. 2006) and the Best Guess formulae (Krieser et al. 2007). It has been shown to be less accurate than parental estimate (Krieser et al. 2007).

The accuracy of Broselow Tape has been shown to be subject to interethnic variation. It underestimates weight in Pacific Island and New Zealand Maori children with a reported mean difference of –1.89 kg with wide limits of agreement (–8.87 to 5.11 kg) (Theron et al. 2005). On the contrary, it has been shown to overestimate weight for Indian children with the size of the overestimation increasing with increasing weight (Ramarajan et al. 2008).

69.4.1.1 Refinements and Adaptations

The approach taken by Broselow and colleagues has been successfully adapted for use in third world countries where the children have different height–weight relationship and the range of treatments is smaller (Molyneux et al. 1999). They report that a locally developed tape correctly estimated actual weight with less than 20% error in 79% of children. This compared favorably with clinician estimates that were only accurate to within 20% in 54% of cases.

Yamamoto et al. (2009) proposed a refinement of the Broselow method using the color-coded section on the tape combined with a body habitus icon to calculate drug doses. The suggested icons

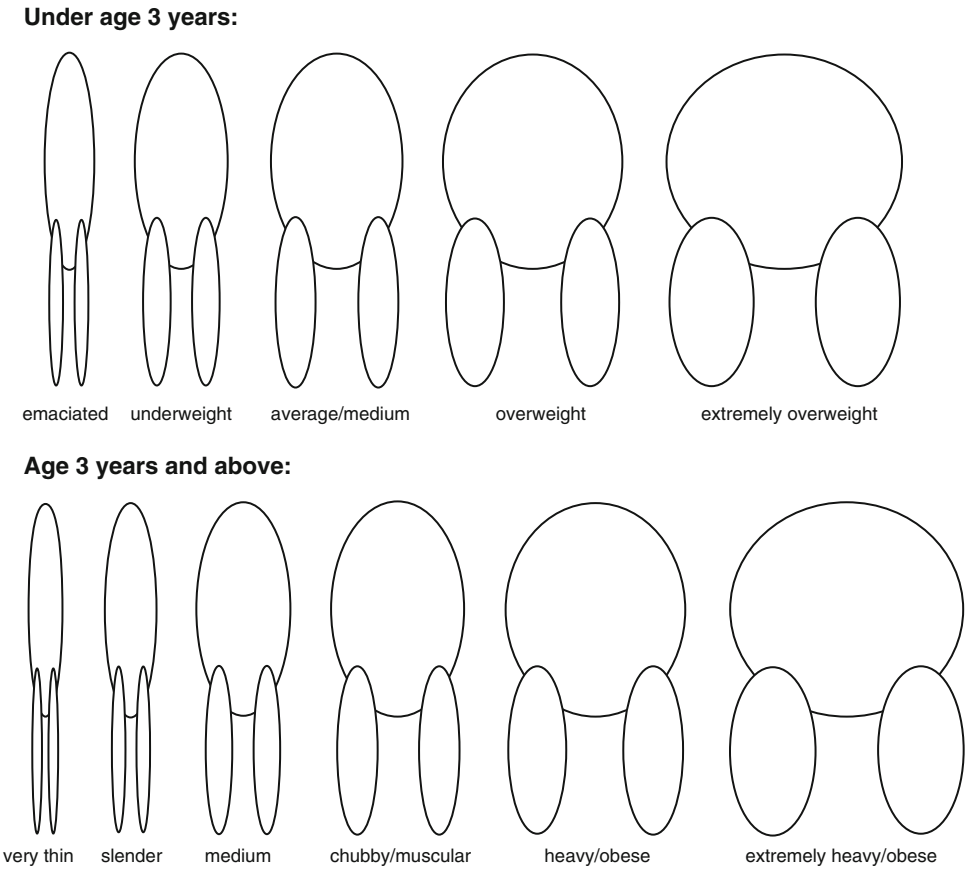

Fig. 69.1 Body habitus icons used by Yamamoto in refinement of Broselow Tape weight estimations. (Reproduced with permission from Yamamoto et al. 2009). This figure shows the body habitus icons used by Yamamoto in a refinement of Broselow Tape weight estimations

are shown in Fig. 69.1. Epinephrine doses estimated using the new method showed significantly smaller mean errors compared to estimations made using the Broselow Tape. No data comparing weight estimations given. The new method requires a subjective assessment of body habitus against charts and a computer program as calculations are quite complex and logarithmic. This will likely limit its application in emergency situations.

69.4.2 Devised Weight Estimation Method

This method, developed by Garland et al. (1986), is based on the height–weight curves and incorporates weight and body habitus to estimate children's weight. Children are subjectively classified as "slim", "average", and "heavy" and weights are estimated from the 5th, 50th and 95th percentiles on the height–weight curves. They reported that using this method 61% of estimated weights were within 10% of actual weights and 95% were within 25% of actual weights. In validation sets, mean percent error has been reported as –3.7% (Dubois et al. 2007) and 0.55% (Black et al. 2002). Error increased at weights above 20 kg (Dubois et al. 2007). A potential weakness of this method is

inter-rater variability in the assessment of body habitus. Both of the validation studies explored this and found good to excellent agreement, with accuracy dependent on experience (Black et al. 2002; Dubois et al. 2007).

69.5 Other Methods Based on Physical Features

Foot length is used in forensic science and archeology to estimate height and weight, but few studies have explored its use in estimation of children's weight, especially in medical emergencies. Bavdekar et al. (2006) collected data from 500 children aged up to 24 months and found good correlation between foot length and weight ($r^2 = 0.88$). They derived a formula for prediction of weight from foot length: Weight (g) = –5.15 + [1.35 × foot-length (cm)]. They tested its accuracy by calculating doses of emergency drugs based on actual weight and weight predicted from foot length and found that the calculated dose exceeded the dose based on actual weight by 2.4%. To date, this method has not been validated or compared for accuracy to other weight estimation methods.

69.6 Estimation by Parents or Clinicians

69.6.1 Parental Estimate

Data regarding accuracy of parental estimation of weight is mixed. Goldman et al. (1999) reported good accuracy of parental estimation with 51.5% of estimates within 5%, 73.4% within 10% and 87.5% within 20% of actual weight. They also found that mothers were in general more accurate than fathers. Harris et al. (1999) reported a mean percent difference between estimated weight and actual weight of –1.3% with there being more than 15% error in 16% of cases. Of concern, however, was the finding that the range of percent error was from –41% to +292%. Leffler and Hayes (1997) found parents to be accurate to within 10% of actual weight in 80% of cases and that parental estimation was more accurate than the age-based formula.

One of the larger studies of parental weight estimation is by Krieser et al. (2007). They found it to be quite accurate when parents were prepared to give an estimate (89% of cases). They report a mean difference of –0.6 kg [RMSE 3.1] and that parental estimate was more accurate than the Argall formula, age-plus-four and Best Guess formulae and the Broselow tape (Table 69.6). Parent estimate maintained its accuracy across the weight range; whereas, the Argall and age-plus-four formulae's performance dropped off sharply with increasing weight (particularly above 40 kg), as did that of the Broselow tape.

69.6.2 Clinician Estimate

It could be suggested that hospital staff see and treat lots of children, so they should be able to accurately estimate a child's weight based on that experience. Evidence, unfortunately, does not support this hypothesis. On the contrary, the data suggests that clinicians are poor at estimating weight and that methods to assist them in weight estimation are required.

Table 69.6 Comparison of weight estimation methods (Reproduced with permission from Krieser et al. 2007)

Method	Mean difference (kg)	RMSE[a]	% agreement within 10% of measured weight
Parent estimate	–0.6	3.1	78
Broselow tape	–1.8	4.4	61
Best Guess formulae	0.7	5.4	42
Argall formula	–1.7	5.7	37
Age-plus-four formula	–4.2	7.5	34

This table compares the accuracy of weight estimation methods including parental estimate, the Broselow Tape, the Best Guess formulae, the Argall formula and the age-plus-four formula
[a]Root mean square error

69.6.2.1 Doctors

Three studies have explored the accuracy of doctors at estimating children's weight. Uesugi et al. (2002) in a study of children undergoing surgery, found that on average 42% of weight estimations by clinical staff were outside an acceptable percent error range. The percent error in estimation was larger for infants and small children (particularly those weighing ≤20 kg) than for older children. Harris et al. (1999) found a mean percent difference from actual weight of –4.8% with more than 15% difference in 29% of cases. Grieg et al. (1997) reported an average difference between estimated and actual weight of 0.21 kg (SD 7.14 kg); however, the range of error was –100% to +300%, with wide individual variation between doctors in accuracy.

69.6.2.2 Nurses and Other Clinicians

Data regarding weight estimation by clinicians other than doctors is sparse. Molyneux et al. (1999) found that clinic staff were only accurate to within 20% of actual weight in 54% of cases. Similarly, Lubitz et al. (1988) found clinical staff to be accurate within 10% of actual weight in 47% of cases. Harris et al. (1999) reported a mean percent difference from actual weight of –7%; however, in 40% of cases there was more than 15% error. Regarding paramedics, Vilke et al. (2001) reported that while the majority of the estimations [82.5%] were within 50% error of the actual weight, 17.5% of cases had between 50% and 100% error.

69.6.3 Summary

Clinician estimate is not sufficiently accurate or consistent to be acceptable in safe clinical practice. Where they are prepared to give an estimate of weight, parents are more accurate than other weight estimation methods.

69.7 Challenges to Weight Estimation Methods

The weight estimation methods that rely on age–height–weight relationships are challenged by how they were developed, interethnic variation and the changing pattern of the age–height–weight relationship.

Most age-based formulae and the Broselow Tape were developed in first world countries with largely Caucasian populations. There has been little exploration of whether they are generalizable to

poorer countries and different ethnic backgrounds. Indeed, there is some data to suggest significant problems with age-based formulae weight estimations between ethnic groups (Theron et al. 2005; Ramarajan et al. 2008; Varghese et al. 2006). How these differences are quantified and adaptions made remain unanswered.

An additional challenge is posed by large for age, small for age and obese children. Two methods have attempted to factor body habitus into weight estimations with some success (Garland et al.1986; Yamamoto et al. 2009). These methods share the potential weakness of inter-rater variability in the assessment of body habitus. More research is needed to address this issue.

The data upon which both of the age and length [height]-based weight estimation methods are based is population data of age–height–weight relationships. This is by no means stable over time. Better nutrition will alter it in developing countries while the trend to childhood obesity may alter it in the first world. Regular re-validation/re-calibration may be necessary to ensure acceptable accuracy for clinical use.

69.8 Practical Considerations

In medical emergency and resuscitation situations, estimation of weight needs to be simple and accurate. Parental estimate fulfils these criteria, if the parent is not too distressed to give a considered answer. The Broselow Tape [or similar] is also easy to use with acceptable accuracy. It has the added advantage of providing drug doses and equipment sizes read directly off the tape. For drugs, this cuts out a calculation step that can be the source of error. Most of the age-based formulae only require simple calculation, but correctly remembering the formula or having it at hand when needed might be problematical. The methods that rely on computer calculations cannot be applied in facilities that do not have this infrastructure, including large parts of the developing world.

Summary Points

- With respect to age-based formulae, available evidence suggests that the most accurate are the Best Guess formulae, with the caveat that they have not been validated outside Australia.
- The Broselow Tape is more accurate than aged-based formulae and has the added advantage that drug doses and equipment sizes can be read directly off the tape.
- Clinician estimation of children's weight has unacceptable error for use in clinical practice.
- Where they are prepared to give an estimate of weight, parents are more accurate than other weight estimation methods.
- In order of descending accuracy, preferred methods for estimating children's weight in medical emergencies are parental estimation, The Broselow Tape [or similar] followed by age-based formulae.

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Chapter 70
Anthropometry and HIV-Infected Children in Africa

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Abstract The epicentre of the HIV/AIDS epidemic is in sub-Saharan Africa. There are few data on the growth and anthropometric indices of HIV-infected children in Africa. HIV-infected children are at risk for malnutrition and have unique nutritional needs due to the physiological demands of growth and the infection. Anthropometry is an affordable and noninvasive method of assessment of body composition and can be used to monitor changes in body composition and nutritional risk of HIV-infected children. Measurements in children should include serial measurements of height/length and weight, mid-upperarm circumference, waist circumference and skinfolds in children older than 1 y to reflect fat and lean body mass. These measurements are often the only option in African countries, because more sophisticated methods of body composition assessment are expensive and seldom available. HIV-infected children not receiving HAART had significantly smaller weight-for-age *z*-score (WAZ) and height/length-for-age *z*-score (HAZ) than control children. After HAART became more generally available around 2004, studies indicated significantly improved WAZ, but not HAZ, in children from the initiation of HAART to 6–24 months of treatment. Before HAART became available, more than 50% of infants died before attaining the age of 2 y in Uganda, whereas 8–9% of children died in equally resource-limited African countries within the first 12–24 months of receiving HAART. There are indications that HAART improves lean body mass in HIV-infected children, with a delayed effect on linear growth and a trend to an increase in fat mass. Such increase in lean body mass is remarkable, because maintenance and increases in lean body mass can be problematic in HIV-infected children. However, HAART has side effects, such as the lipodystrophy syndrome, characterized by peripheral fat wasting, central fat accumulation and metabolic changes. HIV-infected children in the USA and Europe have been shown to develop lipodystrophy syndrome. No published data of lipodystrophy in HIV-infected children receiving HAART in Africa are currently available, probably due to limited availability of HAART in Africa. It is difficult to use anthropometry to measure lipodystrophy in HIV-infected children due to the changes of normal growth and development that occur during childhood and adolescence. The challenge remains to improve height and reduce protein catabolism in HIV-infected children concomitant to a decrease in viral load to undetectable levels. Anthropometry can detect stunted growth, underweight and excessive fat deposition on the trunk. Appropriate interventions can prevent detrimental effects of both undernutrition and overweight in HIV-infected children in Africa.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_70,

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
BMI	Body mass index
BMIZ	Body mass index-for-age *z*-score
d	Day
DXA	Dual energy X-ray absorptiometry
EE	Energy expenditure
FFM	Fat-free mass
HAART	Highly active antiretroviral therapy
g	Gram
HAZ	Height/length-for-age *z*-score
HIV	Human immunodeficiency virus
kg	Kilogram
mg	Milligram
MUAC	Mid-upperarm circumference
NHANES	National Health and Nutrition Examination Survey
TAR	Torso:arm ratio
WAZ	Weight-for-age *z*-score
WHZ	Weight-for-height/length *z*-score
WC	Waist circumference
WHO	World Health Organization
WHR	Waist:hip ratio
Y	Year(s)

70.1 Introduction

Human immunodeficiency virus (HIV) infection progressing to acquired immunodeficiency syndrome (AIDS) is one of the leading causes of death in Africa. The epicentre of the HIV/AIDS epidemic is in sub-Saharan Africa, with an estimated 2.3 million children under the age of 15 y living with HIV in South Africa in 2005 (Shisana et al. 2005). There are still few data on the growth and anthropometric indices of HIV-infected children in Africa. The effects of both HIV infection and antiretroviral (ARV) therapy on body composition had been studied in adults in various studies. The progressive, selective wasting of subcutaneous fat from the face and limbs of HIV-infected adult patients treated with highly active antiretroviral therapy (HAART) first emerged in the 1990s. Lipodystrophy is an abnormality in the metabolism or deposition of fats which is often seen in HIV-infected patients, especially in patients receiving ARV therapy (Viraben and Aquilina 1998). Data are becoming increasingly available about the effects of HIV infection and ARV drugs on body composition in children in Africa (Beau and Imboua-Coulibaly 1997; Berhane et al. 1997; Bobat et al. 2001; Reddi et al. 2007). HIV-infected children are at high risk of malnutrition and have unique nutritional needs due to the physiological demands of growth and development. Malnutrition in children results in growth retardation, increased susceptibility to infection and decreased functional capacity (Berhane et al. 1997; Bobat et al. 2001; Ellis and Molyneux 2007; Ferrand et al. 2007; Berger et al. 2008).

Anthropometry is an affordable and noninvasive method of assessment of body composition and can be used to monitor changes in body composition and nutritional risk of children with HIV infection. Measurements in children should include serial measurements of height (or length) and weight, with calculation of body mass index (BMI) and plotted on the World Health Organization (WHO) growth charts for children (WHO 2005). Mid-upperarm circumference (MUAC), skinfolds and mid-upperarm muscle area in children older than 1 y reflect fat and lean body mass stores. Lean body mass changes measured by anthropometry agree reasonably well with fat-free mass (FFM) changes measured by dual X-ray absorptiometry (DXA) in patients with HIV infection (Knox et al. 2003). Changes in waist circumference (WC) can be measured to detect visceral fat accumulation over time. WC percentiles have been published for children 5–17 y and can be used to monitor 'normal' and excessive increase in WC over time (Fernandez et al. 2004).

70.2 Growth in Healthy and HIV-Uninfected Children

Children have unique nutritional needs due to the physiological demand of growth and physical development. Undernutrition has been related to growth retardation, higher susceptibility to infections and decreased functional capacity (Knox et al. 2003). During adolescence body composition changes take place along with adipose tissue redistribution. Assessment of body fat abnormalities in children is complicated by the difference between abnormal body composition and normal physical development and growth. Serial measurements over time must take normal increases due to growth into account. Similarly, waist:hip ratio (WHR) may not be a useful tool for identification of abnormal truncal obesity in children, because unlike in adults, waist and hip circumferences change with age in children (Knox et al. 2003; Fernandez et al. 2004). In some studies WHR was measured and applied to detect abnormal fat distribution in children. If serial measurements of at least weight and height of HIV-infected children can be done, trends over time can be followed and growth failure can be identified early, so that appropriate interventions can be implemented (Knox et al. 2003).

Undernutrition in children is generally reported in terms of prevalence of stunting, underweight and wasting. Berger et al. (2008) compared these conventional indices with a composite index of anthropometrical failure in a group of HIV-infected and affected orphaned children in Kenya. Because the conventional indices are not mutually exclusive, the total prevalence of undernutrition could not be determined from these indices. When the composite index was used, it was possible to identify children with multiple anthropometric failures, who may have been at risk for poor health outcomes. One-third of the children in this study presented with some form of anthropometric failure. These children were at an increased risk for adverse health outcomes and were in need of nutrition assistance. Furthermore, 22 out of the 170 children (13%) had multiple anthropometric failures and were in urgent need for aggressive nutrition support. If only conventional indices were used to categorize the children, it would not have been possible to identify the 13% of children in urgent need for intervention (Berger et al. 2008). MUAC and mid-upperarm muscle circumference reflect lean body mass, whereas triceps and sub-scapular skinfold thickness in children older than 1 y reflect body fat stores (Miller et al. 2001). These measurements are often the only option in African countries, because more sophisticated methods of body composition assessment are expensive and seldom available (Knox et al. 2003).

70.3 Growth and Body Composition in Children with HIV and Aids

During acute infection HIV-infected children generally lose weight and even when they are not acutely ill, they do not gain weight at the same rate as uninfected children. Poor linear growth is also an indication of advanced AIDS (Verweel et al. 2002). HIV-infected children not receiving HAART had significantly smaller weights and heights than control children (Beau and Imboua-Coulibaly 1997; Berhane et al. 1997; Arpadi et al. 2000; Bobat et al. 2001; Berger et al. 2008; Arpadi et al. 2009). HIV RNA content was positively associated with growth failure in HIV-infected children in the USA and the Netherlands (Arpadi et al. 2000; Verweel et al. 2002).

Children with growth failure had lower energy intakes, but also lower total energy expenditure (EE) and resting EE than children with a normal rate of growth. When resting EE was adjusted for differences in FFM and age, there were no differences between the resting EE of children with and those without growth failure. Rate of growth and FFM, respectively, were inversely related to plasma HIV content (Arpadi et al. 2000). Studies suggest that tissue lost consists of a greater proportion of FFM than would be expected from undernutrition alone, probably due to increased protein catabolism (Beau and Imboua-Coulibaly 1997; Arpadi et al. 2000; Villamor et al. 2005). Factors such as poor oral intake, malabsorption and hypermetabolism may be involved in growth failure of HIV-infected children. It appears that viral replication and possibly inflammatory response could impair dietary intake, disturb normal metabolism and subsequently impede growth of the children. Loss of fat and FFM could both contribute to body weight loss, but studies of their relative contribution have yielded conflicting results (Arpadi et al. 2000). Observations from studies suggest that a preferential loss of FFM occurs early in the disease progression and that cachexia, rather than protein-energy malnutrition, is an important mechanism of weight loss (Moscicki et al. 2006). However, FFM as a percentage of body weight was not significantly different between groups of HIV-infected and non-infected children. These findings suggest that no preferential catabolism of FFM occurs in HIV-infected children. Improved lean body mass is likely to be associated with a reduction in morbidity and mortality (Berhane et al. 1997; Arpadi et al. 2000; Knox et al. 2003), whereas severity of growth failure, indicated by a low weight-for-age *z*-score (WAZ), height/length-for-age *z*-score (HAZ) and weight-for height/length *z*-score (WHZ) or BMI-for-age *z*-score (BMIZ) and loss of lean body mass as measured by low MUAC were associated with an increased risk of mortality (Berhane et al. 1997; Bobat et al. 2001; Villamor et al. 2005). Conservative treatment of HIV infection in children with nutritional support alone apparently helps to increase weight and fat mass, but does not necessarily improve linear growth or lean body mass (Verweel et al. 2002).

70.4 Studies of Growth and Body Composition in Children with HIV Infection in Africa

HIV infection in children in Africa is associated with general undernutrition (Eley et al. 2002; Ferrand et al. 2007). HIV-infected children not receiving HAART had significantly smaller WAZ and HAZ than control children in some studies in South Africa (Bobat et al. 2001) and Uganda, (Berhane et al. 1997) but the difference was not significant in a study in Cote d'Ivoire (Beau and Imboua-Coulibaly 1997). Stunting was not a discriminating factor for HIV infection in this study. The lack of difference may have been due to the endemic malnutrition in the study area (Beau and Imboua-Coulibaly 1997). In studies where children were followed from birth, these differences were already statistically significant at the age of 3 months (Bobat et al. 2001). After HAART became more generally available around

2004, studies indicated significantly improved WAZ and WHZ in children from the initiation of HAART to 6–24 months of treatment (Bolton-Moore et al. 2007; Jaspan et al. 2008; Kabue et al. 2008). In studies in Malawi and South Africa of children with mean age of 7.5 and 5.7 years, respectively, WAZ and WHZ, but not HAZ, improved significantly over 6 months after initiation of HAART (Reddi et al. 2007; Kabue et al. 2008). In this age group, reversal of stunting could not be achieved over the relatively short period of 6 months. Baseline WAZ above +1 was protective against stunting and the most severely undernourished children had a higher prevalence of stunting (Kabue et al. 2008). Before HAART became available, more than 50% of HIV-infected infants died before the age of 2 y in Uganda (Berhane et al. 1997), whereas 8–9% of children died in equally resource-limited African countries within the first 12–24 months of receiving HAART (Bolton-Moore et al. 2007; Ellis and Molyneux 2007; Jaspan et al. 2008). The results of studies describing anthropometric indices of HIV-infected children in Africa are summarized in Tables 70.1 and 70.2.

70.5 Antiretroviral Drugs and Anthropometric Indices

70.5.1 Antiretroviral Drugs and Improved Body Composition

ARV therapy is a combination of medications used to suppress viral replication and progression of HIV disease. A combination of three ARV drugs working synergistically is referred to as HAART. A list of ARV drugs prescribed for HIV-infected children is presented in Table 70.3 and typical ARV drug choices as prescribed in South Africa and other African countries are shown in Table 70.4 (Department of Health 2005; Jaspan et al. 2008). ARV treatment dramatically improved growth and body composition in HIV-infected children after starting treatment (Bolton-Moore et al. 2007; Ellis and Molyneux 2007; Kabue et al. 2008). HIV-infected children treated with HAART exhibit large decreases in plasma HIV RNA concentrations (viral load) and subsequent increases in the number and percentage of circulating CD4 T-lymphocytes. These changes have resulted in significant improvements in clinical outcomes and quality of life, dramatically decreasing the risk of serious opportunistic infections, progression to AIDS, and death. For many HIV disease has been transformed from an acutely life-threatening illness into a manageable chronic disease, allowing children once not expected to survive to live well into adulthood (Miller et al. 2001; Verweel et al. 2002; Reddi et al. 2007; Jaspan et al. 2008). Studies showed that the survival of peri-natally HIV-infected children improved as a result of the introduction of combined ARV therapies (Verweel et al. 2002; Bolton-Moore et al. 2007; Reddi et al. 2007).

Studies reported a positive influence on the growth of HIV-infected children treated with HAART. Height and weight in relation to age improved in children in whom a reduction of the viral load was achieved (Miller et al. 2001; Verweel et al. 2002; Bolton-Moore et al. 2007; Ellis and Molyneux 2007; Kabue et al. 2008). WAZ and WHZ, but not HAZ, improved significantly over 6 months after initiation of HAART in most studies. In contrast to the increase of the BMI in adults on HAART, BMI did not increase in all studies of children effectively treated with HAART (Miller 2001; Verweel et al. 2002; McComsey et al. 2003; Guillen et al. 2007). BMI increased more in children with an advanced stage of infection and who had a poor nutritional status at initiation of HAART (Verweel et al. 2002). Miller et al. (2001) found no significant increase in HAZ, triceps skinfold or mid-upper-arm muscle circumference percentile in HIV-infected children with a mean age of 6.8 y after 2 y of treatment with HAART, including PI. After controlling for age, sex, CD4 *z*-score and viral load, a significant increase in mid-upperarm muscle circumference percentile was found, as well as a

Table 70.1 Results of studies of HIV-infected children in Africa not receiving HAART

Author and country	Study participants	Aim/exposure and outcomes measures	Results
Beau and Imboua-Coulibaly (1997) Ivory Coast	66 children, >15 months, with marasmus, 45% HIV-infected	To assess whether stunting is a discriminating factor for HIV infection	HIV-infected children had lower mean WAZ, WHZ, BMIZ and HAZ than uninfected children, but differences were not significant
Berhane et al. (1997) Kenya	520 infants enrolled at birth from HIV-infected ($n = 84$) and uninfected mothers, followed over 25 months	To study the effect of HIV on somatic growth of infants and the relationship between nutritional status and mortality	Weight-for-age and length-for-age growth curves of HIV-infected infants were significantly lower than those of HIV-uninfected controls; 54% of HIV-infected infants died before attaining the age of 2 y
Bobat et al. (1998) South Africa	48 HIV-infected and 93 uninfected infants, followed for 12 months	To study the effect of HIV infection on somatic growth of infants and the relationship between nutritional status and mortality	HIV-infected infants had significantly lower mean WAZ and HAZ, but not lower WHZ than uninfected infants from 3 months of age; infants who died early had more severe stunting, underweight and wasting than those who survived
Villamor et al. (2004) Tanzania	687 children 6–60 months old, hospitalized with pneumonia, followed up 2 y	To estimate risk of mortality according to HIV status of the children	HIV infection was associated with an adjusted fourfold higher risk of mortality; stunting, wasting and low MUAC were significantly associated with risk of death
Eley et al. (2002) South Africa	60 HIV-infected children, median age 25 months	To document anthropometric and micronutrient disturbances	28% of children had WAZ <–2, 58% had a HAZ <–2; no association between micronutrient status and HAZ or WAZ
Ferrand et al. (2007) Zimbabwe	32 HIV-infected children, 8–19 y	To document anthropometric and clinical features	62% of children had HAZ <–2 and were immune-suppressed
Berger et al. (2008) Kenya	170 children younger than 5 y, orphaned or vulnerable children, impacted by HIV/AIDS	Comparison of conventional indices of undernutrition with a composite index	Conventional index: 31% stunting, 14% underweight, 6% wasting compared to a composite index estimating 38% anthropometric failure. Conventional indices underestimate undernutrition.

This table summarizes results of studies of HIV-infected children in Africa not receiving HAART, including country, aims or exposures and outcome measures

Table 70.2 Results of studies of HIV-infected children in Africa receiving HAART

Author and country	Study participants	Aim/exposure and outcomes measures	Results
Bolton-Moore et al. (2007) Zambia	Cohort of 2,938 HIV-infected children, median age of 81 months at initiation of HAART	To report early clinical and immunological outcomes of children receiving HAART	8.3% of children died, 56% of these within 90 days of initiating HAART; Low WAZ (median –3.5, IQR –4.5 to –2.2) was associated with mortality; mean WAZ increased from –2.2 (95%CI – 1.9, –1.7) to –1.6 (95%CI – 1.7, –1.6) at 6 months
Ellis and Molyneux (2007) Malawi	238 HIV-infected children, 7–212 months old	To assess changes in WAZ, WHZ and survival of the children after initiation of HAART	WAZ and WHZ improved significantly from baseline to 12 months on HAART, 8.4% of children died before 12 months on HAART
Reddi et al. (2007) South Africa	Cohort of 151 children, mean age 5.7 y at initiation of HAART	To report clinical and immunological outcomes of children receiving HAART over at least 8 months	8.6% of children died; median WAZ increased with +1 (p, 0.0001) and HAZ increased with +0.4 ($p = 0.28$) over 8 months
Jaspan et al. (2008) South Africa	Cohort of 391 HIV-infected children, median age of 26 months at initiation of HAART	To report clinical and immunological outcomes of children receiving HAART over 24 months	9% of children died; WAZ increased from median –2.5 (interquartile range –4, –1.2) to –0.1 (interquartile range –1.5, 0) over 24 months
Kabue et al. (2008) Uganda	Cohort of 749 children, mean age 7.5 y at initiation of HAART	To report clinical and immunological outcomes of children receiving HAART over at least 6 months	WAZ increased from mean 7.7th percentile to mean 13.3th percentile, WHZ improved from 7.9th to 13.8th percentile over 6 months, but HAZ remained unchanged at the 8.6th percentile; baseline WAZ >1 was protective against stunting

This table summarizes results of studies of HIV-infected children in Africa receiving HAART, including country, aims or exposures and outcome measures

Table 70.3 A list of ARV drugs prescribed for HIV-infected children

Drug class	Antiretroviral drug
Non-nucleoside reverse transcriptase inhibitors (nNRTI)	Efavirenz (EFV)
	Nevirapine (NVP)
Nucleoside reverse transcriptase inhibitors (NRTI)	Stavudine (D4T)
	Lamivudine (3TC)
	Zidovudine (AZT)
	Didanosine (ddI)
	Abacavir (ABC)
Protease inhibitors (PIs)	Nelfinavir (NFV)
	Indinavir (IDV)
	Lopinavir (LPV)
	Ritonavir (RTV)
	Lopinavir/Ritonavir (LPR/r)

This table lists ARV drugs prescribed for HIV-infected children according to drug class

Table 70.4 ARV drug choices for HIV-infected children in South Africa and other African countries

Regimen	6 months up to 3 years	Over 3 years and >10 kg
First-line	Stavudine (D4T)[a]	Stavudine (D4T)[a]
	Lamivudine (3TC)[a]	Lamivudine (3TC)[a]
	Lopinavir/Ritonavir[b] (LPR/r)	Efavirenz (EFV)
Second-line	Zidovudine (AZT)[a]	Zidovudine (AZT)[a]
	Didanosine (ddI)	Didanosine (ddI)
	Nevirapine (NVP) if age <3 years OR	Lopinavir/Ritonavir[b] (LPR/r)
	Efavirenz (EFV) if age > 3 years	

Department of Health, South Africa (2005)
This table lists ARV drugs prescribed for HIV-infected children in South Africa according to drug class
[a]Abacavir (ABC) may be prescribed if adverse events occur with other NRTIs
[b]If tolerance develops for Lopinavir/Ritonavir, nelfinavir may be prescribed

borderline increase in HAZ of 0.17 SD ($p = 0.1$). The authors concluded that PI therapy in HAART contributed to improved lean body mass in HIV-infected children, with a delayed effect on linear growth and a trend to an increase in fat mass, measured by triceps skinfold thickness. This is in line with experience from nutritional treatment of children with undernutrition from chronic disease, where improved linear growth followed the initial response of an increase in weight (Miller et al. 2001; Verweel et al. 2002). The increase in lean body mass in this study is remarkable, because maintenance and increases in lean body mass can be problematic in HIV-infected children (Arpadi et al. 2000; Villamor et al. 2005). Verweel et al. (2002) found a trend toward significant increases in HAZ and WAZ of HIV-infected children after 96 weeks of HAART. When the results of children who responded to HAART with a significantly reduced viral load to <500 copies/mL and improved CD4 T-cell *z*-score were analyzed separately, significant increases in HAZ and WAZ were found. There was a significant positive correlation between increases in WAZ and BMIZ, respectively, and CD4 T-cell *z*-score increase from baseline. The study showed that improved growth of HIV-infected children receiving HAART can be sustained for at least 96 weeks (Verweel et al. 2002)

70.5.2 Antiretroviral Drugs and Lipodystrophy

However, this therapy has numerous side effects, such as the lipodystrophy syndrome characterized by peripheral fat wasting, central fat accumulation and metabolic changes (Viraben and Aquilina 1998). Two types of lipodystrophy can be distinguished namely lipoatrophy, characterized by localized fat loss in limbs, face and buttocks, and lipohypertrophy characterized by central fat accumulation on the abdomen, breasts and the posterior neck ("buffalo hump"). This syndrome has been well described in adults (Viraben and Aquilina 1998), but HIV-infected children in the USA and Europe have also been shown to develop lipodystrophy syndrome (Amaya et al. 2002; McComsey and Leonard 2004; Hartman et al. 2006; Guillen et al. 2007). No published data of lipodystrophy in HIV-infected children receiving HAART in Africa are currently available, probably due to the short time since the initiation of HAART at pediatric clinics and limited availability of HAART in Africa (Bolton-Moore et al. 2007). It is difficult to measure lipodystrophy in HIV-infected children due to the changes of normal growth and development that occur during childhood and adolescence (McComsey et al. 2003).

Table 70.5 Reference values for hypercholesterolemia and hypertriglyceridemia according to the toxicity scales of the Pediatric AIDS Clinical Trials Group Protocol

Toxicity scale	Hypercholesterolemia		Hypertriglyceridemia	
Grade 0	0–4.4 mmol/L	0–170 mg/dL	0–1.5 mmol/L	0–135 mg/dL
Grade 1	4.41–12.9 mmol/L	171–499 mg/dL	1.51–8.46 mmol/L	136–749 mg/dL
Grade 2	12.95–19.4 mmol/L	500–749 mg/dL	8.5–13.5 mmol/L	750–1,199 mg/dL
Grade 3	>19.4 mmol/L	>750 mg/dL	>13.5 mmol/L	>1,200 mg/dL

Adapted from Amaya et al. (2002)

This table presents reference values for hypercholestrolemia and hypertriglyceridemia according to the toxicity scales of the Pediatric AIDS Clinical Trials Group Protocol

In the absence of a unifying definition for lipodystrophy, children are often assessed based on the individual features associated with lipodystrophy. In a study by Amaya et al. (2002) fat redistribution was defined as fat wasting of extremities, face or buttocks; fat accumulation on the abdomen or dorsocervical spine ("buffalo hump") and/or breast enlargement. Children were categorized into four groups depending on the number of lipodystrophy features observed: no clinical or laboratory abnormalities (Group A), hyperlipidemia alone (Group B), fat redistribution and hyperlipidemia (Group C) and fat redistribution, hyperlipidemia and peripheral insulin resistance (Group D). Hyperlipidemia was defined as the presence of either hypercholesterolemia or hypertriglyceridemia according to the toxicity grading scales of the Pediatric AIDS Clinical Trials Group Protocol as shown in Table 70.5 (Amaya et al. 2002). Hartman et al. (2006) rated lipoatrophy in HIV-infected children in the face, neck, arms, legs and buttocks, whereas lipohypertrophy was rated at the abdomen, breasts and dorsocervical spine as absent, mild (noticeable on close inspection), moderate or severe (readily noticeable). Cases with one or more moderate or severe features of lipodystrophy were classified as cases (Hartman et al. 2006). In persons with lipodystrophy regression equations to calculate percentage body fat based on anthropometry may not be appropriate. Anthropometry may, however, be useful to detect regional fat distribution changes (Knox et al. 2003). The torso:arm ratio (TAR) of skinfold thickness was calculated in a study of Dutch children as the ratio of (subscapular + supra-iliac) to (biceps + triceps) skinfolds and was used as a measure of relative abdominal obesity (Hartman et al. 2006). During acute illness when an increase of tissue fluids occurs, anthropometry may not accurately reflect skinfold thickness. Nutritional risk can be better defined if a marker for lean body mass or body cell mass is available (Knox et al. 2003).

In this study of forty children, 2–16 y old in the USA, seven children (18%) showed evidence of fat redistribution at a mean age of 11.7 ± 0.8 y. The characteristics of the three boys and four girls with fat redistribution were as follows: one had peripheral wasting alone, one had abdominal adiposity alone, one had breast enlargement alone, one had both abdominal and dorsocervical adiposity and the remaining three had both peripheral fat wasting and abdominal adiposity (Amaya et al. 2002). In a study in France children without lipohypertrophy had significantly smaller BMI and skinfold thickness, within the normal range, compared to children with lipohypertrophy. The children with lipohypertrophy also had BMI in the normal range, but greater skinfold thickness at central body sites. Their increased supra-iliac skinfold thickness in relation to peripheral skinfold thickness indicated an abnormal fat distribution for their age (Beregszaszi et al. 2003). A study of Dutch children did not detect any cases of lipohypertrophy or mixed lipodystrophy, but four out of 34 children had lipoatrophy. The children were between 3 months and 18 y of age and received a range of different HAART regimens. The children with lipoatrophy had significantly smaller arm and leg circumferences and thinner skinfolds than children without lipoatrophy, but significantly higher WHR and TAR, indicating relatively higher abdominal fat content (Hartman et al. 2006). In a study in Spain children with lipohypertrophy had a significantly higher BMI than those without lipohypertrophy (Guillen et al. 2007).

Of forty children in the USA study, 29 (73%) had hyperlipidemia at a mean age of 9.4±3.3 y. No organomegaly or ascites was present, but seven children with fat redistribution also had hypertriglyceridemia and hypercholesterolemia. Three children (8%) had laboratory evidence for peripheral insulin resistance. Nine children (23%) successfully completed a 3-day diet history. Eight of these nine children presented with hyperlipidemia, and one had no lipodystrophic features. Four hyperlipidemic patients had elevated dietary fat intake. The remaining four hyperlipidemic children and the single unaffected child had normal dietary fat intakes (Amaya et al. 2002). The sample size in this study was small, but indicates a fairly high prevalence of hyperlipidemia, not necessarily associated with high dietary fat intake.

Although no published data of lipodystrophy in HIV-infected children receiving HAART in Africa are currently available, children should be monitored for the development of lipodystrophy and appropriate interventions should be made.

70.5.3 Putative Factors for the Development of Lipodystrophy

Progressive peripheral subcutaneous fat wasting, truncal fat accumulation, dyslipidemia and insulin resistance in HIV-infected patients on antiretroviral therapy have been attributed to the long-term toxicity of ARVs, especially HIV protease inhibitors (PIs) (Viraben and Aquilina 1998) (Table 70.6). There was no apparent relationship between exposure to a specific antiretroviral agent and the development of lipodystrophic features in some studies (Amaya et al. 2002; Hartman et al. 2006), whereas PIs such as nelfinavir, indinavir and ritonavir as well as zidovudine, stavudine and didanosine have been implicated in other studies (Viraben and Aquilina, 1998; McComsey et al. 2003). The use of a combination of medication containing stavudine and didanosine (NRTI) for longer than 1 year was significantly more often seen in children with lipoatrophy (Hartman et al. 2006).

Fat wasting, however had been observed in patients who have never taken PIs in more recent studies, possibly implicating the effect of nucleoside analogue reverse transcriptase inhibitor (NRTI) therapy. PIs have a predominant influence and may act synergistically with NRTIs. NRTIs appear to predispose individuals to slowly progressive fat loss, which is markedly accelerated when a PI and

Table 70.6 Key features of HAART and lipodystrophy

Anti-retroviral (ARV) therapy is a combination of medications used to suppress viral replication and progression of HIV disease in HIV-infected persons.
HIV-infected persons will not receive treatment with one ARV drug only, but with a combination of three ARV drugs according to standard country-specific protocols.
A combination of three ARV drugs working synergistically is referred to as HAART.
HIV-infected children receiving HAART present with significantly better weight gain than controls not receiving HAART.
HAART may cause side-effects including nausea, vomiting, diarrhea, headache or skin rash
The lipodystrophy syndrome is characterized by fat wasting of the face, arms and legs, central fat accumulation on the trunk, increased blood cholesterol and increased triglycerides.
Two types of lipodystrophy can be distinguished namely lipoatrophy, characterized by fat loss on the limbs, face and buttocks, and lipohypertrophy characterized by central fat accumulation on the abdomen, breasts and the posterior neck (“buffalo hump”).

(Viraben and Aquilina 1998).

This table summarizes key features of HAART and lipodystrophy, including possible side-effects and benefits of HAART

ARV anti-retroviral, *HAART* highly active anti-retroviral therapy

NRTIs are combined. Stavudine leads to an earlier onset of clinically apparent fat wasting and higher serum lactate concentration compared with zidovudine. In the cohort study of Hartman et al. (2006), PI was not related to lipoatrophy (Hartman et al. 2006).

Other risk factors considered to be associated with the development of lipodystrophy in HIV-infected children include age, HIV-1 viral load, exposure to individual ARV medications, duration of ARV therapy and dosing of drug regimens. Patient age, viral load, duration of PI or NRTI therapy did, however, not appear to be associated with the development of lipodystrophy in children (Amaya et al. 2002; Beregszaszi et al. 2003). An important factor that showed a significant association with lipodystrophy was antiretroviral drug dosing. Young children who received pediatric dosing were less likely to develop lipodystrophy than older children with drug dosing based on adult recommendations (Amaya et al. 2002).

Changes in body composition progress with increased exposure to ARV therapy and the degree of peripheral fat loss and visceral fat accumulation were associated with the duration of treatment, but independent of the immunologic stage of the disease or immunologic response (Amaya et al. 2002; Beregszaszi et al. 2003). All children with lipodystrophy in the study of Hartman et al. (2006) were pubertal and had used stavudine and didanosine. Their mean duration of HAART was 70.5 months, compared to 51 months of the children without lipoatrophy (Hartman et al. 2006).

70.5.4 Use of Anthropometry to Detect Lipodystrophy

When considering the measurement of body composition, a precise measure of the regional body composition is essential to distinguish between true central obesity and pseudotruncal obesity. Early detection of lipodystrophy is difficult and there are no clear anthropometric cut-off points (Hartman et al. 2006). In clinical observation the abdomen may appear to be more extended with thinning of the limbs. Anthropometry can help to monitor changes in MUAC, WC and skinfold thickness over time in children receiving HAART, but cannot be regarded to give a precise characterization of these changes (Amaya et al. 2002; Knox et al. 2003). It was observed that the children with lipodystrophy had significantly smaller arm and leg circumference, and their skinfolds were thinner. They could also be distinguished from controls by a WHR *z*-score of +1 standard deviation or higher and a sum of skinfolds *z*-score of at least -1 standard deviation (Hartman et al. 2006).

The physical examination and anthropometric measurements that were performed in the study of Hartman et al. (2006), rated the fat redistribution in the arm, back and abdominal areas. The biceps and triceps skinfold thicknesses were measured at the upper arm midway between elbow and shoulder, the subscapular skinfold at the back, at the lower tip of the scapula and in the abdominal region above the iliac crest. The torso:arm ratio (TAR) of skinfolds was measured for an indication for relative abdominal obesity. Children with lipoatrophy had borderline, significantly lower median BMI *z* scores than controls, and median arm and leg circumference *z*-scores were also lower. Median triceps skinfold, suprailiac skinfold and the sum of skinfold *z*-scores were also lower, whereas median waist:hip ratio (WHR) *z*-score was significantly higher. Median TAR *z*-score was increased in children with lipoatrophy, but the difference was not statistically significant (Hartman et al. 2006).

Children with lipoatrophy had a normal waist circumference, but WHR was significantly higher compared with controls, showing that the abdominal circumference was relatively greater than hip circumference. These findings suggest a relatively greater intra-abdominal fat content. However, normal waist circumference implies that the abdomen seems extended through thinning of the limbs and the higher WHR represents pseudotruncal obesity, which is in concordance with a large study in adults (Hartman et al. 2006).

70.5.5 Treatment of Lipodystrophy in HIV-Infected Children

Longitudinal studies of the consequences of lipodystrophy in children are lacking, but the expected outcome would be premature cardiovascular disease. There are also no published data regarding the treatment of hyperlipidemia in HIV-infected children receiving HAART. Dietary changes and exercise are generally recommended as the first intervention in uninfected children with hyperlipidemia. Lipid-lowering drugs may interact with ARV drugs. The best strategy may be to switch from a PI to a PI-sparing regimen (McComsey et al. 2003). A study in 17 HIV-infected children showed that a switch from a PI to efavirenz was associated with significant lowering of fasting total cholesterol, low-density lipoprotein cholesterol, triglycerides and the total cholesterol:high-density lipoprotein cholesterol ratio after 24 and 48 weeks of efavirenz treatment. None of the children received lipid-lowering drugs. No indication of insulin resistance was found in the children, and neither fasting insulin nor C-peptide changed significantly over the duration of the study. No changes in body fat content, mid-thigh and mid-upperarm circumferences, triceps or thigh skinfolds, or waist:hip ratio was found over the 48 weeks of the study. Lean body mass, measured by BIA did, however, increase significantly. Throughout the study period virologic suppression was maintained (McComsey et al. 2003). Children should be monitored for early signs of lipodystrophy and appropriate interventions should be done. In most cases ARV drugs may be switched, but dietary changes may be recommended by a dietician in children with hyperlipidemia.

70.6 Applications to Other Areas of Health and Disease

Detection of undernutrition by using anthropometry is useful to identify children in need for nutrition support. Prevalence of undernutrition in a community or population provides the necessary information on which to base nutrition policy and programmes. Instead of conventional indices of undernutrition, it is recommended that a composite index of undernutrition should be applied to identify children with multiple anthropometric failure. These children are in need for urgent nutrition intervention and can be targeted for nutrition support. If anthropometric failure is found in >30% of a community or population, this may be an indication for blanket intervention (Berger et al. 2008). A study on infants born to HIV-infected mothers indicates that children with a WAZ <-1.5 were at an increased risk of death. The poor nutritional status of these infants may have represented the association between infection-induced cachexia, associated with poor food intake, malabsorption and mortality (Berhane et al. 1997; Arpadi et al. 2000; Bolton-Moore et al. 2007). Alternatively poor nutritional status may have accelerated the progression from HIV infection to AIDS and death. Early aggressive nutrition support for undernourished children may delay HIV progression to AIDS and death (Berhane et al. 1997; Bobat et al. 2001; Bolton-Moore et al. 2007).

The influences of changes in body composition (weight, height, growth, body fat, muscle mass or fat and muscle distribution) on the pharmacokinetic parameters of the antiretroviral drugs need to be explored. These changes in body composition can be monitored using anthropometric measurements and should be used to calculate appropriate pediatric dosages of HAART and other medications. Dosages are currently mainly calculated on the basis of body weight, but adjustment of dose for the proportion of lean mass to fat mass may be more appropriate.

Fat redistribution is associated with metabolic alterations in glucose homeostasis and lipid metabolism, even in HIV-uninfected persons. Insulin resistance occurred only in HIV-infected

lipodystrophic children, but dyslipidemia was also found in non-lypodystrophic children receiving ARVs (Beregszaszi et al. 2003). Children with lipodystrophy could be distinguished from controls by an increased C-peptide level, an indication of increased insulin resistance (Hartman et al. 2006). In children with C-peptide above the upper limit of normal, median *z* scores of the waist circumference were significantly increased when compared with children with normal C-peptide. Children with C-peptide above upper limit of normal had significantly increased median *z* scores of the BMI, arm and waist circumference in comparison with the controls that had normal C-peptide (Hartman et al. 2006).

Grade 1 hyperlipidemia, hyperglycemia, hyperinsulinemia and glucose intolerance were evaluated in a study of lipodystrophy by Amaya et al. (2002). There were no significant differences in the values between the children with lipoatrophy and the controls (Amaya et al. 2002). High-density lipoprotein cholesterol, free fatty acids, glucose and insulin were not above the upper limit of normal for patients or controls (Hartman et al. 2006). A study in France also found no glucose intolerance in HIV-infected children receiving HAART, but signs of insulin resistance in the children in this group with lipohypertrophy (Beregszaszi et al. 2003). These results underline the importance of monitoring of HIV-infected children receiving HAART for signs of lipodystrophy and early treatment.

70.7 Practical Guidelines

Anthropometry should be used to monitor growth and nutritional status of HIV-infected children, independent of whether they are receiving HAART or not. In resource-poor settings at least height, weight and MUAC should be measured. If children receive HAART, WC and/or WHR should also be measured in an attempt to detect lipodystrophy. Because children are growing, an increase in all parameters is expected. It is thus important to calculate *z*-scores or use percentiles on growth charts or tables to assess progress of children according to their age and gender (WHO 2005).

70.8 Conclusion

Significant differences in body composition were found between HIV-infected children and age-matched controls, although wasting was rare. Treatment with HAART had a positive effect on height and weight in children with HIV-infection. This effect is sustained for at least 2 y and is associated with the successful application of HAART. Contrary to the BMI increase in adults treated with HAART, BMI in children does not increase in all patients successfully treated with HAART, but only in those with a low BMI at initiation of HAART (Verweel et al. 2002). FFM decreased relatively to age in some children receiving HAART, while there is redistribution of fat mass and these changes resulted in the BMI remaining relatively constant. The challenge remains to improve height and weight and reduce protein catabolism in HIV-infected children concomitant to a decrease of viral load to undetectable levels (Arpadi et al. 2000). HIV-infected children have a longer life span with the use of HAART, but the effective and safe treatment of the adverse effects of ARV therapy is imperative. Nutritional assessment, including anthropometry can help to detect stunted growth, as well as excessive fat deposition on the trunk and appropriate interventions can prevent detrimental effects of both undernutrition and overweight.

Summary Points

- Measurements in HIV-infected children should include serial measurements of height/length and weight, mid-upperarm circumference, waist circumference and skinfolds in children older than 1 y to reflect fat and lean body mass.
- HIV-infected children not receiving HAART were significantly more underweight and stunted than control children.
- With HAART undernutrition improved significantly in children from baseline to 6–24 months of treatment and a smaller percentage of children died before the age of 2 y.
- HAART has side effects, such as the lipodystrophy syndrome, characterized by peripheral fat wasting, central fat accumulation and metabolic changes. No published data of lipodystrophy in HIV-infected children receiving HAART in Africa are currently available.
- Anthropometry can help to detect stunted growth, underweight and excessive fat deposition on the trunk, so that interventions can prevent detrimental effects of both undernutrition and overweight in HIV-infected children in Africa.

Acknowledgments All work for this review was undertaken as part of the academic work of the author at the North-West University, Potchefstroom campus, South Africa.

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Chapter 71
Waist Circumference Measures and Application to Thai Children and Adolescents

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Abstract The prevalence of childhood obesity has been increasing worldwide. Assessment of changing trends in nutritional and health status of the child population could be achieved using accurate and reliable body composition techniques. Waist circumference is a simple anthropometric measure that is useful for the detection of abdominal obesity which reflects the sum of subcutaneous and visceral adipose tissues in the trunk region. Research evidence shows that waist circumference is highly correlated with weight-for-height and body mass index. Waist circumference is also a good predictor of cardiovascular risk factors. Measurement of waist circumference can be performed at different sites of the trunk region and the measurement technique requires a standardized procedure. Reference data of percentile distributions of waist circumference among children and adolescents are now available in many countries, including Thailand. Waist circumference cut-off can be an advantageous tool for a large-scale screening of children who are at risk for overnutrition and for tracking child growth. Future studies need to address the universal waist circumference benchmark and the application of waist circumference as well as weight-to-height ratio for growth monitoring and public health intervention program towards promoting a healthy child population.

Abbreviations

AUC	Area under curve
BMI	Body mass index
CT	Computerized tomography
DBP	Diastolic blood pressure
FFM	Fat-free mass
HDL-C	High-density lipoprotein cholesterol
IAAT	Intra-abdominal adipose tissue
LDL-C	Low-density lipoprotein cholesterol
MRI	Magnetic Resonance Imaging

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_71,

NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristic
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
TBF	Total body fat
TG	Triglycerides
VAT	Visceral adipose tissue
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
WHZ	Weight-for-height *Z* score

71.1 Introduction

The prevalence of childhood obesity has been strikingly increasing worldwide (Dehghan et al. 2005; Ogden et al. 2006). Overweight and obesity in children have significant impact on both physical and psychological health. Children who are obese tend to become obese adults and are at great risk of developing non-communicable chronic diseases. The increase in childhood obesity rate stimulates clinicians and nutritionists to search for reliable and appropriate anthropometric techniques to use for identifying children and adolescents who are at risk. Biological factors regarding child age, gender, and ethnic differences also influence changes in body composition during child growth. In general, girls accumulate body fat more than boys, and much more during pubertal development. With respect to fat-free mass (FFM), gender difference is negligible until the age of 14 years after which males will have more FFM than female adolescents (Ellis 1997; Malina 2005). Obese children tend to have greater total body fat (TBF) with excess fat on the trunk region than normal weight children. Assessment of intra-abdominal adipose tissue (IAAT) can be directly quantified with sophisticated imaging techniques, that is, computerized tomography (CT) and magnetic resonance imaging (MRI), and the amount of adipose tissue is measured as cross-sectional area or volume of fat mass. However, these are seldom used due to their high cost and radiation exposure in the CT technique, and they may not be appropriate for health screening in a large population. Among many reference methods, waist circumference (WC) has been proved to be an indirect anthropometric index to determine body fat distribution (Goran 1998a) and change in WC could predict risk for adverse health consequences. In this chapter, the authors will present WC measurements associated with fat distribution as well as measurement technique. The use of WC as a tool for childhood overweight and obesity screening in many countries including Thailand will also be highlighted.

71.2 Significance of Waist Circumference

Waist circumference (WC) is an anthropometric measure of fat distribution, particularly abdominal obesity, and is widely used. The inter-subject variation in WC reflects the variation in IAAT. The use of WC as an index of adiposity provides additional health information to weight-for-height or body mass index (BMI) since WC is tracked on the given abdominal fatness.

71.2.1 Factors Influencing Intra-Abdominal Adipose Tissue

71.2.1.1 Gender and Ethnic Differences in Fat Distribution

The anatomical distribution of adipose tissues shows different patterns of change with age and gender. Sexual dimorphism of fat distribution is clearly explicit during pubertal development. Generally, subcutaneous adipose tissue (SAT) deposition increases in the trunk in boys leading to the phenotype known as "android" and SAT deposition increases in the gluteal–femoral region in girls, the "gynoid" fat pattern. A study by Fox (Fox et al. 2000) in adolescents using the MRI technique indicated that IAAT and SAT areas are significantly increased in boys and girls by the second year of follow-up period. Boys had deposited greater IAAT and the IAAT/SAT ratio increased significantly, but this ratio decreased in girls. The influence of ethnicity on body fat distribution has been investigated in a few studies. Huang (Huang et al. 2001), based on a CT study, estimated that the rate of change of abdominal visceral adipose tissue (VAT) was greater in White than Black prepubertal children but no difference in SAT between ethnic groups was found. Change rates for VAT and SAT did not differ between boys and girls. He (He et al. 2002) showed that African–American and Caucasian prepubertal girls had greater arm, leg, and gynoid fat compared with boys whereas Asian girls and boys had greater trunk fat compared with African–American and Caucasian adolescents. A study in adolescents using skinfold measurement also found more trunk SAT deposition in Asian than White and Black children (Malina et al. 1995).

71.2.1.2 Total Body Fat Mass

Total body fat is an important determinant factor of IAAT. The difference in adiposity between obese and non-obese children is remarkably found in SAT (Fox et al. 1993) and the portion of the variance in IAAT is explained by total fat mass (Goran et al. 1998b).

71.2.1.3 Hormones

The change in hormone levels, particularly female sex hormones, during puberty is known to affect regional fat distribution (de Ridder et al. 1992) and at different Tanner stages, puberty was associated with greater fat mass which was more accumulated in the trunk region (Goulding et al. 1996).

71.2.2 The Relation of Waist Circumference to Fat Distribution and Metabolic Disorders

Increased abdominal adiposity in children and adolescents is associated with dyslipidemia, diabetes, insulin resistance, and high blood pressure whether the fat distribution is assessed with advanced techniques (Caprio et al. 1995; Gower et al. 1998; Huang et al. 2002) or assessed with WC (Savva et al. 2000; Maffeis et al. 2003; Lee et al. 2006; Kim and Park 2008). As mechanism underlying these metabolic disorders, it has been explained that IAAT is more sensitive to lipolysis than adipose tissue at other sites, thereby, releasing the increased free fatty acids into the portal circulation. Excess of circulating free fatty acids may induce an increase in hepatic triglycerides (TG) synthesis leading

to hyperinsulinemia and insulin resistance (Bjorntorp 1992). Attempts have shifted toward the use of simple anthropometric tools, for example, WC and/or trunk-to-extremity subcutaneous fat ratio, to describe fat distribution. In addition, enlarged WC has been proved to be a reliable anthropometric index for screening the metabolic syndrome in children and adolescents (Moreno et al. 2002).

71.3 The Relation of Waist Circumference to Other Anthropometric Indices

While WC has been proved to be a reliable index of abdominal adiposity, waist-to-hip ratio (WHR) has been shown to be a less sensitive proxy measure of central adiposity in prepubertal and adolescent children (Goran et al. 1998b; Taylor et al. 2000). One study found the WHR was not consistently associated with cardiovascular risk in prepubertal children (Gillum 2001). A few studies found a relationship between combined WC and BMI on health outcomes. Janssen (Janssen et al. 2005) found in children 5–18 years old that combined BMI and WC provided greater predictive value on cardiovascular risk than BMI or WC alone. Moreover, WC and BMI showed a relatively strong positive correlation (r = 0.68–0.73) (Neovius et al. 2005; Fredriks et al. 2005).

Another measure, the waist-to-height ratio (WHtR), has been recently shown to be positively associated with abdominal obesity and cardiovascular risk factors in children (Savva et al. 2000; Kahn et al. 2005; Yan et al. 2007). Freedman (Freedman et al. 2007) also indicated that WHtR rather than BMI provided a higher predictive value on serum cholesterol while BMI was slightly better in predicting children with high systolic blood pressure (SBP). In adults, the WHtR value of ≤ 0.5 is proposed as cut-off value for normal weight persons (Hsieh and Yoshinaga 1995). WHtR can be easily obtained by measurement of WC and height and then calculated by dividing WC by height. WHtR permits the same boundary values for gender and ethnicity in the adult population. However, the application of this ratio index and its relation to metabolic disorders should be investigated in children and adolescents.

71.4 Practical Guidelines for Waist Circumference Measurement

Accurate measurement of pediatric body composition is challenging. Waist circumference correlates well with body fat mass and is a good predictor of intra-abdominal fat. Waist circumference can be used alone or combined with body weight, height and subcutaneous skinfold to reflect child growth and over-nutrition problems. Owing to its simplicity, children can measure and evaluate WC themselves. However, such measurement still requires standardized procedures and well-trained staff to get accurate and reliable values.

The measurement technique involves several important practical points. The measuring tape should be flexible but inelastic and it is recommended to be about 0.7 cm wide. Measuring WC with tape that has a spring-retractable mechanism should be carefully done and the retraction spring tension on the tape should not affect the measurement. Prior to measurement, the subject should wear light clothing and stand erect with the abdomen relaxed with both arms at sides and the feet together. The positioning of the tape on the trunk region is important because this can affect the reliability. The plane of the tape around the trunk must be perpendicular to the long axis of the body and the tape is held around the body part but not compressing the subcutaneous tissue. Waist circumference should be taken at the end of normal expiration with measurement recorded to the nearest 0.1 cm (Callaway et al. 1988). Measurements should be performed in triplicate.

The locations of WC measurement have varied according to the anatomical site of body. Many investigators have documented the reference site of WC: midway between the lowest rib and the iliac crest is recommended by the Word Health Organization (World Health Organization 1998); the smallest circumference of the torso which is at the level of natural waist (Lohman et al. 1988), at the level of the umbilicus (Savva et al. 2001), and at the level immediately above the iliac crest (National Institute of Health 2000).

71.5 Waist Circumference of Children and Adolescents in Different Countries

In children and adolescents, body fat distribution can be described by WC, by WHtR and/or extremity-to-trunk skinfold ratio. Since the evidence shows that enlarged WC is positively associated with high risk for metabolic complications and morbidity, the use of WC as an anthropometric tool for identifying children at risk gains more attention in research and intervention applications. Waist circumference distribution and reference data have been widely studied in many countries (Table 71.1). The differences in location sites of measurement make it somewhat difficult to compare the results among countries and a single standardized location site should be considered as an important point to overcome this problem. Waist circumference can be easily determined by practitioners and/or children and adolescents themselves and it is an informative index in addition to BMI and weight-for-height measures. However, measurement of WC should be carefully done because child age, gender, and ethnicity as well as the abdominal site of measurement affect the variation of the WC values.

71.6 Risk Classification Based on Waist Circumference Cut-Off Value

Research on WC cut-offs for predicting adverse health consequence in children and adolescents is limited. Most studies had been carried out to determine the cut-off values of WC derived from maximization of sensitivity and specificity of the measure and the value corresponding to ≥75th percentile was found to be more associated with adverse fasting blood glucose, lipid profile, and elevated blood pressure (Table 71.2). The WC cut-off that should be adopted for different child age groups remains open for discussion and research. Even though gender and ethnic difference are considered as the determinant factors, the common site for measurement should be chosen in accordance with the selected procedure in order that the comparison among countries can be done. Development of a universal WC cut-off is the ideal goal and cross-validation of the results is needed for other children's populations.

71.7 Application of Waist Circumference Measurements to Thai Children and Adolescents

In Thailand, childhood obesity is becoming a major public health problem. Results from one national representative survey conducted in 8,655 children from 17 provinces, including Bangkok, found the prevalence of obesity in 2–5, 6–12, and 13–18 years children were 7.9%, 6.7%, and 8.6%, respectively (Mo-suwan et al. 2004). In 2006, the National Statistical Office conducted a nutrition survey in 9,404 children aged under 5 from 26 provinces of Thailand that also indicated the proportion of

Table 71.1 Study on waist Circumference in different countries

Region	Country	Study subjects	Age range	No. of subjects	Site of measurement	Reference
North America	Canada	1981 Canada Fitness Survey	11–18 years	3,064	Midway between the 10th rib and the iliac crest	Katzmarzyk (2004)
	USA	NHANES III (1988–1994)	2–18 years	9,713	Above the uppermost lateral border of right ileum	Fernandez et al. (2004)
	USA	NHANES 1999–2004	2–19 years	24,216	High point of iliac crest	Li et al. (2006)
	Mexico	School children from middle-income area of Mexico City	6–10 years	833	At the level of the greatest frontal extension of the abdomen between the bottom of the rib cage and the top of iliac crest	Gomez-Diaz et al. (2005)
	Cuba	Three municipal areas of the Havana City	4.5–20.5 years	7,285	Midway between the lower rib and iliac crest	Martinez et al. (1994)
South America	Brazil	School children from City of Santa Catarina, South Brazil	7–10 years	2,919	Midway between the 10th rib and the iliac crest	de Assis et al. (2007)
Europe	Italy	School children in a region of Central Italy	6–14 years	2,858	Not indicated	Zannolli and Morgese (1996)
	Spain	School children from Central part of Spain	6.0–14.9 years	1,728	Midway between the lowest rib and iliac crest	Moreno et al. (1999)
	UK	School children from geographical regions of Great Britain	5.0–16.9 years	8,355	Midway between the 10th rib and the iliac crest	McCarthy et al. (2001)
		Avon Longitudinal Study of Parents and Children (ALSPAC) 1995–1998	2–5 years	1,821	Midway between the 10th rib and the iliac crest	McCarthy et al. (2005)
Europe	Greece	Primary and secondary school children in 5 districts of Cyprus	6–17 years	2,472	At the level of umbilicus	Savva et al. (2001)
	Germany	Elementary schools in Nuremberg	3–11 years	3,531	Midway between the lowest rib and iliac crest	Schwandt et al. (2008)
	Netherlands	Fourth Dutch Growth Study	3 months–21 years	14,500	Midway between the lowest rib and the top of iliac crest	Fredriks et al. (2005)

Middle East	Iran	School children from 23 province; urban and rural areas	6–18 years	21,111	Midway between the lower border of rib cage and the iliac crest	Kelishadi et al. (2007)
	Turkey	Primary and secondary schools from 2 urban and 10 suburban areas of Kayseri	7–17 years	4,770	Midway between the lowest rib and the top of the iliac crest	Hatipoglu et al. (2008)
Asia	Japan	National survey	6–18 years	10,614	WC1 = at the level of maximal waist narrowing WC2 = at the level of the top of the iliac crest	Inokuchi et al. (2007)
	Hong Kong Chinese	Sampling primary and secondary school children from 18 districts	6–18 years	14,842	Midway between the lowest rib and the superior border of the iliac crest	Sung et al. (2008)
Australia	Australia	School children from Australian Health and Fitness Survey (AHFS)	7–15 years	8,439	At the level of umbilicus	Eisenmann (2005)

This table lists the research studies on waist circumference (WC) in various age groups of children and adolescents; it was found that the anatomical sites for WC measurements varied among countries

Note: Iliac crest is the prominent bony ridge at the top of the hip bone

Table 71.2 Studies on Waist Circumference Cut-offs in Children and Adolescents

Country	Age range (years)	No. of subjects	Ethnicity	Gender	Waist circumference cut-off (cm.)	Biomarker end points	Reference
USA	5–9	1,068	White-American		WC corresponding to 90th percentile	LDL-C, HDL-C, TG, plasma insulin	Freedman et al. (1999)
				Boys	59–77		
				Girls	57–73		
			Black-American	Boys	56–74		
				Girls	56–78		
	4–11	87	White and Black	Boys and Girls	WC corresponding to the highest L_{pos}	Fasting insulin, LDL-C, HDL-C, TG	Higgins et al. (2001)
					≥71		
	12–19	2581	Hispanic	Boys	84.3	Lipid profile, fasting glucose, insulin and high BP	Messiah et al. (2008)
				Girls	80.9		
			Non-Hispanic White	Boys	76.6		
				Girls	80.5		
			Non-Hispanic Black	Boys	82.0		
				Girls	78.4		
Mexico	6–10	833			WC corresponding to 85th percentile	BMI > 85th percentile	Gomez-Diaz et al. (2005)
				Boys	69.5		
				Girls	66.2		
Japan	9–15	124		Girls	77.0	TG, Alanine amin-otransferase, fasting insulin	Asayama et al. (2000)
	6–15	194		Boys	79.4	TG, Alanine amin-otransferase, fasting insulin	Asayama et al. (2005)
China	6–12	2,593	Hong Kong		WC corresponding to 85th percentile	Four of the six risk factors (SBP and/or DBP, TG, HDL-C, LDL-C, glucose, Insulin	Sung et al. (2007)
				Boys	58–76 cm		
				Girls	57–71 cm		

China	12–19	2,102	Hong Kong	Boys	WC corresponding to 76th percentile 12–15 years; 71.6–75.4 cm 16–19 years; 76.4–79.3 cm	Fasting glucose, LDL-C, HDL-C, TG, SBP or DBP	Ng et al. (2007)
				Girls	WC corresponding to 77th percentile 12–15 years; 67.8–69.6 cm 16–19 years; 69.7–69.8 cm		
China	7–18	4,224	Han		WC corresponding to 85th percentile	Based on study by Sung et al. (2007)	Yan et al. (2008)
				Boys	7–18 years; 62.9–84.2 cm.		
				Girls	7–18 years; 59.0–75.6 cm		
			Uygur	Boys	7–18 years; 57.7–77.2 cm.		
				Girls	7–18 years; 54.8–75.4 cm		

This table shows the results from some countries that demonstrated the association between WC cut-off points and the occurrence of cardiovascular risk factors in children and adolescents. The ethnicity of the population also influenced the variation of WC value

Note: *LDL-C* low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol; *TG* triglycerides, alanine aminotransferase: one liver enzyme used for the diagnosis of liver function, *SBP* systolic blood pressure; *DBP* diastolic blood pressure; A percentile: a value on a scale that indicates the percent of a distribution that is equal to it or below it, for example; 85th percentile is the value (score) below which 85% of the observation may be found

obesity in young children at 13.7% (National Statistical Office 2006). These figures were derived from nutritional assessment using weight-for-height index. Since WC data of Thai children and adolescents are less available, therefore, the authors performed analysis using recent data from three cross-sectional studies.

71.7.1 Preschool Children

Saraburi is a province located in the central region of Thailand. The Saraburi project was aimed to explore the prevalence of obesity in preschool children and parental feeding practices. The study was conducted during July–September 2008. Subjects were children aged between 3 and 6 years and they were randomly enrolled from nine kindergartens. Anthropometric measurements in children were performed by the same researcher. Body weight, height, and WC were measured in children. Waist circumference measurement was done in each child by positioning horizontally an inelastic tape at midway between the lowest rib and the iliac crest. Table 71.3 shows the anthropometric characteristics of the preschool Thai children. There were increasing trends in body weight, height, waist, and hip circumference with age. The results of percentile distribution of WC and WHtR of children are also shown in Tables 71.4 and 71.5. Waist circumference values were relatively greater in boys than in girls and the values increased with age. The WHtR value of boys was also slightly greater than that of girls and the values increased with age (Yamborisut et al. unpublished data).

71.7.2 Prepubertal Children

The dual form malnutrition project was carried out between June 2003 and March 2004. The study was to explore risk factors associated with obesity and wasting in prepubertal children in Nakhon Pathom and Bangkok. Subjects were 107 obese and 51 normal weight children whose age ranged between 6 and 10 years. They were enrolled from primary schools located in six districts of Nakhon Pathom province and in four nearby districts of Bangkok. An obese child was categorized by weight-for-height Z score (WHZ) of >+2SD and a normal weight child by WHZ of between -1.5SD and +1.5SD of median, Thai Growth Reference (Department of Health 1999). Waist circumference was measured at midway between the lowest rib and the iliac crest. Twelve-hour fasting blood samples were also obtained from subjects for the determination of plasma glucose and serum lipids. Results demonstrated that among boys and girls, obese children tended to have more cardiovascular risk factors, that is, high blood level of TG and LDL-C and low HDL-C (Table 71.6). In this study, WC was found to be highly positive correlated with weight-for-height index in children (Fig. 71.1); therefore, it has been suggested that WC could be used as a proxy measure to identify health risk in children. The results also indicated that girls who had WC value of ≥75th percentile (≥78.2 cm) had significantly higher blood TG and lower HDL-C level than girls who had WC value of less than 75th percentile (Table 71.7).

71.7.3 Adolescents

The authors conducted one cross-sectional study to determine WC cut-off points that correlated with over-nutrition in Thai adolescents. This work was done as a part of a research study on the reliability

Table 71.3 Anthropometric characteristics of preschool Thai children (Yamborisut et al., unpublished data)

Age (months)	No. of subjects	Weight (kg)	Height (cm)	WHZ	BMI (kg/m^2)	Waist circumference (cm)	Hip circumference (cm)	WHR	WHTR
Boys									
36–47	7	17.0 ± 3.3	101.8 ± 5.6	0.42 ± 1.1	16.3 ± 1.7	50.4 ± 4.6	54.5 ± 5.4	0.93 ± 0.01	0.49 ± 0.03
48–59	328	18.1 ± 3.7	106.1 ± 4.8	0.24 ± 1.5	16.0 ± 2.3	51.5 ± 5.6	54.8 ± 5.4	0.94 ± 0.03	0.49 ± 0.04
60–71	382	20.4 ± 5.0	111.6 ± 4.9	0.35 ± 1.7	16.2 ± 2.9	53.6 ± 7.6	57.2 ± 6.6	0.93 ± 0.04	0.48 ± 0.05
72–85	66	21.4 ± 5.2	114.9 ± 6.1	0.22 ± 1.5	16.0 ± 2.7	53.8 ± 7.3	58.0 ± 6.8	0.93 ± 0.05	0.47 ± 0.05
Total	783	19.5 ± 4.7	109.5 ± 5.9	0.29 ± 1.6	16.1 ± 2.7	52.7 ± 6.8	56.3 ± 6.3	0.94 ± 0.04	0.48 ± 0.05
Girls									
36–47	11	15.8 ± 2.1	99.6 ± 3.5	0.27 ± 1.2	15.9 ± 1.9	49.7 ± 4.2	54.0 ± 3.6	0.93 ± 0.01	0.49 ± 0.03
48–59	305	17.5 ± 4.4	105.4 ± 4.8	0.12 ± 1.5	15.6 ± 2.7	50.6 ± 6.2	54.7 ± 5.9	0.94 ± 0.03	0.48 ± 0.04
60–71	400	19.7 ± 5.3	111.2 ± 5.6	0.14 ± 1.5	15.8 ± 2.9	52.6 ± 7.3	57.3 ± 6.6	0.93 ± 0.04	0.48 ± 0.06
72–85	81	20.4 ± 4.6	114.1 ± 5.1	0.02 ± 1.3	15.5 ± 2.4	52.3 ± 6.0	58.0 ± 6.0	0.90 ± 0.04	0.46 ± 0.04
Total	797	18.9 ± 5.0	109.1 ± 6.2	0.12 ± 1.5	15.7 ± 2.7	51.8 ± 6.8	56.4 ± 6.4	0.92 ± 0.04	0.47 ± 0.05

This table shows the average value (as mean ± standard deviation) of anthropometric parameters of preschool Thai children. Body weight, height, WC, and hip circumferences of children increase with age

Note: *WHZ* weight-for-height *Z*-score, can be calculated by observed value-median reference value/standard deviation of reference population; *BMI* body mass index, can be calculated from body weight and height (kg)/ht^2(m); *WHR* waist-to-hip ratio; WHtR waist-to-height ratio

Table 71.4 Percentile distribution of WC for preschool Thai children (Yamborisut et al. unpublished data)

Gender	Age (months)	No. of subjects	Percentiles						
			5th	10th	25th	50th	75th	90th	95th
Boys	36–47	7	46.8	46.8	46.8	49.4	50.9	60.4	60.4
	48–59	328	45.3	46.2	47.9	50.2	53.6	59.9	63.9
	60–71	382	46.1	47.2	48.8	50.7	55.3	65.5	71.0
	72–85	66	45.9	46.5	48.9	51.6	56.6	64.1	71.9
Girls	36–47	11	46.4	46.4	46.7	48.6	50.6	59.3	60.6
	48–59	305	44.4	45.3	46.9	49.2	51.9	57.7	61.4
	60–71	400	45.4	46.3	48.1	50.6	54.5	61.7	67.1
	72–85	81	46.2	47.1	48.2	51.0	54.2	59.2	68.4

This table shows the distribution of WC as percentile value by gender- and age-specific group of children. Waist circumference values increased with age and boys had greater WC than girls

Note: A percentile is a value on a scale that indicates the percent of a distribution that is equal to it or below it, for example; 85th percentile is the value (score) below which 85% of the observation may be found

Table 71.5 Percentile distribution of waist-to-height ratio (WHtR) for preschool Thai children (Yamborisut et al. unpublished data)

Gender	Age (months)	No. of subjects	Percentiles						
			5th	10th	25th	50th	75th	90th	95th
Boys	36–47	7	0.46	0.46	0.47	0.49	0.52	0.55	0.55
	48–59	328	0.43	0.44	0.46	0.48	0.50	0.54	0.58
	60–71	382	0.42	0.43	0.44	0.46	0.50	0.56	0.61
	72–85	66	0.41	0.42	0.43	0.45	0.49	0.53	0.58
Girls	36–47	11	0.44	0.45	0.48	0.49	0.50	0.60	0.61
	48–59	305	0.43	0.44	0.45	0.47	0.49	0.53	0.57
	60–71	400	0.42	0.43	0.44	0.46	0.49	0.53	0.57
	72–85	81	0.41	0.42	0.44	0.45	0.47	0.52	0.54

This table shows the distribution of waist-to-height ratio (WHtR) as percentile value by gender- and age-specific group of children. Children who had greater WHtR have high body weight and normal height or high body weight and/or short stature

Note: A percentile is a value on a scale that indicates the percent of a distribution that is equal to it or below it, for example; 85th percentile is the value (score) below which 85% of the observation may be found

and validity of nutrition tool development for the prediction of body fat and physical activity of Thai children and adolescents. Subjects were 509 adolescents, aged 10–18 years and they were enrolled from four primary schools and five secondary schools in Bangkok and Nakhon Pathom province. Anthropometric parameters of subjects are shown in Table 71.8. Waist circumference was measured at four different sites of the trunk region: WC1, midway between the lowest rib and the iliac crest; WC2, at the narrowest waist; WC3, at immediately above the iliac crest; and WC4, at the umbilicus level. Trunk fat and TBF were measured with whole-body dual energy X-ray absorptiometry. Results indicated that WCs measured at all four sites were correlated well with trunk fat mass in adolescent boys (R^2 = 0.81–0.85) and girls (R^2 = 0.80–0.86). Because WC measured at the umbilicus level (WC4) could be easily located and self-evaluated by practitioner themselves, further data analysis was done to determine the strength of association between WC4 and trunk fat mass. Figure 71.2 demonstrated the highly positive correlation between WC4 and trunk fat mass in adolescent boys and girls and it was shown that the variance of trunk fat mass explained by WC measured at the umbilicus level was 85% for boys and 83% for girls. By receiver operating characteristic (ROC)

Table 71.6 Anthropometric and biochemical parameters of prepubertal Thai children (Yamborisut et al. unpublished data)

	Boys		Girls	
Parameters	Obese	Normal weight	Obese	Normal weight
Number of subjects	66	23	41	28
Age (years)	8.1 ± 1.2	8.3 ± 0.9	8.3 ±1.1	8.1 ± 0.9
Body weight (kg)	45.0 ± 8.5*	24.0 ± 3.9	43.0 ± 7.3*	24.4 ± 3.8
Height (cm)	133.0 ± 7.3*	125.1 ± 6.8	132.1 ± 6.8*	125.2 ± 6.7
WHZ	3.6 ±1.2*	–0.35 ± 0.8	3.0 ± 0.8*	–0.11 ± 0.7
Body mass index (kg/m^2)	25.3 ± 3.1*	15.2 ± 1.4	24.5 ± 2.5*	15.5 ± 1.3
Waist circumference (cm)	81.1 ± 7.6*	54.1 ± 4.7	76.7 ± 5.9*	54.9 ± 4.2
WHtR	0.61 ± 0.05*	0.43 ± 0.03	0.58 ± 0.04*	0.44 ± 0.03
Fasting plasma glucose (mg/dL)	87.6 ± 5.4	85.2 ± 9.9	85.0 ± 7.2	81.8 ± 6.7
Total cholesterol (mg/dL)	209.2 ± 33.8*	192.4 ± 25.6	213.4 ± 32.5	201.7 ± 21.7
LDL-cholesterol (mg/dL)	140.5 ± 34.6*	126.5 ± 26.0	140.5 ± 31.9	132.8 ± 22.0
HDL-cholesterol (mg/dL)	48.4 ± 8.0	51.6 ± 8.6	48.2 ± 10.4*	52.8 ± 7.3
Triglycerides (mg/dL)	101.8 ± 50.9*	71.8 ± 18.7	123.8 ± 51.1*	80.4 ± 39.3

This table shows that within each gender, obese children had significantly greater body weight, height, weight-for-height Z-score, WC, and weight-to-height ratio than the normal weight children. Similarly, high blood levels of TG were found in obese boys and girls and significantly higher blood levels of total cholesterol and LDL-C were also found in the obese than normal weight boys. Results were expressed as mean ± standard deviation

Note: *WHZ* weight-for-height *Z* score was calculated by observed value-median reference value/standard deviation of reference population; *WHtR* waist-to-height ratio; *LDL-C* low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol

*Significant mean differences between the obese and normal weight children, by Student's *t*-test at $p < 0.05$

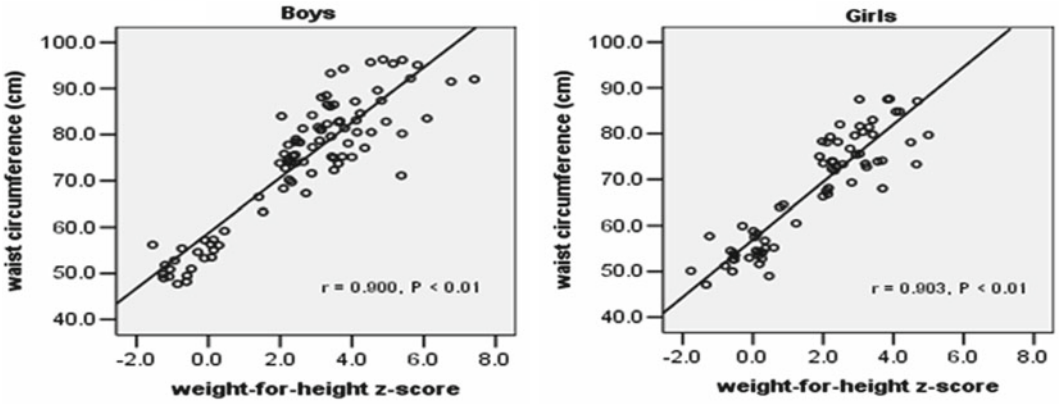

Fig. 71.1 Waist circumference index was found to be highly positively correlated with weight-for-height of children in both genders. Boys $n = 89$ and girls $n = 69$ (Yamborisut et al. unpublished data)

curve analysis, WC cut-offs that predicted the overweight adolescents were 73.5 cm for boys and 72.3 cm for girls (Table 71.9). The WC threshold to detect obesity was increased to 75.8 cm for boys and 74.6 cm for girls (Yamborisut et al. 2008). However, when considering the low positive predictive value (PPV) of WC in adolescent girls, 53.2% for overweight and 54.2% for obesity detection, these cut-off values might misclassify some girls as in fact they did not have high adiposity as expected. In such cases, other anthropometric indicators such as trunk skinfold and/or WHtR would be helpful to identify the problem. It is also suggested that further studies need to address the relationship between WC cut-offs and morbidity in adolescents.

Table 71.7 Cardiovascular risk factors in children according to WC at 75th percentile cut-off (Yamborisut et al. unpublished data)

	Waist circumference	
Cardiovascular risk factors	<75th percentile	≥75th percentile
Boys		
Number of subjects	67	22
Plasma fasting glucose (mg/dL)	87.2 ± 7.4	86.4 ± 5.2
Triglycerides (mg/dL)	91.4 ± 49.0	101.9 ± 38.3
Total cholesterol (mg/dL)	202.4 ± 30.8	212.2 ± 37.4
LDL-C (mg/dL)	134.9 ± 32.1	142.6 ± 35.8
HDL-C (mg/dL)	49.2 ± 8.4	49.2 ± 7.8
Girls		
Number of subjects	52	17
Plasma fasting glucose (mg/dL)	82.9 ± 6.9	86.3 ± 7.6
Triglycerides (mg/dL)	97.5 ± 47.1	132.8 ± 54.9*
Total cholesterol (mg/dL)	209.2± 26.5	206.8 ± 36.6
LDL-C (mg/dL)	138.2 ± 26.6	134.8 ± 33.9
HDL-C (mg/dL)	51.5 ± 9.9	45.5 ± 6.4*

This table indicates the girls who had WC at or higher than 75th percentile (≥78.2 cm) would have high blood levels of TG with low HDL-C level compared with girls who had WC less than 78.2 cm. Results were expressed as mean ± standard deviation

Note: *LDL-C* low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol

*Significant mean difference between two groups by Student's *t*-test

Table 71.8 Anthropometric characteristics of Thai adolescents (Adapted by permission, from Yamborisut et al. 2008, Copyright ©2008 Medical Association of Thailand, All right reserved)

	All subjects	
	Boys	Girls
No. of subjects	238	271
Age (years)	13.3 ± 2.3**	13.8 ± 2.4
Body weight (kg)	48.2 ± 12.9*	45.6 ± 10.9
Height (cm)	154.8 ± 13.4**	152.4 ± 8.6
WHZ score	0.55 ± 1.56**	0.18 ± 1.48
BMI (kg/m^2)	19.8 ± 3.7	19.5 ± 3.8
Waist circumference (cm)		
WC1	69.8 ±10.1*	67.4 ± 8.7
WC2	67.7 ± 9.0*	64.0 ± 7.9
WC3	72.4 ± 9.9	72.9 ± 9.5
WC4	70.8 ± 10.4	69.2 ± 9.2
Total body fat (%)	20.4 ± 10.6**	28.1 ± 8.1
Total body fat mass (kg)	10.1 ± 6.7**	13.4 ± 6.6
Trunk fat (%)	20.1 ± 12.1**	27.4 ± 9.7
Trunk fat mass (kg)	4.43 ± 4.4**	5.85 ± 3.3

This table shows anthropometric parameters of Thai adolescents. Waist circumference value measured at immediately above the iliac crest (WC3) was greater than WC value measured at other sites of trunk of subjects. Waist circumference measured at midway between the lowest rib and iliac crest (WC1) and WC measured at the narrowest waist (WC2) of boys were greater than that of girls. Data are expressed as mean ± standard deviation

*Significant mean differences between adolescent boys and girls by *Student's *t*-test and ** Mann-Whitney test, at $p < 0.05$

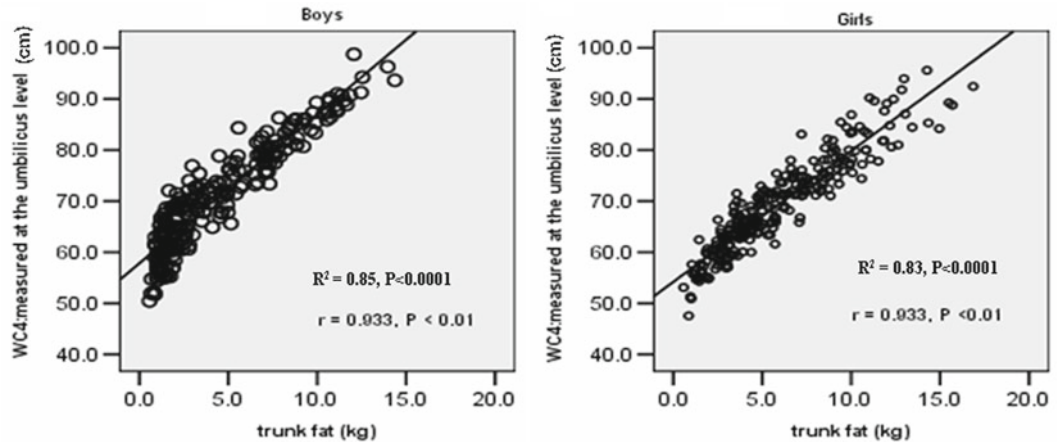

Fig. 71.2 Waist circumference measured at the umbilicus level was shown to be strongly positively correlated with trunk fat mass in both genders. Boys $n = 238$ and girls $n = 271$. (Adapted, by permission, from Yamborisut et al. 2008, Copyright © 2008, Medical Association of Thailand, All rights reserved)

Table 71.9 Proposed WC cut-offs for screening overweight and obese Thai adolescents (Adapted by permission, from Yamborisut et al. 2008, Copyright ©2008 Medical Association of Thailand, All right reserved)

	AUC[a] (95% CI)	WC Cut-off[b] (cm)	Sensitivity[c] (%)	Specificity[d] (%)	PPV[e] (%)	NPV[f] (%)
Boys						
Thai WHZ >+1.5 SD	0.971 (0.953–0.989)	73.5	96.8	85.7	70.9	98.6
Thai WHZ > +2.0 SD	0.968 (0.948–0.988)	75.8	96.3	86.4	67.5	98.8
Girls						
Thai WHZ > +1.5SD	0.969 (0.944–0.993)	72.3	96.1	80.5	53.2	80.4
Thai WHZ > +2.0 SD	0.983 (0.970–0.997)	74.6	95.1	85.7	54.2	98.8

Note: *WHZ* weight-for-height *Z*-score, was calculated by observed value-median reference value/standard deviation of reference population. *WC* waist circumference

[a]AUC: Area under the curve indicates the probability that an adolescent with over-nutrition has a higher value of the WC than an adolescent without over-nutrition; 95% confidence intervals are given within parentheses

[b]Cut-off producing equal values of sensitivity and specificity

[c]Sensitivity: true positive rate, the proportion of the overweight or obese adolescents who are correctly identified as "positive" by the test

[d]Specificity: the proportion of non-overweight or non-obese adolescents who were correctly identified as "negative" by the test

[e]Positive predictive value (PPV): The probability of adolescents become overweight or obese when the test results are positive

[f]Negative predictive value: The probability of adolescents are non-overweight or non-obese when the test results are negative

71.8 Application of Waist Circumference Measure for Public Health Intervention

Waist circumference is considered as a simple tool and reliable anthropometric index to identify children and adolescents who become at risk for overweight and obesity, particularly abdominal obesity. Research evidence shows that WC is positively correlated with weight-for-height index and BMI.

Table 71.10 Key features of WC

- Waist circumference is a simple anthropometric index that can be used as a proxy of abdominal obesity.
- Waist circumference is highly positive correlated with intra-abdominal adiposity and an increase in WC predicts the risk for diabetes, insulin resistance, dyslipidemia, and high blood pressure.
- Waist circumference measurement involves several important techniques: the measuring tape should be inelastic, the positioning of tape held on the trunk must be perpendicular to the long axis of the body, and measurement should be taken at the end of normal expiration.
- Waist circumference measurement can be performed at midway between the lowest rib and the iliac crest of hip bone, at the narrowest waist, at the umbilicus level or at the level immediately above the iliac crest.
- Waist circumference distribution has been studied in both developed and developing countries and WC values vary depending on ethnicity, gender, and pubertal development.
- Universal WC cut-offs are needed for general use in the detection of children and adolescents at risk for over-nutrition and cut-off points should be established against multiple health risk indicators

This table indicates that WC is an anthropometric index that reflects the accumulation of fat tissues in the abdominal cavity and the increase in WC is associated with increased risk for chronic diseases. Factors that influence change in WC are ethnicity, gender, and pubertal development. Techniques for WC measurement also require standardized procedures

Note: Dyslipidemia: a condition involving an abnormal concentration of blood lipids, for example, excess levels of total cholesterol, low-density lipoprotein cholesterol (bad cholesterol), and TG concentration and a low level of high-density lipoprotein cholesterol (good cholesterol). Both elevated levels of LDL-cholesterol and low levels of HDL-cholesterol can cause the clogging or hardening of blood vessels; insulin resistance: a condition in which the body does not respond to insulin properly, for example, the decreased ability of body cells to respond to the action of insulin in transporting glucose (sugar) from the blood stream into muscle cells and other tissues. Insulin resistance typically develops with obesity and can induce the onset of type 2 diabetes. Insulin resistance is also linked to high blood lipids and high blood pressure; iliac crest: the prominent bony ridge at the top of the hip bone

Children who have greater WC will be more susceptible to have multiple cardiovascular risk factors, such as hypertriglyceridemia, diabetes dyslipidemia and elevated blood pressure, leading to mortality in later life. The difference in WC cut-off points derived from studies in many countries are affected by ethnicity, child age, and pubertal development. The optimal WC cut-off derived from maximization of sensitivity and specificity can provide useful information related to health outcomes. However, an age-specific cut-off point is suggested because using single cut-off point to identify children at risk, particularly when interpretation is based on age range, may pose a problem such as a value may overestimate in young child and underestimate in the older child. The establishment of a WC and weight-to-height ratio reference would be advantageous for public policy as WC could be applied as a nutrition tool for tracking child growth and screening children who are at risk for over-nutrition. In addition, WC can be used as a self-monitoring index for the evaluation of intervention programs such as school nutrition and physical fitness program.

71.8 Summary

The majority of research evidence shows that abdominal obesity is associated with increased cardiovascular risk factors leading to morbidity and mortality. Among many anthropometric methods, WC is found to be well correlated with subcutaneous and visceral trunk fat and is highly correlated with weight-for-height and BMI. Age and sex-specific WC percentile distribution has been widely studied in many countries and WC cut-off points have been proposed by studies in some countries. Future research need to address the universal WC cut-off that could have far-reaching application for child monitoring, health screening, and public intervention programs.

Summary Points

- Waist circumference is a reliable anthropometric tool that correlates well with trunk fat and serves as an index to identify excess abdominal fat in children and adolescents.
- Enlarged WC could contribute to the risk for non-communicable chronic diseases such as diabetes, dyslipidemia, high blood pressure, and cardiovascular disease in later life.
- Measurement of WC can be easily performed using standardized procedures. The common site for measurement is at the midway between the lowest rib and the iliac crest of hip bone.
- Waist circumference reference data have been generated in many countries. Regarding Asian countries, percentile distribution of WC has been studied in prepubertal children and adolescents and that of preschoolers in one cross-sectional study in Thailand.
- In addition to weight-for-height index and BMI, WC should be adopted as an important nutritional index for child screening in intervention programs and for monitoring child growth. The optimal WC cut-offs points should be derived based on health outcomes.

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Chapter 72
Secular Changes in Craniofacial Dimensions of Indigenous Children in Southern Mexico

Bertis B. Little and Robert M. Malina

Abstract Studies of adult European immigrants by Franz Boas early in the twentieth century indicated secular change in craniofacial dimensions, suggesting plasticity of the craniofacial skeleton. Subsequent analyses of the original Boas data and data for other populations have shown variation in the pattern of change in craniofacial dimensions and indices over time. Cranial length tends to increase while width tends to decrease, resulting in brachycephalization (increase in the cranial or cephalic index). A generalized trend toward brachycephalization and upper and lower facial narrowing has been noted across adult populations that were also experiencing a secular increase in height. Cranial height has also increased, resulting in a taller, narrower skull and cranial vault. Secular trends in craniofacial dimensions in a rural indigenous community in the Valley of Oaxaca in southern Mexico have followed the general population trends. Facial changes probably reflected environmental change associated with diet (softer, processed foods) while cranial vault changes were more likely associated with genetic variation. Although growth of the cranial vault is largely established prenatally, craniofacial remodeling extends throughout the growth period with major changes occurring in conjunction with rapid growth of neural tissues between birth and 5 years. Secular changes observed in indigenous children of school age (6–14 years) were extrapolated to young adulthood using a longitudinal component in the data set. Review of the limited literature suggests that environmental and genetic influences on craniofacial dimensions established early during growth are reflected in corresponding dimensions in young adulthood.

Abbreviations

R^2	R-squared
cm	Centimeter
Est.	Estimated
SE	Standard error
B	Unstandardized regression slope
P	Probability of Type I statistical error
N	Number of subjects

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_72,

72.1 Introduction

Secular gains in height are well documented in children and adults and are generally interpreted as reflecting improvements in living conditions, specifically related to health, nutrition and associated economic circumstances (Malina 1979). However, some populations have experienced either no secular change or a secular decline in height indicating no change in or decline in living conditions, respectively. Positive secular changes are thus not universal and are reversible. The proximate causes of secular trends in height remain unresolved but are generally agreed to be multifactorial (Susanne and Bodzsar 1998; Susanne et al. 1988), but proportions of the secular increase attributable to genetic and environmental factors or their interactions are controversial. The worldwide epidemic of obesity has shifted attention to recent gains in weight-for-height. The secular increase in body weight in the presence of minimal or no change in height reflects environmental conditions related to energy balance i.e., increased intake in the presence of reduced expenditure (Malina and Little 2008).

Secular trends in craniofacial dimensions are more complex. The well-known early study of European immigrants by Boas (1912, 1940) has been cited for almost a century as evidence of cranial plasticity associated with environmental change (Sparks and Jantz 2002, 2003). Specifically, exposure to different environments during the growing years was postulated as the proximate cause of differences in the craniofacial complex between American-born and European-born children of immigrants (Gravlee et al. 2003).

Changes that occur over the relative short-term, i.e., two or three generations, are usually assumed to be environmental (Smith et al. 1986). Changes over longer intervals (i.e., brachycephalization) are assumed to involve genetic and environmental components (Ruff 2002; Schwidetzky and Rösing 1990). Brachycephalization has slowed over the past 145 years in European populations (Jantz and Jantz 2000). In Japanese populations, the trend toward brachycephalization may be reversing while a trend toward dolicocephalization may be emerging (Kouchi 2000; Zellner et al. 1998). Climate has been linked to long-term changes in the cranial vault (Beals 1979; Beals et al. 1983; Croninger 1981). More recently, it has been suggested that a large proportion of changes in skull shape on account of climate occurs in "extremely cold regions," and that "…if genetic drift is not explicitly accounted for, the effect of natural selection can be greatly overestimated" (Betti et al. 2010).

Secular changes in height of the cranial vault are associated with corresponding changes in body height (Jantz and Jantz 2000). Dimensions of the facial skeleton are also correlated with height and long bone length (Smith et al. 1986), so that increases in height and leg length are associated with narrower and taller faces (Mizoguchi 1992).

72.1.1 Literature Review of Secular Trend in Child Craniofacial Dimensions

The literature on secular trends on craniofacial dimensions in children is limited to only two studies. In one study from Croatia, craniofacial measures of schoolchildren were taken 13 years apart (Gazi-Coklica and Muretic 1991). In another investigation, Zapotec school-aged children from the Valley of Oaxaca, southern Mexico, were compared across a 30-year period (Little et al.2006b). A comparison of these two studies yielded conflicting findings. Over time the faces of Croatian children became broader and shorter, the skull longer, and cranial index decreased (debrachycephalization). In Zapotec children, change in the opposite direction occurred, with narrower faces, shorter skulls, and increased cranial indices (brachycephalization).

In southern Mexico, the living conditions in the community where the Zapotec children were reared improved over time, as indicated by childhood mortality figures that decreased significantly

over time. In parallel, growth in children's stature and weight increased over the same 30-year period. In contrast, living conditions in Croatia probably deteriorated over time. Economic conditions in the Eastern European Bloc were generally worsening during the final decade of communist rule, the period when the Croatian secular trend study was conducted. The Zapotec children had a pattern of change consistent with improvement in health and nutritional conditions (i.e., brachycephalization, gracilization of the face). In contrast, craniofacial changes over time in Croatian children reflect a worsening of health and nutritional conditions (debrachycephalization, robustness of the face). Thus, the two published studies of secular trend in craniofacial dimensions are congruent with one another given changes in living conditions. In order to further discuss craniofacial dimensions in children and their secular changes given the paucity of information, the investigation in Zapotec children is reviewed and augmented in this chapter.

This review of secular change in craniofacial dimensions concentrates on school children aged 6–13 years from a genetically isolated Amerindian population in the Valley of Oaxaca in southern Mexico between 1968 and 2000. The data for school children are complemented with a longitudinal component of individuals measured in 1968 as children and in 1978 as young adults. Using equations developed from the 1968–1978 longitudinal component, craniofacial dimensions of young adults in 2000 were predicted for children who were measured in 1978.

72.1.1.1 Review of Secular Trend of Craniofacial Dimensions Among Children

In this review of the extremely limited literature on the secular trend of craniofacial dimensions among children, the focus is a rural Zapotec-speaking community in the Valley of Oaxaca. Characteristics of the valley and community have been previously described (Malina et al. 2008a, b). The community is indigenous to the Valley and was listed by name in a census (Tribute Rolls) dating to 1536 (Iturribarria 1955). Their lifestyle is typical of traditional Middle America. Socially, the population is based on kinship and is largely endogamous. Economically, the community is characterized by small-scale farmers working relatively small plots of individually owned land which fits the subsistence model. Population size has increased over time, somewhat rapidly from 1960 (1,086) through 1970 (1,423) and 1980 (1,823) and then at a slower rate to 1990 (1,954) and 2000 (1,939). Population size, however, has historically been influenced by a high rate of out-migration, especially of males, starting about 1940. Migration and an increase in adults working outside of the community underlie the changing conditions in the community, perhaps a shift from the traditional lifestyle.

Families typically work small plots (<1 acre) of individually or communally owned land. About 90% of heads of households were full-time farmers in 1978, but the proportion had declined to about 30% by 2000. By inference, many are now part-time farmers; other occupational activities include vendors, artisans, construction workers, and industrial workers. Daily household chores, walking and leisure activities of youth 9–17 years of age in the community suggest a moderately active lifestyle for girls and moderately-to-vigorously active lifestyles for boys (Malina et al. 2008c). Household activities of boys are related to animal care and agriculture; those of girls are related to cleaning, washing and food preparation. With increased out-migration of adult males, youth are more often involved in family subsistence activities.

This review is focused on the genetic and environmental associations of secular change in craniofacial dimensions and indices of school children 6–13 years who were surveyed in 1968, 1978 and 2000. The projects were approved by the respective committees at the University of Texas at Austin and Michigan State University. Community authorities also granted permission for each survey. Parents granted permission for primary school children (grades 1–6). Self-assent was obtained from older individuals (10+ years).

Table 72.1 Population genetics of study community

	1978	2002	Comparative rank	References
Estimated gene flow	3.3%	4.7%	Very low	Little et al. (1989, 2008)
Selection for body size	0.0	–	Low average	Little et al. (1989)
Selection potential	110%	–	10% above average	Little and Malina (1989, 2006)
Genetic drift	25.4	–	Moderate-high	Little and Malina (1989)
Inbreeding	0.01	–	Moderate-high	Little and Malina (1989)

As previously published, the growth status of school children was the primary focus of three surveys: (1) 1968, 331 children: 166 boys and 165 girls (Malina et al. 1972); (2) 1978, 363 children: 175 boys and 188 girls (Malina et al. 1980); and (3) 2000 (late 1999 early 2000, for convenience 2000), 363 children: 179 boys and 184 girls (Peña Reyes et al. 2003a, b). The primary school population was largely 6–14 years in the earlier surveys but the number of 14-year-old children in 2000 was small. Hence, the analyses were limited to children 6–13 years of age. Height and sitting height were measured with a field anthropometer. Intra-observer technical errors of measurement for height were 0.33 and 0.32 cm in the 1978 and 2000 surveys, respectively, while those for sitting height were 0.48 and 0.40 in the two surveys, respectively. Inter-observer technical errors between anthropometrists in the 1968 and 1978 surveys were 0.23 cm for height and 0.35 cm for sitting height. Leg (subischial) length was estimated as standing height minus sitting height.

During the 1978 survey, an attempt was made to locate the sample of school youth surveyed in 1968. Of the 1968 sample, 184 (56%), 91 males and 93 females, were still resident in the community in 1978. These individuals comprise the longitudinal component of most of the investigation on craniofacial measures in this community.

Age of children was obtained from school records. For the follow-up sample, date of birth was obtained at the time of measurement and age was calculated. For those who could not recall their birth date, age as of last birth day was recorded and was indicated at mid-year.

Prior analyses indicated that the population was genetically isolated (i.e., gene flow was very low), perhaps experienced a greater potential for natural selection than was average for similar subsistence agrarian communities, and the probability for random inbreeding was moderately high (Table 72.1). Interestingly, social mating practices (non-random inbreeding) reduced observed inbreeding by 41% (Little and Malina 2005).

Four craniofacial dimensions were measured in each survey of school children and the follow-up sample in 1978: head length (glabella-opisthocranion), head breadth (euryon-euryon), bizygomatic breadth (zygion-zygion) and bigonial breadth (gonion-gonion). Intra-observer technical errors of measurement based on replicates in the 1978 and 2000 surveys, respectively, were as follows: head length, 0.15 and 0.12 cm; head breadth 0.11 and 0.10 cm; bizygomatic breadth, 0.11 and 0.12 cm; and bigonial breadth, 0.24 and 0.13 cm. Inter-observer technical errors between anthropometrists in the 1968 and 1978 surveys were 0.13 cm for head length, 0.08 cm for head breadth and bizygomatic breadth, and 0.17 cm for bigonial breadth. The cranial index (head breadth/head length × 100) and zygomandibular index (bigonial breadth/bizygomatic breadth × 100) were calculated (Little et al. 2006).

Heritability of craniofacial measures was high for the four dimensions: head length > head breadth > bizygomatic ~ bigonial (Table 72.2). Heritability of growth velocity based on a one-year longitudinal study from 1978 to 1979 was zero for bigonial and bizygomatic breadths but significantly greater than zero for head length (0.16) and breadth (0.48).

A secular trend in craniofacial dimensions of children 6–13 years across the three surveys was previously reported (Little et al. 2006a). The trend indicated a shorter skull, narrower mid-face,

Table 72.2 Estimated heritability of craniofacial dimensions based on sibling correlations in 1978

	Estimated heritability[a]	
	Growth status	Growth velocity
Head length	0.98	0.16
Head breadth	0.72	0.48
Bigonial breadth	0.52	0.00
Bizygomatic breadth	0.50	0.00

[a]Little et al. (1991)

Table 72.3 MANCOVA of secular effects on craniofacial dimensions

	Covariate adjusted means*			
Dimension	1968	1978	2000	Secular Effect
Males				
Head length	17.1	16.9	16.7	Shorter head†‡§
Head breadth	14.2	14.2	14.3	No change
Bizygomatic breadth	12.1	12.1	11.8	Narrower mid-face‡§
Bigonial breadth	9.4	9.3	9.0	Smaller mandible‡§
Cephalic index	83.1	84.1	85.6	Brachycephaly†‡§
Zygomandibular index	77.6	76.8	76.9	Narrower face†‡
Females				
Head length	16.7	16.6	16.4	Shorter head‡§
Head breadth	13.8	13.9	14.0	Broader skull†‡
Bizygomatic breadth	11.9	11.9	11.7	Narrower mid-face‡§
Bigonial breadth	9.1	9.1	8.9	Smaller mandible‡§
Cephalic index	82.8	83.7	85.4	Brachycephaly†‡§
Zygomandibular index	76.7	76.7	76.3	No change

Modified after Little et al. (2006a)
*Adjusted for age, age^2, and body height
†$P < 0.05$ or lower for 1968 vs. 1978
‡$P < 0.05$ or lower for 1968 vs. 2000
§$P < 0.05$ or lower for 1978 vs. 2000

smaller mandible, increased brachycephalization and a narrower face over time in males, and a shorter broader skull, narrower mid-face, smaller mandible and increased brachycephalization over time in females (Table 72.3).

72.2 Synthesis of Prior Studies

Secular changes in craniofacial dimensions and indices observed in children 6–13 years (Table 72.3) are ultimately reflected in adult status (Table 72.4). Prediction of 1978 dimensions from 1968 measurements in males had R^2 values of 0.40 for head length, 0.73 for head breadth, and 0.59 for the two facial measurements. Corresponding R^2 values for females were 0.85 for head length, 0.57 for head breadth, and 0.48 for the two facial dimensions. The predicted values for young adults in 2000 compare favorably with observed values for children in 2000. They also reflect the same trend for young adults as for children in 2000, but the magnitude of the difference is less. This suggests that the equations

Table 72.4 Longitudinal craniometric analysis: 1968–1978 and 1978–2000[a]

					1968 Child		1978 Young adult	
	B	SE	*P*	R^2	Mean	SE	Mean	SE
Males: Children in 1968 as young adults in 1978 (n = 91, 12.6±1.7 years; n = 41, 23.2±2.3 years)								
Head length	0.913	0.033	0.001	0.40	17.2	0.11	18.1	0.10
Head breadth	0.882	0.058	0.001	0.73	14.3	0.07	15.0	0.07
Bizygomatic breadth	0.915	0.123	0.001	0.59	12.5	0.09	13.9	0.08
Bigonial breadth	0.756	0.103	0.000	0.59	9.8	0.10	10.7	0.09
Cepahlic index	–	–	–	–	83.1	0.54	82.8	0.48
Zygomandibular index	–	–	–	–	78.3	0.52	76.9	0.54

	1978 Child		2000 Young adult (Est.)	
	Mean	SE	Mean	SE
Males: Children in 1978 as young adults in 2000, *Estimated* (n = 106, 12.0 ± 1.4 years)				
Head length	17.1	0.06	18.0	0.05
Head breadth	14.3	0.04	15.0	0.04
Bizygomatic breadth	12.4	0.04	14.0	0.04
Bigonial breadth	9.6	0.04	10.6	0.03
Cepahlic index	83.8	0.39	83.3	0.32
Zygomandibular index	77.0	0.28	76.0	0.21

					1968 Child		1978 Young adult	
	B	SE	*P*	R^2	Mean	SE	Mean	SE
Females: Children in 1968 as young adults in 1978 (n = 73, 12.1 ± 1.3 years; n = 46, 22.3 ± 1.9 years)								
Head length	0.904	0.040	0.001	0.85	16.9	0.10	17.3	0.06
Head breadth	0.710	0.066	0.001	0.57	14.0	0.07	14.3	0.06
Bizygomatic breadth	0.742	0.119	0.001	0.48	12.3	0.06	13.1	0.06
Bigonial breadth	0.690	0.110	0.001	0.48	9.6	0.03	10.2	0.07
Cepahlic index	–	–	–	–	82.6	0.65	82.8	0.50
Zygomandibular index	–	–	–	–	77.6	0.42	77.6	0.35

	1978 Child		2000 Young adult (Est.)	
	Mean	SE	Mean	SE
Females: Children in 1978 as young adults in 2000, *Estimated* (n = 73, 12.0 ± 1.5 years)				
Head length	16.8	0.06	17.3	0.06
Head breadth	14.0	0.05	14.4	0.04
Bizygomatic breadth	12.3	0.06	13.1	0.04
Bigonial breadth	9.4	0.05	10.1	0.03
Cepahlic index	83.5	0.40	83.4	0.33
Zygomandibular index	77.0	0.31	77.2	0.23

Estimated – regression estimates using formulae from 1968 to 1978 observed values
[a]Age range: 10–15 years in 1968

for predicting young adult craniofacial dimensions in 2000 are sensitive to detecting the secular trend and permit a reasonable extrapolation of the magnitude of change. The cephalic index observed for young adults in 1978 was 82.8 for males and females, while the predicted index for young adults in 2000 was 83.3 for males and 83.4 for females, reflecting a trend toward brachycephalization. Similarly, the zygomandibular index observed in 1978 was 76.9 and 77.6 for males and females,

Table 72.5 Age-adjusted means and standard errors for height, estimated leg length and craniofacial indices in 1968, 1978, and 2000*

	Height		Leg length		Cranial index		Zygoman index	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Males:								
1968	122.0	0.41	55.9	0.25	83.1	0.32†‡	77.5	0.25
1978	121.9	0.38	55.6	0.23	84.2	0.31§	76.5	0.24
2000	128.2	0.39‡§	59.2	0.24‡§	85.5	0.31‡§	77.3	0.24
Females:								
1968	120.7	0.41	54.3	0.25	82.9	0.29†‡	76.7	0.24
1978	120.1	0.37	54.4	0.23	83.8	0.26§	76.6	0.22
2000	128.2	0.39‡§	58.2	0.23‡§	85.0	0.27‡§	76.6	0.23

*Adjusted for age and age^2 by ANCOVA
†$P < 0.05$ or lower for 1968 vs. 1978
‡$P < 0.05$ or lower for 1968 vs. 2000
§$P < 0.05$ or lower for 1978 vs. 2000

Table 72.6 Regression of craniofacial on leg length and sitting height *z*-scores

	B	SE	*P*	R^2
Leg length				
Head length	0.22	0.03	0.0001	0.05
Head breadth	0.14	0.03	0.0001	0.02
Bizygomatic	0.26	0.03	0.0001	0.07
Bigonial	0.29	0.03	0.0001	0.08
Sitting height				
Head length	0.18	0.03	0.0001	0.04
Head breadth	0.14	0.03	0.0001	0.02
Bizygomatic	0.24	0.03	0.0001	0.06
Bigonial	0.24	0.03	0.0001	0.06

*Pooled gender, age specific *z*-scores, $n = 1{,}037$

respectively, while the predicted index for young adults in 2000 was 76.0 for males and 77.2 for females, consistent with the trend toward a narrower face (Table 72.4).

Secular changes in linear dimensions (height and estimated leg length) and craniofacial indices are summarized in Table 72.5. Height and leg length did not increase between 1968 and 1978, but the cranial index did change over this interval. Both the linear dimensions and cranial index increased between 1978 and 2000. On the other hand, the zygomandibular index did not change among the three surveys spanning 32 years. Moreover, the relationship between long bones (leg length) and specific craniofacial dimensions was not different from the relationship with sitting height (trunk length) (Table 72.6). The relationship of leg length to birth year for the study sample showed that only the 2000 cohort of children experienced a marked secular increase in leg length (Fig. 72.1). Interestingly, the trends observed among Zapotec children are opposite of those reported among Croatian children. Croatian children tend toward debrachycephalization and more robust facial parameters. Speculating, it may be possible that the inconsistency of results between the Croatian and Zapotec children is related to increase or decrease in the standard of living for the majority of the population, and is associated with the variation within the two groups.

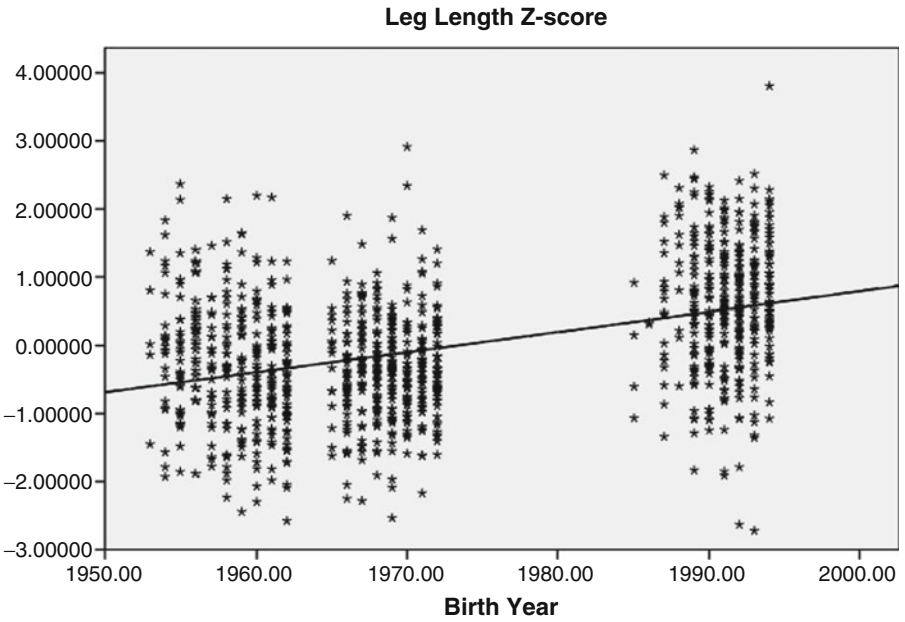

Fig. 72.1 Leg length z-scores by birth year for 1968, 1978, and 2000 cohorts. Note that leg length increase is apparent only in 2000 (n = 1037)

72.3 Discussion

An analysis of the longitudinal series of individuals observed in 1968 as children and in 1978 as young adults indicated an increase in absolute size of craniofacial dimensions (Table 72.4). The longitudinal series also indicated that trends in craniofacial dimensions and indices observed among adults were established during childhood prior to six years of age. Thus, observations for the indigenous population were consistent with prior postulates that secular trends in craniofacial dimensions are established early in child growth (Jantz and Jantz 2000). Although absolute differences established during childhood were absolutely larger in young adults, the trends were similar. Relative measures (indices) followed a similar trend.

It has been posited that changes in cranial vault dimensions must occur by early childhood because of the early development of the vault (Jantz and Jantz 2000). This is based upon logical deduction from adult data rather than actual analysis of data for children. A review of the craniofacial secular trend for indigenous children in Oaxaca who were observed as young adults included a longitudinal component that was analyzed to test the hypothesis that differences in cranial vault and facial dimensions originate in childhood. The differences observed in young adulthood were established in childhood. The data are, however, limited, since the age of the youngest subjects was 6 years. Thus, it is likely the differences observed at 6 years were established at younger ages.

In the present review, investigators suggest that prediction of young adult status has implications for the timing of the onset of differences in craniofacial dimensions. First, the observed trends indicate that differences in dimensions have their origins early in child growth, before the age of six which is the youngest group of children in studies reviewed. Secondly, the trends observed seem to be part of a continuum because the 1968–1978 equations give the impression that the trend they model is a reasonable estimate of young adults in 2000. Interestingly, the young adults in 2000 are similar to children in 2000. This indicates that the same trend (direction, magnitude) observed for

Table 72.7 Cephalic index in Zapotec adults between 1899 and 1978

Males		Females			
N	Mean	*N*	Mean	Year of survey	Source
100	81.0	25	82.0	1899	Starr (1902)
99	81.1	25	82.5	1899	Starr (1902)
50	81.1 ± 3.4	–	–	1933	Leche (1936)
236	84.7	–	–	1941	Gomez-Robleda et al. (1949)
41	82.8 ± 3.1	46	82.8±3.4	1978	Unpublished data[a]

[a]Youth 10–15 years in 1968 who were seen in 1978 as young adults: males 23.2 ± 2.3 years and females 22.3 ± 1.9 years

1968–1978 is observed for 1978–2000, implying that the secular trend is a process which builds on size and shape changes not only across ages (ontogenetically) but across time (generations).

The first systematic and quantitative craniometric analysis was conducted by Boas in 1899 (Boas 1899) and in the early 1900s (Boas, 1912, 1940) on European immigrants in America. Boas concluded that the change in size and shape of human crania over time among immigrants was a response to changes in environmental conditions and genetic influences exerted during childhood. Craniofacial dimensions and indices differed between those whose childhood growth occurred in Europe compared to those who grew up in the United States; Boas attributed the differences to "cranial plasticity." Re-analysis of the Boas dataset with more sophisticated techniques led to a quite different conclusion and shifted focus from high environmental effects to a very high degree of genetic influence (Sparks and Jantz 2002). The interpretation of the re-analyses, however, is not universally accepted; others argue that the environment played a larger role than genetics (Gravlee et al. 2003). Sibling analyses reveal that for indigenous children, head length was under high genetic control (98%) and head breadth was under moderate genetic influence (> 75%), whereas facial measures (bizygomatic and bigonial) reflected a high environmental influence (> 50%) (Little et al. 1987, 1991).

Brachycephalization has been noted over time in a number of populations (Kobyliansky 1983; Mikic 1990; Susanne et al. 1988), but a counter trend, 'de-brachycephalization,' has also been observed (Kouchi 2000; Zellner et al. 1998). Brachycephaly means literally "short skull" (length/breadth). An unresolved issue is the contribution of environmental or genetic influences, or genetic-environmental interactions in the observed trends (Sparks and Jantz 2002; Gravlee et al. 2003). Advances in standards of living are associated with brachycephalization (Jantz and Jantz 2000; Gyenis et al. 2003; Mikic 1990). Some studies also suggest that gene flow (admixture) may be associated with brachycephalization, including increased cranial height (Billy 1975, 1979; Hulse 1957; Palsson and Schwidetzky 1973). Cranial plasticity posited by Boas (1912, 1940) suggested a major role for the effect the American environment on immigrants from Europe. By inference, the conditions in Europe from which the individuals migrated were relatively impoverished and were associated with a shorter, narrower skull (lower cranial index). Among Zapotec children, the secular trend was toward brachycephaly (Table 72.3, Little et al. 2006b), while in Croatian children the trend was in the opposite direction, toward debrachycephalization (Gazi-Coklica and Muretić 1991). The cranial index of Zapotec adults in the Valley of Oaxaca also showed a trend to increase from 1899 to 1978 (Table 72.7).

Changes in craniofacial dimensions are correlated with changes in stature in forensic skeletal collections; long bone length (leg length) is highly correlated with skull length and cranial height (Jantz and Jantz 2000). Among children in the Oaxaca study an interesting observation is that the cranial index increased between 1968 and 1978 (Table 72.3, Little et al. 2006) while height and leg length did not change (Fig. 72.1) in subsequent years, the cranial index continued to increase while height

and leg length increased between 1978 and 2000 (Table 72.5, Little et al. 2006b). This suggests that changes in cranial dimensions are possibly a leading indicator that future changes in leg length in the next interval (decade or so) are possible. In other words, secular changes in cranial dimensions may predict the onset of secular increase in the post-cranial skeleton. Previous investigators have noted that secular changes in cranial dimensions were larger than in the post-cranial skeleton (Jantz and Jantz 2000).

Of interest is that the zygomandibular index was unchanged across the three surveys. However, relationships between the four craniofacial dimensions and leg/trunk length were not as strong as expected from the literature (Table 72.6). The regression slopes were not different between estimated leg length or sitting height.

Increase in body size including height, particularly leg length, and body weight characterize the secular trend (Malina 1979). The longitudinal component of the data for an indigenous population demonstrated that changes in cranial dimensions observed in adults were established early in child growth. It was previously noted that secular trends in cranial and post-cranial skeletons follow a similar course in the secular trend (Jantz and Jantz 2000). The unexpected finding was that secular change in cranial dimensions may be a leading indicator for secular increase in leg length and height. However, it is important to consider that cranial vault morphology and secular trends are population-specific.

Cranial size and shape are established early in child growth, including prenatal growth. Secular changes are associated with improved health and nutritional conditions, and include: (1) brachycephaly, (2) narrower mid-face, (3) narrower cranial vault and (4) narrower lower face. Craniofacial anthropometry data in the Oaxaca studies of Zapotec schoolchildren did not include measures of cranial height or facial height, but published data associate the secular trend with increased cranial vault height and a taller face. Analysis of changes in craniofacial dimensions and leg length suggest craniofacial changes in an indigenous Amerindian population may be leading indicators for onset of the secular increase in the post-cranial skeleton (height) in the next interval (10–20 years).

72.4 Synthesis of Studies Reviewed

The secular trend in craniofacial dimensions of the two populations for which data have been reported yield opposite results. Among Croatian children the trend was toward a more robust face and debrachycephalization (Gazi-Coklica and Muretić 1991), perhaps related to environmental conditions under communism. Zapotec children's craniofacial dimensions tended toward a more gracile face and brachycephalization (Little et al. 2006). Among the Zapotec children transition to softer, smoother food over time was associated with facial gracilization and brachycephaly. Among the Zapotec children the trend was analyzed even further because observations of secular change in craniofacial dimensions in children (ages 6–13 years) in the Valley of Oaxaca, southern Mexico (Little et al. 2006b) were extended to an analysis of a longitudinal series of individuals observed in 1968 as children and in 1978 as young adults. Equations developed from the longitudinal component were applied to the year 2000 cohort to predict their values as young adults. The analysis showed a relatively stable absolute increase in size of the craniofacial dimensions. Hence, trends in craniofacial dimensions and indices observed among adults were established during early childhood. The proportional change in dimensions was consistent from early childhood to young adulthood, similar to prior postulations that secular trends in craniofacial measures are established early in child growth, as early as during fetal development. Possible clinical implications of the findings may be that

treatment of craniofacial growth anomalies among children (craniofacial syndromes, orthodontics, helmeting, etc.) may require consideration of possible secular trends in absolute and relative measures. Craniofacial anthropometrics have been used to evaluate hypothesized syndromes (Little et al. 1996). Clinically, it may be important to note the trend for consistent proportions with increase in absolute size from early childhood into adulthood in the case of secular trend. Ultimately, children will likely not resemble their parents to the extent that may be expected to in the absence of a secular trend.

Summary Points

- Secular change in body size (positive secular trend) – An increase in body size that is associated with improved health and nutritional conditions, but some authorities have suggested that gene flow confounds the direction relationship between the environment and the secular trend. Generally, it is agreed that the secular trend is multi-factorial in causation. The post-cranial skeleton secular trend is toward taller and heavier individuals, with much of the increase in stature due to increased leg length.
- Secular change in cranial skeleton – Secular changes in the cranial skeleton have tended toward a shorter, taller skull, also termed brachycephaly. These are trends that span hundreds or even thousands of years. However, in some modern populations, the trend toward brachycephalization has slowed (Northern Europe) or even halted (Japan).
- Secular change in facial skeleton – The secular change in the facial skeleton is a change from robust short and wide faces to a more gracile, taller, narrower face. Some authorities have argued that change in diet from hard, rough food sources (nuts, seeds, stone ground food, etc.) to softer, smoother food (processed grains and seeds, machine ground food, etc.) is mechanically related to facial changes over generations.
- Secular change in cranial index – The cranial index tends to increase over time and indicates the tendency toward brachycephaly. Franz Boas analyzed the cranial index among immigrants to the United States and those who were born in America.
- Inter-relationships of secular changes – Increases in stature are associated with craniofacial changes. Leg length is strongly correlated with increased skull height, increased cranial index and taller, narrower faces. Within the craniofacial skeleton, narrower, shorter and taller skulls are associated with taller, narrower faces, reflecting the secular trend for robust features to become gracile across time.

Key Points

Secular change in body size (positive secular trend)
Increased height
Increased leg length
Secular change in cranial skeleton
Narrower skull
Shorter skull
Taller skull

Secular change in facial skeleton
- Narrower face
- Taller face
- Narrower mandible
- Narrower mid-face

Secular change in indices
- Brachycephalization (higher cephalic index)
- Gracilization of face (lower facial indices such as zygomandibular)

Inter-relationships of secular changes
- Cranial changes associated with post-cranial skeleton
- Secular changes in cranial dimensions occur before post-cranial skeleton

Interpretations
- Secular increase in size associated with improved living conditions

Acknowledgment The field research upon which this study is based was supported in part by the Institute of Latin American Studies at the University of Texas at Austin and National Science Foundation grants BNS 78–10641, 1978–1980 and BCS 9816400, 1999–2002.

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Chapter 73
Anthropometric Indexes of Low-Income Brazilian Children

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Abstract Brazil is a very large country, with more than eight million square kilometers, and comprises five different regions with distinctive social and economic characteristics. This gives rise to considerable inter-regional disparities in the analysis of child health status. In the last four decades, five surveys were conducted nationwide, and the first survey showed that protein–energy malnutrition was the most serious nutritional problem among Brazilian children. However, these rates have been declining sharply in all Brazilian regions as a result of an improvement in the social and economic conditions of families and in the sanitation coverage, and of wider offer of and access to health services, education, and food supplementation programs. More recent studies indicate that although there has been a reduction in height deficit in all Brazilian regions, it is still significant among Brazilian children and affects 7.0% of them. In addition to socioeconomic, biological, and quality-of-life determinants, the prevalence of low height can be partially attributed to the high frequencies of iron deficiency anemia and vitamin A deficiency among Brazilian children (20.9% and 17.4%, respectively), considering the importance of these micronutrients on linear growth and immune response. Child obesity affects 6.6% of Brazilian children and should be addressed immediately by the National Food and Nutrition Policy.

Abbreviations

ENDEF	National Study on Family Expenses
H/A	Height for age
IBGE	Brazilian Institute of Geography and Statistics
INAN	National Institute of Food and Nutrition
NCHS	National Center of Health Statistics
PNDS	National Survey on Demographics and Health
PNSN	National Health and Nutrition Survey
POF	Family Budget Survey
PPV	National Survey on Standard of Living
UNICEF	United Nations Children's Fund

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_73,

W/A Weight for age
W/H Weight for Height
WHO World Health Organization

73.1 Introduction

73.1.1 Characterization of the Group

The child group includes newborns, infants, preschool and school children, that is, all individuals below10 years. This phase of life is characterized by intense growth and development, which is determined by genetic factors and by extrinsic factors such as eating habits; social, economic, and household (water supply and sewage) conditions; access to health services; and others. Fast growth and greater susceptibility to diseases are characteristics of this group, especially of children aged under 5, who are a major and primary target of the initiatives of the health system.

Brazil is a very large country, with more than eight million square kilometers, and comprises five different regions with distinctive social and economic characteristics. This gives rise to considerable inter-regional disparities in the analysis of child health status. The greatest social differences are found between the South region, where slightly more that three million people have a per capita family income below the poverty line, and the Northeast region where the population under this condition corresponds to approximately 22 million individuals (Brasil 2009a).

Approximately one-fourth of the Brazilian population has a per capita family income below the poverty line (Brasil 2009a). Thirty-nine per cent of children below 6 years live in families that are considered poor and this proportion is 61.5% in the Northeast (UNICEF 2004). Therefore, conditions affecting the child population are still related to nutritional deficiencies and diseases spread through inadequate sanitation systems.

Malnutrition, iron deficiency anemia, and vitamin A deficiency are the nutritional deficiencies that are the major causes of concern as regards public health, due to their high prevalence and deleterious effects on child health. The World Health Organization (WHO 2009) estimates that approximately 2,405,000 (13.3%) of Brazilian preschool children are affected by vitamin A deficiency, which is a moderate public health problem. Estimates for the number of anemic children in Brazil, in turn, point at 9,923,000 (55.0%), and this is considered a severe public health problem (WHO 2008).

73.2 Nutritional Profile

According to the United Nations Children's Fund (UNICEF 2007), 8% of Brazilian newborns are low-weight (weight below 2.5 kg at birth), a percentage that is similar to that of industrialized countries (7%), and lower than that of developing countries (15%).

In developing countries, the World Health Organization estimates that the prevalence of weight-to-age, weight-to-height, and height-to-age deficits are 20.2%, 10.0%, and 32.0%, respectively, and in South America, they are 4.1%, 0.6%, and 13.8%, respectively (Black et al. 2008).

In the last four decades, five surveys were conducted nationwide, and the first survey showed that protein–energy malnutrition prevailed as the most serious nutritional problem among Brazilian children. However, these rates have been declining sharply in all Brazilian regions as a result of an

improvement in the social and economic conditions of families and in the sanitation coverage, and of wider offer of and access to health services, education, and food supplementation programs (Monteiro et al. 1993). According to Monteiro et al. (2009), two-thirds of the reduction in the prevalence of malnutrition can be attributed to increase in maternal educational level (25.7%), greater purchasing power of families (21.7%), health-care expansion (11.6%), and improvement of basic sanitation (4.3%).

The survey of the nutritional status of Brazilian children at the national level started in the 1970s with the National Study on Family Expenses [*Estudo Nacional de Despesas Familiares*] (ENDEF), conducted in 1974–1975, by the Brazilian Institute of Geography and Statistics [*Instituto Brasileiro de Geografia e Estatística*] (IBGE). Children were assessed according to the weight-to-age ratio using the anthropometric reference recommended and used by the National Center for Health and Statistics (NCHS) at that time. The results indicated that 18.4% of children presented malnutrition (weight-to-age ratio below – 2 *Z*-score), in that the North and Northeast regions had the highest prevalence and the South region had the lowest (Monteiro et al. 1993).

In the following decade, national anthropometric data were obtained from the National Health and Nutrition Survey [*Pesquisa Nacional sobre Saúde e Nutrição*] (PNSN), conducted in 1989, by the National Institute of Food and Nutrition [*Instituto Nacional de Alimentação e Nutrição*] (INAN), with the cooperation of the Government Management Planning Institute [*Instituto de Planejamento de Gestão Governamental*] and the Brazilian Institute of Geography and Statistics. The age group assessed and the method used were the same of the survey described above. The comparison of the ENDEF and PNSN studies showed a drop of approximately 61% in the prevalence of malnutrition rates in children below 5 years for weight-to-age ratio (18.4% in 1975 and 7.1% in 1989). The North and Northeast regions had the highest prevalence and the South region had the lowest. However, the lowest decline in malnutrition rates was observed in the North and Northeast regions, whereas the highest decline was observed in the South region, which widened inter-regional inequality. The drop in malnutrition prevalence was substantial in all quartiles of per capita family income, but was sharper in the highest quartiles (Monteiro et al. 1993).

In 1996, the National Survey on Demographics and Health [*Pesquisa Nacional sobre Demografia e Saúde*] (PNDS) analyzed the nutritional status of children under 5, according to the weight-to-age, weight-to-height and height-to-age ratios, using the same anthropometric reference of the previous surveys. The survey showed that 5.7% had low weight for their age, 10.5% had low height for their age, and 2.3% had low weight for their height.

According to the study, 18.0% of children in the Northeast region had height deficit, whereas in the South region, 5.1% had it, evidencing that the wide gap between the regions of the country remained. The height deficit rate was 19.0% in children living in rural areas, and 7.8% in those living in urban areas. The prevalence of this deficit dropped as maternal educational level increased (PSNS 1997).

The publication of the data of the latest Family Budget Survey [*Pesquisa de Orçamentos Familiares*] (POF), conducted in 2002–2003 by the IBGE in partnership with the Ministry of Planning, Budget and Management, made known the nutritional status of Brazilian children below the age of 10 years. The anthropometric ratio assessed was weight-to-age and the reference used was the same as that used for other surveys, i.e., that of the NCHS. According to the data, the prevalence of low weight-to-age in children under 10 was 5.8%, and in those below 5 years the prevalence was 7.0%. Prevalence was similar in rural and urban areas, but the North region continued to present the highest rates: 11.4% for children below 5 years, and 8.5% for children between 5 and 9 years. It is important to highlight that the situation is especially worrisome in the rural North region where 15.0% of children were malnourished (Brasil 2006).

The most recent data on the nutritional status of Brazilian children come from the latest National Survey on Demographics and Health (PNDS), conducted in 2006 (Table 73.1). Just as the 1996 PNDS,

Table 73.1 Prevalence of protein–energy malnutrition and obesity among Brazilian children

Characteristics	H/A < -2 *Z*-score %	W/H < -2 *Z*-score %	W/H ≥ +2 *Z*-score %	W/A < -2 *Z*-score %
Gender				
Male	8.1	2.0	6.4	1.8
Female	5.8	1.4	6.8	2.0
Area of residence				
Urban	6.9	1.7	6.7	2.0
Rural	7.6	1.9	6.3	1.5
Region of Brazil				
North	14.8	0.7	5.2	3.4
Northeast	5.7	2.1	6.0	2.2
Southeast	5.7	1.8	6.7	1.4
Midwest	5.6	1.1	7.0	1.6
South	8.5	2.0	8.8	2.0
Total	**7.0**	**1.98**	**6.6**	**1.7**

Source: Brasil (2008)

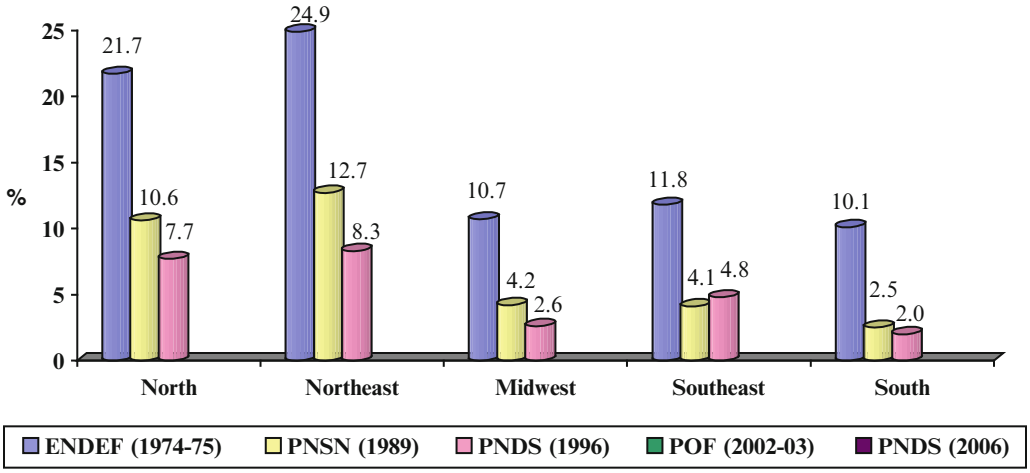

Fig. 73.1 Trend of the prevalence of weight-to-age deficit in children under 5 years of age for each Brazilian region. 1974–2006 (*Sources*: IBGE, National Study on Family Expenses (ENDEF) 1974–1975; National Institute of Food and Nutrition, National Health and Nutrition Survey (PSNS) 1989; *Sociedade Civil Bem-Estar Familiar no Brasil*, National Survey on Demographics and Health (PNDS) 1996 and 2006; IBGE, Department of Surveys, Coordination of Work and Income, Family Budget Survey (POF) 2002–2003)

this survey assessed children under 5 according to the weight-to-age, weight-to-height, and height-to-age ratios, but it used the 2006 international recommendation of the World Health Organization (WHO) as its anthropometric reference. The survey evidenced that the deficits in the weight-to-age, weight-to-height, and height-to-age ratios were 1.7%, 2.0%, and 7.0%, respectively (Brasil 2008).

Figure 73.1 shows the trend of malnutrition in Brazilian children below 5 years, in time, for each Brazilian region. The reduction in the prevalence of weight-to-age deficits in all regions especially in the North and Northeast regions is worthy of notice. These regions were heavily targeted by government initiatives.

73.3 Current Nutritional Status of Brazilian Children

Table 73.1 presents the current nutritional status of Brazilian children, according to the latest survey conducted in 2006, the National Survey on Demographics and Health [*Pesquisa Nacional sobre Demografia e Saúde*].

Table 73.1 shows that the primary nutritional problems currently affecting Brazilian children are height deficit and excess weight. The low prevalence of weight-to-age deficit and acute malnutrition, which is evidenced by the weight-to-height ratio, stands out.

Also worthy of notice is the high frequency of low height in the North region, and its higher prevalence among males compared to females.

The data presented in Table 73.2 come from recent *ad hoc* studies, and aim to demonstrate the prevalence of malnutrition in specific groups. Although there has been a drop in prevalence of malnutrition over the last four decades and in all Brazilian regions, prevalence is still very high in some specific groups, such as indigenous children and children living in shanty towns, where height deficit also stands out.

Height is an important indicator of quality of life, and reflects the cumulative nutritional status. Data from the National Health and Nutrition Survey (1989) indicated that the average growth of Brazilian children was beginning to decline compared to North American children who were used as anthropometric reference (NCHS) as of the fourth month of age, which indicated the importance of the environment in the expression of growth potential in childhood. Therefore, considering the high prevalence of height deficits in certain groups of Brazilian children, children living in the North of the country (Table 73.1), low-income and indigenous children (Table 73.2) should be prioritized in government initiatives designed to fight child malnutrition in the country.

Obesity has become a very worrisome nutritional problem even in developing countries like Brazil. This recent epidemics has been attributed to changes in children's eating habits, such as early weaning and increased consumption of sugar and fats from industrialized products, in addition to changes in life style, such as increased sedentarism.

The most recent data on overweight in childhood come from the 2006 PNDS (Table 73.1), which indicates an obesity prevalence of 6.6%, with the highest prevalence in the South region (8.8%).

Table 73.2 Data on the prevalence of malnutrition in indigenous children and low-income children

Age group	Population characteristics	Place of study	Prevalence (%)	Authors
<5 years	Indigenous children in the Amazon	Rondonia (North region) and Mato Grosso (Midwest region)	H/A: 45.5 W/A: 16.2 W/H: 1.2	Orellana et al. (2009)
<5 years	Kaingáng indigenous children	Mangueirinha Indigenous Land, Parana (South region)	H/A: 24.8 W/A: 9.2 W/H: 2.1	Kühl et al. (2009)
6 months to 6 years	Shanty-town residents	Municipio de Sao Paulo (Southeast Region)	H/A: 13.1 W/A: 15.5 W/H: 4.8	Santos et al. (2008)
6–30 months	Low-income families	Duque de Caxias, Rio de Janeiro (Southeast region)	H/A: 8.6 W/A: 2.8 W/H: 3.3	Barroso et al. (2008)

H/A height to age, *W/A* weight to age, *W/H* weight to height

The age group with the highest frequency of overweight was the group between 36 and 47 months and the prevalence was similar for females and males, 6.8% and 6.4%, respectively (Brasil 2008).

73.4 Specific Nutritional Deficiencies

73.4.1 Iron Deficiency Anemia

The data presented in Table 73.3 are from a compilation of studies published between 1997 and 2009, in Brazil, and aim to demonstrate the prevalence of anemia in Brazilian children in different Brazilian regions.

Until 2006, when the National Survey on Demographics and Health [*Pesquisa Nacional sobre Demografia e Saúde*] was conducted, there was no study in Brazil on the prevalence of anemia in Brazilian children with a nationwide representation. This survey assessed the levels of hemoglobin of 3,455 children aged below 5 years using the cyanmethemoglobin method in different regions of the country. Those with hemoglobin below 11 g/dL were considered anemic. The prevalence of anemia was 20.9%. The Northeast region had the highest prevalence (25.5%) and the North the lowest (10.4%). Although no statistical association has been observed between the economic classification and prevalence of anemia in children, there was a lower prevalence of anemia in higher-income children. The prevalence of anemia was higher in children living in urban areas and in those under 24 months of age (Brasil 2009b).

73.4.2 Vitamin A Deficiency

The compilation of the data of 23 *ad hoc* studies published on the prevalence of vitamin A deficiency in the country over the last 10 years, with a total sample of more than 6,500 children, showed a minimum prevalence of 7.0% and a maximum prevalence of 75.4% in these studies.

As in the case of iron deficiency anemia, the country lacked a nationwide survey on vitamin A deficiency in Brazilian children until 2006, when the National Survey on Demographics and Health was conducted. The survey studied 3,499 children below 5 years, and their serum retinol concentrations were determined using the dried droplet technique, with high-performance liquid chromatography (HPLC), and 0.70 μmol/L was considered as an indication of inappropriate nutritional status for vitamin A (low levels).

According to the study, 17.4% of children had inadequate levels of this micronutrient. The highest prevalence of vitamin A deficiency was found in the Northeast (19.0%) and Southeast (21.6%) regions of the country. Children living in urban areas and those with mothers aged over 35 years presented a higher prevalence of retinol deficiency as compared with their peers (Brasil 2009b).

Table 73.3 Prevalence of anemia in children aged 0–10 years in different Brazilian regions (1997–2009)

Region	Number of studies considered	Total number of children studied	Prevalence (%) (min – max)
North and Northeast	14	6,804	20.2 – 73.2
Midwest	04	1,084	11.9 – 60.9
Southeast	22	5,485	11.2 – 69.5
South	07	2,461	25.7 – 63.7

73.5 Conclusions

Anthropometric indicators of Brazilian children point to a reduction of protein–energy malnutrition over the last four decades, especially as regards the weight-to-age and weight-to-height ratios. However, despite these reductions, height deficit still affects 7.0% of Brazilian children, and the children of the northern region suffer more (15%). Indigenous and low-income children present a higher rate of malnutrition, especially low height. In addition to the classic determinants of child malnutrition, the significant prevalence of iron deficiency anemia (20.9%) and of low and marginal levels of vitamin A (17.4%) in Brazilian children stands out. These micronutrients play an important role in linear growth and these deficiencies have an impact on the immune system. Therefore, individuals with such deficiencies present higher morbidity due to infectious processes with a deleterious effect on their nutritional status. More recent studies indicate that child obesity has become a major nutritional problem in the country and requires immediate action under the National Policy on Food and Nutrition [*Política Nacional de Alimentação e Nutrição*.]

Summary Points

- **Characterization of the Group:** Child group includes newborns, infants, preschool and school children, that is, all individuals below 10 years. This phase of life is characterized by intense growth and development, which is determined by genetic factors and by extrinsic factors such as eating habits, social, economic, access to health services, and others.
- **Nutritional Profile:** In the last four decades, five surveys were conducted nationwide, and the first survey showed that protein–energy malnutrition prevailed in the Brazilian children and, nowadays, it is decreasing.
- **Current Nutritional Status of Brazilian Children:** The low prevalence of weight-to-age deficit and acute malnutrition, which is evidenced by the weight-to-height ratio, is worthy of notice. Also is high the frequency of low height in the North region, and presents higher prevalence among males than females.
- **Specific Nutritional Deficiencies:** The prevalence of anemia was higher in children living in urban areas those under 24 months of age. The highest prevalence of vitamin A deficiency were found in children living in urban areas, and those with mothers above 35 years of age presented a higher prevalence of retinol deficiency.
- **Conclusions:** More recent studies indicate that childhood obesity has become a major nutritional problem in the country and requires immediate action of Brazilian Government.

Key Points

Key features of protein-energy malnutrition in children

1. Protein–energy malnutrition is characterized by low-energy ingestion.
2. If children are classified with protein–energy malnutrition, they have low macronutrient and micronutrient ingestion.
3. Its distribution changes according to gender, whether urban or rural area, and the specific Brazilian region.

Table 73.1 lists the key factors of protein–energy malnutrition and obesity among Brazilian children. An anthropometric index was used to assess children with protein–energy malnutrition and obesity as recommended by WHO

Key features of prevalence of malnutrition in indigenous children and low-income children

1. Prevalence of malnutrition in indigenous children is higher in the northern region than southern region, but is high in both regions.
2. Children with low-income residents in shanty town (Sao Paulo) present higher prevalence of malnutrition than children with low-income families living in Rio de Janeiro.
3. All indexes (H/A, W/A, and W/H) are higher in the shanty-town than of children who live in low-income families.

Table 73.2 lists the key factors of malnutrition in indigenous children and those who live with low-income families in Sao Paulo and Rio de Janeiro cities, respectively

Key features of prevalence of anemia in children from 0 to 10 years in different Brazilian regions (1997–2009)

1. Prevalence of anemia is high in all Brazilian regions.
2. The prevalence of anemia is high – in the north and northeast, the less developed regions, and also in the southern region, the region that is more developed.
3. Anemia is present in all social classes in the Brazil.
4. Children are considered anemic when the hemoglobin level is below 11g/dl.

Table 73.3 lists the key factors of distribution of anemia in children from 0 to 10 years in several Brazilian regions (1997–2009)

Key features of the trend of malnutrition in Brazilian children under 5, in each Brazilian region

Figure 73.1 reveals the data on the nutritional status of Brazilian children come from the latest National Survey on Demographics and Health (PNDS), conducted in 2006 and lists the keys facts that reveal the reduction in the prevalence of weight-to-age deficits in all regions especially in the North and Northeast regions

Acknowledgments Thanks for the support provided by the *Universidade Federal de Ouro Preto* and *Universidade Federal de Viçosa*.

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Chapter 74
Adipokines and Anthropometry: Childhood and Adolescent Obesity or Adipocytokines and Anthropometry in Childhood and Adolescence

Panagiota Pervanidou, Makarios Eleftheriades, and Ioannis Papassotiriou

Abstract Adipose tissue is no longer considered an inert tissue simply devoted to energy storage, but it has emerged as an active organ in regulating a variety of physiological processes. Adipokines, such as leptin, adiponectin, resistin, adipsin, and visfatin, are proteins secreted by the adipocytes and released into the circulation, participating in the regulation of insulin sensitivity, food intake, inflammation, immunity, and vascular sclerosis. The prevalence of obesity is dramatically increasing worldwide in both children and adults and, along with the increase of obesity, is a parallel increase in the prevalence of comorbid disorders such as hyperlipidemia, arterial hypertension, insulin resistance, and diabetes type 2. In obesity, adipocytes enlarge and macrophages infiltrate adipose tissue, resulting in the large-scale release of several adipokines and in an imbalance between molecules and peptides secreted by the adipose tissue. The proinflammatory cytokines contribute to the "low-grade inflammatory state" of obese individuals, especially those with the Metabolic Syndrome (MetS), a clustering of metabolic abnormalities related to obesity, in both adults and children. Leptin and adiponectin are the two most studied adipokines in neonates, children, and adults and the majority of studies in obese individuals have shown hyperleptinemia and hypoadiponectinemia compared to normal-weight individuals. Furthermore, levels of circulating leptin are negatively associated with insulin sensitivity and conversely, adiponectin improves insulin sensitivity by stimulating glucose uptake and fatty acid oxidation in skeletal muscle. However, anthropometric changes during growth and puberty as well as changes in endocrine and metabolic parameters may contribute to the varied effects of adipokines on insulin sensitivity and the metabolic profile.

Abbreviations

AdipoR1	Adiponectin Receptor 1
AdipoR2	Adiponectin Receptor 2
BMI	Body Mass Index
BMI-SDS	Body Mass Index Standard Deviation Scores

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_74,

BF	Body Fat
CRP	C-Reactive Protein
Db gene	Diabetes gene
FMI	Fat Mass Index
HDL	High Density Lipoprotein
HMW	High Molecular Weight
HOMA	Homeostasis Model Assessment
IL-6	Interleukin-6
IDF	International Diabetes Federation
IOTF	International Obesity Task Force
LCPUFAs	Dietary long-chain polyunsaturated fatty acids
LMW	Low Molecular Weight
MetS	Metabolic Syndrome
NAHNES	National Health and Nutrition Examination Study
NT-proBNP	N-terminal pro-brain Natriuretic Peptide
Ob gene	Obesity gene
RBP4	Retinol-Binding Protein 4
TF	Trunk Fat
TNF-α	Tumor Necrosis Factor-alpha
TZD	Thiazolidinedione
TTR	Transthyretin
WC	Waist Circumference

74.1 Introduction

An innovative concept in the past few years was that the adipose tissue is not simply a reservoir of energy, but also serves as an active secretory organ, releasing a variety of peptides, complement factors, and cytokines into the circulation (Trayhurn and Wood 2004). These "adipokines" participate through endocrine, paracrine, and autocrine mechanisms of action in a variety of physiological processes such as insulin sensitivity, food intake, inflammation, and vascular sclerosis (Trayhurn and Wood 2004; Trayhurn 2005). Since the discovery of the protein leptin, product of the *obese* (ob) gene, the adipose tissue was found to produce more than 50 molecules (Lago et al. 2007) including adiponectin, resistin, visfatin, and other factors.

There is now convincing evidence that obesity, the state of excessive fat mass in the organism, is related to elevated markers of inflammation and it is now considered as a proinflammatory state. In the presence of excessive fat mass, with enlarged adipocytes and macrophages inserted within them, the balance between these peptides and molecules is altered and more proinflammatory cytokines, such as TNF-α and IL-6, and fewer anti-inflammatory peptides, such as adiponectin (Wellen and Hotamisligil 2005) are secreted (Fig. 74.1). The proinflammatory adipokines seem to contribute to the "low-grade inflammatory state" of obese individuals, especially those with the Metabolic Syndrome (MetS), a clustering of metabolic abnormalities related to obesity, including insulin resistance, dyslipidemia, increased blood pressure, and type 2 diabetes (Trayhurn et al. 2006).

Fewer studies have examined the relations between obesity and adipokines in childhood and adolescence. Though the same principals apply in younger individuals, the effects of linear growth and puberty as well as the normal changes in anthropometric and metabolic parameters from childhood

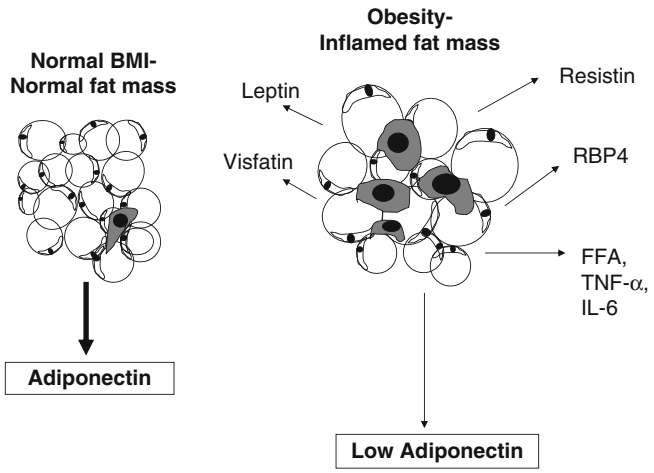

Fig. 74.1 The adipose tissue and secretion of adipokines in lean vs. obese individuals. The adipose tissue of lean individuals contains few macrophages and secretes relatively high levels of adiponectin and low levels of inflammatory cytokines. In obesity and insulin resistance, the adipose tissue contains many macrophages and secretes high levels of a variety of adipokines and low levels of adiponectin

to adulthood may differentiate the physiologic and pathophysiologic role of those molecules. The present chapter aims to review studies investigating the role of the adipokines in pediatric and adolescent obesity and in relation to the normal changes of growth and pubertal development.

74.2 Anthropometric Measures of Obesity in Childhood and Adolescence: Practical Methods and Techniques

Obesity is generally defined as the excessive accumulation of fat in the adipose tissue, to the extent that health may be impaired (WHO 2000). The ability to accurately estimate the level of adiposity, together with the simplicity of the measure, the easiness of use, the cost, and acceptability to the subject are important criteria for an effective measure of obesity (Power et al. 1997). Furthermore, the measure has to be well documented with published reference values. The two most popular methods in the clinical practice are the estimation of Body Mass Index (BMI) and the measurement of Waist Circumference (WC) and are outlined below; however, none of these methods meet all these standards.

74.2.1 Body Mass Index for Age

Body Mass index (BMI) is the ratio of the body weight in kilograms divided by the square of the height in meters. BMI is a good indicator of adiposity in adults and adequate evidence supports that an increased BMI is associated with an increased risk of morbidity and mortality in adults. Similar to adults, BMI seems to be a useful tool for identifying overweight and obese children. However, its value has been limited by the lack of standard reference values. Not all countries have developed reference growth charts, which includes BMI for age and gender percentiles. Most countries have chosen the 85th and 95th percentiles of BMI for age and gender to define overweight and obesity (Cole et al. 2000). However, this definition has limitations as it has not been proven that BMI for age is associated with ill health. Furthermore, regardless of the absolute amount of fat mass, children and adolescents are defined as overweight or as obese based on the median and BMI distribution of the

national reference curve they belong. This means that BMI percentiles are not comparable among different countries, or within the same country after several years, because the mean, the median, and the distribution of BMI are not the same.

BMI-z score (BMI of the individual-mean BMI of the population/Standard Deviation) measures the distance of a value from the mean in a specific population and it represents a more accurate practical measure of obesity in childhood and adolescence. The use of BMI-z score allows us to not only measure childhood obesity in a more accurate manner but also to follow-up patients more precisely, compared to percentiles. Furthermore, using the BMI-z score, the clinician is able to calculate fatness in the very obese children, those with a BMI over the 97th percentile. However, despite the advantages of this method, defining childhood obesity in BMI-z-scores is based on a specific national population chart and suffers from the same limitations as percentiles.

To overcome this limitation, a Workshop organized by the International Obesity Task Force (IOTF) in 1997 proposed a set of BMI percentile curves based on an international reference population and by defining cutoff points in relation to the percentiles that equate to the adult cutoff points, 25 for overweight and 30 for obesity. Based on this approach, Cole et al. developed the international cutoff points and data for this development were obtained from growth surveys in six different countries worldwide (Bellizzi and Dietz 1999; Cole et al. 2000).

74.2.2 Waist Circumference (WC)

Central (abdominal) obesity has been determined as a key factor in the etiology of diabetes type 2 and cardiovascular disease in adults. WC is a well-established anthropometric parameter of measuring intra-abdominal fat and has a clear association with the risk of metabolic disease in adults. Its value is less clarified in children; however, recent evidence has suggested that WC is associated with cardiovascular risk markers. Thus, the additional inclusion of WC measure to the BMI percentile has improved the prediction of obesity-related health risks in youth. Similar to BMI, WC values in childhood can only be used in relation to reference values from national WC percentile curves. The importance of WC as a pediatric anthropometric parameter of obesity has been highlighted in the relatively new consensus on pediatric Metabolic Syndrome by the International Diabetes Federation, where a WC ≥ 90th percentile has replaced the BMI ≥ 95th percentile (Zimmet et al. 2007).

74.3 Adiposity and the Metabolic Syndrome

The Metabolic Syndrome (MetS), a clustering of clinical and metabolic parameters, such as central obesity, dyslipidemia, impaired glucose tolerance, and arterial hypertension, is highly prevalent among overweight and obese adults, whereas studies in children are limited (Fig. 74.2). Insulin resistance seems to be the key pathophysiologic mechanism in the development of MetS. The MetS is associated with the subsequent development of diabetes type 2 and cardiovascular disease in adults: Adults with MetS are twice as likely to die from and three times as likely to develop cardiovascular complications compared to those without the syndrome. Furthermore, adults with MetS have a fivefold greater possibility of developing type 2 diabetes (Pervanidou et al. 2006). Although there are no studies directly connecting the MetS in childhood to the above-mentioned conditions, it is believed that the pediatric MetS leads to adult MetS and that young individuals presenting multiple risk factors related to obesity are at a great risk of developing disease in later life.

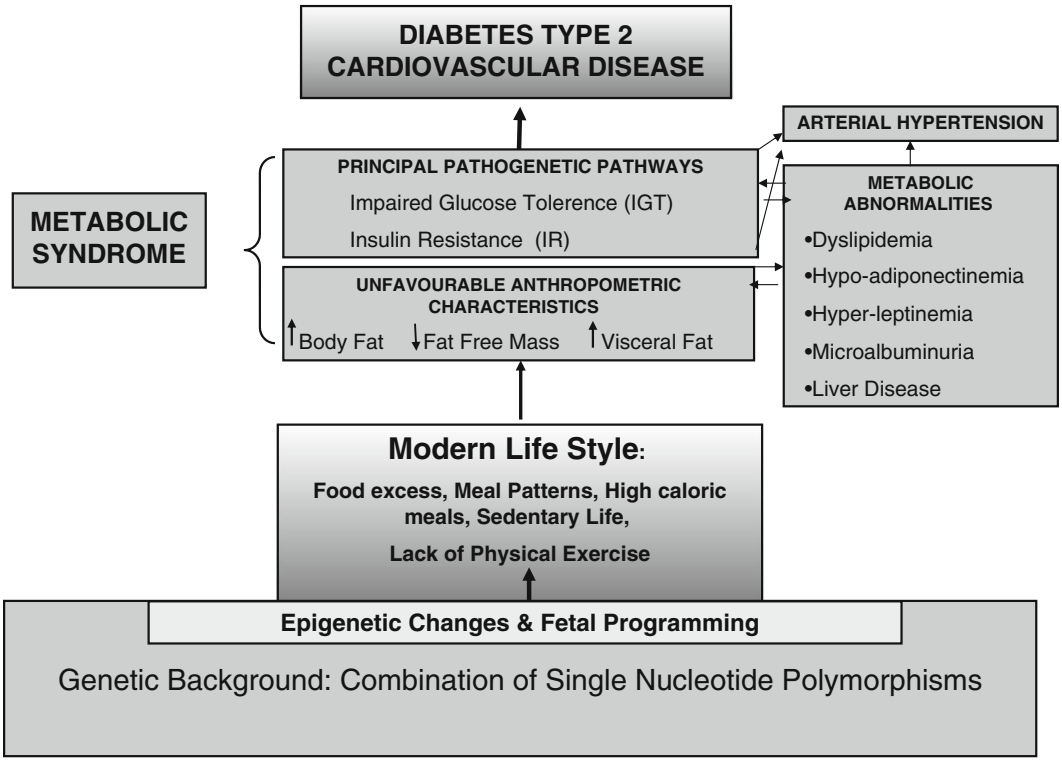

Fig. 74.2 Pathophysiologic mechanisms in the development of the Metabolic Syndrome. The interaction between the genetic background with epigenetic changes and the modern life style can lead to unfavorable anthropometric characteristics, such as obesity, increased visceral fat, and low fat-free mass, in children and adults. The Metabolic Syndrome, a clustering of obesity-related clinical and metabolic manifestations, is associated with insulin resistance and the development of diabetes type 2 and cardiovascular disease

Similar to adults, several definitions of MetS in children and adolescents aim at including as many individuals at risk as possible; however, no general consensus exists. The majority of pediatric studies on MetS use percentile charts for BMI or Waist Circumference, blood pressure, and lipid profile (HDL and triglycerides), while a standard cutoff is recommended for fasting glucose concentrations or glucose intolerance. At least three criteria are required to fulfill the definition of pediatric MetS. Recently, in 2007, a consensus on criteria for pediatric MetS was published by the International Diabetes Federation (Zimmet et al. 2007). This definition includes the measurement of waist circumference (WC) and requires a WC ≥ 90th percentile to define obesity. According to the IDF report, cutoff values for triglycerides, HDL, blood pressure, and glucose are expressed in absolute numbers instead of percentiles, depending on age and gender (Table 74.1).

Worldwide, the growing prevalence of diabetes type 2 in the youth, in parallel with the obesity epidemic, has highlighted the importance of MetS diagnosis in children and adolescents as a high-risk condition for developing disease in later life. The National Health and Nutrition Examination Study (NHANES) 1999–2000, using the ATP III definition modified for age, identified that the prevalence of the MetS among US adolescents increased from 4.2% in NHANES III (1988–1992) to 6.4% in NHANES (1999–2000). The prevalence of MetS was found high almost exclusively among obese adolescents (Cook et al. 2008).

However, pediatric definitions of the MetS use criteria extrapolated from the adult definitions and, in general, do not take into account the influences of growth and puberty. Thus, the MetS as an entity

Table 74.1 Key features of the pediatric metabolic syndrome (MetS)

1. The Metabolic Syndrome is a clustering of clinical and metabolic manifestations related to obesity. Insulin resistance is the key pathophysiologic pathway in the development of MetS, while an alteration in the secretion of several adipokines is also involved.
2. Though the prevalence of MetS is not high in the general population, it is highly prevalent among overweight and obese individuals. The MetS is associated with an increased risk for diabetes type 2 and cardiovascular disease.
3. A range of published pediatric definitions of the MetS suggests three or more of the following criteria: obesity, arterial hypertension, high triglycerides, low HDL, and increased fasting glucose/impaired glucose tolerance.
4. Central obesity is measured by Body Mass Index (BMI), or Waist Circumference (WC), age and gender specific. In pediatrics, a BMI ≥ 95th percentile, or a BMI-z score ≥2.0 in the national BMI charts is considered as a positive criterion for obesity. According to the IDF definition, a WC ≥ 90th percentile is also a measure of obesity.
5. Arterial hypertension is considered a systolic or diastolic blood pressure (BP) ≥ 90th or the 95th percentile for age, gender, and height. Based on the IDF definition, a fixed cutoff of systolic BP ≥130 or diastolic BP ≥ 85 mmHg is required to define hypertension, or treatment of previously diagnosed hypertension in adolescents older than 16.
6. Hypertriglyceridemia is a triglyceride level ≥ 90th or the 95th percentile for age and gender. The recent IDF definition recommends a cutoff of ≥150 mg/dl for triglycerides, or specific treatment for high triglycerides in adolescents older than 16.
7. HDL-Cholesterol ≤5th or the 10th percentile for age and gender, or, according to the IDF, an HDL <40 in both genders <16 years old and <40 in males and <50 in females or specific treatment for low HDL in adolescents older than 16 is a positive criterion for MetS
8. Impaired glucose tolerance is defined as a glucose level >140 mg/dl, but <200 in the oral glucose tolerance test. According to the IDF definition, a fasting glucose ≥100 mg/dl or the presence of known Type 2 Diabetes Mellitus is a positive criterion to define pediatric MetS.

This table lists the key features of the pediatric metabolic syndrome, including obesity, arterial hypertension, dyslipidemia, and increased fasting glucose/impaired glucose tolerance. Criteria for diverse pediatric MetS definitions described in this table are based on Zimmet et al. (2007)

is developing progressively and in accordance to age and pubertal changes, so that the full MetS cannot be easily diagnosed in childhood, especially when using cross-sectional assessments. Furthermore, the "normal" insulin resistance during puberty, in addition to changes in fat and fat-free mass observed during puberty, as well as changes in growth and sex steroids hormone secretion may play an important role in MetS stability.

74.4 Developmental Origins of the Metabolic Syndrome and the Adipocyte

Both human and animal studies have shown that being exposed to inappropriately low or high nutrition levels during crucial periods of fetal and postnatal development is associated with an increased risk for obesity, MetS, and diabetes type 2 in children and adults. The concept of fetal origins of obesity and the metabolic syndrome supports that exposure to excessive or deficient nutrition before birth alters the development of the adipocyte resulting in a permanent increase in the capacity to form new cells in the adipose tissue or to store lipids in existing adipocytes (lipogenesis) (Muhlhausler and Smith 2008).

Adipogenesis, the process of adipocyte development, occurs mainly during late fetal and early postnatal life, and it is highly sensitive to the nutritional environment at this time frame. It was also suggested that the number of adipocytes is relatively fixed in adulthood, with a very low turnover rate of adipose cells, supporting further the idea that fetal and early postnatal periods are crucial for the development of adipose tissue.

Experimental and human data have shown that infants suffered from fetal growth restriction, resulting most often from a compromised placental function, have lower adipose stores at birth. However, the postnatal exposure of the growth restricted infant to a nutrient-rich environment results in growth acceleration (catch up) and increased visceral adipose tissue accumulation.

Apart from fetal growth restriction, maternal obesity and/or maternal diabetes constitute major risk factors for childhood obesity and related disease. Based on animal data, it has been hypothesized that changes in gene expression within visceral adipocytes before birth influence the subsequent properties of subcutaneous adipose tissue that continues to develop. These "programmed" adipocytes may secrete factors that promote preadipocyte differentiation in other depots, resulting in further increase in adipocyte number (Muhlhausler and Smith 2008).

74.5 Obesity, Adipose Tissue and Inflammation

Obesity in adults and children is characterized by a state of chronic, low-grade systemic inflammation. Indeed, inflammatory markers, such as CRP and IL-6 are increased in obese individuals compared to controls, though not to the same extent observed in inflammatory diseases. This state of chronic inflammation in obesity has been successfully associated with a risk of developing diabetes type 2 and cardiovascular disease in later life. In the last few years, a large body of evidence has supported the role of the adipose tissue as an active secretary organ and an active participant in regulating the organism's physiologic and pathophysiologic processes (Fantuzzi 2005) (Fig. 74.3).

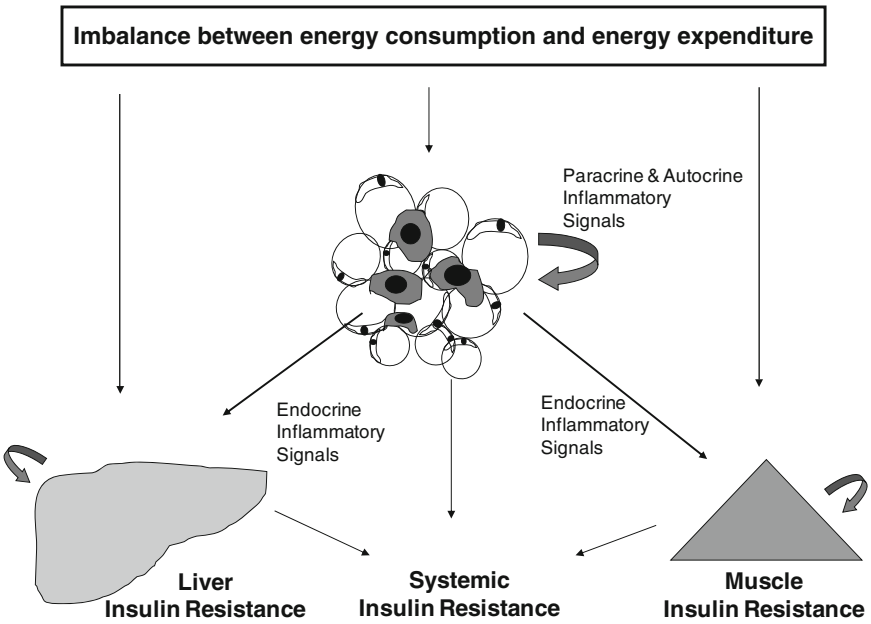

Fig. 74.3 Autocrine, paracrine, and endocrine function of the adipose tissue and the development of systemic insulin resistance in obesity. In obesity, adipocytes release cytokines, adipokines, and free fatty acids. These molecules act in a paracrine or autocrine function to augment the proinflammatory state within adipose tissue and cause localized insulin resistance. Furthermore, adipose tissue is considered as an endocrine organ, since these molecules act in liver and muscle and may decrease insulin sensitivity. In addition to the adipokines, independent inflammatory signals within the liver and muscle can result in local insulin resistance

Table 74.2 The pathophysiologic role of molecules secreted by the adipose tissue (in alphabetical order)

Adiponectin	Metabolic regulator; anti-inflammatory role; inhibition of monocyte adhesion to endothelial cells–macrophage transformation to foam cells
Agouti protein	Adipocyte lipid metabolism and differentiation
Adipsin	Stimulation of glucose transport; Stimulation of triglyceride storage in adipose cells; inhibition of lipolysis
Apelin	Regulator of cardiovascular functions; upregulated in obesity
FABP4/AFABP	Fatty acid–binding protein; lipid transport
IL-6	Inflammatory cytokine; promotes angiogenesis; regulates insulin sensitivity; increases hepatic *de novo* synthesis of fatty acid and cholesterol
Leptin	Metabolic regulator; promotes proliferation and angiogenesis; satiety signal; stimulation of lipolysis; inhibition of lipogenesis; improvement of insulin sesnsitivity
Lipocalin-2/NGAL	Antagonist of inflammatory adipokine secretion
MIF	Inflammatory cytokine
PPAR gamma/NRIC3	Nuclear regulator of metabolism
Retinol-binding Protein 4 (RBP4)	Regulator of insulin sensitivity
Resistin	Metabolic regulator; proinflammatory role
Serpin A8/Angiotensinogen	Serine protease inhibitor; promotes adipose tissue growth
Serpin A12/Vaspin	Serine protease inhibitor; regulates insulin sensitivity
Serpin E1/PAI-1	Serine protease inhibitor; extracellular matrix remodeling
Serum amyloid A1/SAA1	Apolipoprotein; low-grade inflammation
TGF-beta	Inhibitor of adipocyte differentiation
TNF-alpha	Inflammatory cytokine; regulates leptin; Promotes angiogenesis; regulates insulin sensitivity
Visfatin	Insulin-like and proinflammatory effects

This table summarizes the main actions of the molecules secreted by the adipose tissue in alphabetical order

The adipose tissue consists of white adipose tissue (WAT), which is the most prevalent type, and brown adipose tissue, participating mainly in thermogenesis. WAT consists mainly of adipocytes and a small number of macrophages. The number of macrophages infiltrated in WAT is directly associated with adiposity and with adipocyte size in human and rats (Weisberg et al. 2003). Adipocytes and macrophages are distinct types of cells. Macrophages are the major source of WAT derived TNF-alpha and IL-6 whereas circulating concentrations of these molecules are directly associated with adiposity, insulin resistance, and the metabolic syndrome. The pathophysiologic role of molecules secreted by the adipose tissue is presented in Table 74.2.

74.6 Leptin

Leptin (Greek word *leptos* meaning thin) is a 16 kDa protein encoded by the *ob* gene and it belongs to the class 1 cytokine superfamily, consisting of a bundle of four α-helices (Zhang et al. 1994). It is mainly produced by adipocytes, and circulating leptin levels are directly correlated with the mass of adipose tissue. Leptin is mainly involved in the control of appetite: it decreases food intake and increases energy consumption by acting on hypothalamus and inducing anorexigenic factors and inhibiting orexigenic neuropeptides (Lago et al. 2007) (Figs. 74.4 and 74.5). The synthesis of leptin is mainly regulated by food intake and eating-related hormones but also by sex steroid hormones and a variety of inflammation mediators. Leptin levels are higher in women than in men even after

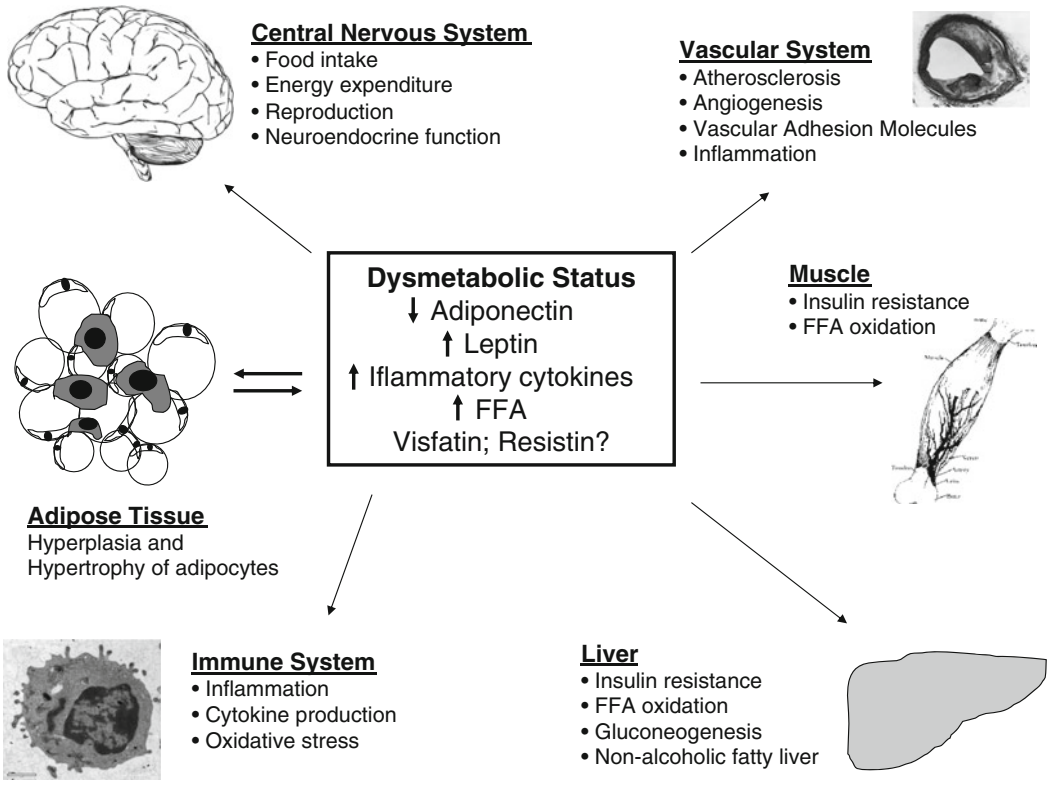

Fig. 74.4 Effects of obesity-related dysmetabolic status on other organs and systems. Hyperplasia and hypertrophy of adipocytes, caused by obesity, lead to an unfavorable metabolic status, with low adiponectin, high leptin, high inflammatory cytokines, and high free fatty acids. This dysmetabolic status effects on different organs and systems, such as the central nervous, the vascular, and the immune system as well as the muscle and the liver, regulating a variety of physiologic processes, as indicated in the figure

adjusting for BMI, as a result of sex steroid hormones' action (being inhibited by testosterone and increased by ovarian sex steroids).

Leptin exerts its biological actions by binding to its receptors, which are encoded by the gene *diabetes* (*db*) and belong to the class I cytokine receptors superfamily. Mice with a mutation in the leptin (*ob/ob*) or leptin receptor (*db/db*) genes, as well as humans with a mutation in the same genes have excessive obesity. Leptin is now considered as a pleiotropic hormone involved in a variety of physiologic processes, such as regulation of food intake, glucose metabolism, synthesis of glucocorticoids, the proliferation of CD4+ T lymphocytes, cytokine secretion, phagocytosis, endocrine functions, inflammation and immune response, and reproduction and angiogenesis (Lago et al. 2007).

A vast majority of studies has investigated the role of leptin in childhood and adolescent obesity and obesity-related disorders. A recent study (Zhang et al. 2009) examining plasma leptin concentrations in relation to different adiposity measurements has shown similar associations of leptin with BMI, WC, fat mass index (FMI), and percentage body fat (%BF) in females. In males, %BF and FMI were more strongly associated with leptin levels than BMI and WC. Trunk fat (%TF) had the weakest associations with leptin in both genders.

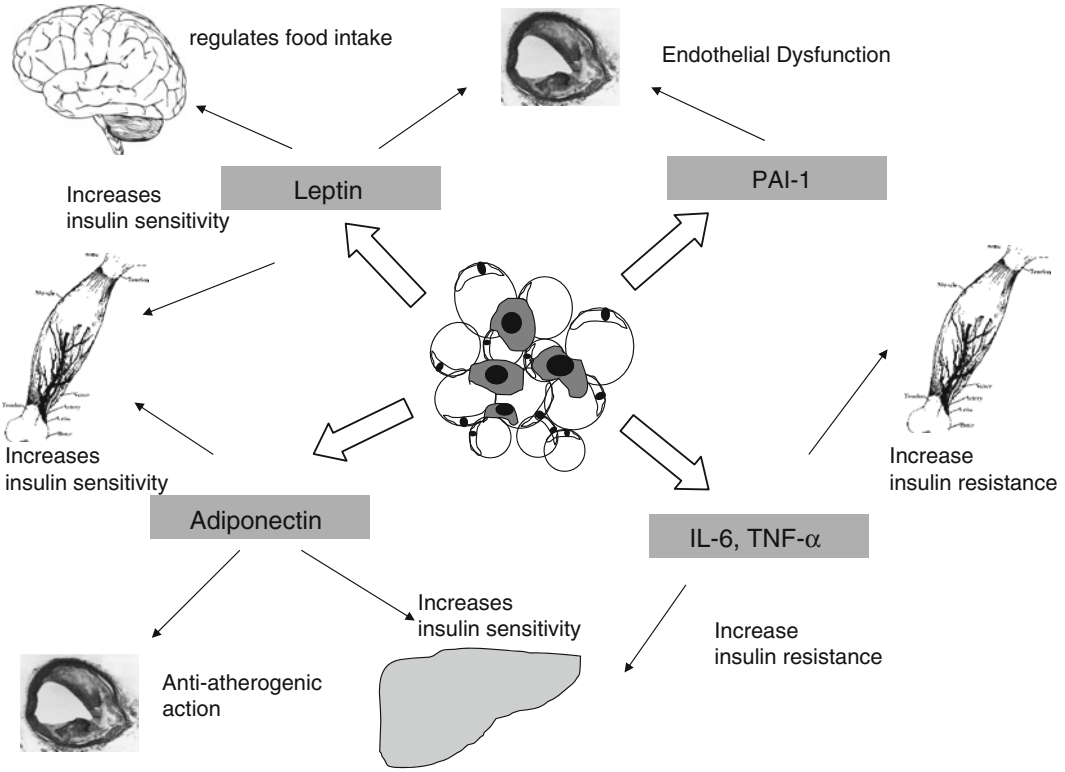

Fig. 74. 5 Actions of leptin, adiponectin, PAI-1, IL-6, and TNF-alpha. This figure indicates the diverse actions of each adipokine and inflammatory cytokine on different organs and systems

74.7 Adiponectin

Adiponectin is a 244-residue protein prevalently produced in the white adipose tissue. It increases the oxidation of fatty acids and reduces the synthesis of glucose in the liver (Berg and Scherer 2005). Adiponectin circulates in human blood in the form of multimers, with specific molecular sizes, a trimeric low-molecular-weight (LMW), a hexameric medium-molecular-weight, and a high-molecular-weight (HMW) adiponectin (Araki et al. 2006). It has been suggested that adiponectin molecules have different biological actions and that the HMW-form is the one with the higher activity. It acts, as far as it is known, via two receptors, the AdipoR1, mainly found in skeletal muscle, and the AdipoR2 found in the liver. It has profoundly insulin-sensitizing effects and an important role in regulating energy metabolism. Studies in knock-out mice have shown that ablation of the adiponectin gene has no dramatic effects on animals being in a normal diet. However, when those mice are given a high-fat, high-sucrose diet they develop severe insulin resistance and lipid accumulation in muscles (Whitehead et al. 2006).

Circulating levels of adiponectin are lower in obese than nonobese individuals (Arita et al. 1999). A significant negative correlation has been found between serum adiponectin levels and BMI, percent body fat, waist-to-hip ratio, and intra-abdominal fat. Adiponectin levels have also been studied in obesity-related disorders such as type 2 diabetes, where plasma adiponectin concentrations are lower than in age- and BMI-matched individuals. Finally, plasma adiponectin concentrations are lower in

patients with clinical manifestations of coronary heart disease (Ouchi et al. 2003) and several cardiovascular risk factors, including hyperlipidemia, high blood pressure, and C-reactive protein (CRP) levels. In addition to traditional obesity-related risk factors, such as lipid profile, glucose, and insulin, it appears that this cytokine has emerged as a powerful cardiometabolic risk factor.

One of the first studies in pediatric obesity examined the role of adiponectin (Winer et al. 2006) in childhood obesity and its associations with inflammatory markers and the metabolic syndrome. This study involved a multiethnic cohort of 589 obese children and adolescents. An association was found between adiponectin and CRP levels, which was independent of insulin resistance and adiposity. Low levels of adiponectin were associated with high levels of CRP and with components of the metabolic syndrome, such as low high-density-lipoprotein (HDL) and high triglyceride-to-high-density-lipoprotein ratio. Hypoadiponectinemia appeared to be related to a low-grade systemic chronic inflammatory state and it was suggested as a signal linking inflammation and obesity. Furthermore, high adiponectin levels were associated with a favorable lipid profile (high HDL and low triglyceride to HDL ratio). It has been suggested that these effects might result from the significant positive relation to lipoprotein lipase activity.

Few other studies have investigated the relation between adiponectin and the metabolic syndrome in children and found that hypoadiponectinemia is an independent risk factor for MetS (Gilardini et al. 2006) and adiponectin has been proposed as a potential biomarker of metabolic syndrome in children. Ethnic differences have also been reported in adiponectin levels in children: It has been shown that obese African-American and Hispanic children have lower adiponectin concentrations and this may be related to insulin sensitivity and may contribute to an increased risk for developing type 2 diabetes in these ethnic groups (Bush et al. 2005; Winer et al. 2006). Age and puberty seem also to impact on adiponectin levels: among children and adolescents, adiponectin levels were lower in older children (Winer et al. 2006) whereas another study found that adiponectin levels decline with age in relation to changes in sex steroid hormones and growth factors. These "normal" changes of adiponectin during puberty may contribute to the "normal" pubertal insulin resistance (Butte et al. 2005).

A few recent studies also suggest a positive association between adiponectin and the N-terminal pro-brain natriuretic peptide (NT-proBNP). NT-proBNP is considered a well-established diagnostic and prognostic marker of heart failure and coronary heart disease in adult patients with peripheral arterial disease, chronic heart failure, and coronary heart disease (Pervanidou et al. 2009). In investigating associations between adiponectin and NT-proBNP in obese adolescents, we found a significant positive correlation between NT-proBNP and adiponectin concentrations only in females. This association was stronger in adolescents with a greater degree of obesity, in girls having a BMI-z-score >2.5. In the same study, adiponectin showed a significant negative correlation with BMI-z-scores, triglycerides, HDL, and fasting insulin levels. This association was not found in males, suggesting a potential role of sex steroid effects during puberty. Although associations between adiponectin and NT-proBNP concentrations cannot be fully understood, a lipid-mobilizing effect of NT-proBNP that indirectly stimulates adiponectin could be a possible explanation. Indeed, in a recent study, intravenous infusion of natriuretic peptide increased glycerol concentrations in human subcutaneous adipose tissue suggesting a direct lipid-mobilizing effect.

A number of studies have also investigated circulating levels of adiponectin in neonates, in relation to gestational age and birthweight. In a sample of preterm infants at discharge, lower levels of adiponectin were found in the preterm than the full-term group. However, after adjustment for body weight, the influence of prematurity was no longer significant. Levels of adiponectin were influenced by being born small for gestational age, weight gain, and possibly by dietary intake of long-chain polyunsaturated fatty acids (LCPUFAs). In the same group, serum adiponectin levels did not correlate with insulin or leptin levels. Another study in preterm neonates showed that adiponectin was higher

in those infants fed long-chain polyunsaturated fatty acids (LCPUFA)-supplemented formula, than infants fed the LCPUFA-free formula, indicating that early dietary manipulation – supplementation with LCPUFA – may have a beneficial effect on serum adiponectin in preterm infants (Siahanidou et al. 2008). Regarding the distribution of adiponectin multimers in infants, a recent study in full- and preterm infants showed that high-molecular-weight adiponectin is the most prevalent form in infants, while the distribution of low- and medium-molecular-weight molecules differ between full- and preterm molecules (Siahanidou et al. 2009).

74.8 Resistin

Resistin is a 12 kDa peptide that was originally discovered when examining differential gene expression of mouse adipose tissue after treatment with thiazolidinedione (TZD) (Steppan et al. 2001). Resistin was increased in insulin resistant mice and decreased by TZD treatment. Additionally, treatment with a antiresistin antibody improved insulin sensitivity and glucose transport in mice and mouse adipocytes. However, data in humans are less clear: a number of studies investigated resistin concentrations in plasma or adipose resistin expression and have found variable results. In summarizing experimental and clinical data till now, resistin is an important adipokine in the development of insulin resistance; however, it seems to be quantitatively less important in humans in comparison with other adipokines (Rasouli and Kern 2008).

74.9 Visfatin

Visfatin was originally identified as a protein involved in B-cell maturation (Resouli and Kern 2008) and most recently was discovered as a protein with insulin-like functions. Visfatin is predominantly found in visceral adipose tissue, from which its name was derived (Fukuhara et al. 2005). Studies in mice revealed that injection of visfatin decreases blood sugar, while animals with a mutation in visfatin gene have high glucose levels.

74.10 Retinol-Binding Protein 4 (RBP4)

RBP4 is a small, 21 kDa protein that circulates bound to transthyretin (TTR) in a form of 80 kDa protein complex. RBP4 was initially considered to be only the transporter of retinol (Vitamin A), but recent experimental and clinical studies have shown that the soluble form of RBP4 is an adipokine involved in systemic insulin resistance: Studies in obese, insulin resistant, type 2 diabetic adults revealed high levels of this adipokine, while reduced concentrations of RBP4 were associated with improved insulin action. Two recent studies reported increased RBP4 concentrations in obese adolescents, although a correlation between RBP4 and the HOMA was not demonstrated. In children, a study in 80 girls (Kanaka-Gantenbein et al. 2008) showed that, in contrast to adult studies, RBP4 concentrations correlated negatively with BMI-SDS (Fig.74.6). This discrepancy in findings of RBP-4 levels between adult and pediatric obesity, may be due to the development of protective mechanisms of the organism during childhood.

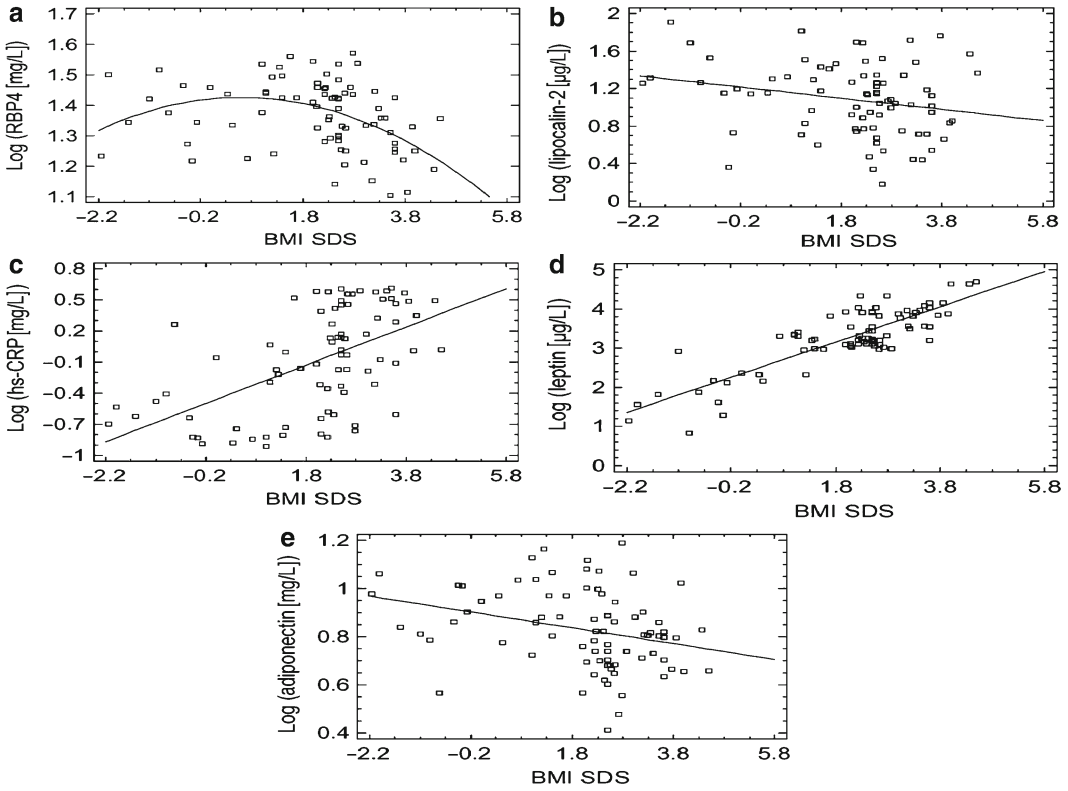

Fig. 74.6 Associations between childhood obesity and adipokines. Relations between childhood obesity, expressed in BMI-SDS, and leptin, adiponectin, ultra-sensitive CRP, RBP4, and lipocalin-2. This pediatric study suggests that with the exception of RBP4 and lipocalin-2, other cytokines follow the adult pattern of association (Kanaka-Gantenbein et al. 2008)

74.11 Lipocalin-2

Lipocalin-2 is a protein, belonging to the same family as RBP4, with inflammatory actions. It is positively correlated to BMI and several parameters of the MetS. Similarly to RBP4, lipocalin-2 was found to promote insulin resistance. In a recent pediatric study (Kanaka-Gantenbein et al. 2008), and similar to RBP4, lipocalin-2 concentrations correlated negatively with BMI-SDS. This finding was in contrast to adult studies, and a counter-regulatory effect was hypothesized to protect the organism from insulin resistance.

74.12 Applications to Other Areas of Health and Disease, and Conclusions

A large amount of clinical and experimental data supports that WAT is an active secretory organ, participating in a variety of physiologic and pathophysiologic processes. It is now clear that adipokines play multiple roles and participate in the function on several organs and systems, revealing a

continuous interplay between the adipose tissue and metabolic and inflammatory disorders. Research in adipose tissue and adipokines has enhanced our understanding of the relations between obesity, inflammation, insulin resistance, and the development of diabetes type 2 and cardiovascular disease and has led to the development of new therapeutic approaches. Prevention of leptin-induced inflammation is a potential therapeutic aim, through the development of a leptin-binding protein or by blocking the leptin receptor. Adiponectin, the promising molecule with antiatherosclerotic effects, is another obvious target for therapeutic interventions. The development of drugs acting in enhancing the endogenous production of this molecule would be of great importance for the treatment of obesity and obesity-related disorders. Further studies focused on mechanisms related to the infiltration of adipose tissue with macrophages and the secretion of inflammatory cytokines and adipokines are needed. However, the field is still too young to allow for therapeutic interventions related to adipokine and cytokine production, especially in childhood and adolescent obesity.

Summary Points

- The adipose tissue is no longer considered as an inert reservoir of energy but as an active secretory organ, releasing a variety of peptides and other molecules, the adipokines, into the circulation.
- In the presence of obesity, the adipose tissue, with enlarged adipocytes and macrophages inserted within them, secretes more proinflammatory cytokines, such as TNF-alpha and IL-6, and fewer antiinflammatory peptides, such as adiponectin.
- The Metabolic Syndrome, a clustering of clinical and metabolic manifestations related to obesity, is associated with an imbalance in the secretion of molecules secreted by the adipose tissue. These molecules act on several organs and systems, such as the central nervous, the immune, the vascular system, the muscle, and the liver, and regulate a variety of pathophysiologic functions.
- In children and adolescents, the same pathophysiologic mechanisms link obesity to the Metabolic Syndrome, however, there is some evidence that the effects of growth and puberty in these critical periods of change may differentiate the normal values as well as the physiologic role of the adipokines.
- Leptin, the prototypic adipokine, is mainly involved in the control of appetite: by acting on the hypothalamus, it decreases food intake and increases energy consumption. Leptin is higher in women than in men, independently of BMI, and higher in obese than normal-weight individuals, adults, and children.
- Adiponectin increases the oxidation of fatty acids and reduces the synthesis of glucose in the liver. Circulating levels of adiponectin are lower in obese adults and children and low levels of this cytokine are also associated with diabetes type 2.
- Retinol-Binding Protein 4 (RBP4) and lipocalin-2 are two novel adipokines involved in insulin resistance. In contrast to adult studies, where RBP4 and lipocalin-2 are high in obesity, it was found that these adipokines correlated negatively with BMI-SDS in obese children.

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Chapter 75
Anthropometric Measures in Children with Renal Failure

Andreas Nydegger and Julie E. Bines

Abstract Anthropometric and body composition assessments provide important information about the nutritional status of dialysis patients. A nutritional assessment by a trained dietitian is therefore recommended for patients diagnosed with renal disease because they are frequently in poor nutritional health. Knowledge of the nutritional health of patients with renal disease is necessary to prescribe and monitor appropriate clinical and nutrition therapies. Anthropometrical methods occupy a meaningful role in assessing the nutritional status of patients with renal disease, are cost-effective screening techniques for describing body size, and they are well suited for identifying levels of body composition, nutritional status or risk for disease. However, children with renal disease present special problems for anthropometry, including decreased functional status and increased comorbidity, which challenge nutrition assessment methodology. Measures of weight, stature, calf circumference, arm circumference and triceps and subscapular skinfolds have therefore been reported for dialysis patients, who tend to be shorter, lighter and have less adipose tissue than healthy persons of the same age. Other techniques to assess body composition are dual energy X-ray absorptiometry (DEXA), bioelectrical impedance, total body water (TBW) and prediction equations. However, irrespective of the technique to be used, all are validated in healthy individuals based on the assumption that body composition parameters are relatively static, which isn't the case in renal patients. Anthropometric measurements should be an integral component of the routine care of the child and adolescent with renal disease.

Abbreviations

CRF	Chronic renal failure
ESRD	End stage renal disease
BMI	Body mass index
DEXA	Dual energy x-ray absorptiometry
TBW	Total body water
FFM	Fat free mass
BIA	Bioelectrical impedendance

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_75,

GH Growth hormone
IGF-1 Insulin-like growth factor-1
TBK Total body potassium

75.1 Introduction

Accurate assessment of nutritional status is an essential component in the management of children with chronic renal failure (CRF) and following renal transplantation. Despite advances in dialysis technique and in adjunct therapies, protein-energy malnutrition is still encountered in up to 50% of children on chronic hemodialysis and may progress despite regular dialysis (Nydegger et al. 2007). The etiology of malnutrition in children with renal failure is multifactorial. Anorexia, side-effects of medications and uraemia can contribute to the development of malnutrition in children with renal disease. Hyperglucagonemia, hyperparathyroidism, or metabolic acidosis is associated with accelerated protein catabolism and a reduction in muscle mass (Kuizon et al. 1997). Alterations in nutritional, metabolic and fluid homeostasis negatively impact the long-term clinical outcome and quality of life of patients with CRF (Rigden et al. 1987). Assessment of nutritional status and body composition in the early stages of renal disease is important to detect nutritional disturbance at its onset and target interventions aimed at preventing the development of malnutrition.

Assessment of weight and height is routinely performed in children in both inpatient and outpatient settings. Using standardised growth charts, growth and weight, body mass index and growth velocity in a child with renal disease can be compared to normal expectations based on age and sex. These simple and practical measures can identify changes in nutritional status and growth impacting the normal growth of the child with CRF (Norman et al. 2000) (Fig. 75.1). However, faltering in

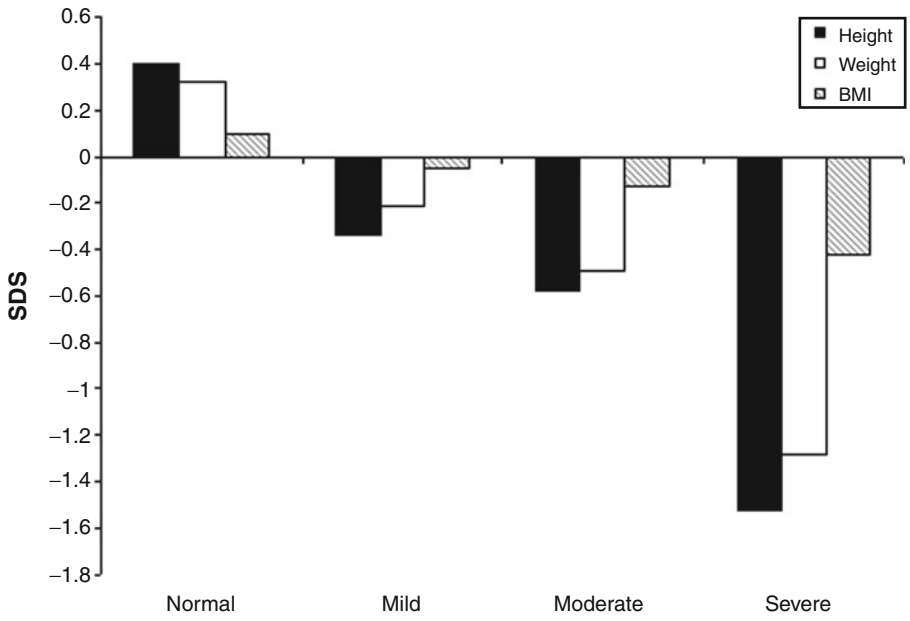

Fig. 75.1 Comparison of weight, height and body mass index standard deviation score (BMI SDS) in relation to severity of chronic renal insufficiency. Anthropometric assessment is a simple and practical measure to identify changes in nutritional status and growth impacting on the normal growth of the child with chronic renal failure (Reprinted from Norman et al. (2000), with permission)

Table 75.1 Features of anthropometric measurements used in infants and children with chronic renal failure

Measurement	Assessment	Accuracy	Reliability	Utility
Weight	Total body	●●●●	●●●●	●●●●
BMI	Total body	●●●●	●●●●	●●●
Height/length	Total body	●●●●	●●●●	●●●●
Sitting height	Spinal length	●●●●	●●●●	●●
Head circumference	Head growth	●●●●	●●●●	●●●●
Growth velocity	Active growth	●●●●	●●●●	●●●
Sitting: standing height ratio	Disproportionate skeletal growth	●●●●	●●●	●●
Triceps skin fold	Adipose tissue	●●	●●●	●●
Subscapular skinfold	Adipose tissue	●●	●●	●●
Mid arm circumference	Fat-free mass and adipose tissue	●●●	●●	●●
Knee height	Lower limb length	●●●	●●●	●●●
Bicondylar femur	Upper leg	●●	●●	●
Bicondylar humerus	Upper arm	●●	●●	●

Adapted for children from Chumlea (2004)
●●●● Very high
●●● High
●● Moderate

height growth often lags 3–6 months after weight loss or failure to gain and is not considered a sensitive, early marker of decline in nutritional status. In view of the frequency of growth impairment in children with renal disease, correction for "height-age" is important in monitoring growth expectations in children with CRF (Wells 2001). Measurements of skinfolds and limb circumference are practical, cost-effective techniques that describe body size and can identify levels of fatness and leanness in patients with renal failure. The accuracy and reliability of these measurements in children on dialysis have been adapted from data in adults and children and are summarised in Table 75.1 (Chumlea 2004).

75.2 Effects of Renal Disease on Anthropometric Measurements and Interpretation in Children and Adolescents with Renal Disease

Anthropometric measurements are standardised and validated for age, gender and ethnicity in the healthy population (Lohman et al. 1988). However, when extrapolating this data to children with renal disease a number of key considerations need to be considered.

75.2.1 Site of Measurement

Traditionally, measurements are performed on the right side of the body based on the methodology used to establish the reference data. However, in a patient with a vascular access for dialysis or any other limitations of the right side (i.e. past cerebrovascular accident, localised oedema) (Fig. 75.2), measurements may need to be performed on the left side. The change in location of the vascular access for hemodialysis may necessitate changing the location for subsequent measurements of circumferences and skinfolds.

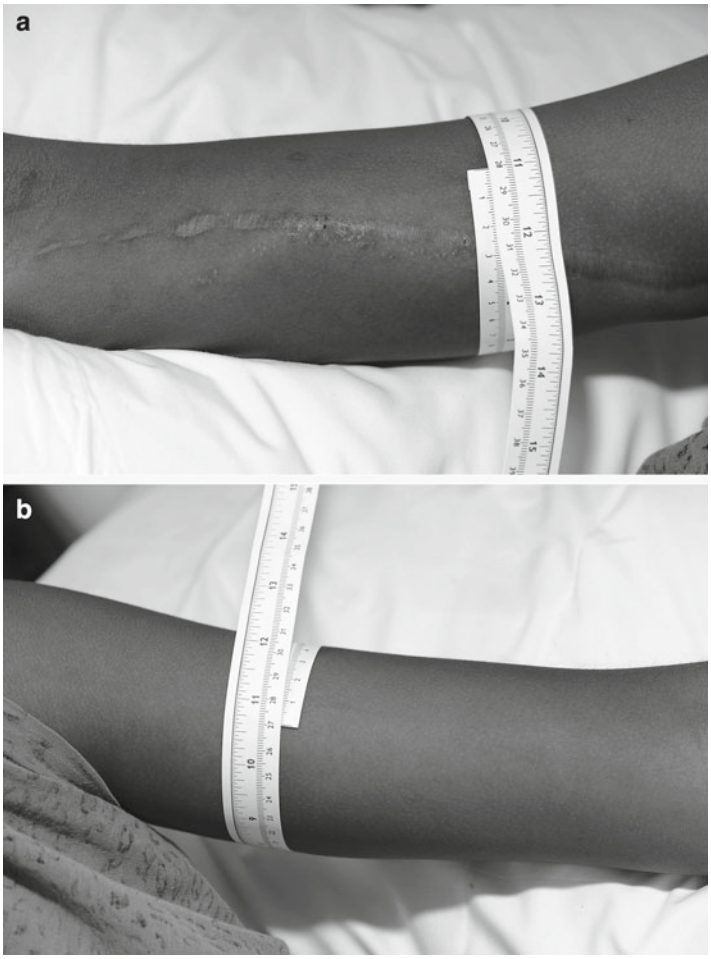

Fig. 75.2 Patient with a vascular access for dialysis on the right arm. (**a**) Increasing its diameter and rendering correct measurement impossible, (**b**) left arm of the same patient (with written consent of the patient)

75.2.2 Hydration Status

Changes in weight reflect changes in hydration status, energy and protein balance. This presents a challenge in patients on regular dialysis where large shifts in extracellular fluids may occur over a few hours. It is recommended that serial measurements be performed at the same time in the dialysis cycle, usually after dialysis is completed. Fluid overload in CRF can affect both skinfold and midarm circumference measurements as well as altering the assumptions for body composition validated in healthy individuals. Hydration status, abnormal regional body composition or an abnormal ratio of subcutaneous to visceral fat could also result in an overestimation of fat mass estimated from skinfold measurement. Estimates of fat free mass (FFM) are based on the assumption that the body water content is 73%; therefore, an estimate of edema-free FFM may be a more useful nutrition parameter than FFM in children with CRF.

75.2.3 Skeletal Disproportion in Children with CRF

Impaired linear growth is a major complication of childhood-onset CRF and is a significant obstacle to successful long-term rehabilitation. Growth failure in children with CRF can be caused by effect

of the disease and its treatment on the somatotrophic axis. It may also occur as a direct result of uremia at the level of the growth plate (Schaefer and Mehls 1998). An improved understanding of the factors affecting growth in CRF and following transplant has led to the introduction of growth-promoting strategies with recombinant human growth hormone (Haffner et al. 2000; Maxwell and Rees 1998). But, even with recombinant GH treatment, children and adolescents with CRF may not grow well during puberty and catch-up growth following renal transplantation may be suboptimal (Haffner et al. 2000; Fine 1997).

The spine has a greater number of epiphyses than any other part of the axial skeleton. Therefore, spinal measurements may be a more sensitive indicator of abnormal growth than total height, especially in the assessment of differential growth. A significant proportion of spinal growth occurs during puberty and delayed puberty may be associated with skeletal disproportion, impacting final height. Skeletal disproportion is assessed by calculating the ratio of sitting height to standing height (SH:HT). A significant proportion of children with CRF have relative shortening of the spine (Qayyum et al. 2003). Altered skeletal proportions can be identified at puberty and can persist, despite renal transplantation (Qayyum et al. 2003). Medications, in particular corticosteroids, inhibit growth directly at the level of the growth plate or via the growth hormone axis (Mushtaq and Ahmed 2002). The impact of corticosteroids on bone resorption is marked in cancellous bone and glucocorticoid-induced osteoporosis may present with loss of vertebral height as well as spinal deformity.

75.3 Effects of Age, Gender and Ethnicity on Interpretation of Anthropometric Data in Children and Adolescents with Renal Disease

The normal variability in anthropometric measurements occurring with age, gender and race further confounds the interpretation of anthropometric measurements in children with renal disease. Changes in body composition occur throughout the lifespan and are associated with changes in metabolism, nutrient intake, physical activity and the risk of chronic disease. Throughout childhood, there is an increase in the mineralisation of the skeleton with growth and increase in the density of FFM (Lohman 1986). In addition, the changes in the hormonal milieu alter the distribution and proportions of adipose, muscle and skeletal tissues in children as they mature into adults. These changes are further affected by the variation in the onset and duration of puberty.

Bone mineral accounts for as much as 6% of FFM but decreases substantially after menopause. However, levels of FFM and bone mineral also decrease as physical activity decreases with CRF and chronic hemodialysis and therefore, must also be considered in interpreting results of anthropometric measurements in children and adolescent with renal disease.

75.4 Effects of Hormone Deficiency on the Interpretation of Anthropometric Measurements in Children and Adolescents with Renal Disease

Although the etiology of growth failure in children with renal disease is multifactorial, endocrine-related factors, including abnormalities in the growth hormone (GH) and insulin-like growth factor-1 (IGF-1) axis may be may play an important role in the pathogenesis of growth impairment. Even after transplantation, alterations of the GH-IGF-1 axis are impacted by the use of corticosteroids, which suppress GH production and secretion and decrease cell responsiveness to IGF-1

(Hokken-Koelega et al. 1993). Whilst trunk and head measurements are usually preserved, the extremities are the most affected. Zivicnjak and colleagues reported a marked decrease in *z*-scores for bone dimensions of the legs (e.g. leg length –2.22; bicondylar femur diameter -1.87) and arms (e.g. arm length -1.996; bicondylar diameter of humerus –1.53) in children with CRF (Zivicnjak et al. 2000). However, these results need to be interpreted with caution as there was no correction for delayed puberty, which occurred in 34% of the study cohort. Nevertheless, growth hormone therapy was effective in improving impaired longitudinal dimensions of the body and the restoration of growth reported occurred predominantly in the extremities. Growth hormone therapy has been associated with improved growth and decreased the risk for death due to cardiovascular disease in children with CRF (Wong et al. 2000).

75.5 Other Limitations and Sources of Error

Measurement error may occur due to patient, observer and equipment factors. Children are notoriously difficult to measure and cooperation for repeat measurements can sometimes be challenging. The assistance of a parent and an experienced observer can help minimise these problems. Equipment should be well maintained and calibrated to limit the risk of malfunction. Estimation of fat mass and fat free mass should be based on established methodology validated in this specific patient group. The limitation of standardised data in normal children across a range of ages is a major barrier in the interpretation of measurements in children with renal disease. This may be further compounded by ethnic and disease specific factors that may influence linear growth potential or body composition. Also the treatment of an individual with renal disease may vary from year to year with alterations in medications, dialysis requirements or transplantation. This may limit the ability to interpret the influence of nutritional status on growth and body composition outcomes. In interpreting measurements of anthropometrics, both body size, irrespective of chronological age, and pubertal status are important variables that must be considered.

75.6 Other Techniques to Assess Body Composition in Children with Renal Disease

A range of methods is available to measure body composition and these provide options for monitoring nutritional status in children with renal disease. Direct methods use electro-magnetic radiation to quantify specific tissues and chemical and molecular elements in the body and include neutron activation, computer X-ray tomography and magnetic resonance imaging. Indirect methods involve measures of body density from water or air, dual energy X-ray absorptiometry (DEXA), total body water (TBW), bioelectrical impedance (BIA) and the use of predictive equations. However, irrespective of the technique to be used, all are validated in healthy individuals based on the assumption that body composition parameters are relatively static. For example, the measurement of TBW is based on the assumption that the average proportion of water in the body is 73%. However, body water in the normal adult can range from 67% to 80% (Chumlea et al. 1999). This range is even larger in infants and small children in whom the proportion of total body water changes dramatically in the first months of life (Davies 1993). As approximately 15–30% of TBW is present as extracellular fluid, variations in the distribution of TBW will also impact estimates of FFM and total body fat in patients with renal disease. Pre-dialysis patients have high levels of extracellular fluid and electrolytes. The impact of these variables on the accuracy of body composition methods is not well understood and may be clinically relevant in children with renal disease. Therefore, it is recommended that body

Table 75.2 Body composition of children with CRF and ESRF [*z*-scores; mean ± SD]

	CRF	ESRF	*P*-value
Number (%)	8 (53%)	7 (47%)	–
Weight-for-age *z*-score	–0.30 ± 0.87	–0.39 ± 0.49	0.823
Height-for-age *z*-score	–0.97 ± 0.98	–1.45 ± 1.14	0.397
Triceps skin fold thickness *z*-score	–0.71 ± 1.07	–0.28 ± 0.83	0.404
Body mass index *z*-score	–0.31 ± 1.13	+0.31 ± 0.73	0.357
Total body potassium *z*-score	+0.52 ± 0.81	+0.99 ± 0.81	0.279
Total body protein *z*-score	–0.72 ± 0.83	–0.71 ± 0.62	0.981
DEXA fat free mass *z*-score	+0.68 ± 1.51	+0.40 ± 0.87	0.674

Reprinted from Nydegger et al. (2007), with permission

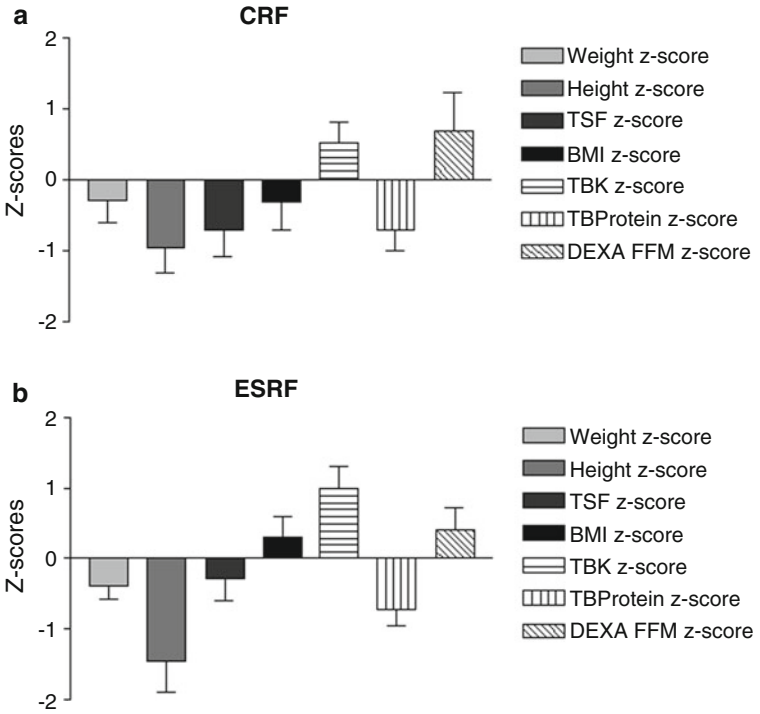

Fig. 75.3 Comparison of CRF and ESRF, using child and adolescent body composition reference data (matched for age, gender and ethnicity). Fluid overload and altered body potassium and urea levels in children and adolescents with CRF may lead to an overestimation of lean body mass as was found in a study comparing methodologies for the assessment of body composition in children with renal failure. *TSF* triceps skinfold, *BMI* body mass index, *TBK* total body potassium, *TBProtein* total body protein, *DEXA FFM* DEXA fat free mass (Reprinted from Nydegger et al. (2007), with permission)

composition measurements be performed immediately after dialysis when body fluid compartments may be closer to healthy levels. The clinical use of isotope dilution in children with renal disease may be limited by fluid overload and may result in an underestimation of fat and lean mass. Techniques such as densitometry, neutron activation analysis and total body potassium measurement may offer some advantages (Nydegger et al. 2007) (Table 75.2). Fluid overload and altered body potassium and urea levels in children and adolescents with CRF may lead to an overestimation of lean body mass as was found in a study comparing methodologies for the assessment of body composition in children with CRF (Nydegger et al. 2007) (Fig. 75.3).

75.7 Anthropometric Measures as Predictors of Outcome and Mortality

Renal disease is associated with significant morbidity and mortality (Childhood mortality rate: Renal disease 1.9% versus total population 0.48%) (Guyer et al. 1998). Anthropometric measurements, including height, growth velocity, weight and BMI, can predict outcome in children with renal disease.

75.7.1 Height and Growth Velocity

Wong et al. reported that paediatric patients with end stage renal disease (ESRD, defined as glomerular filtration rate <10 mL/min/1.73 m^2) have a mean height 2.5 standard deviations less than the mean (Fig. 75.4), growth velocity 0.38 standard deviation less than the mean and BMI 0.24 standard deviation less than the mean of healthy children reported in the Third National Health and Nutrition Examination Survey (NHANES III) (Wong et al. 2000; NHANES-III 1996). Using multivariate analyses, height, linear growth velocity and BMI were identified as significant predictors of death among children with ESRD. However, height and growth velocity were better predictors of mortality in younger (0- to 5-years and 6- to 14-years) children, than in adolescents (15- to 18-years). Over all age strata, for every one standard deviation decrease in height, the adjusted risk for death increased by 14%. After adjusting for sex, age, race, treatment modality and duration of ESRD, for every one standard deviation decrease in growth velocity, the risk for death increased by 12%. Hemodialysis was associated with an 11-fold increase in risk for death compared to transplantation. Interestingly, weight, sex and ethnicity were not significantly associated with mortality in children with ESRD (Wong et al. 2000).

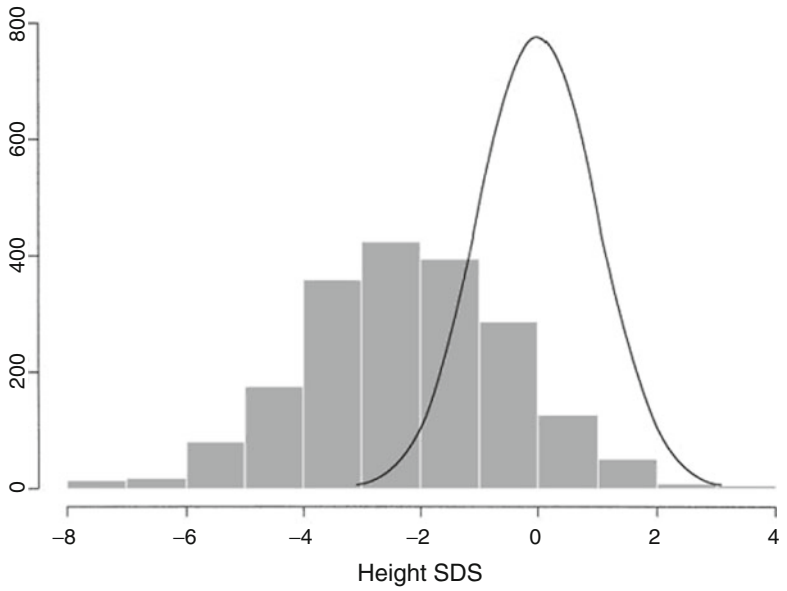

Fig. 75.4 Distribution of height standard deviation scores in patients with end stage renal failure compared with children in the US general population. The distribution of height standard deviation scores of 1949 patients in the study sample of Wong et al. compared with children in the US general population shows a mean height 2.5 standard deviation less than the mean (Reprinted from Wong et al. (2000), with permission)

75.7.2 Weight and BMI

Excessive weight gain in children with CRF may be associated with an increased risk of cardiovascular morbidity (Oh et al. 2002). Originally body mass index (BMI) was developed to assess body fat in community-based studies. Age-matched BMI data have aided the use of BMI in paediatric population studies and have increasingly been used to assess nutritional status in children with chronic disease (Cole et al. 1995; Wong et al. 2000). However, the clinical usefulness of BMI in the assessment of children with chronic diseases that place them at increased risk of growth retardation has been questioned (Schaefer et al. 2000). Reduced levels of physical activity, dialysis and glucocorticoid therapy may further confound the interpretation of BMI in children with renal disease. Wong et al. suggested that the relationship between BMI and mortality among both dialysis and transplant patients followed a "U" shaped distribution (Wong et al. 2000). Using the BMI standard deviation of 0.50 as the reference BMI, moving either above or below the referent point by two standard deviations was associated with a 26% increased risk for death. Moving from the referent point either above or below three standard deviations was associated with a 67% increased risk for death (Wong et al. 2000). However, caution must be used in interpreting BMI in children with renal disease. A high BMI may occur due to co-morbidities such as volume overload, edema or obesity, whereas a low BMI is likely to represent malnutrition. Rashid et al. showed that children with CRF and post renal transplantation have a high fat mass, which may be associated with an increased risk of cardiovascular morbidity, insulin resistance and diabetes (Rashid et al. 2006). Interestingly, these patients exhibited central obesity, suggesting that nutritional factors, chronic inflammation and lack of physical activity, as well as corticosteroid therapy, all contribute to the increased fat mass.

75.8 Applications to Other Areas of Health and Disease

The application of anthropometric techniques and the interpretation of results in children with CRF reflect similar challenges observed in children with chronic disease involving other organ systems. However, a key distinction in CRF is the specific impact of this disease on protein metabolism and bone mineralisation. Consideration of marked changes in hydration status with dialysis provides an insight into the interpretation of anthropometric measurements in children experiencing significant shifts in fluid balance such as occurs in assessing nutritional status in a child with acute gastroenteritis.

75.9 Conclusions

Renal disease in children is associated with significant morbidity and death. Not only can anthropometric measurements predict outcome in children with renal disease but they also provide a practical tool to detect early signs of nutritional and growth faltering and monitor response to nutritional and therapeutic interventions. However, the results of anthropometric measurements in children with renal disease need to be interpreted with consideration of hydration status, growth failure, skeletal abnormalities and delayed development. Early disturbance in growth and nutritional status can be identified even in children with mild chronic renal insufficiency. Identification and nutritional intervention at this early stage may present a window of opportunity to overt or limit the growth failure

often associated with CRF of childhood. Anthropometric measurements are safe, cost-effective and easy to perform and should be an integral component of the routine care of the child and adolescent with renal disease.

Summary Points

- Chronic malnutrition occurs in up to 50% of children on chronic hemodialysis and may progress despite regular dialysis
- Early assessment of nutritional status and body composition are important to detect nutritional disturbance at its onset and target interventions aimed at preventing the development of malnutrition
- Growth faltering often lags 3–6 months after weight loss or failure to gain weight and is not a sensitive, early marker of decline in nutritional status
- Key considerations in performing anthropometric measurements in children with CRF include the site of measurement due to vascular access needed for dialysis, hydration status and skeletal disproportion
- Key considerations in interpreting results of anthropometric measurements in children with CRF include age, gender, ethnicity, pubertal stage, bone mineral density, physical activity and hormone deficiencies such as growth hormone and IGF-1 deficiency
- Other methods of body composition measurement can provide useful data on early changes in nutritional status in children with CRF
- Anthropometric measurements including height, weight, growth velocity and BMI can predict outcome in children with CRF

Key Features of Chronic Renal Failure in Children

- Fluid retention
- High blood pressure
- Poor urine output
- Imbalance of blood electrolytes (high serum potassium and phosphate, low serum calcium)
- Imbalance of acid-base balance (metabolic acidosis)
- Poor appetite
- Lethargy
- Poor growth
- Disturbance in bone growth and strength
- Poor muscle mass

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Chapter 76
Measures of Body Surface Area in Children

Janusz Feber and Hana Krásničanová

Abstract Body surface area (BSA) is an important index of body size in both adults and children. The use of BSA allows for standardization of the important physiological parameters such as cardiac function, glomerular filtration rate and proteinuria, which are indexed by BSA. This in turn enables comparison of these parameters among children of various ages and sizes. In addition, BSA has been frequently used in children for the dosing of diagnostic and therapeutic drugs. The estimation of a correct BSA is therefore of crucial importance in both diagnostic and therapeutic aspects of pediatric medicine.

Methods for direct estimation of BSA, such as coating methods, alginate methods or three-dimensional scanning, yield precise results but are not suitable for bedside use where only indirect methods for BSA estimation can be used. They are mostly based on mathematical formulae containing weight alone or both weight and height as parameters. Although there are numerous BSA formulae published in the literature, only few have been validated in children. Formulae with weight as the only parameter tend to underestimate or overestimate the BSA. Most published pediatric formulae with both weight and height yield similar results with only minor, yet not clinically important differences. Therefore, the BSA formulae are suitable for use in all children up to the age of 18 years, with the exception of newborns in whom the selection of suitable BSA formulae is limited. The formula by Mosteller et al., where the BSA (m^2) = square root of [height (cm) × weight (kg)/3,600], seems to be the most universal and user friendly formula for children of all age categories.

Abbreviations

BSA Body surface area
GFR Glomerular filtration rate

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_76,

76.1 Introduction

Body surface area (BSA) is the total area of a human's skin. BSA changes significantly with age and growth, which is especially important in pediatric medicine where the patients' BSA gradually increases from 0.2 m^2 at birth to 1.73 m^2 in adulthood (Fig. 76.1) along with maturation of organ function. Consequently, BSA has been extensively used in clinical medicine as an index of physiologic processes (Table 76.1) such as glomerular filtration rate (GFR) (Bird et al. 2003; Blake and Grewal 2005), proteinuria (Nagasako et al. 2007), left ventricular mass (Daniels et al. 1988) and cardiac output (Bergstra et al. 1995). The indexation by BSA enables standardization of normal values and allows for the comparison of variables between individuals of different weight and height. Moreover, BSA is an important index for calculation of both maintenance and replacement fluid requirements in resuscitation setting and burn injury (Milner et al. 1993). BSA serves as a marker/guide for the therapeutic use of various drugs such as anticancer medications (Gao et al. 2008), prednisone (Feber et al. 2009), cyclophosphamide, cyclosporine, valganciclovir (Vaudry et al. 2009) and many others.

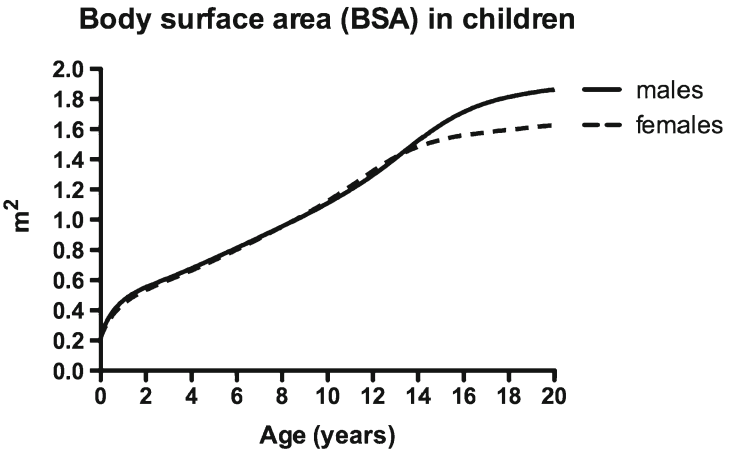

Fig. 76.1 Body surface area (BSA) in healthy persons aged from 0 to 20 years. This figure shows evolution of the BSA from the age of a newborn to the age of 20 years. The *x* axis represents age in years; the y axis represents BSA in m^2

Table 76.1 Examples of use of body surface area in pediatrics

Parameter	Description	Reference
Body structure	Liver volume	Yoshizumi et al. (2003)
	Central vein dimensions	Twardowski and Seger (2003)
	Left ventricular mass	Daniels et al. (1988)
Body functions	Glomerular filtration rate	Bird et al. (2003)
	Proteinuria	Nagasako et al. (2007)
	Cardiac output	Bergstra et al. (1995)
Fluid requirements	Maintenance fluids	
	Replacement fluids	Milner et al. (1993)
Medication dosing	Anticancer medications	Gao et al. (2008)
	Prednisone	Feber et al. (2009)
	Cyclophosphamide	
	Cyclosporine	
	Valganciclovir	Vaudry et al. (2009)
Diagnostic imaging	Radio contrast for CT scan	Bae et al. (2008)

This table illustrates various examples where body surface area is used as an index of body structure, body function, physiologic processes and medication doses. This allows for standardization of values/doses in patients with various body weight and height

BSA has also been used as a guide for estimation of liver volume (Yoshizumi et al. 2003) in transplant medicine and central vein catheter dimensions (Twardowski and Seger 2002). In addition, the use of BSA allows for the adjustment in dosage of radio contrast material for CT scanning (Bae et al. 2008).

The estimation of BSA belongs to the daily routine of clinicians, especially pediatricians who deal with constantly growing/changing body size and function. Therefore, the correct estimation of BSA is of primary importance for diagnosis and therapy in clinical medicine.

76.2 How Is BSA Measured?

The list of methods for measurement of BSA is shown in Table 76.2.

76.3 Direct Measurement of BSA

Typical practices used to measure BSA include coating methods (using paper, elastic tape, plaster bandage or aluminum foil), surface integration and geometric (or triangulation) methods (Lee et al. 2008). However, these methods are too laborious and tiresome for both subjects and researchers. Recently, three dimensional (3D) whole body scanning for estimating BSA has been proposed (Tikuisis et al. 2001; Yu et al. 2003). However, the accuracy of studies using 3D whole body scanning have also been questioned, because the method cannot recognize overlapping or shading body parts such as fingers, armpits, toes, and underneath the breasts. 3D scanning underestimates the BSA of overweight people because of the skin's folds. Lee and Choi suggested a new method using alginate to measure BSA (Lee and Choi 2006). This method has many advantages that are less time-consuming than traditional coating methods and can even measure skin folds of overweight and thin patients, in addition to small body parts such as fingers, toes and ears. Alginate (Jeltrate® Regular set. DENTSPLY LTD, England), a fine powder mainly used in forming artificial teeth in dentistry, is evenly coated on the skin. After only a couple of minutes, the material hardens to a certain degree and the alginate piece is separated from the surface of the skin. The alginate pieces are then copied on the paper, scanned by a 2D scanner and transformed into an electronic file containing the calculation of the surface area. The validity and reliability of the alginate method has been evaluated (Lee and Choi 2006). This precise measure of the BSA cannot be used

Table 76.2 Methods of estimation of body surface area in humans

Method	Details	Reference
Direct measurement	Coating method	Lee et al. (2008)
	Surface integration method	
	Geometric method	Tikuisis et al. (2001)
	3D scanning	Lee and Choi (2006)
	Alginate method	
Indirect measurement	Mathematical formulas:	Lee et al. (2008)
	Weight only	
	Square root of weight × height	
	$\text{Weight}^a \times \text{height}^b$	
	Weight + height	
	Weight, height, head circumference	

This table shows examples of direct and indirect measurements of body surface area in humans

in clinical practice due to its complexity, but serves as a reference measure for comparison of precision of various mathematical formulae used to calculate BSA in adults (Lee et al. 2008).

76.4 Indirect Measurement of BSA

76.4.1 BSA in Adults

The formulas for calculation of BSA can be divided into several categories based on the number of variables and the mathematical expression used (Lee et al. 2008) (Table 76.2):

weight only
square root of weight × height
weight^{a} × height^{b}
weight + height
weight, height and head circumference

Most of these formulae have been developed and validated for adults. In contrast, only few formulae have been validated for use in children. The list of formulae suitable for use in children is shown in Table 76.3.

76.4.2 BSA in Children

The most widely used formula of Du Bois and Du Bois (1916) increasingly underestimated BSA as the values fell below 0.7 m^2; the disparity was greatest in newborn infants (7.96%) (Haycock et al. 1978). Haycock et al. therefore developed a pediatric formula where BSA (m^2) = weight (kg)$^{0.5378}$ × height (cm)$^{0.3964}$ × 0.024265 (Haycock et al. 1978). This formula was derived from the measured data by multiple regression analysis and provided an adequate fit for all values of BSA from less than 0.2 m^2 to greater than 2.0 m^2 (r = 0.998). Consequently, this formula was used to construct nomograms for the estimation of BSA in infants, children and adults using a derivative from their height (length) and weight (Haycock et al. 1978).

In order to simplify the calculation of BSA for bedside use, Lindahl et al. proposed the following approach: for infants below 20 kg, the BSA (m^2) =3.6 × weight (kg) + 9, whereas for infants with a body weight between 20–40 kg, the BSA (m^2) =2.5 × weight (kg) + 33 (Lindahl and Okmian 1981). However, this formula was validated against the formula by Du Bois and Du Bois, which may underestimate the BSA as discussed above.

In 1987, Mosteller et al. (Mosteller 1987) described a simplified calculation where the BSA (m^2) = square root of [height (cm) × weight (kg)/3,600]. This formula gained wide acceptance in the pediatric community due to its precision and simplicity.

Also based on the formula by DuBois and DuBois, Ogunranti et al. (Ogunranti 1990) described a simplified method for BSA calculation in children based on their study of 920 Nigerian adults and children. Wang et al. studied 60 women and 148 neonates and concluded that several BSA formulas, including the DuBois and DuBois formulas, adequately predicted measured BSA over a wide range of patient populations. Although the original subjects studied by DuBois and DuBois excluded extremes of height and weight, their formula still appears to be a valid predictor (Wang et al. 1992). This is in contrast to an earlier study by Haycock et al. (1978), who stated that the formula by DuBois and DuBois is not suitable for children.

Table 76.3 Formulas for BSA estimation in children

Authors	Year of publication	Equation to calculate BSA
DuBois and DuBois	1916	BSA (cm^2) = 71.84 × height $(cm)^{0.725}$ × weight $(kg)^{0.425}$
Haycock et al.	1978	BSA (m^2)= weight $(kg)^{0.5378}$ × height $(cm)^{0.3964}$ × 0.024265
Lindahl and Okmian	1981	<20 kg: BSA (m^2) = 3.6 × weight (kg) + 9 20–40 kg: 2.5 × weight (kg) + 33
Meban	1983	BSA (m^2) = 6.4954 × weight $(g)^{0.562}$ × height $(cm)^{0.320}$
Mosteller	1987	BSA (m^2) = square root of [height (cm) × weight (kg)/3,600]
Current	1988	BSA (m^2) = (weight (kg) +4)/30
Shuter and Aslani	2000	BSA (cm^2) = 94.9 × [weight $(kg)^{0.441}$] × [height $(cm)^{0.655}$]

This table shows the most frequently used formulas for BSA calculation in children

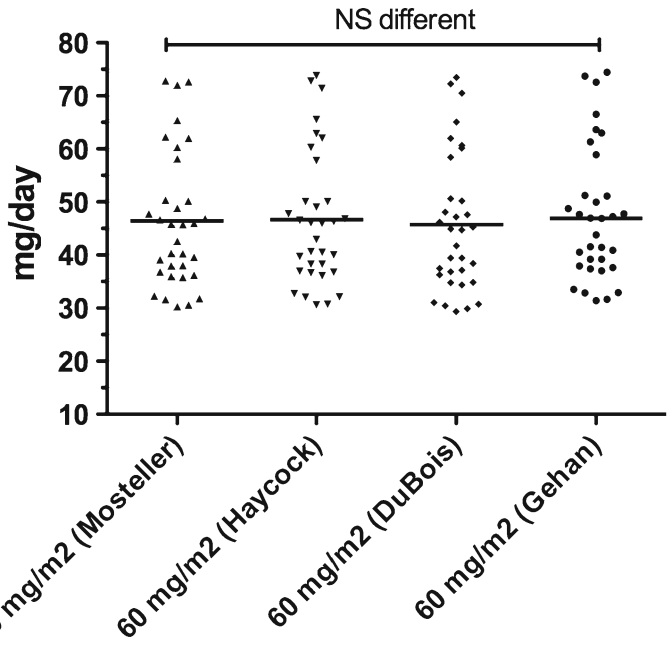

Fig. 76.2 Comparison of the oral prednisone dose (60 mg/m^2 BSA) calculated with various BSA formulae in children with nephrotic syndrome. The dose of oral prednisone was calculated as 60 mg/m^2 BSA using various formulas for BSA (*x* axis). The resulting total daily prednisone dose in mg/day is shown on the *y* axis. There is no significant difference in the total daily prednisone dose when calculated with various BSA formulae containing body weight and height as parameters for BSA estimation

Shuter et al. performed a critical revision of the DuBois and DuBois formula with modern statistical methods and stated that although the original equation obtained by Du Bois and Du Bois was found to be adequate in adults, it should not be used in daily practice based on the low number of subjects used in its derivation (Shuter and Aslani 2000).

More recently, Ahn et al. (Ahn and Garruto 2008) compared four different formulae for BSA in newborns against their mean and concluded that the formula by Meban (1983) is possibly the best BSA estimate for newborns among the existing formulae today; closely followed by the Mosteller formula (Mosteller 1987). Due to either overestimation or underestimation, the two formulae of Boyd (1935) and DuBois (1916) were not recommended for the surface estimation of newborns. The formula by Mosteller continued to provide very accurate estimates in newborns from Saudi Arabia (Nwoye and Al-Shehri 2005).

In older children with nephrotic syndrome, three commonly used BSA formulae (DuBois and DuBois 1916; Haycock et al. 1978; Mosteller 1987) that include weight and height in the calculation of BSA, were not significantly different – (Fig. 76.2). However, the formula using weight only

(Current 1998) significantly underestimated the BSA when compared to the formulae using both weight and height in the calculation of BSA (Feber et al. 2009).

Based on literature and personal experience, it seems that BSA is more of a function of both weight and height, rather than weight alone. The advantage in using both weight and height may override the single use of weight for surface estimation, regardless of the clinical and methodological simplicity of using only weight (Ahn and Garruto 2008).

The use of BSA rather than weight alone is likely more suitable for obese patients in whom the correct estimation of BSA and dosing of cytostatic drugs is a matter of debate (Verbraecken et al. 2006; Hunter et al. 2009). Similarly, adjustment of radio contrast-medium dosing for CT scanning by the BSA (which accounts for both the body weight and height factors) provides a more accurate iodine dosing over a wide range of body sizes (Bae et al. 2008).

In summary, accurate estimates of body surface area are clinically important in pediatric medicine for indexing cardiac and renal function, calculating maintenance and replacement fluid therapy and drug dosing. Although the formulae using both weight and height for the calculation of BSA are more mathematically complicated, they provide a more accurate estimation of the BSA when compared to formulae with weight as the only parameter. A simplified formula proposed by Mosteller et al. (Mosteller 1987) (BSA (m^2) = square root of [height (cm) × weight (kg)/3,600] offers the advantage of both parameters, which encompase the simplicity of use and precision over a wide range of body sizes. It may therefore be proposed as the preferred formula for bedside use in pediatrics.

76.5 Application to Other Areas of Health and Disease

An accurate estimation of body surface area (BSA) in children has a huge impact on many diagnostic and therapeutic procedures in pediatrics. BSA is frequently used as an index to standardize cardiac and renal function and to quantify urine protein excretion. The use of BSA therefore allows for comparison of results in children of various size and body composition. In addition, the dosing of many drugs and diagnostic substances such as radio contrast drugs for imaging used in pediatrics, is based on body surface area rather than weight alone.

76.6 Practical Methods and Techniques

BSA in children can be easily estimated from body weight and height using the following formula: BSA (m^2) = square root of [height (cm) × weight (kg)/3,600].

Summary Points

- The use of BSA allows for standardization of cardiac and renal function in children with various body compositions
- BSA is frequently used for the dosing of diagnostic and therapeutic drugs in pediatrics
- Direct measurements of BSA are not clinically useful
- BSA can be indirectly estimated with many mathematical formulae, with only a few having been validated in children

- Formulae for BSA containing weight and height as parameters, provide a more accurate estimate of the BSA when compared to formulae using weight as the sole parameter
- The formula proposed by Mosteller et al., BSA (m^2) = square root of [height (cm) × weight (kg)/3,600], offers reasonable precision and convenience for bedside use in pediatrics

Key Facts

Table 76.4 Key fact of body surface area estimation

1. BSA can be precisely measured using direct methods such as coating methods, the alginate method or 3D scanning
2. Only indirect methods for BSA estimation can be used in clinical practice
3. The selection of formulae suitable for calculation of BSA in children is limited, but the formula proposed by Mosteller et al. (Table 76.3) offers sufficient precision at all age categories and ease of use. It can be therefore recommended as the formula of choice for children

This table lists the key facts of measuring the body surface area in children

Table 76.5 Key facts of nephrotic syndrome in children

1. Nephrotic syndrome is characterized by an increased protein loss, low serum albumin level and high serum cholesterol level
2. The most common type of childhood nephrotic syndrome is associated with only minimal structural changes of cells along the glomerular basement membrane; it is also referred to as 'minimal change disease'
3. The therapy of childhood nephrotic syndrome consists of prednisone, with a standardized initial recommended dose of 60 mg/m^2/day or 2 mg/kg/day.

This table lists the key facts of childhood nephrotic syndrome

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Chapter 77
Skinfold Thickness in Sri Lankan Children

V.P. Wickramasinghe

Abstract Skinfold thickness has been used as a method of assessment of body composition. It reflects the subcutaneous fat distribution of body. Assessment of the SFT is useful in nutritional assessment as well as in assessing changes in the distribution of fat in the body during treatment of certain illnesses. Furthermore, it provides information on regional body composition, which is important in certain illnesses, such as metabolic syndrome. Prediction equations can be used to assess body density, total FM and percent FM. Skinfold thickness is a user-friendly and cost effective method for assessment of body composition with significant accuracy. There are conventionally agreed sites for the measurement of skinfold thickness and they will represent central as well as peripheral fat distribution in the body. It is important to apply standardized techniques to assess the SFT for accuracy as well as for reproducibility of measurements.

Skinfold thickness shows ethnic variations which could be explained by the theories of evolution. Subcutaneous fat distribution also changes with age and gender. It is important to understand such changes when interpreting results of research studies. In Sri Lankan children, the peripheral (assessed by tricep + biceps SFT) and central (assessed by subscapular + suprailiac SFT) subcutaneous fat distribution was lowest at six years of age and increased with age with the increase being more marked in girls. In Sri Lankan children, while total fat mass was increasing with age, the ratio of peripheral SFT: total FM and central SFT: total FM showed a reduction denoting that more fat is deposited as visceral adipose tissue than subcutaneous adipose tissue.

Centile charts can be used to interpret measurements of SFT. Furthermore, SFT equations can be used in the assessment of body composition. It is important to first validate these prediction equations on the specific population under study before using them for body composition assessment. It would be most prudent to use prediction equations developed on the same study population as they would give more accurate assessments. SFT-based prediction equations available in the published literature did not provide accurate assessment of body composition in Sri Lankan children; therefore these were developed specifically for Sri Lankan children, which estimated body fat accurately not only in native Sri Lankan children but also in Australian children of Sri Lankan origin.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_77,

Abbreviations

ANOVA	Analysis of variance
CV	Coefficient of variation
FM	Fat Mass
SFT	Skinfold thickness
NHANES	National Health and Nutrition Examination Survey
Tri	Triceps
SS	Sub Scapula

77.1 Introduction

History of body composition assessment can be traced back to the 5th century BC when Hippocrates proposed that the whole body is composed of blood, phlegm, black bile and yellow bile. (Wang et al. 1999). For many years people studied the structure of tissues of the body and determined whether it was of normal morphology or affected by any disease. The beginning of body composition analysis in early twentieth century enabled scientists to describe changes in a parameter that occur in different pathophysiological states. Although technically advanced methods for body composition analysis are available, anthropometric methods such as height, weight, skinfold thickness and circumferences are useful tools in day-to-day clinical practice. They are easy to use and cost effective. However, each anthropometric method has its own advantages and disadvantages in the assessment of body composition.

Scientists have appreciated the anthropometric value of subcutaneous fat in the assessment of nutritional status of humans for many years. In 1953 Tanner first described the use of Harpenden's skinfold caliper, enabling measurement of skinfold thickness which is a proxy measure of total body fat (Durnin et al. 1997). Since then the instrument has evolved, yet preserving its original mechanics and measurement techniques. Skinfold thickness represents a double layer of adipose tissue and skin. When measured at specific sites, it gives estimates of central (Sub-Scapular and Supra-Iliac) and peripheral (triceps and biceps) fat distribution. There are numerous equations described in the literature to predict fat mass as well as body density using skin fold thickness (vide infra).

Skinfold thickness is considered superior to mid upper arm circumference measurement for nutrition screening as the latter leads to errors in measurements due to soft tissue compression. Skinfold thickness measurements can be obtained with greater accuracy (Owen 1982). Skinfold thickness measurements taken at the NHANES I study in USA showed an inter-observer technical error of 1.89 mm (CV 15.4) for triceps and 1.53 mm (CV 15.4) for sub-scapular readings. Intra-observer technical error of 0.8 mm (CV 6.5) and 1.83 mm (CV 18.3) was observed for triceps and sub-scapular skinfold thickness measurements respectively (Owen 1982).

Subcutaneous fat deposition is influenced by sex, chronological age, race, state of maturation and nutritional status (Harsha et al. 1980; Shalitin and Phillip 2003). Skinfold thickness is more useful in the long-term follow-up of children with obesity and other medical conditions (growth hormone replacement) than for simple nutritional screening in the community (Owen 1982). Centile standards are used to compare data (Tanner and Whitehouse 1962, 1975). The new World health Organisation (WHO) growth reference charts are available for skinfold thickness assessment (http://www.who.int/childgrowth/en/). Regression equations are used to calculate body composition such as body density or percent fat mass (Annexure). However, as all these prediction equations were based on mathematical relationships, it will predict body composition only if the test population resembles the reference population that was originally used in the development of the equation. Most of the prediction equations were developed on Western European or North American populations of white Caucasian or black

African origins. There are a few equations that have been validated on populations of Chinese ancestry. These equations have been cross-validated on different populations and some showed satisfactory agreement while others did not (Janz et al. 1993; Reilly et al. 1995). There is no prediction equation developed on populations of South Asian origin. As fat distribution in body is influenced by the ethnic origin it is doubtful that currently available equations would predict body composition accurately in South Asian populations.

Skinfold thickness, which has the ability to directly assess the subcutaneous fat mass, would give a good estimate of body fat stores. However, concern over several technical issues has discouraged its use. The main concerns are in applying the technique, observer variability, influences of different types of callipers and difficulties in locating the correct measuring site.

Durnin and co-workers (1997) reviewed the published literature addressing technical errors on skinfold thickness measurements and found that inter-observer error accounted for less than 2–3% in estimation of percent fat mass. Furthermore, it was noted that the side of the body used for the measurement or instrument variability accounted for an error of less than 3%. They also looked at the effect of measuring skinfold thickness at imprecise locations other than what is considered to be standard sites for the measurement of four skinfold thickness measurements (triceps, biceps, subscapular and supra-iliac) in assessing percent fat mass. They showed that deviations as much as 20mm from the standard anatomical site gave an error of less than 3%. They concluded that the degree of error caused by picking up the wrong skinfold in assessing percent fat mass is of minimal importance. However, they expressed caution that precision is required if skinfold thickness is intended to examine local pathology. However in obese individuals locating the correct anatomical site as well as holding skinfold calliper jaws in place may be quite difficult.

Assessment of regional body composition is important in determining the onset of certain illnesses. This refers to anatomical variation in the distribution of major compartments of body mass, adipose tissue, skeletal muscle mass and skeletal tissues. Regional body composition varies with sex, age, development, physiological state and ethnicity. Regional fat distribution can be used as a determinant of risk for certain non-communicable diseases e.g. abdominal fat deposition associated with the metabolic syndrome (Alberti et al. 2006). Skinfold thickness is a good tool that can be used to assess regional body composition in detail. It is important to adopt standardized techniques in the assessment of skinfold thickness for reproducibility (Table 77.1). Standard equipment with standard caliper pressure needs to be applied. Standard pressure applied by caliper jaws is 10 g/cm^2 and should be kept for about 2–3 s before taking the measurement to the closest 1 mm. (Owen 1982). By convention certain sites have been identified for the assessment of skin fold thickness. It is important to adopt a standardized protocol in order to reproduce and compare measurements.

Table 77.1 Key feature in taking a skinfold thickness measurement

1. Identify the standard anatomical site to measure the skinfold thickness
2. Hold the skinfold between the thumb and the index finger.
3. Slide the skin with subcutaneous tissue over the underlying muscles to produce a skinfold just above or below the site marked for the measurement.
4. Apply the jaws of the calliper at the site marked to take the measurement.
5. Release your fingers from the skinfold.
6. Keep the calliper jaws for about 2–3 seconds to stabilize before taking the reading.

This table lists the key steps one has to follow when making a skinfold measurement

Following are the standardized techniques that have been described for making skinfold thickness measurement at some predetermined anatomical sites.

Triceps skinfold thickness is measured at the mid point between the lateral projection of the acromion and inferior surface of the olecranon process with the arm flexed to 90° at the elbow.

The measurement is taken with the arm hanging freely at the side of the trunk and the palm facing the lateral aspect of the thigh. A vertical skinfold over the triceps muscle is measured.

Biceps skinfold thickness is measured as the thickness of a vertical fold raised on the anterior aspect of the arm over the belly of the biceps muscle at the same level as is used for the triceps skinfold thickness measurement. Arm should be hanging by the side with the palm directed anteriorly while taking the measurement.

Forearm skinfold thickness is measured with the subject standing erect with arms relaxed and palms facing the lateral aspect of the thigh. A vertical skinfold in the midline of the posterior aspect of the forearm at the level of the maximum circumference is measured.

Mid anterior thigh skinfold thickness is measured by grasping a vertical fold of skin midway between the mid point of the inguinal crease and the proximal border of the patella. Measurement is taken with the subject standing erect and body weight evenly distributed on both legs.

Medial calf skinfold thickness is measured with the subject seated and the measured foot kept on the ground and flexed to 90° at the knee joint. A vertical skin-fold on the medial side of the calf at the level of maximum girth is measured.

Subscapular skinfold thickness is measured on an oblique line (approximately 45° to the horizontal plane), inclined infero-laterally, immediately below the inferior angle of the scapula.

Suprailiac skinfold thickness is measured in the mid axillary line. An inferomedially aligned oblique (45° to the horizontal plane) skinfold immediately superior to the iliac crest is grasped and measured (Harrison et al. 1988).

77.2 Ethnic Differences in Skinfold Thickness

Body composition varies with ethnicity, and Harsha and co-workers (1980) showed that there is a racial difference in subcutaneous fat distribution. Skinfold thickness measurement in a group of 7–15 year old American children of European and African origin showed differences in their fat distribution despite having similar weights and dietary habits. Black children had thinner skinfold thickness than white children except for the sub-scapular skinfold thickness which was similar in the two groups. This distribution could perhaps be explained by the influence of environment, both thermal and nutritional, on evolution. Europeans needed a heat conserving body composition. Therefore they have short limbs and long trunk with uniform deposition of subcutaneous fat for heat conservation and maintenance of energy stores. On the other hand Africans needed to dissipate more heat and keep body temperature down. This could be achieved by having a thin tall body with long limbs. Therefore they have lesser subcutaneous fat. However, they also need to stores energy with minimum interference to its cooling mechanism. This was achieved by depositing fat in the back of the trunk which would interfere only minimally with the cooling effort. This explains why Africans and Europeans have similar patterns of subcutaneous fat distribution in the subscapular region (Harsha et al. 1980). Robson and co-workers (1971) found similar results when comparing Caribbean island children of African origin with European children.

Body fat distribution of 12–17 year old American girls living in San Diego, of Mexican, European, Asian and African origins were compared by Malina and co-workers (1995). Based on skinfold thickness, girls of Asian and Mexican origins had more centrally distributed fat than girls of European and African origins. Central to peripheral skinfold thickness was larger in Asians. There was no significant ethnic difference between upper extremity (triceps) and lower extremity (medial calf) skinfold thickness. However, there were significant differences in upper trunk (sub-scapular) and lower trunk (supra iliac) skinfold thickness of children of Asian, Mexican and African origin when compared to children of white Caucasian origin (Malina et al. 1995).

77.3 Adipose Tissue Changes with Age and Sex

Physiologically normal amounts of fat mass depend on age and gender. Distribution of fat in the body also depends on age (Table 77.2). At birth, infants have equal amounts of central and peripheral subcutaneous adipose tissue. This ratio of central to peripheral tissue reduces to the lowest point at about 5 years of age. Up to about 13 years, similar increases are seen in both gender groups. During adolescence males gain more central subcutaneous adipose tissue than peripheral subcutaneous adipose tissue (C:P > 1), whereas females gain fat in both areas (C:P = 1) (Rolland-Cachera et al. 1990). This pattern of central to peripheral subcutaneous fat distribution remains thoughout life in both gender groups. Therefore males have proportionally more subcutaneous adipose tissue on trunk than extremity during adolescence and adulthood and females have similar subcutaneous fat distribution in both trunk and extremity (Table 77.3).

Subcutaneous adipose tissue to fat mass ratio is more or less similar for both boys and girls of 9–15 years of age. Thereafter, in males, it increases till about 20 years of age and then steadily declines. Therefore adult males have less subcutaneous adipose tissue and more visceral adipose tissue with advancing age. Contrary to this, female subcutaneous adipose tissue to fat mass ratio declines during adolescence and then remains static.

Table 77.2 Key features in changes in subcutaneous fat in with age

1. At birth infants have similar amount of subcutaneous fat in the central (trunk) and peripheral (extremity).
2. The ratio of central to peripheral skinfold thickness reduces and will be at its lowest point at around 5 years of age.
3. Till adolescence (about 13 years) both central and peripheral fat increases in similar amounts in both girls and boys
4. During adolescence, more subcutaneous adipose tissue gets deposited in the trunk than in the limbs in boys. Therefore central to peripheral subcutaneous fat ratio is more than one.
5. During adolescence, subcutaneous adipose tissue deposition in both trunk and limbs are seen in similar amounts in girls. Therefore central to peripheral subcutaneous fat ratio is equal to one.

This table shows main changes that occur in subcutaneous fat with age in both sex groups

Table 77.3 Key features in changes in body fat during puberty

1. Till puberty (about 9–15 years) subcutaneous fat (fat under the skin) to the total fat in the body (fat mass) are seen in similar proportions in both girls and boys.
2. In boys more subcutaneous fat deposition takes place till about 20 years. Therefore subcutaneous fat to fat mass ratio increases.
3. After 20 years this ratio decreases denoting that more fat get deposited inside (visceral) the body than under the skin (subcutaneous).
4. In girls subcutaneous fat to fat mass ratio increases till about 20 years denoting more fat is deposited under the skin.
5. Thereafter the ratio is static showing that fat deposition takes place in both subcutaneously as well inside body at an equal rate.

This table shows how body fat and subcutaneous fat changes during and after puberty in both girls and boys

In Sri Lankan children the peripheral subcutaneous tissue distribution measured by triceps and biceps skin fold thickness was shown to have the lowest distribution at six years of age and thereafter it shows an increase with age (Fig. 77.1). A similar pattern of distribution was seen in central adipose tissue measured by subscapular and suprailiac skinfold thickness. The increase is more marked in girls than in boys.

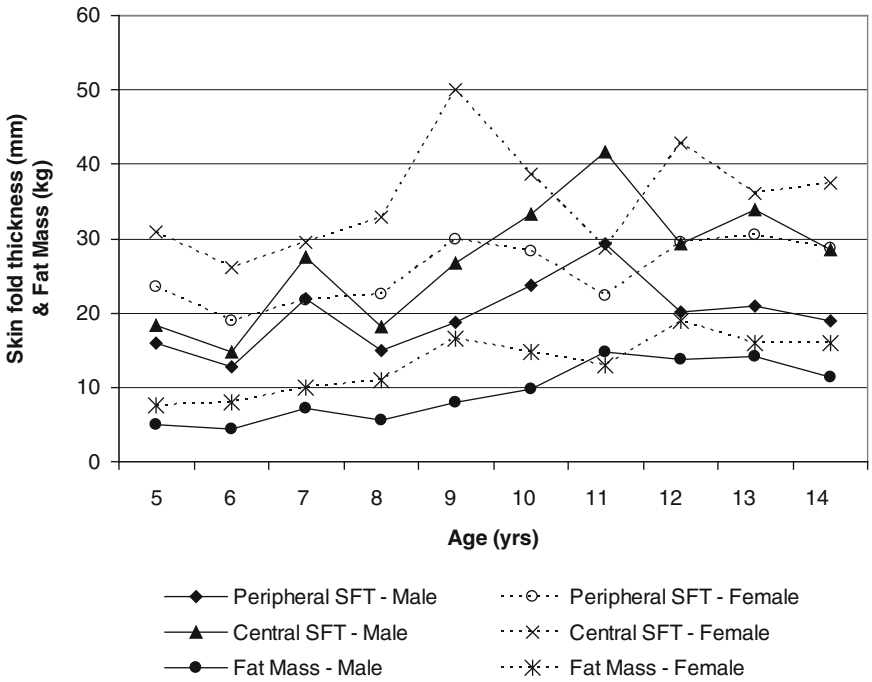

Fig. 77.1 Pattern of change in main skinfold thickness of the body and fat mass with age for each gender in a group of Sri Lankan children. Subcutaneous fat in both trunk and extremities are lowest at 6 years and gradually increases with age. Total FM also increased with age. Females always had a greater fat content than males

Central to peripheral skinfold thickness ratio remains more or less static during 5–14 years of age but it is more than one denoting that there is more central fat deposition than peripheral fat deposition (Fig. 77.2). Malina (1996) studied a group of female children from Quebec and noted that with maturation, from young pre-menarcheal to older post-menarcheal age, total fat mass increased. Although subcutaneous adipose tissue, as assessed by 6 skinfold thickness measurements at sub-scapular, supra iliac, abdominal, triceps, biceps and medial calf sites, increased while the subcutaneous adipose tissue to fat mass ratio reduced, denoting that more visceral adipose tissue accumulation occurred with advancing maturity. This denotes that females accumulate more visceral adipose tissue during sexual maturation (Malina 1996). Significant ethnic differences in body fat distribution have been noted. More central pattern of subcutaneous adipose tissue distribution is seen among adolescent girls of Asian and Mexican origin than their counterparts of European or African origin (Malina 1996).

Among Sri Lankan children also the total fat mass increased with age as assessed by isotope dilution technique using D_2O (Bell et al. 1998) (Please see Fig. 77.1.). The ratio of peripheral skinfold thickness to total fat mass and central skinfold thickness to total fat mass showed a reduction despite an increase in total fat mass with increase in age (Fig. 77.2). This denotes that more fat is deposited as visceral adipose tissue than subcutaneous adipose tissue.

77.4 Studies of Body Composition of Sri Lankan Children

South Asians are highly susceptible to metabolically related noncommunicable diseases and it is postulated to be directly related to regional body composition, namely abdominal fat distribution. South Asians have a higher amount of fat in the anterior abdominal wall for any given circumference

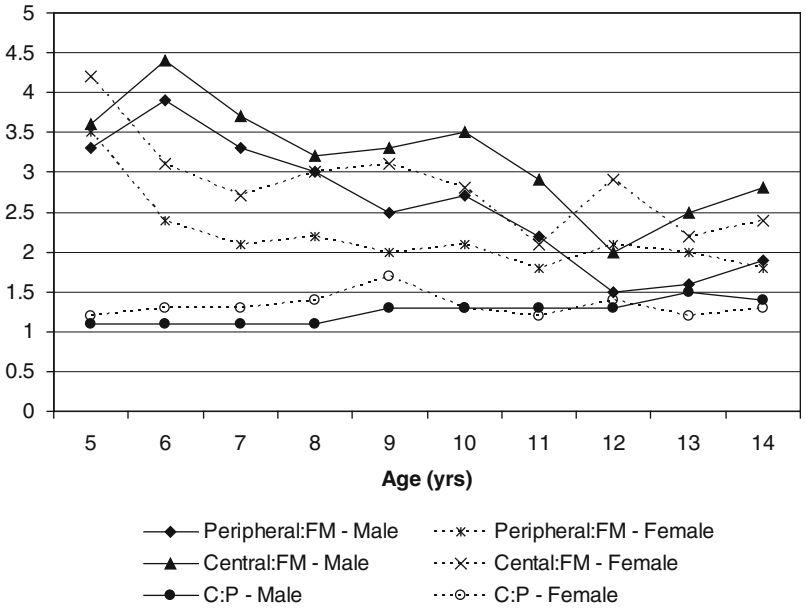

Fig. 77.2 Distribution of skinfold thickness ratios with age in both genders in a group of Sri Lankan children. Both peripheral subcutaneous fat to total FM and central subcutaneous fat to total FM are high at a younger age and decreases with advancing age. Central to peripheral subcutaneous fat ratio is static throughout growth in both gender groups

compared to other races (Alberti et al. 2006). Wider understanding of their body composition would help in controlling many of these illnesses. There had always been some doubt about the ability to use body composition assessment techniques without validating them on different ethnic groups. It is important to validate the existing body composition techniques and if not suitable, develop new equations/techniques for field use on populations.

As prediction equations for body composition assessment works best in the population they were originally developed for, it is important to validate them in the test population prior to their use. There are many skinfold thickness based prediction equations in the published literature for the assessment of body composition (Annexure). Several prediction equations were cross-validated on a group of Sri Lankan children to identify their suitability with this population. Nine skinfold thickness prediction equations in boys, described in the literature by five different authors and seven equations described by four authors for assessment of body composition in girls, were cross-validated on a group of 5–15 year old Sri Lankan children. Sarria and co-workers (1998) studied a group of Spanish boys and derived the equation to be used exclusively on boys. Therefore this equation was not included in the assessment of percent fat mass in girls. Some equations are ethnic specific (Slaughter et al. 1988) while some are gender specific (Deurenberg et al. 1990). Except for the equation of Yuan and co-workers (1987), other equations were developed on Western European or North American populations. Yuan et al. developed a set of equations on a group of Japanese children.

Table 77.4 shows the mean percent fat mass level for each gender of a group of Sri Lankan children assessed by different prediction equations (Annexure) and compared with the percent fat mass assessed by isotope dilution technique (D_2O) (Wickramasinghe et al. 2008a). All prediction equations in both

Table 77.4 Mean percent FM, Correlation (*r*) between percent FM assessed by each SFT equation and criterion method (D_2O) and comparison of mean percent FM assessed by each SFT equation, for each gender in a group of Sri Lankan children

	Male (158)		Female (124)	
	Mean±SD	*r***	Mean±SD	*r***
Durenberger et al. 2 SFT	17.4 ± 5.3	0.743*	22.1 ± 5.5	0.289*
Durenberger et al. 4 SFT	18.1 ± 5.7	0.729*	23.9 ± 6.1	0.343*
Slaughter et al. (Tri+SS) White	20.2 ± 12.0	0.729*	25.4 ± 9.6	0.356*
Slaughter et al. (Tri+SS) Black	17.9 ± 10.4	0.754*	25.4 ± 9.6	0.356*
Slaughter et al. (Tri+Calf)	21.6 ± 10.9	0.725*	25.5 ± 8.3	0.356*
Brooks	24.5 ± 9.5	0.748*	29.2 ± 10.2	0.360*
Sarria et al. 1	16.2 ± 9.5	0.724*	N/A	N/A
Sarria et al. 2	15.6 ± 8.6	0.711*	N/A	N/A
Yuan et al.	23.7 ± 9.4	0.567*	26.7 ± 7.9	–0.228*
D_2O method	26.2 ± 10.6	–	37.0 ± 10.3	–

Mean percent FM assessed by each equation and by the established method (deuterium water) is shown. Also it shows the correlation between the percent FM assessed by each equation and the established method

*$p < 0.05$

**Correlation between %FM assessed by each prediction SFT equation and criterion method (D_2O)

Table 77.5 Mean bias and limits of agreement in the estimation of percent FM by SFT equations and isotope dilution technique in a group of Sri Lankan children

Comparison of %FM from D_2O vs % FM from	Bias[a] Mean ± SD (%)	Correlation coefficient[b]	Limits of agreement of bias[c]
Male			
Durenberger et al. 2 SFT	8.5 ± 4.4	0.000	–0.1 to 17.1
Durenberger et al. 4 SFT	9.2 ± 4.7	0.000	0.0 to 18.4
Slaughter et al. (Tri+SS) White	5.9 ± 8.4	0.000	–10.6 to 22.4
Slaughter et al. (Tri+SS) Black	–8.2 ± 7.3	0.000	–22.5 to 6.1
Slaughter et al. (Tri+Calf)	–4.6 ± 8.0	0.000	–20.3 to 1.1
Brooks	–1.6 ± 7.2	–0.156	–15.7 to 12.1
Sarria et al. 1	–10.0 ±7.5	–0.156	–24.7 to 4.7
Sarria et al. 2	–10.5 ± 7.5	–0.194	–25.2 to 4.2
Yuan et al.	–2.5 ± 8.0	0.920	–18.2 to 13.2
Female			
Durenberger et al. 2 SFT	8.8 ± 5.5	0.000	–2.0 to 19.6
Durenberger et al. 4 SFT	10.6 ± 5.6	0.000	–0.3 to 21.5
Slaughter et al. (Tri+SS) White	–11.6 ± 11.3	0.000	–33.7 to 10.5
Slaughter et al. (Tri+SS) Black	–11.6 ± 11.3	0.000	–33.7 to 10.5
Slaughter et al. (Tri+Calf)	–11.7 ±10.7	0.000	–32.7 to 10.3
Brooks	–7.8 ± 10.2	–0.015	–27.8 to 12.2
Sarria et al. 1 & 2	NA		
Yuan et al.	–10.3 ± 102	0.784	–30.3 to 9.7

The mean bias or the difference between the percent FM assessed by the equation and the established method is given in the table. Limits of agreement show the range of bias with 95% confidence interval. The correlation shown is the relationship between the bias and the mean percent FM assessed by the two methods [(equation + established method)/2]

[a]"Bias"; difference of the %FM assessed by the indirect technique minus %FM assessed by isotope dilution technique.

[b]Correlation coefficient and 'significance, of the bias of percent fat mass between the two methods and the mean fat mass derived by the two methods (skin fold thickness and isotope dilution technique).

[c]Mean bias ± SD × *t* (*t* is the confidence coefficient at 95% level of confidence for *n* - 1 degrees of freedom in a two tailed test).

gender groups underestimated the percent fat mass. The equation of Brook had the highest estimate of percent fat mass out of the equations tested; 24.4% (9.5) and 29.2% (10.2) for boys and girls respectively. The correlations between percent fat mass assessed by criterion method and each skinfold thickness equations are shown in Table 77.4. Except for the equation described by Yuan and co-workers for the prediction of percent fat mass, all other equations in boys had a very good correlation with the percent fat mass assessed by criterion method (D_2O). Highest association in both groups was with the Brook equation. However, in females although there was statistically significant correlation the strength was low. Yuan and co-workers equation gave a low correlation in boys and a negative correlation in girls.

Percent fat mass assessed by criterion method and each skinfold thickness equation were compared using one way ANOVA (data not shown). Estimations made by the equations of Brook and Yuan agreed with the criterion method in males. However, none of the equations gave percent fat mass estimates agreeable with the criterion method in females (Wickramasinghe et al. 2008a).

Bias is used to evaluate the effectiveness of predicting a parameter (Bland and Altman 1986). It is calculated by subtracting the percent fat mass assessed by criterion method, from the percent fat mass estimated by prediction equations (predicted – actual) (Table 77.6).

Table 77.6 Key features in Bland Altman plot

1. A Bland and Altman plot is used to evaluate the agreement between the value predicted by a new diagnostic or test procedure and the assessment made by the established (criterion) method.
2. A graph (scatter plot) is drawn between the value obtained by the established method and the new method for each individual.
3. Correlation between the two methods is calculated to identify the closeness between the two assessment methods in giving the results.
4. Similarly the Bland and Altman plot is drawn to assess the distribution of bias between the value assessed by the new method and value assessed by the established method.
5. Bias is calculated by subtracting value obtained by the established method from the value obtained by the new method. This value is taken to the y axis.
6. Mean value for each parameter is calculated. That is the sum of the value obtained from the criterion method and new method, divided by 2. This value is plotted on x axis.
7. Correlation between the two parameters is calculated. It would be ideal to have no significant relationship. This means that the bias or difference is not affected by the value and therefore the new method is good to assess the parameter even at extremes.

This table lists the steps in performing a Bland Altman plot and its interpretation

Mean bias and limits of agreement for each method, for each gender is shown in Table 77.5. In boys the lowest mean bias was seen for estimation made by the equation of Brook. However, in boys, the limits of agreement were quite high denoting that values could be underestimated by 15.7% or overestimated by 12.1%. The narrowest limits of agreement was provided by the two equations described by Deurenberg et al. The equation which used the sum of triceps and susbscapular skinfold thickness, underestimated by 0.1% and overestimated by 17.1% while the equation which used the sum of four skinfold thickness overestimated by 18.4%. In girls also a similar pattern was observed. Whilst the equation of Brook gave the lowest bias, both equations of Deurenberg et al. gave the narrowest limits of agreement which was slightly wider in girls than in boys (Wickramasinghe et al. 2008a). Although Yuan and co-workers studied an Asian population it had very high limits of agreement, which perhaps denotes that significant differences exist between the body composition of populations of south Asian and Chinese origins.

The relationship between bias and mean percent fat mass, assessed by the criterion method and the specific prediction equation, is used to evaluate whether extremes of percentage fat mass in the

Table 77.7 Correlation between different skinfold thicknesses and fat mass/percent fat mass assessed by isotope dilution techniques (D_2O) in a group of Sri Lankan children

	Male		Female	
	Fat mass	Percent fat mass	Fat mass	Percent fat mass
Triceps SFT	0.85*	0.74*	0.72*	0.29**
Sub-scapular SFT	0.84*	0.67*	0.77*	0.40*
Supra iliac SFT	0.84*	0.71*	0.66*	0.41*
Biceps SFT	0.76*	0.76*	0.66*	0.30*

Table shows the relationship between different skinfold thicknesses and fat mass and percentage fat mass of the body for both male and female Sri Lankan children of 5–15 year age group
*$p < 0.001$
**$p < 0.01$

body would influence assessment made by skinfold thickness prediction equations (Bland and Altman 1986). Equations of Deurenberg et al. and Slaughter and co-workers did not show a relationship in both males and females. This denotes that extremes of percent fat mass did not influence the bias. The equation published by Brook had a statistically significant negative association denoting that at lower levels of percent fat mass the equation overestimates while at higher levels of percent fat mass the equation underestimates.

Brook gave the closest prediction value for percent fat mass when compared with the assessment made by isotope dilution method, which was considered as the criterion method in this study. Brook also used isotope dilution technique to develop the equation. The age groups were similar to our study but the sample size was only 23 children and some were obese and suffered from short stature. Therefore, the validity of such equations being used on the general public is questionable. Although Brook gave the lowest bias for the estimation of percent fat mass in both girls and boys the limits of agreement were quite wide. On the other hand both equations described by Deurenberg and co-workers had a fairly high bias, but 95% limits of agreement were the lowest. Furthermore, the correlation between bias and the mean percent fat mass assessed by criterion method and skinfold thickness equation was zero, denoting that there was no association between bias and percent fat mass assessed. In other words, extremes of measures of percent fat mass did not influence the bias. Equations of Slaughter and co-workers gave a relatively small bias in the assessment of percent fat mass, especially in males, but the limits of agreement were quite wide.

It is quite evident from this data that prediction equations cannot be used freely just because they have been developed on a group of children. The prediction equations we have tested were developed using 3 different ethnic groups namely white Caucasians (Brook 1971; Slaughter et al. 1988; Deurenberg et al. 1990; Sarria et al. 1998), black Americans (Slaughter et al. 1988) and those with Chinese ancestry (Yuan et al. 1987). Therefore it is possible to postulate that ethnic groups may have a significant influence on fat distribution of the body. Another factor that could lead to the difference in results would be the diversity in the age groups. Of the equations we validated, none of the equations matched each study population in its entirety with the age of the original population.

Table 77.7 shows the Pearson's correlation between different skinfold thickness measures and percent FM and FM assessed by isotope dilution techniques (D_2O). Statistically significant associations were seen in both groups but the power was weaker in females.

Although the equations predicted the percent fat mass poorly, the correlation between different skinfold thickness and percent fat mass was significant, denoting that skinfold thickness could be used to predict percent fat mass, but population/ethnic specific equations are required to do so.

Many factors could have contributed to the poor agreement of skinfold thickness prediction equations in the assessment of percent fat mass. Ethnic differences in body composition as well as

socioeconomic influence could have been the two main factors. Furthermore, a shortcoming of the study could be the criterion method we used. However, of the equations we validated, some used two-compartment body composition model with isotope dilution technique (Brook 1971) while some used underwater weighing (Sarria et al. 1998; Deurenberg et al. 1990). One study used a multi-component body composition model (Slaughter et al. 1988).

77.5 Development of Prediction Equations

As existing prediction equations showed poor estimation of percentage fat mass in Sri Lankan children, a prediction equation developed on this population would be very useful in the assessment of body composition.

Prediction equations are constructed by step wise multiple regression on an identified dependent variable(s) and a set of independent variables. Best predictive variables are selected by measure of goodness-of-fit statistics including coefficient of determination (R^2), root mean squared error (RMSE) and Mallows' Cp statistics. Best prediction equation should have a high R^2 with minimum RMSE. Mallows' Cp statistics give the appropriate number of independent variables to an equation. Mallows' Cp statistics is an index to identify the optimum number of independent variables. A prediction equation is considered suitable when the number of independent variables is close to the value of Cp statistics (Dawson and Trapp 2001). Increase in the number of independent variables increases the precision of the equation. However, the magnitude of improvement gradually decreases.

Several preliminary prediction equations were developed and after validating on an independent group of subjects, the best predictive equation was identified (Wickramasinghe et al. 2008b). After identifying the best independent predictor variables, the final prediction equation is developed. Final prediction equation is statistically validated using PRESS (prediction of sum of squares) statistical method (Guo and Chumlea 1996; Sun et al. 2003). The PRESS statistic is a measure of how well an equation performs when applied to an independent sample. The process of applying PRESS statistics is:

1. Regression equation is made after excluding one observation
2. Obtain the predicted value of the observation that was excluded
3. Calculate the residual or difference for that excluded observation (observed – predicted)
4. Steps 1–3 is repeated for all the observations
5. Sum of the squares of all the residuals are taken and
6. PRESS statistic is calculated by taking the mean square root of the sum of squared of the residuals divided by the total number of observations.

Validation using the PRESS technique is almost equal to validating against an independent sample as PRESS residual is obtained for the observation that was not included in forming the equation. Pure error was used to evaluate the predictability of the derived equation when applied to the Validation Group. It is calculated as square root of the mean sum of squared differences (bias) between observed and predicted value. Smaller values denote better prediction. There is no defined way to assess success of validation using pure error. However, the general rule is that the RMSE value obtained from the development group should be similar to the pure error obtained in the validation group (Guo and Chumlea 1996).

77.6 Development of a Skinfold Thickness Prediction Equation for Sri Lankan Children

Body composition assessment with skinfold thickness is based on prediction equations derived using statistical methods rather than biological properties of human anatomy and physiology. Therefore it is very important to choose the appropriate equation to convert the skinfold thickness to a body composition parameter. The best would be to have prediction equations derived from populations which are closely linked to the population under study. As most of the existing equations are developed on white Caucasian populations, it is very important to either derive a specific set of equations or validate the existing equations on the target population prior to its clinical use.

Two separate sets of preliminary equations based on skinfold thickness were constructed for the prediction of fat mass and percent fat mass (Wickramasinghe et al. 2008b). In each set there was a gender non-specific and gender-specific equation. Gender non-specific equation had a higher coefficient of determination in the prediction of both fat mass and percent fat mass than gender-specific equations. Root mean squared error did not differ significantly in any of these equations.

On cross-validation, results of mean fat mass and percent fat mass assessed by all equations, in both males and females, did not differ significantly from each other. However, gender non-specific equation gave minimum bias and minimum pure error when compared with gender-specific equations for the assessment of fat mass in both groups. In the assessment of percent fat mass, gender non-specific equation gave low bias but high pure error when compared with gender-specific equation. Gender non-specific equation either under- or overpredicted fat mass by very small amounts and it was always less than 1,000 g. Similarly gender non-specific equation for the prediction of percent fat mass also had prediction accuracy within 1.1% units. A statistically significant ($p < 0.001$) association existed between the criterion method and the predicted values of fat mass and percent fat mass assessed by each of the new prediction equations. Fat mass and percent fat mass was better predicted by gender combined equations than gender-specific equations. However, the variables in the prediction of fat mass were responsible for a variance of 70.2% while for prediction of percent fat mass it was only 40.8%.

Fat mass and percent fat mass assessed by each skinfold thickness equation and the criterion method showed statistically significant correlations. The association with fat mass was much stronger and results were similar in both gender groups. When preliminary prediction equations were validated they gave minimum bias and had significant agreement with the criterion method. A single gender combined equation for the prediction of fat mass and percent fat mass would also be more acceptable in day-to-day practice.

Table 77.8 shows the final prediction equation derived using the 282 subjects. The R^2 and root mean squared error (RMSE) showed good agreement between independent variables (impedance index, weight and sex) and dependent variables (fat mass and percent fat mass). Although PRESS statistics were closer to pure error in both gender groups, PRESS statistics were slightly higher than pure error for both fat mass and percent fat mass assessment in boys but slightly lower in girls. However, PRESS residual of final prediction equation was slightly higher than mean bias of validation of the preliminary prediction equations for fat mass and percent fat mass. PRESS R^2 is also comparable to the R^2 of the multiple regression of variables. PRESS residuals of the final prediction equation were compared with bias in validation of preliminary equations. PRESS residuals were higher than the mean bias in the assessment of both fat mass and percent fat mass in both gender groups. Variables showed strong agreement with the R^2 for the prediction of fat mass (75%) but low agreement for the prediction of percent fat mass (44.8%).

Fat mass and percent fat mass assessed by the criterion method plotted against the fat mass and percent fat mass predicted by each final prediction equations are shown in Figs. 77.3 and 77.4.

Table 77.8 Final, gender-combined, SFT prediction equation for FM and percent FM in Sri Lankan children

FM = (0.68 × age) + (0.246 × SFT-triceps) + (0.383 × SFT-sub-scapular) – (1.61 × Sex Code[a]) – 3.45
% FM = (–0.28 × Age) + (0.49 × SFT-triceps) + (0.34 × SFT-sub-scapular) – (7.97 × Sex Code[a]) + 26.8

The two equations developed on Sri Lankan children based on skinfold thickness are shown. These can be used to calculate the FM or Percent FM
[a]Sex code: male = 1; female = 0

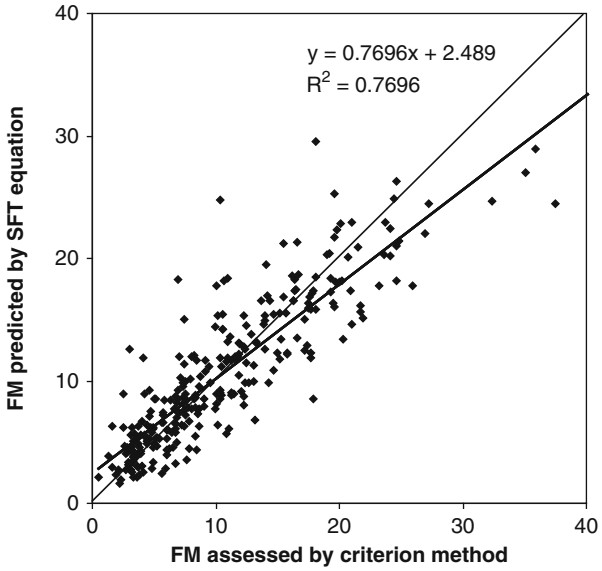

Fig. 77.3 Fat mass assessed by criterion method (D_2O) versus that predicted by final gender combined skinfold thickness equation, line of identity and regression line in a group of Sri Lankan children. FM assessed by established (criterion) method and new prediction equation is plotted on the graph. The values are concentrated closer to the mid line denoting that there is very good agreement between the two methods (Reprinted from Wickramasinghe et al (2008b), with permission)

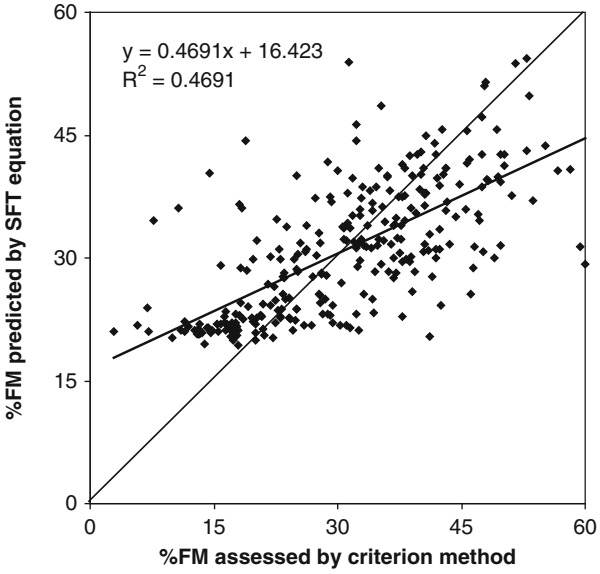

Fig. 77.4 Percentage fat mass assessed by criterion method (D_2O) versus predicted by final gender combined skinfold thickness equation, line of identity and regression line in a group of Sri Lankan children. Percent FM assessed by established (criterion) method and new prediction equation is plotted on the graph. The values are relatively concentrated to the mid line denoting that there is good agreement between the two methods. But it is not as impressive as in the assessment of FM (Reprinted from Wickramasinghe et al (2008b), with permission)

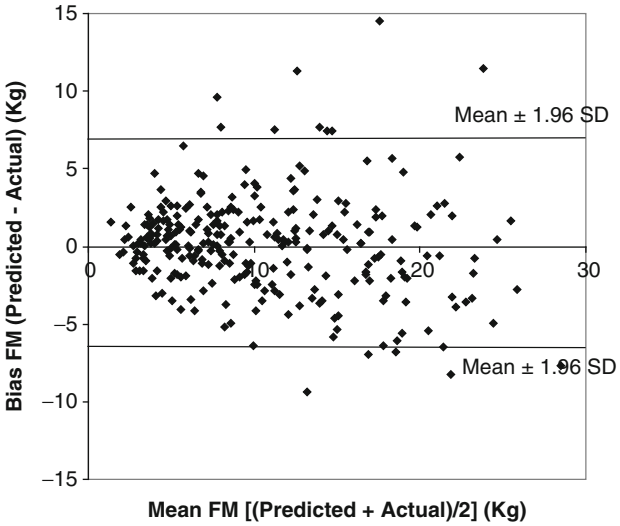

Fig. 77.5 Bland Altman plot for mean fat mass assessed by skinfold thickness prediction equation and D_2O method and fat mass assessment bias (predicted – actual) in a group of Sri Lankan children. Mean bias was 3.05×10^{-7} L (~0) and SD of 3.38. The bias in the assessment of FM (assessed by equation - established methods) is plotted against the mean FM assessed by the two methods [(equation + established methods)/2]. Values are scattered closer to mean and spreads across the whole of *X*-axis. This shows that bias in not dependent on the value of total FM of body (Reprinted from Wickramasinghe et al. (2008b), with permission)

Assessment of fat mass shows strong agreement with values obtained from the criterion method and most of the values were falling along the line of identity. However, in the assessment of percent fat mass values at extreme ends, there were deviations from the line of identity. Figure 77.5 shows the Bland Altman plot for mean fat mass assessed by the criterion method and final prediction equation and bias between the criterion method and final prediction equation. Most of the bias was close to zero. Figure 77.6 shows the Bland Altman plot for mean percent fat mass assessed by the criterion method and final prediction equation and bias between criterion method and final prediction equation. In this instance also the distribution was mainly around zero, but less condensed than for fat mass. In both instances most of the values remained within mean bias ± 1.96 SD.

Fat mass of the body as well as its distribution is influenced by maturity. Therefore, fat deposition of body could depend on pubertal stage of the individual. Thus, the prediction of body fat mass based on skinfold thickness equations could be influenced by the pubertal stage of the child. The initial prediction equation did not consider the influence of maturity on the assessment of fat mass and percent fat mass. A set of equations to assess fat mass as well as percent fat mass based on pubertal stage were also developed and validated to find the most appropriate set of skinfold thickness equation for Sri Lankan children (Table 77.9 and 77.10). The fat mass and percent fat mass were assessed by each of the maturation specific prediction equations. They are:

1. The gender and maturity non-specific common childhood equation (common equation to be used without taking pubertal stage and gender into consideration
2. Maturity-specific but gender non-specific common equation (equation is based on pubertal stage but irrespective of gender)
   and
3. Maturity and gender-specific equation (equation is selected taking into consideration both pubertal stage and gender).

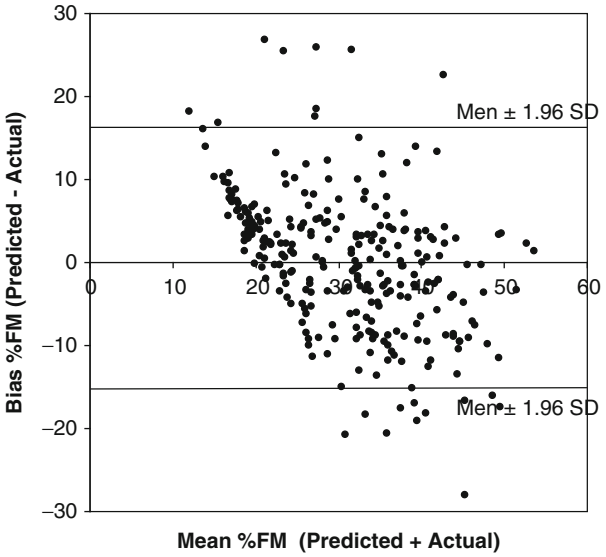

Fig. 77.6 Bland Altman plot for mean percent fat mass assessed by skinfold thickness prediction equation and D_2O method and percent fat mass assessment bias (predicted – actual) in a group of Sri Lankan children. Mean bias was $–1.11\times 10^{-7}$ L (~0) and SD of 8.6. The bias in the assessment of percent FM (assessed by equation – established methods) is plotted against the mean percent FM assessed by the two methods [(equation + established methods)/2]. Values are scattered evenly all over the graph denoting that bias is highly variable (Reprinted from Wickramasinghe et al. (2008b), with permission)

Table 77.9 Preliminary SFT equation developed on a group of Sri Lankan children: gender-combined and gender-specific equations for the prediction of fat mass and percent fat mass in *prepubertal children*

	Equation	R^2	RMSE
Fat mass prediction equations	**Gender non-specific**		
Fat mass	(0.41 × age) + (0.29 × SFT-triceps) + (0.28 × SFT-sub-scapular) – (2.2 × sex code[a]) – 0.48	75.9	2.09
	Gender-specific		
Fat mass: male	(0.26 × age) + (0.57 × SFT-triceps) + (0.026 × SFT-sub-scapular) – 2.26	72.0	1.8
Fat mass: female	(0.78 × age) – (0.08 × SFT-triceps) + (0.55 × SFT-sub-scapular) – 1.32	80.0	2.2
Percentage fat mass prediction equations			
	Gender non-specific		
Percentage fat mass	(0.09 × age) + (1.12 × SFT-triceps) + (0.10 × SFT-sub-scapular) – (10.4 × sex code[a]) + 22.0	50.2	8.9
	Gender-specific		
Percentage fat mass: male	11.53 – (0.53 × age) + (2.02 × SFT-triceps) – (0.42 × SFT-sub-scapular)	51.5	7.3
Percentage fat mass: female	22.46 + (1.48 × age) – (0.53 × SFT-triceps) + (1.02 × SFT-sub-scapular)	29.0	10.2

The table shows different equations developed to assess FM and percent FM in *prepubertal* children. Some equations are meant for a specific sex group (gender specific) while some equations can be used for both sex groups (gender non-specific)

[a]Sex code: male =1; female = 0

Table 77.10 Preliminary SFT equation developed on a group of Sri Lankan children: Gender-combined and gender-specific equations for the prediction of fat mass and percent fat mass in *pubertal children*

	Equation	R^2	RMSE
Fat mass prediction equations	**Gender non-specific**		
Fat mass: common	(0.57 × age) + (0.39 × SFT-triceps) + (0.27 × SFT-sub-scapular) – (2.17 × Sex code[a]) – 2.89	70.7	3.66
	Gender specific		
Fat mass: male	(0.69 × age) + (0.43 × SFT-triceps) + (0.8 × SFT-sub-scapular) – 5.7	75.1	3.1
Fat mass: female	(0.51 × age) + (0.37 × SFT-triceps) + (0.38 × SFT-sub-scapular) – 3.7	62.4	4.1
Percentage fat mass prediction equations			
	Gender non-specific		
Percentage fat mass: common	28.6 – (0.28 × age) + (0.5 × SFT-rtriceps) + (0.22 × SFT-sub-scapular) – (8.5 × sex code[a])	44.4	8.3
	Gender specific		
Percentage fat mass: male	9.7 – (0.5 × age) + (0.81 × SFT-triceps) – (0.07 × SFT-sub-scapular)	45.0	7.3
Percentage fat mass: female	48.8 – (1.53 × age) - (0.006 × SFT-triceps) + (0.37 × SFT-sub-scapular)	24.9	8.7

The table shows different equations developed to assess FM and percent FM in *pubertal* children. Some equations are meant for a specific sex group (gender specific) while some equations can be used for both sex groups (gender non specific)

[a]Sex code: male =1; female = 0

They were developed and validated on an independent group. Fat mass and percent fat mass predicted by each equation was quite similar to the results obtained by the criterion method (Table 77.11). One way ANOVA was used to compare the results obtained by the 3 different prediction equations and the criterion method in the validation group. None of the predicted values differed significantly from the values obtained from the criterion method (Table 77.11).

This denotes that although pubertal stage influenced the fat distribution in the body, the results obtained by pubertal stage specific and gender specific equation did not differ from the results obtained from gender and maturity non-specific equation in this group of children. It must be stressed that the assessment of maturity in a field or clinic setting is not easy. According to this study evaluations made by a common equation (that does not take gender and pubertal stage into account) does not seem to affect body fat assessment. Therefore, it would be more practical to use a single equation for children of both gender groups and without taking development stage into account. Therefore, body fat mass can be assessed using a single equation without having to assess the maturity of the child.

Of the equations that we validated, only the equations of Deurenberg and co-workers (1990) and Slaughter and co-workers (1988) used equations to suit different pubertal stages of subjects. Yuan et al (1987) used different equations based on age and sex, but not on pubertal stage. Brook (1971) used gender-specific equation while Sarria and co-workers (1998) developed equations only for boys. This shows the diversity of equations that are available in the published literature. Assessment of pubertal stages as well as applying gender-specific equations is not easy in busy clinics or field settings. Therefore, having a common equation which gives agreeable results is much more acceptable in day-to-day clinical practice.

Table 77.11 Validation results for the assessment of fat mass and percent fat mass using different skinfold thickness equations based on maturity (pubertal status) in a group of Sri Lankan children

	Fat mass	Percentage fat mass	Fat mass	Percentage fat mass
Pre-pubertal children	**Male (n = 25) Mean ± SD**		**Female (n = 16) Mean ± SD**	
Criterion method	6.6 ± 6.04	24.8 ± 10.8	8.02 ± 3.3	33.1 ± 8.5
Maturity specific common equation for prepubertal children	5.9 ± 4.7	24.6 ± 8.7	9.4 ± 3.6	37.6 ± 6.2
Maturity and gender specific equation for prepubertal children	5.7 ± 4.3	24.2 ± 10.4	9.9 ± 4.3	38.8 ± 6.7
Gender and maturity non specific common equation	6.1 ± 5.5	24.7 ± 6.2	9.1 ± 4.2	34.7 ± 5.5
Pubertal children	**Male (n = 28) Mean ± SD**		**Female (n = 25) Mean ± SD**	
Criterion method	11.7 ± 8.5	27.4 ± 13.1	16.4 ± 6.7	37.8 ± 10.9
Maturity specific common equation for prepubertal children	10.2 ± 6.5	27.3 ± 5.6	15.6 ± 4.8	37.6 ± 4.7
Maturity and gender specific equation for prepubertal children	11.0 ± 6.5	27.9 ± 11.4	15.6 ± 5.0	43.6 ±5.9
Gender and maturity non specific common equation	11.4 ± 6.5	27.3 ± 7.0	15.8 ± 4.8	38.1 ± 5.6

The above equations (in Tables 77.9 and 77.10) and the equation which was developed initially (Table 77.8) were tested on an independent group of children and results are shown in this table. Assessment by any of the equations did not significantly differ from the assessment made using established (criterion) method

77.7 Assessment of Body Composition of Sri Lankan Children Residing in Australia

Children of South Asia living in Western societies have been shown to develop metabolic derangements due to affluent life styles (Whincup et al. 2002). A significant Sri Lankan expatriate community lives in Australia. Therefore, having robust techniques to assess body composition of these groups of children is important. Equations developed on Sri Lankan children were validated on Australian children of Sri Lankan origin.

Table 77.12 shows the results obtained by each of the prediction equations and the criterion method. Except for the equation described by Yuan et al. to assess percent fat mass in both gender groups and estimation of percent fat mass in females children using fat mass estimation equation, all other equations gave high correlation for the assessment of percent fat mass in Sri Lankan children residing in Australia. Estimation of fat mass and percent fat mass in such Sri Lankan children residing in Australia, using skinfold thickness equations developed in Sri Lanka, provided a high degree of accuracy.

Skinfold thickness can be used in the assessment of body composition with fair accuracy. This is useful especially in low resource settings. Its accuracy in using on Sri Lankan children living in Australia suggests that ethnicity is a more influential factor on body composition assessment than the socio-economic environment that they are living in.

Table 77.12 Assessment of body composition in a group of Australian children of Sri Lankan origin, using Sri Lankan skinfold thickness equations

	Male (27)			Female (15)		
	Mean±SD	*r**	Bias	Mean±SD	*r**	Bias
Fat mass						
D_2O method	6.9 ± 4.6			10.2 ± 5.5		
Sri Lankan equation for fat mass estimation	6.9 ± 4.2	0.92	–0.3 ± 1.8	11.7 ± 5.5	0.88	1.5 ± 2.7
Percentage fat mass						
D_2O method	22.9 ± 8.7			29.0 ± 6.0		
Sri Lankan equation for fat mass[a]	22.4 ± 7.8	0.76	–0.4 ± 9.5	34.1 ± 8.1	0.40	5.4 ± 4.1
Sri Lankan equation for percent fat mass[b]	24.9 ± 4.3	0.86	1.9 ± 7.9	35.9 ± 5.0	0.80	6.9 ± 5.7
Slaughter et al. (Triceps+Calf)	17.2 ± 7.5	0.84	–5.7 ± 4.2	23.2 ± 5.5	0.82	5.8 ± 4.1
Sarria et al. 2	13.3 ± 6.6	0.83	–9.6 ± 5.3	–	–	–
Yuan et al.	21.4 ± 7.6	0.35	–1.5 ± 7.9	24.7 ± 6.1	0.46	–4.2 ± 6.7

The newly developed equation was tested on a group of Australian children of Sri Lankan origin with some other equations published in the literature. Results in the assessment of FM and percent FM using newly developed equations were quite similar to the results obtained by the established (criterion) method. Assessment results obtained from other equations did not agree

[a]Percent fat mass is calculated secondarily from the estimated fat mass based on Sri Lankan equation

[b]Percent fat mass is estimated directly from the equation derived to estimate the percent fat mass based on Sri Lankan equation

*$p < 0.001$

77.8 Clinical Application of Skinfold Thickness Measurements

Skinfold thickness measurements can be used in the assessment of nutritional status and also to assess improvement in nutritional rehabilitation of children with undernutrition. Although not very accurate, skinfold thickness also can be used to estimate the volume of muscle in a region of body such as a limb. When it is assumed that the cross-section of the limb is circular, skinfold thickness are equal to the thickness of subcutaneous adipose tissue and maintains a uniform thickness around the limb, then muscle bulk with the bone can be estimated. However, when compared to CT and MRI scans, it is less accurate (Roche 1996). Skinfold thickness is also useful in follow-up of patients with obesity. In the management of obesity one has to primarily reduce fat stores in the body. Therefore, fat stores could be objectively assessed based on skinfold thickness using either centile charts or prediction equations and calculating the absolute fat mass or percent fat mass of the body.

Children with growth hormone deficiency are obese with excess subcutaneous fat in the body. In such situations, response to growth hormone therapy could be assessed by serial skinfold thickness measurements.

Summary Points

- Subcutaneous fat deposits act as an energy store and reflect the nutritional status of the body.
- Measurement of skinfold thickness is useful in the assessment of nutritional status as well as follow-up of medical conditions for response to treatment.

- Skinfold thickness measures a double layer of skin and subcutaneous tissue and it can be used to assess muscle mass in a limb as well.
- Standard callipers should be used to measure skinfold thickness and the correct technique should be employed.
- Standard sites are used to measure skinfold thickness to improve accuracy and reproducibility.
- Subcutaneous fat distribution is dependent on age, sex, maturity and ethnicity.
- Centile charts can be used to compare data and new WHO reference charts are available.
- Skinfold thickness based prediction equations can be used for the assessment of body composition, mainly body density, fat mass and percent fat mass.
- Prediction equations need to be validated prior to their use on a given population if the equations were originally developed in a population different from the study population.

Annexure

Prediction equation of Deurenberg et al. for assessment of %FM

Boys	Prepubertal	= –14.61 + 26.51 × log (bicep + triceps)
		= –22.23 + 26.56 × log (biceps + triceps + SS + SI)
	Pubertal	= –9.78 + 21.9 × log (bicep + triceps)
		= –11.91 + 18.7 × log (biceps + triceps + SS + SI)
	Post pubertal	= –6.81 + 17.77 × log (bicep + triceps)
		= –15.58 + 18.88 × log (biceps + triceps + SS + SI)
Girls	Prepubertal	= –16.84 + 29.3 × log (bicep + triceps)
		= –25.87 + 29.85 × log (biceps + triceps + SS + SI)
	Pubertal	= –14.79 + 26.21 × log (bicep + triceps)
		= –18.89 + 23.94 × log (biceps + triceps + SS + SI)
	Post pubertal	= –27.71 + 36.53 × log (bicep + triceps)
		= –43.49 + 39.02 × log (biceps + triceps + SS + SI)

Prediction equation of Sarria et al. for the assessment of body density in boys

Equation 1 = 1.1579 – [0.0685 × log (biceps + triceps + SS + SI)] (13)
Equation 2 = 1.0728 + (0.0007 × BMI) – (0.0028 × triceps SFT) (14)

Conversation of body density to %FM

$$\%\text{FM} = \frac{\left[562 - 4.2\left(\text{Age} - 2\right)\right]}{\text{body density}} - \left[525 - 4.7\left(\text{Age} - 2\right)\right]$$

Prediction equation of Slaughter et al. equation for prediction of %FM

From triceps and calf SFT

Boys = 0.735 × (triceps + calf) + 1.0
Girls = 0.610 × (triceps + calf) + 5.1

From Triceps and Subscapular

Prepubertal	White males = 1.21 × (triceps + SS) – 0.008 × (triceps + SS) – 1.7
	Black males = 1.21 × (triceps + SS) – 0.008 × (triceps + SS) – 3.2

Pubertal	White males = 1.21 × (triceps + SS) – 0.008 × (triceps + SS) – 3.4
	Black males = 1.21 × (triceps + SS) – 0.008 × (triceps + SS) – 5.2
Post pubertal	White males = 1.21 × (triceps + SS) – 0.008 × (triceps + SS) – 5.5
	Black males = 1.21 × (triceps + SS) – 0.008 × (triceps + SS) – 6.8
	All females = 1.33 × (triceps + SS) – 0.013 × (triceps + SS) – 2.5

For sum of triceps and subscapular >35 mm, the following equation was used

$$\text{All males} = 0.783 \times (\text{triceps} + \text{subscapular}) + 1.6$$
$$\text{All females} = 0.546 \times (\text{triceps} + \text{subscapular}) + 9.7$$

Prediction equation of Brook equation for prediction of body density

$$\text{Males} = (1.1533 - 0.0643) \times \log (\text{biceps} + \text{triceps} + \text{SS} + \text{SI})$$
$$\text{Females} = (1.1369 - 0.0598) \times \log (\text{biceps} + \text{triceps} + \text{SS} + \text{SI})$$

Conversation of body density to %FM

$$\%\text{FM} = \left\{\frac{4.95}{\text{body density}} - 4.5\right\} \times 100$$

Prediction equation of Yuan et al. for prediction of %FM

10–12 years	Males = 9.0870 + 0.6616 × (triceps + SS)
	Females = 11.2657 + 0.5311 × (triceps + SS)
13–15 years	Males = 4.8942 + 0.5311 × (triceps + SS)
	Females = 10.8048 + 0.3614 × (triceps + SS)

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Chapter 78
Use of Segmental Lengths for the Assessment of Growth in Children with Cerebral Palsy

Kristie L. Bell, Peter S.W. Davies, Roslyn N. Boyd, and Richard D. Stevenson

Abstract Measurement of height or recumbent length is essential for the assessment of linear growth in children. Children with cerebral palsy (CP) often grow poorly and assessment of growth in this population is further complicated by two main difficulties. Firstly, children may have joint contractures, muscular weakness, scoliosis, and/or involuntary movements that make standing or lying straight difficult, if not impossible. Hence, accurate and reliable measures of height or recumbent length are not always attainable in this population. Secondly, as a result of atypical growth patterns, generally accepted reference charts for typically developing children may not be appropriate for use in children with CP. Due to these difficulties segmental lengths such as knee height, tibial length or upper arm length are frequently used as alternatives. These measures are all reliable and valid alternative measures for height in children with CP. They have been recommended for inclusion in the routine growth assessment of this group when accurate or reliable direct measurements of height or recumbent length are difficult or not possible (Spender et al. 1989; White and Ekvall 1993; Chumlea 1994; Stevenson 1995; Gauld et al. 2004). Segmental lengths can be compared directly with growth charts developed from data collected from children with normal growth or children with CP (Spender et al. 1989; White and Ekvall 1993; Stevenson et al. 2006). Alternatively, they may be used to estimate height using published equations, thus enabling comparison with height-for-age reference charts developed from typically developing children or children with CP (CDC 2000; Stevenson et al. 2006; WHO 2006; Day et al. 2007).

Abbreviations

A	Age
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
CP	Cerebral Palsy

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CV	Coefficient of Variation
GMFCS	Gross Motor Function Classification System
NAGCPP	North American Growth in Cerebral Palsy Project
RMSE	Root Mean Square of the Error
SEE	Standard Error of the Estimate
TE	Technical Error
WHO	World Health Organisation

78.1 Introduction

Physical growth is a fundamental aspect of health and an indicator of physical wellbeing in children. Abnormal growth may occur for a number of reasons and may be indicative of illness or chronic inadequate nutrient intake (Stevenson et al. 2006). Physical growth and development in children have been assessed for many years using classic anthropometric measurements. These include measures of height or supine length, weight and other simple measures (WHO Expert Committee on Physical Status 1995). In typically developing individuals, assessment of linear growth is relatively straightforward where values for recumbent length or height can be compared to a growth reference or standard (CDC 2000; WHO 2006). Measures of length or height are also frequently used with measures of body weight to assess body proportions through use the body mass index (BMI) or weight-for-height growth charts (WHO Expert Committee on Physical Status 1995). Other applications include calculation of predicted energy requirements using published formulae (Schofield 1985); and prediction of reference ranges for the assessment of pulmonary function and glomerular filtration rate (Gauld et al. 2004).

Growth and nutritional status of children and adolescents with CP have been the subject of numerous investigations over the past 50 years (Tobis et al. 1961; Spender et al. 1989; Stevenson et al. 1994; Krick et al. 1996; Stevenson et al. 2006; Day et al. 2007). In general, children with CP are shorter and lighter than their typically developing peers (Krick et al. 1996; Stevenson et al. 2006; Day et al. 2007). The largest study, to date, of the growth parameters of children and adolescents with CP was based on retrospective data relating to height and weight obtained from the patient records of 24,920 children and adolescents with CP aged 2–20 years (Day et al. 2007). A combination of cross-sectional and longitudinal data was included, totalling 141,961 different observations. The 10th, 50th and 90th percentile curves for height, weight and BMI were determined by age, sex, and five levels of functional ability. This study was the first to develop growth curves for children with CP stratified by gross motor skills and feeding ability (Day et al. 2007).

Height and weight percentile curves for the highest functioning groups (i.e. group 1: walks well alone for at least 6 m and balances well) approximated those of the general population. Trends for lower weight and height for age were apparent for the lower functional groups and deviated further from those of the general population with increasing functional impairment. Interestingly, in the lowest functioning groups (groups 4 and 5), the presence of a feeding tube was associated with greater height and weight (Day et al. 2007). The most significant limitation of this study was that the methods utilised to measure height were of unknown validity and reliability in this population. The authors acknowledge this limitation and conclude that the height curves presented for children with significant motor impairment (i.e. groups 3, 4 and 5) should be viewed with some caution.

Table 78.1 Key facts about the use of segmental lengths in children with cerebral palsy

Measurement of height or recumbent length in children with cerebral palsy may be difficult and sometimes impossible.
Segmental lengths are frequently used as alternative measures to height or length in children with cerebral palsy for the assessment of growth.
Commonly used segmental lengths in children with cerebral palsy are knee height, upper arm length and tibial length.
The landmarks for segmental lengths may be difficult to identify. Training and practice is required to develop skill and competence in their measurement.
All measurements should be taken twice and on the left hand side of the body. The average of the two measurements should be used.
Upper arm length and knee height should be measured using specialised equipment. Knee height should be measured using a sliding calliper or anthropometer. Upper arm length should be measured with an anthropometer or Vernier callipers, depending on the size of the child.
Tibial length can be measured accurately using steel or plastic measuring tapes.

This table describes some key facts related to the use of segmental lengths in children with cerebral palsy including those measures commonly used, equipment required and basic concepts

78.2 Difficulties with Conventional Assessment of Height or Length in Children with CP

Direct measurement of recumbent length or height may be inaccurate, unreliable and frequently impossible in children and adolescents with physical disabilities, such as cerebral palsy (CP), due to joint contractures, muscular weakness, scoliosis, involuntary movements or poor cooperation. Difficulty obtaining conventional measures of height or recumbent length have been reported in 53% of children with CP participating in a study of growth parameters (Spender et al. 1989); furthermore, reliable measurements of either recumbent length or height were unable to be obtained in 52% of a clinical population of children with CP (Stevenson 1995). In this study, the population in which a reliable measure of length or height was possible was those of the younger children with less severe motor impairment than the larger clinic population; suggesting that difficulties with obtaining direct measures of height or recumbent length in children with CP increase with increasing age and severity of motor impairment (Stevenson 1995). In order to overcome these difficulties, various segmental lengths including upper arm length, ulna length, forearm length, knee height and lower leg (tibial) length have been identified as potential alternatives or proxy measures in different populations. Key facts regarding the use of segmental lengths in children with CP are included in Table 78.1. To be clinically useful as a proxy measure for recumbent length or height in the population of interest, the measure must be (1) measurable in the population (2) reproducible (3) highly correlated with recumbent length or height and (4) able to be compared to a growth reference.

78.3 Use of Segmental Lengths in Children with Cerebral Palsy

Knee height, lower leg length and upper arm length have all been shown to be both reproducible and clinically useful as proxy measures for height or recumbent length in children and adolescents with CP (Spender et al. 1989; Chumlea 1994; Stevenson 1995; Hogan 1999; Bell and Davies 2006). In typically developing children, correlations between height and knee height, upper arm length and tibial length are very high (r = 0.97, 0.98 and 0.98, respectively) (Spender et al. 1989; Chumlea

Table 78.2 Reliability of segmental lengths in children with cerebral palsy

	Intra-observer error $N = 307$		Inter-observer error $N = 18$	
	TE (cm)	CV (%)	TE (cm)	CV (%)
Upper arm length[a]	0.27	1.07	0.52	2.32
Tibial length[b]	0.28	1.04	0.33	1.31
Knee height[a]	0.22	0.61	0.29	0.89

This table shows reliability data for measurements of segmental lengths in children with CP. All data presented here were obtained as part of the North American Growth in Cerebral Palsy Project

[a]Published data (Stevenson et al. 2006)

[b]Previously unpublished data. TE indicates the technical error = $\sqrt{\Sigma d^2/2n}$, where d = difference between paired measures on n subjects, CV is the coefficient of variation = 100 × (TE/mean of measures taken)

1994; Gauld et al. 2004). In children with CP, correlations between height or recumbent length and knee height, upper arm length and tibial length are similarly high ($r = 0.98$, 0.97, and 0.97, respectively, $p < 0.05$) (Stevenson 1995). In addition, knee height has been found to correlate significantly with recumbent length in a group of wheel chair dependent children, adolescents and adults with CP ($r = 0.88$, $p < 0.05$) (Hogan 1999).

78.4 Reliability

Reliability of anthropometric data may be expressed in many ways. Two commonly utilised statistics are the technical error of the measurement (TE) and the coefficient of variation (CV). The TE is calculated as $\sqrt{(\Sigma d^2/2n)}$, in which d is the difference between the same measure on the same child done by the same observer (intraobserver observer) or different observers (interobserver error) (Cameron 1986). The TE will be greater for measures of larger magnitude. For example, the TE for measurements of height will be greater than the TE for measurements of knee height due to the magnitude of the measure itself. The CV is the TE of measurement divided by the overall mean of all subjects for the particular variable under study. It is a measure of relative variability, i.e., variation relative to the overall magnitude of the measure (Malina et al. 1973).

Acceptable levels of intra- and inter-observer repeatability have been reported for measures of knee height, upper arm length and tibial length, when conducted by trained observers, in children with CP, as shown in Table 78.2 (Stevenson et al. 2006). The data reported here were obtained as part of the North American Growth in Cerebral Palsy Project (NAGCPP). This was a multicentre study that investigated the growth, body fat stores and physical development of children with moderate to severe CP (Gross Motor Function Classification System (GMFCS) Levels III–V). Data were collected across six different sites throughout the United States and Canada. Values reported for TE and CV for segmental lengths were similar to those obtained for measurement of height in typically developing children from the National Health Examination Survey cycle II. This large scale study reported TE and CV for height measured by the same observer (TE = 0.68 cm, CV = 0.42) and different observers (TE = 0.49 cm, CV = 0.30) (Malina et al. 1973).

78.5 Interpretation of Segmental Lengths

78.5.1 Use of Growth Charts for Segmental Lengths

The interpretation of anthropometric data is facilitated by comparison to a growth reference and/or to earlier measurements from the same child. Reference charts for lower leg length, upper arm length, knee height, and ulna length have been developed for healthy typically developing children and can be used to assess the linear growth of children with CP and other physical disabilities (Spender et al. 1989; White and Ekvall 1993; Gauld et al. 2004). For example, growth charts for upper arm length and tibial length were developed by Spender and colleagues using data obtained from 1,298 typically developing children (Snyder et al. 1977; Spender et al. 1989). These growth charts have not been commercialised and are not readily available in most clinical settings.

Growth charts for knee height have been developed from data collected specifically from children with CP as part of the NAGCPP (Stevenson et al. 2006). These charts, and additional charts for tibial length and upper arm length for boys and girls, are the first charts to allow clinicians to make comparisons with segmental length measurements obtained from a group of children with CP (Appendix 1–6). They were developed from data collected from 156 boys and 114 girls aged 2–18 years. All children were diagnosed with CP and classified as having moderate to severe motor impairment (GMFCS levels III–V only). The reference curves were estimated using the LMS method (Cole and Green 1992) Some key facts regarding the NAGCPP are included in Table 78.3.

78.5.2 Equations to Predict Height from Segmental Lengths

An alternative to direct comparisons with growth charts for segmental lengths is to predict height from the segmental length measure using published equations. Formulae have been developed from data collected from healthy, typically developing individuals to predict height from segmental lengths in different ethnic groups (Chumlea 1994; Cheng et al. 1998; Gauld et al. 2004) and from data collected specifically from children with CP (Stevenson 1995). These allow comparisons of predicted height with standard height-for-age growth references or standards for typically developing children (CDC 2000; WHO 2006) and children with CP (Day et al. 2007).

Equations to predict height from ulna, forearm, tibial and lower leg lengths have been developed from a large dataset of 2,343 healthy, typically developing Australian school children and adolescents aged 5–19 years as shown in Table 78.4 (Gauld et al. 2004). In addition, prediction equations for height from radius, humerus, tibia and ulna lengths have been developed from measurements conducted in a group of 3,647 healthy, typically developing Chinese elementary, middle and high school children and adolescents aged 3–18 years (Table 78.5) (Cheng et al. 1998). However, the largest data set to date from which equations to predict height have been developed was collected from 1960 to 1970 in cycles I, II and III of the United States National Health Examination Survey (Table 78.6) (Chumlea 1994). These surveys included nationally representative samples of free living United States civilian adults (cycle I, $n = 5{,}414$), children aged 6–11 years (cycle II, $n = 7{,}087$) and adolescents aged 12–18 years (cycle III, $n = 6{,}734$). Equations were developed by age, sex and ethnicity (Caucasian and African-American). Population specific equations have been developed to predict height from knee height, upper arm length and tibial length from data obtained from a group of 172 children with CP aged 2–12 years, 48% of which were non-ambulatory (Stevenson 1995) and are included in Table 78.7. Available reference data for measurements of segmental lengths are summarised in Table 78.8.

Table 78.3 Key Facts of the North American Growth in Cerebral Palsy Project

Study Design	The North American Growth in Cerebral Palsy Project (NAGCPP) was a multicentre, region based study established in 1996.
Location	Six regional geographic locations throughout the United States and Canada
Aims	The long term goal of NAGCPP was to optimise the growth, nutrition, functional outcome and overall quality of life in children with CP by: 1. Defining expected growth patterns 2. Determining the nutritional, endocrinological, neurological and physical factors that influence growth, and 3. Determining how growth affects function, general health status, cognitive and motor development, family stress, health care use, morbidity and mortality.
Eligibility	All children with CP between the ages of 2 and 18 years residing in the designated geographical regions and classified as Gross Motor Function Classification Levels III, IV or V were eligible to participate.
Participants	235 children participated. Average age was 9.7 ± 4.6 years. 59% were male GMFCS Levels were: III – 56; IV – 55; V – 122
Measures	• Anthropometry: weight, head circumference, length, upper arm length, tibial length, knee height, calf circumference, mid-arm circumference, triceps skinfold thickness, calf skinfold thickness, subscapular skinfold thickness • Child Health Questionnaire • Medical history • Feeding abilities • Cognitive functioning • Health care use • General health

This table describes some of the key features of the North American Growth in Cerebral Palsy Project (NAGCPP) (Liptak et al. 2001)

Table 78.4 Equations to estimate height from segmental lengths in typically developing children and adolescents

Segmental measure	Estimation equation (cm)	RMSE
Males		
Ulna length	Height = (4.605 × UL) + (1.308 × A) + 28.003	3.896
Forearm length	Height = (2.904 × FL) + (1.193 × A) + 20.432	3.556
Tibial length	Height = (2.758 × TL) + (1.717 × A) + 21.818	3.791
Lower leg length	Height = (2.423 × LL) + (1.327 × A) +21.818	3.062
Females		
Ulna length	Height = (4.459 ×UL) + (1.315 × A) + 31.485	3.785
Forearm length	Height = (2.908 × FL) + (1.147 × A) + 21.167	3.344
Tibial length	Height = (2.771 × TL) + (1.457 × A) + 37.748	3.383
Lower leg length	Height = (2.473 × LL) + (1.187 × A) + 21.151	2.717

Equations to estimate height from measurements of segmental lengths obtained from 2,343 healthy, typically developing Australian school children and adolescents aged 5–19 years (Gauld et al. 2004)
UL ulna length, *A* age, *FL* forearm length, *TL* tibial length, *LL* lower leg length, *RMSE* root mean square of the error

Table 78.5 Equations to estimate height from segmental lengths in typically developing Chinese children and adolescents

Segmental measure	Estimation equation (cm)
Radius length	Height = 40.45 + (4.45 × A) – (0.28 × Sex) + (4.15 × RL)
Humerus length	Height = 31.15 + (1.48 × A) + (0.30 × Sex) + (3.52 × HL)
Tibia length	Height = 41.05 + (1.64 × A) + (0.84 × Sex) + (2.55 × TL)
Ulna length	Height = 30.35 + (1.29 × A) + (0.77 × Sex) + (4.32 × UL)

Equations to estimate height from measurements of segmental lengths obtained from a group of 3,647 health, typically developing Chinese elementary, middle and high school students aged three – 18 years (Cheng et al. 1998). Sex = 0 for girls and 1 for boys
RL radius length, *HL* humerus length, *TL* tibia length, *UL* ulna length, *A* age

Table 78.6 Equations to estimate height from knee height in typically developing children and adolescents (6–18 years)

Group	Estimation equation (cm)	RMSE	SEE (cm)
Caucasian boys	Height = 40.54 + (2.22 × KH)	4.16	4.21
African-American boys	Height = 39.60 + (2.18 × KH)	4.44	4.58
Caucasian girls	Height = 43.21 + (2.15 × KH)	3.84	3.90
African-American girls	Height = 46.59 + (2.02 × KH)	4.25	4.29

Equations to estimate height from measurement of knee height developed from data collected from 13,821 children and adolescents in the United States (Chumlea 1994)
RMSE root mean squared of the error, *SEE* standard error of the estimate, *KH* knee height

Table 78.7 Equations to predict height from segmental lengths in children with cerebral palsy (under 12 years of age)

Segmental measure	Prediction equation (cm)	SEE (cm)
Upper-arm length	Height = (4.35 × UAL) + 21.8	±1.7
Tibial length	Height = (3.26 × TL) + 30.8	±1.4
Knee height	Height = (2.69 × KH) + 24.2	±1.1

Equations to predicted height from segmental lengths obtained from 172 children with cerebral palsy aged 2–12 years (Stevenson 1995)
UAL Upper-arm length, *TL* tibial length, *KH* knee height, *SEE* standard error of the estimate

Table 78.8 Key features of reference data for measurements of segmental lengths

Author	Population	Growth charts developed for	Prediction equations developed for
Cheng et al. (1998)	*N* = 3,647 Healthy, typically developing Chinese children and adolescents Aged 3–18 years		Radius length Humerus length Tibia length Ulna length
Chumlea (1994)	*N* = 13,821 Typically developing children and adolescents aged 6–18 years from cycles II and III of the United States National Health Examination Survey		Knee height

(continued)

Table 78.8 (continued)

Author	Population	Growth charts developed for	Prediction equations developed for
Gauld et al. (2004)	*N* = 2,343 Healthy, typically developing Australian children and adolescents 5–19 years of age	Ulna length	Radius length Humerus length Tibia length Ulna lengths Knee height
Spender et al. (1989)	*N* = 1,298 Typically developing United States children and adolescents (Snyder et al. 1977)	Upper arm length Tibial length	
Stevenson et al. (2006)	*N* = 273 North American children with Cerebral Palsy (GMFCS III–V) Aged 2–19 years	Knee height Tibial length Upper arm length	
Stevenson (1995)	*N* = 172 North American children with Cerebral Palsy (GMFCS III–V) Aged 2–12 years 48% non-ambulatory		Knee height Tibial length Upper arm length
White and Ekvall (1993)	*N* = 1,298 Typically developing United States children (Snyder et al. 1977)	Knee height	

This table shows key information relating to currently available reference data for segmental lengths in various populations. Included in the table are: descriptions of the populations in which measurements have been conducted (sample size, nationality, diagnosis of cerebral palsy), as well as identification of datasets used to develop growth charts for segmental lengths and equations to estimate height from segmental lengths

GMFCS Gross Motor Function Classification System

78.5.3 Evaluation of Prediction Equations

The accuracy of equations to predict height from segmental lengths in individuals with CP has been evaluated (Spender et al. 1989; Hogan 1999; Bell and Davies 2006). The ability of the Chumlea equations (Chumlea 1994) and the Stevenson equation (Stevenson 1995) to predict height from knee height was investigated in a group of 17 ambulatory children with CP (Gross Motor Function Classification System I and II) and 20 typically developing children (Bell and Davies 2006). At the population level, the Stevenson (1995) equation performed best with height predicted to within, on an average, 0.4% of measured height. Again, at the population level, the Chumlea equation also performed well with height predicted to within 1%; however, the bias in predicted height using the Chumlea equation increased with increasing height. Importantly, whilst the mean bias produced by the equations may have been acceptable, the limits of agreement for both equations remained relatively large. As a result, at the individual level height predicted by the Stevenson equation can vary by as much as 12.7 cm (10%) below to 11.8 cm (9%) above actual measured height for children with CP and 10.9 cm (9%) below to 12.3 cm (10%) above that for typically developing children. Thus the equations may be accurate at the group level; however, they may lead to unacceptable error for any one individual and caution should be exercised when using these equations in that way. Johnson and Ferrara (Johnson and Ferrara 1991) also found equations derived from healthy typically developing individuals to predict height from knee height were not sufficiently accurate for use in a group of adolescents with CP (Table 78.7 and 78.8).

These studies highlight the long known and well accepted concern relating to the application of equations to populations from which they were not derived. Equations to predict height or recumbent length from segmental lengths assume a strong relationship between the segmental length and height or recumbent length. Due to the heterogeneous nature of CP and known alterations in growth patterns, it is unlikely that this relationship is constant between children with different types and severities of motor impairment, let alone in children with CP and typically developing children (Krick et al. 1996; Stevenson et al. 2006; Day et al. 2007). Obviously, the Stevenson (1995) equations were derived from a group of children with CP where measurement of recumbent length or height was possible. The appropriateness of applying these equations to ambulatory children with CP has been confirmed (Bell and Davies 2006). Caution should be exercised when using these equations in children with more severe motor impairments where measures of height or recumbent length are not possible, such as those with severe scoliosis and contractures, the precise group for whom an alternative assessment of linear growth is necessary. The validity of prediction equations for use in these populations may never be determined since direct measurement of height or length is not possible. For these children it would be more appropriate to use growth charts for knee height, upper arm length or tibial length to assess linear growth, thereby avoiding any of the potential error associated with prediction equations.

78.5.4 Choice of Segmental Length in Individuals with CP

When an accurate measure of height or recumbent length is difficult, or impossible, the choice of alternative measure is likely to be determined by the resources available and the abilities of the child. To be accurate and reliable, both upper arm length and knee height require specialised measuring equipment (anthropometer or knee height calliper), whereas, tibial length can be measured using a flexible measuring tape (Spender et al. 1989; Rogerson et al. 2000). Of the three alternatives, the landmarks for knee height are the easiest to identify and indeed knee height has been found to be the most reproducible (Stevenson 1995). Since measurement of tibial length does not require specialised equipment, is not impacted on by knee and ankle contractures and the landmarks are relatively easy to palpate in lean individuals, it may be the most suitable alternative measure for height in children with CP. It is important to note however, that training of observers is required to ensure reliable and accurate results.

78.6 Practical Methods and Techniques

Detailed methods for the measurement of knee height, upper arm length and tibial length are described below (refer to Table 78.9). By convention, all anthropometric measures for the assessment of growth in children should be conducted on the left hand side of the body and in duplicate with the mean of the two measurements used for interpretation and analysis (WHO Expert Committee on Physical Status 1995). Where duplicates are not within an acceptable level of accuracy a third measurement may be taken and the mean of the two closest measurements used. In children with CP with marked asymmetry, investigators have conducted measurements on the less impaired side (Stevenson 1995; Bell and Davies 2006).

Table 78.9 Measurement of segmental lengths

Segmental measure	Equipment required	Distance of measurement
Upper arm length	Anthropometer or Vernier calliper in smaller children (Spender 1989)	From the acromium process to the head of the radius (Cameron 1986)
Tibial length	Flexible tape measure or Anthropometer (Stevenson 1995)	From the superomedial edge of the tibia to the inferior edge of the medial malleolus (Stevenson 1995)
Knee height	Anthropometer or Knee height calliper (Rogerson 2000)	From the heel to the anterior surface of the thigh over the femoral condyles (Cameron 1986)

This table describes the equipment required for measurement of different segmental lengths as well as the distance to be measured

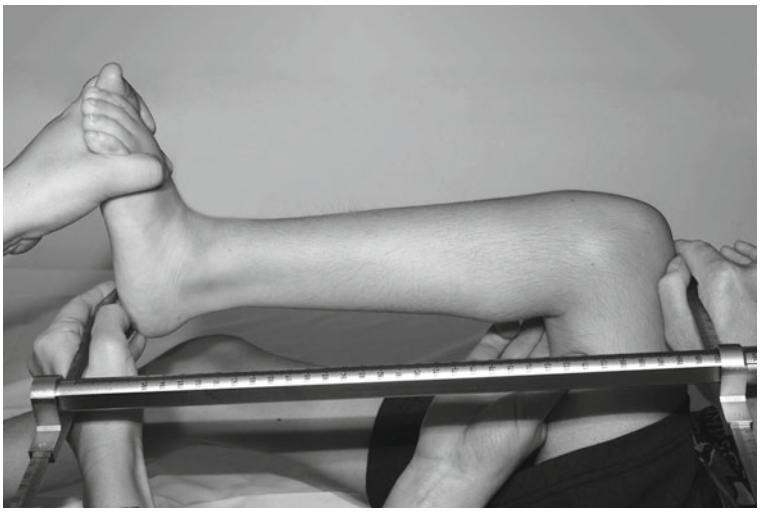


Fig. 78.1 Measurement of knee height in a child with CP in the supine position. Measurement of knee height in the recumbent position requires two observers. Care must be taken to ensure that the child's knee and ankle should both be held at 90° angles

78.6.1 Knee Height

Knee height is the distance from the heel to the anterior surface of the thigh over the femoral condyles. Both the knee and ankle must be flexed at 90° angles with the subtabular joint in neutral. This can be achieved in one of two ways:

(a) The child may be seated upright with feet flat on the floor and both the knee and ankle joints flexed at 90° angles. In this instance, the measurement is taken as the distance from the floor, or foot rest, to the anterior surface of the thigh just proximal to the patella. The shaft of the caliper should be held parallel to the tibia and gentle pressure applied to the blades of the caliper to blanch the skin and compress the tissue (Chumlea 1994).

(b) Recumbent knee height is measured with both the knee and ankle held at 90° angles while the child is in a supine position (see Fig. 78.1). One of the blades of the calliper or anthropometer should be positioned under the heel of the left foot and the other placed over the anterior surface of the thigh above the femoral condyles, just proximal to the patella. Once again, the shaft of the calliper is held parallel to the shaft of the tibia and gentle pressure is applied to the blades of the calliper to compress the tissue (Stevenson 1995).

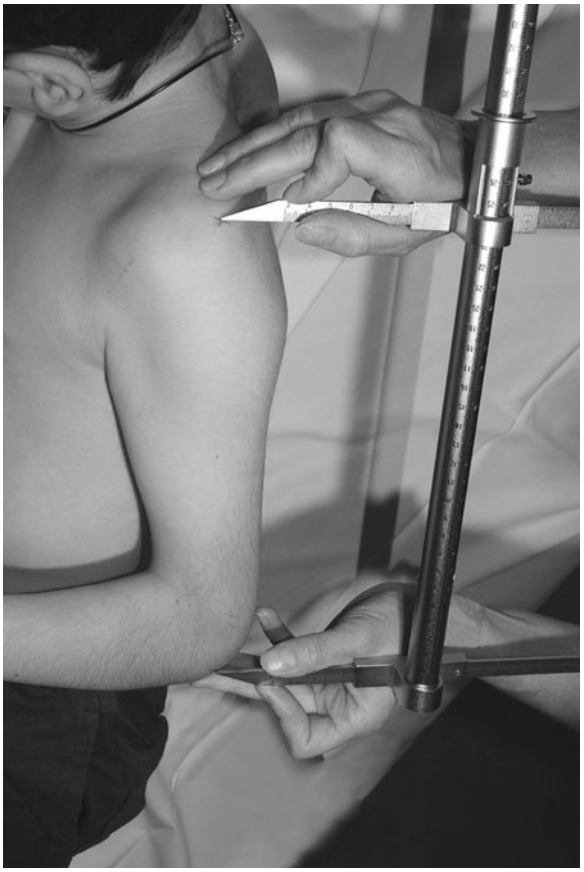


Fig. 78.2 Measurement of upper arm length in a child with CP. For children who are unable to sit independently, adequate positioning for measurement of upper arm length may be best achieved with the child lying on their right side

Accurate and reliable measurements of knee height may be difficult to achieve in children with contracture of the soleus resulting in equinovarus deformity or in children with a proximally displaced patella. Knee height should be measured using a sliding calliper or anthropometer, as accuracy is impaired when using a flexible measuring tape. Values for knee height collected using a flexible tape measure have been found to be on average 1.3 cm greater than those conducted using specialised equipment in a group of 56 non-ambulatory adults with developmental disabilities ($p < 0.001$) (Rogerson et al. 2000).

78.6.2 Upper Arm Length or Humerus Length

Upper arm length is the distance from the acromion process to the head of the radius (Cameron 1986) (see Fig. 78.2). The measurement should be made when the child is upright (either seated or standing) with their back to the observer, arms relaxed and vertical and the elbow flexed to 90°. This position can be difficult to achieve in children with physical disabilities who are unable to sit independently. The landmarks can be challenging to identify, and the measure requires significant practice to develop competence. Upper arm length should be measured with an anthropometer or may be measured with Vernier callipers in smaller children. Steel and plastic measuring tapes should

Fig. 78.3 Landmarks for the measurement of tibial length in a CP in the supine position. Landmarks for measurements of segmental lengths should be identified and marked prior to the measurement being taken

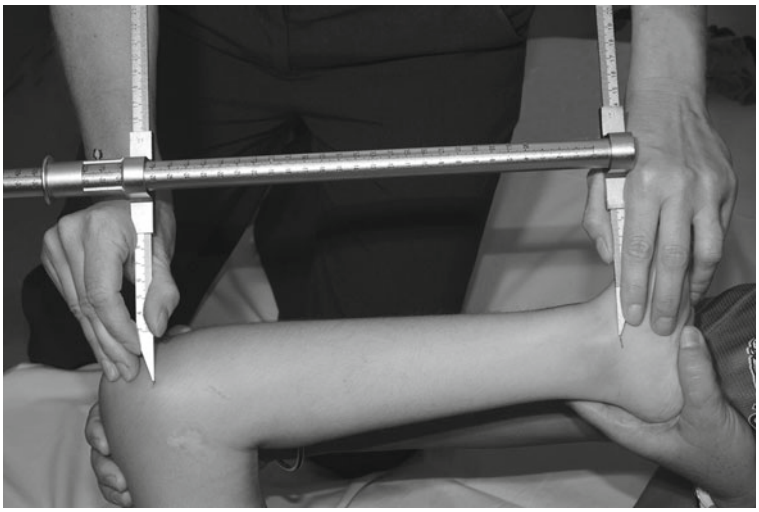


Fig. 78.4 Measurement of tibial length in a child with CP in the supine position. Adequate positioning for measurement of tibial length may be achieved with the child in a supine position with their left leg held so that the medial aspect of the tibia faces upwards

be avoided when measuring upper arm length as accuracy is impaired with their use (Spender et al. 1989). In children with CP, measurements of upper arm length obtained using steel and plastic measuring tapes have been found to be on average 1.03 cm (±0.2 cm) and 1.1 cm (±0.25 cm) greater than those obtained using an anthropometer (Spender et al. 1989).

78.6.3 Tibial Length

Tibial length is the distance from the superomedial edge of the tibia to the inferior edge of the medial malleolus (Stevenson 1995). The measurement should be conducted with the child in a seated position facing the observer with the left ankle or calf resting on the right knee so that the medial aspect of the tibia faces upwards (see Figs. 78.3 and 78.4) (Cameron 1986).

78.7 Applications to Other Areas of Health and Disease

Segmental lengths have proven to be clinically useful in other populations of children with physical disabilities such as Duchenne muscular dystrophy and myelomeningocele. The use of segmental lengths (ulna length, forearm length, tibial length, lower leg length) was investigated in a group of 20 children with Duchenne muscular dystrophy between 7 and 19 years of age, 17 of whom were wheelchair dependant (Gauld et al. 2004). Adequate positioning was not attainable for forearm and lower leg length measures in children with wrist or ankle deformities. Measurement of tibial length was difficult in children with equinovarus deformities of the ankle. Ulna length measurements were possible in all children and were not affected by wrist contracture; however, reliability was not reported. The usefulness of forearm length, ulna length, and arm span in children with idiopathic scoliosis and children with Duchenne muscular dystrophy was evaluated by Miller and colleagues (Miller and Koreska 1992). They concluded that for children who were unable to stand and who had proximal upper extremity contractures, height should be calculated from measurement of forearm segment. If there are finger or wrist contractures, height can be calculated from measurement of ulna length.

Arm span measurements are frequently used for the assessment of linear growth in children with myelomeningocele; however it is difficult to obtain accurate and reliable measurements in children with high level spinal lesions (Belt-Niedbala et al. 1986). For this reason other upper limb measurements have been proposed as alternatives including upper arm length, forearm length and total arm length, for use in this population (Belt-Niedbala et al. 1986). These measures have been shown to correlate significantly with recumbent length in a group of 44 children with myelomeningocele between three and 12 years of age ($r = 0.96$, 0.95 and 0.85, respectively), suggesting that these may be suitable proxy measures for linear growth in this population. Equations to predict height from segmental lengths are yet to be evaluated in children with myelomeningocele.

78.8 Clinical Usefulness of Measures of Body Height or Body Segments

Assessment of physical growth is an important aspect of routine health care maintenance for all children and is used by physicians primarily (1) as a screen for general endocrine and medical integrity and health and (2) as a marker of nutritional status (Stevenson 1996). For the assessment of physical growth *per se*, direct comparison of the segmental measure with its corresponding growth reference is recommended (Spender et al. 1989; White and Ekvall 1993; Gauld et al. 2004; Stevenson et al. 2006). This will avoid any potential error associated with the use of prediction equations. There is growing evidence that children with CP have different growth patterns as compared to typically developing children and that growth patterns in this population are influenced by both nutritional factors as well as factors related to the severity of CP (frequently referred to as non-nutritional factors) (Stevenson et al. 1994; Day et al. 2007). Due to the influence of non-nutritional factors on growth in this group, even well-nourished children with CP should not be expected to exhibit the same growth patterns as the general paediatric population. One major issue facing clinicians who treat children with CP is determining whether a child who is growing poorly according to a growth reference, is actually growing as expected for a child with CP, or whether a potentially treatable medical problem, such as malnutrition, is present that is limiting growth.

Most readily available growth references or growth standards have been derived from the general paediatric population and application to children with growth disorders may be problematic. In rec-

ognition of the requirement for diagnosis specific reference data, specialised growth charts have been developed for children with CP, as previously discussed (Krick et al. 1996; Stevenson et al. 2006; Day et al. 2007). These charts are not necessarily reflective of the "optimal growth" of well-nourished children as they were derived from populations with potentially high degrees of undernutrition. As a result they should be viewed with some caution. They do allow comparisons of the growth of individuals with CP with other large groups of children with CP; however they should by no means be used to determine "ideal" growth in this population.

78.9 Use of Segmental Lengths in the Assessment of Nutritional Status in Children with CP

For the evaluation of nutritional status in the clinical setting, measures of length or height are frequently used in combination with measures of body weight. Indices have been developed to provide simple estimates of body size, in both children and adults, and also to infer levels of body fatness (Benn 1971). Those most commonly utilised indices are weight-for-height (i.e. weight/height^1) and the BMI (weight/height^2). The BMI is the index which removes the most influence of height on weight and is highly correlated with skinfold thicknesses and total body fatness in typically developing children (Mei et al. 2002). As a result, BMI cut points to identify overweight, obesity and underweight in children and adolescents have been determined and are commonly utilised in clinical settings (WHO Expert Committee on Physical Status 1995; Cole et al. 2000, 2007). Use of these cut points in children with CP is problematic for a number of reasons. Firstly, the prediction of height from segmental lengths in children where this is necessary, introduces potential error associated with the prediction equation. Secondly, the BMI may not be a sensitive measure of body fatness in children and adolescents who are particularly short for their age or who have an unusual body composition. For example, a wheel chair dependent child with CP may have a low BMI but may in fact have a high level of body fatness in comparison to a typically developing child. In this instance, limitations in physical activity participation would result in a reduction in lean body mass and a subsequent increase in the proportion of body fat. Use of the BMI and other weight for height indices as indicators of adiposity in children with CP is an area that requires further investigation (Table 78.9).

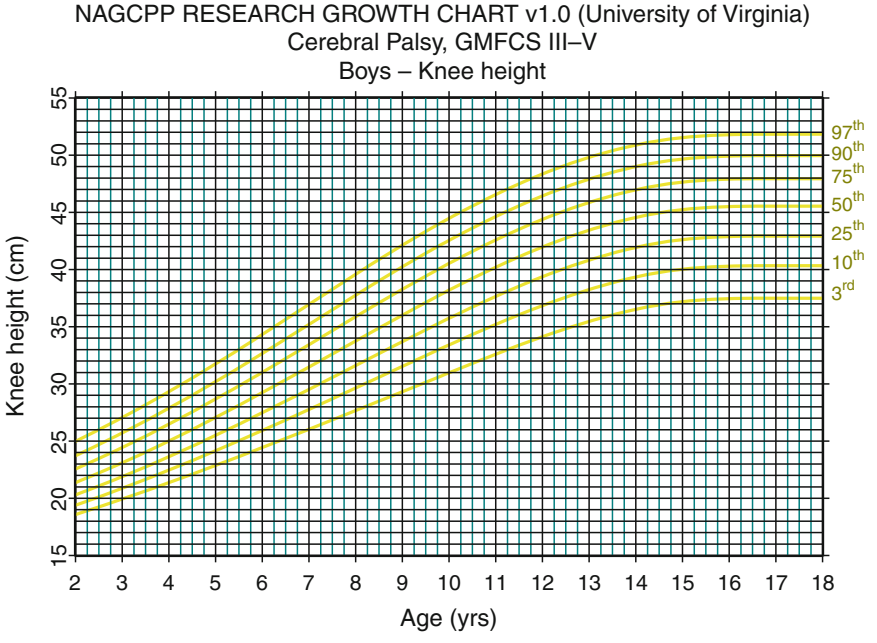
The inclusion of a more direct measure of body fat when assessing the nutritional status of children with CP will allow for more accurate identification of poorly nourished children. Measures such as skinfold thicknesses are frequently utilised in this group; however, they do require specialised equipment and adequate training to be performed accurately and reliably. Further research is required to determine the most appropriate methods for the assessment of nutritional status in children with CP, in the clinical setting, and to establish links between nutritional status and health related outcomes in this group; with a view to establishing standards that reflect "ideal" patterns of growth for this population.

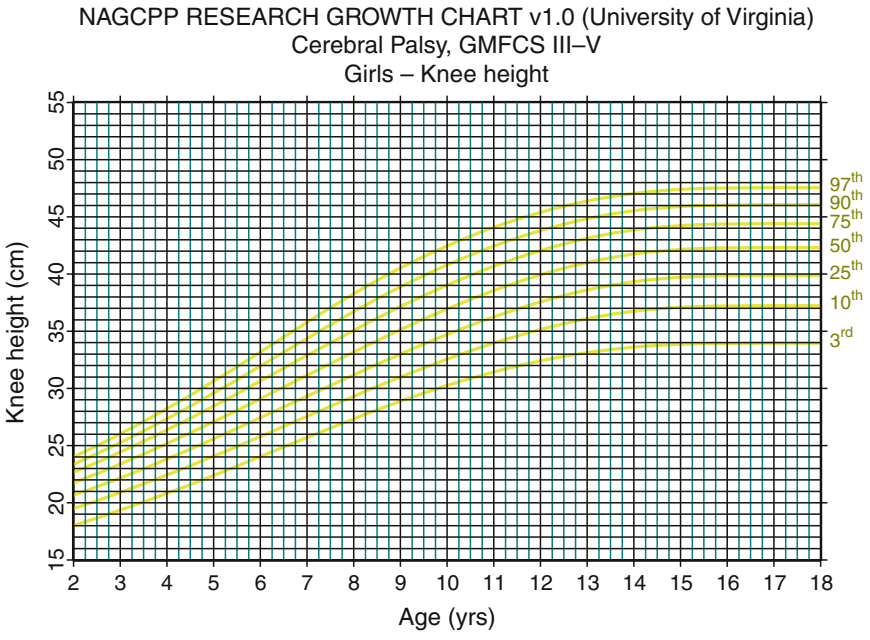
Summary Points

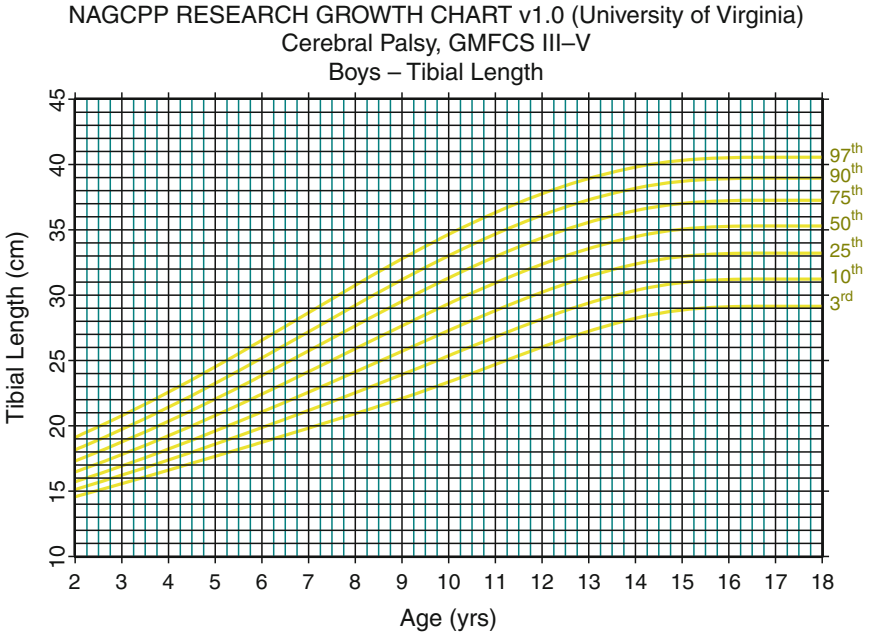
- Measurement of height or recumbent length in children with CP may be difficult and sometimes impossible due to joint contractures, muscular weakness, scoliosis, involuntary movements and poor cooperation.

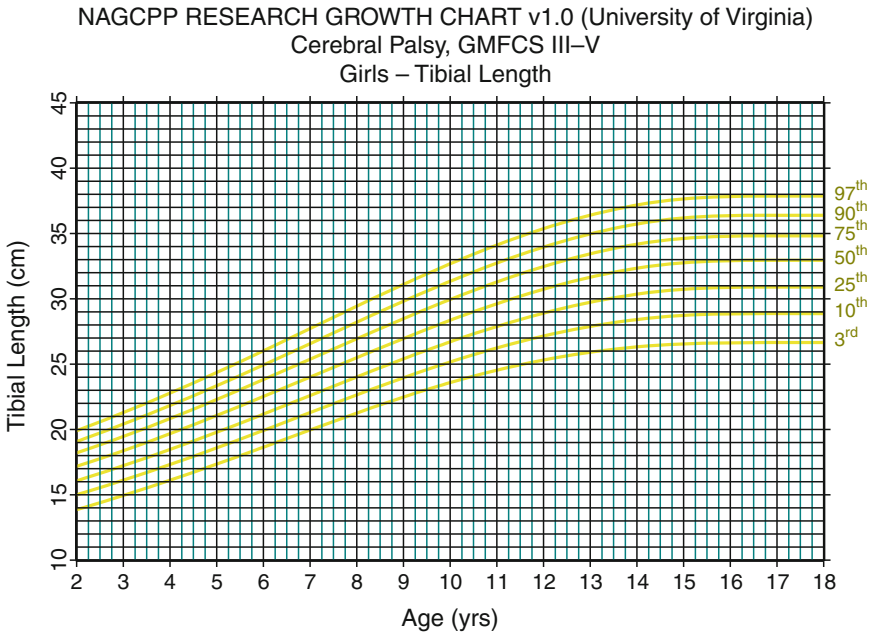
- Correlations between height or recumbent length and knee height, upper arm length and tibial length are high in both typically developing children and children with CP.
- Knee height, lower leg length and upper arm length have been shown to be both reproducible and clinically useful as alternative measures for height or recumbent length in children with CP.
- Reference charts for lower leg length, upper arm length, knee height, and ulna length have been developed from data obtained from typically developing children.
- Reference charts for knee height, tibial length, and upper arm length have been developed from data obtained from children with CP.
- Height can be predicted from knee height, upper arm length or tibial length in children with cerebral palsy to facilitate comparison with standard height-for-age growth charts.
- Population specific equations to predict height from knee height perform better in children with cerebral palsy than equations developed from typically developing children.
- Whilst knee height is the most reproducible proxy measure and the landmarks are easily identified, it may be difficult or impossible to obtain an accurate measurement in some children with severe contractures of the lower limb, as the distance to be measured crosses two joints.
- Upper arm length and knee height should always be measured using either an anthropometer or a knee height calliper. Tibial length can be measured using a flexible measuring tape.

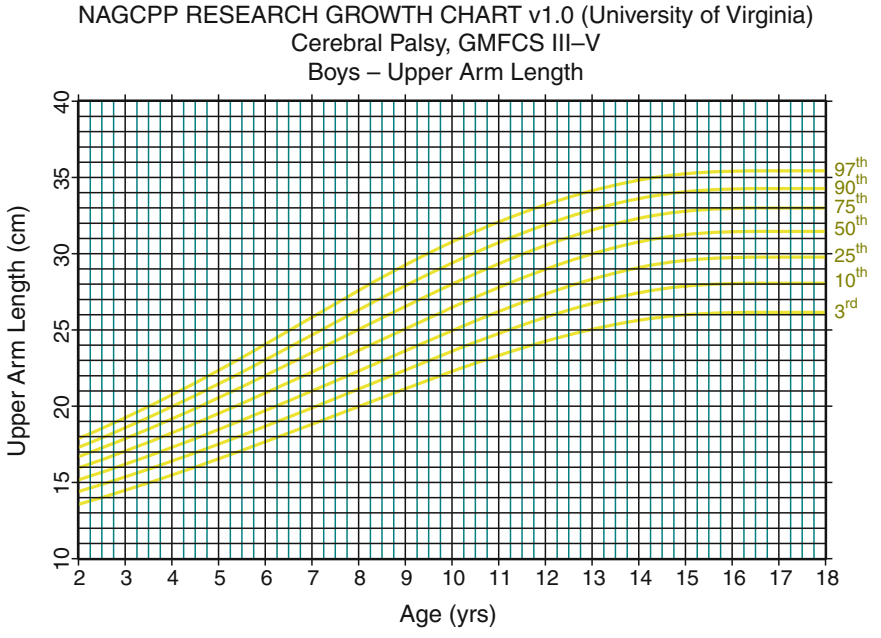
Appendix

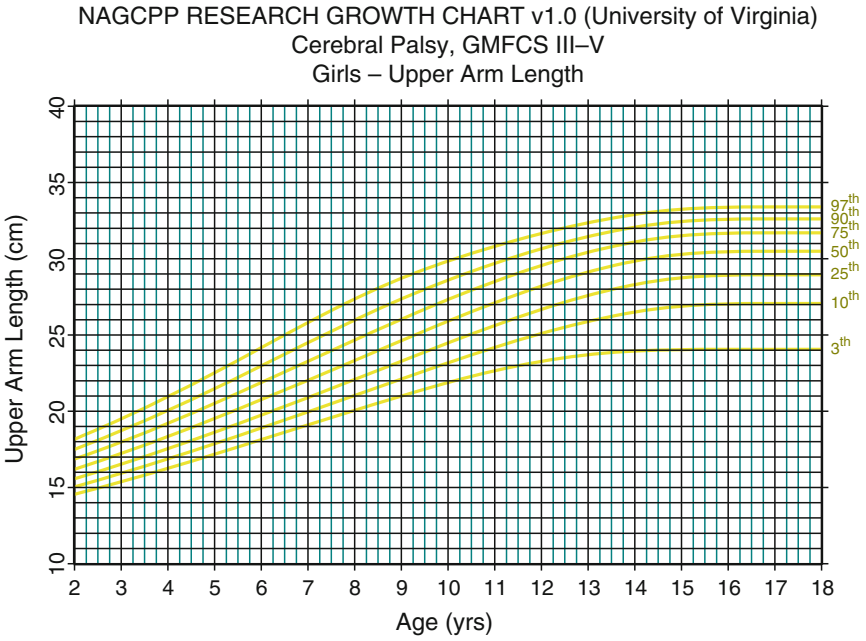



NAGCPP RESEARCH GROWTH CHART v1.0 (University of Virginia)
Cerebral Palsy, GMFCS III–V
Girls – Knee height
Knee height (cm)
15 20 25 30 35 40 45 50 55
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Age (yrs)
97th
90th
75th
50th
25th
10th
3rd


NAGCPP RESEARCH GROWTH CHART v1.0 (University of Virginia)
Cerebral Palsy, GMFCS III–V
Boys – Tibial Length
Tibial Length (cm)
10 15 20 25 30 35 40 45
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Age (yrs)
97th
90th
75th
50th
25th
10th
3rd


NAGCPP RESEARCH GROWTH CHART v1.0 (University of Virginia)
Cerebral Palsy, GMFCS III–V
Girls – Tibial Length
Tibial Length (cm)
10
15
20
25
30
35
40
45
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
Age (yrs)
97th
90th
75th
50th
25th
10th
3rd


NAGCPP RESEARCH GROWTH CHART v1.0 (University of Virginia)
Cerebral Palsy, GMFCS III–V
Boys – Upper Arm Length
Upper Arm Length (cm)
10
15
20
25
30
35
40
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
Age (yrs)
97th
90th
75th
50th
25th
10th
3rd



Acknowledgements We thank the School of Medicine, University of Queensland and the Royal Children's Hospital Foundation, Brisbane, Australia for financial support; the National Health and Medical Research Council (NHMRC) for the Project Grant "Growth, Nutrition and Physical Activity of Young Children with Cerebral Palsy" (NHMRC 569605) and Career Development Award for A/Professor Boyd (NHMRC 473860). The North American Growth in Cerebral Palsy Project (NAGCPP; Prof. Stevenson) was supported by the Kluge Research Fund and the Children's Hospital Committee of the University of Virginia (UVA), the Genetech Foundation for Growth and Development, the National Center for Medical Rehabilitation Research (Grants # 5 R01 HD35739–04, 1 F32 HD08615–01A1, 1 R24 HD39631–01, K24-HD041504–01) and the UVA General Clinical Research Center (GCRC, #M01RR00847). In addition, NAGCPP was supported by: the University of North Carolina GCRC (#M01RR00046) and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (#K24AR02132); the GCRC (M01RR00240) and the Nutrition Center at the Children's Hospital of Philadelphia; the Jones-Guerrero Fund at Duke University, the Children's Hospital Fund at the University of British Columbia, and the GCRC at the University of Rochester (#M01 RR00044). The authors acknowledge Mark Conaway, PhD, who created the growth chart figures.

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Part XIII
Anthropometry of Puberty and Adolescence in Health and Disease

Chapter 79
Anthropometric Indices and Cardiovascular Disease Risk in Children and Adolescents: CASPIAN Study

Roya Kelishadi

Abstract For the first time in the Eastern Mediterranean region, we assessed the anthropometric indices most closely correlated to cardiovascular disease risk factors in a large nationally representative sample of children and adolescents to be used as a simple tool for identifying those at risk. We also developed the first age- and gender-specific reference curves for waist and hip circumferences in an Asian population of children and adolescents. This cross- sectional population survey was conducted in 2003–2004 on a nationally representative sample of 21,111 school-students living in urban (84.6%) and rural (15.4%) areas of 23 provinces in Iran. Biochemical variables were determined in a subsample of 4,811 participants. The correlation of anthropometric indexes and cardiovascular disease risk factors were determined by using Receiver Operator Characteristic (ROC) curves and partial correlation. Furthermore, smoothed reference curves for waist and hip circumference and waist-to-hip ratio were developed by the LMS method. In both genders, waist and hip percentile values increased with age. For girls, the 50th–95th percentile curves for waist circumference had a sharp increase between 8 and 13 years and 11–15 years, respectively, and began to plateau after this age, whereas for boys, these curves had a persistent and less sharp increase with age until the age of 18 years. The most prevalent cardiovascular disease risk factors were low levels of high-density lipoprotein-cholesterol (28%), followed by hypertriglyceridemia (20.1%), and overweight (17%). Among anthropometric indexes, body mass index (BMI) and waist circumference (WC) had the highest correlation ($r = 0.77$, $p < 0.0001$ in boys, and $r = 0.82$, $p < 0.0001$ in girls).The ROC analyses showed that among boys, all anthropometric indices had the same association with cardiovascular disease risk factors in 6–9.9-year-age group, while in the 10–13.9 and 14–18-year-age groups, respectively WC and BMI had the strongest association. Among girls, these indices were BMI and waist to stature ratio (WSR), WC and WSR, and WC, respectively. The obtained curves can provide baseline data for analysis of time trends, as well as for international comparisons. In the CASPIAN study, BMI, WC and WSR were more closely correlated with cardiovascular disease risk factors. Considering the close correlation between different anthropometric indices studied, and differences in the best predictive index according to age and gender, it may be clinically useful in the pediatric population to routinely measure WC and WSR in addition to BMI as a screening tool to identify high risk youths.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_79,

Abbreviations

BMI	Body mass index
BP	Blood pressure
CASPIAN Study	***C***hildhood & ***A***dolescence ***S***urveillance and ***P***revent***I***on of ***A***dult ***N***on-communicable disease
HDL-C	High density lipoprotein-cholesterol
HiC	Hip circumference
LDL-C	Low density lipoprotein-cholesterol
ROC	Receiver operating characteristic
WC	Waist circumference
WHR	Waist-to-hip ratio
WSR	Waist-to-stature ratio

79.1 Introduction

Childhood obesity is reaching a global epidemic, but the dispute about the most valid anthropometric index related to its health hazards remains to be resolved. An improved understanding of body composition and factors influencing its development may help to plan strategies for reducing the risk factors of various diseases from early life onward. For early screening, various anthropometric measurements have been proposed to identify children and adolescents at risk. Body mass index (BMI) is perhaps the index most thoroughly studied; its relation with cardiometabolic risk factors and outcomes has been well documented. Nonetheless, as this index cannot distinguish fat from muscle mass and cannot represent the body fat distribution, the appropriateness of this overall obesity index in predicting cardiometabolic risk factors has been investigated in several studies.

Population-based surveys have documented that, similar to adults, in children and adolescents, abdominal or upper body fat is associated with an increased risk for cardiometabolic complications (Daniels 2000).

Ethnic differences are documented in several aspects of body size and proportions. Ethnic-specific references of anthropometric measures are generated, and are considered suitable for their respective populations, and corresponding to increases in body fat and associated health risks. Because of such ethnic differences in body size, especially in height, and variation in body fat distribution, different cutoff values are considered for anthropometric measures among diverse populations, and ratios of these measures are considered to provide a more appropriate index than simple measures in predicting cardiometabolic risk factors. This is of special concern for Asian populations with smaller body size, notably shorter statures than Western populations, and a genetic predisposition to visceral or abdominal obesity (WHO 2000). Similar to adults, anthropometric indices such as waist-to-hip ratio (WHR) and waist-to-stature ratio (WSR) and various cutoff values for anthropometric measures have been considered in children and adolescents as well (KC 2004).

Although the epidemiologic transition along with rapid lifestyle changes resulted in a rapidly growing prevalence of childhood obesity in the Eastern Mediterranean region (Kelishadi 2007a), experience regarding anthropometric indices of children and adolescents is very limited in this region. Therefore, for the first time in this region, we determined the anthropometric index most closely correlated to cardiometabolic risk factors in a large nationally representative sample of children and adolescents in Iran to be used as a simple tool for identifying those at risk.

79.2 Study Methods

79.2.1 Participants

The present study was performed as part of the baseline survey of a longitudinal national project titled: "***C****hildhood &* ***A****dolescence* ***S****urveillance and* ***P****revent****I****on of* ***A****dult* ***N****on-communicable disease*"*:* ***CASPIAN***[1] Study (Kelishadi et al. 2007b, c).

The first phase of this multicenter study was conducted at the national level in 2003–2004 among 21,111 school students (96% participation rates) living in urban and rural areas of the central cities of 23 (out of 28) provinces, as a joint collaboration of the World Health Organization (WHO/EMRO) and the National Ministry of Health and Ministry of Education. The present paper describes the findings obtained from a subsample of 4,811 school-students selected from six provinces located in diverse parts of the country (a 91% participation rate). In these counties, biochemical variables were examined in addition to the risk behaviors and biological risk factors evaluated in all the subjects studied.

Students were selected by multistage, random cluster sampling from elementary, middle, and high schools of urban and rural areas of different counties. These areas were defined according to the national population census. Initially, census blocks based on data from the Ministry of Health were randomly selected. Schools were randomly selected from different randomly selected clusters of these blocks, and, within schools, the students were selected at random. Schools were stratified according to location (urban/rural) and the socioeconomic character of its uptake area, with consideration of the proportion of the different types of schools (public/private) in order to avoid socioeconomic bias. From each stratum, a proportional, two-stage cluster sample of students was selected. The primary units (clusters) were the schools. The secondary units were the students within the schools. Students were allocated code numbers and randomly selected using random number tables.

Ethics committees and other relevant national regulatory organizations approved the study. Written informed consent was obtained from parents and oral assent from students, after full explanation of the procedure involved.

79.2.2 Quality Control/Quality Assurance

Considering that collecting data of high quality was critical to the success of our multicenter project, The Data & Safety Monitoring Board (DSMB) of the project has taken into account different levels of quality assurance and quality control (QA/QC). In addition to training, we developed a detailed operation manual and distributed it among the project team. A supervisor and a team of external evaluators nominated by the two collaborating ministries regularly monitored the performance of the personnel, and checked and calibrated equipment according to standardized protocols. Repeat studies were designed and conducted at specified time points on a student subsample. These repeat studies required taking multiple measurements on the same participant in order to quantify variability and to identify its sources, as well as to implement corrective action, as appropriate, in a timely manner to minimize measurement errors. The data entry staff entered data for all forms and questionnaires twice and checked for completeness and inconsistencies.

[1] Caspian is the name of the world's largest lake, located in Northern Iran.

79.2.3 Physical Examination

The field examinations of the survey were carried out by a specially trained team consisting of expert healthcare professionals trained for the survey. The questionnaires were filled out confidentially under the supervision of trained nurses. The age and birth date of subjects were recorded. Height and weight were measured twice to ±0.2 cm and to ±0.2 kg, respectively, with subjects being barefoot and lightly dressed; the averages of these measurements were recorded. Body mass index (BMI) (weight in kilograms divided by the square of height in meters) was calculated. Waist circumference (WC) was measured with a non-elastic tape at a point midway between the lower border of the rib cage and the iliac crest at the end of normal expiration. Hip circumference (HiC) was measured at the widest part of the hip at the level of the greater trochanter to the nearest half-centimeter. Next, WHR and the WSR were computed by dividing the WC by the HiC and Ht, respectively.

Blood pressure (BP) was measured using mercury sphygmomanometers after 5 min of rest in the sitting position. The subjects were seated with the heart, cuff, and zero indicator on the manometer at the level of the observer's eye. All readings were taken in duplicate on the right arm. Appropriate size cuffs were used with cuff width 40% of mid-arm circumference, and cuff bladders covering 80–100% of the arm circumference and approximately two-thirds of the length of the upper arm without overlapping. The procedure was explained to the students and the cuff inflated and deflated once; the first BP measured was not used in the analysis of this study. The readings at the first and the fifth Korotkoff phase were taken as systolic and diastolic BP (SBP and DBP), respectively. The average of the two BP measurements was recorded and included in the analysis.

79.2.4 Laboratory Examination

For blood sampling, students were invited to the health center nearest the school, in accordance with the rules of the national MoE. The students were instructed to fast for 12 h before the screening; compliance with fasting was determined by interview on the morning of examination. While one of parents accompanied his/her child, blood samples were taken from the antecubital vein between 8:00 and 9:30 a.m. After collecting blood samples, the participants were served a healthy snack provided by the project team.

The blood samples were centrifuged for 10 min at 3,000 rpm within 30 min of venipuncture. In each county, the biochemical analysis was performed in the Central Provincial Laboratory, which met the standards of the National Reference Laboratory, a WHO collaborating center in Tehran. Fasting blood sugar (FBS), HDL-C, and triglyceride (TG) were measured enzymatically by autoanalyzers. HDL-C was determined after dextran sulfate-magnesium chloride precipitation of non-HDL-C (Mc Namara 1987). Low-density lipoprotein-cholesterol (LDL-C) was calculated in serum samples with TG ≤ 400 mg/dL, according to the Friedwald equation (Friedewald 1972).

79.2.5 Definition of Risk Factors

The BMI percentiles provided by the Centers for Disease Control and Prevention (CDC) were used for the classification of the children and adolescents as undernourished, normal, and overweight and obese (Kuczmarsk 2000). Abnormal serum lipids were defined as TC, LDL-C, and TG higher than

Table 79.1 Age- and gender-specific percentiles of waist circumference (WC) of a national sample ($n = 21,111$) of Iranian children and adolescents in comparison to the British percentiles: CASPIAN study

Age		5th		10th		25th		50th		75th		90th		95th	
(year) (n)	Gender	Iranian	British	Iranian	British	Iranian	British	Iranian	British	Iranian	British	Iranian	British	Iranian	British
6	Girl	48	46.3	49	47.3	51	49.2	54	51.5	57	54.2	62	57	67	58.9
($n = 814$)	Boy	46	47.2	48	48.2	51	50.7	55	52.2	58	54.6	63.4	57.1	67.2	58.7
7	Girl	46	47.4	49	48.4	52	50.3	55	52.7	59	55.6	64	58.7	69	60.8
($n = 1330$)	Boy	45	47.9	49	48.9	52	50.9	56	53.3	60	56.1	66	58.8	70	60.7
8	Girl	49	48.5	50	49.6	53	51.5	56	54.1	60	57.1	65	60.4	69	62.7
($n = 1499$)	Boy	47	48.7	50	49.9	53	52.1	57	54.7	61	57.8	65	60.9	69	62.9
9	Girl	49	49.5	51	50.6	54	52.7	58	55.3	63	58.5	70	62	73	64.5
($n = 1435$)	Boy	49	49.7	51	51	55	53.4	58	56.4	62	59.7	68	63.2	73	65.4
10	Girl	50	50.7	52	51.8	56	53.9	60	56.7	65	60	71	63.6	75.4	66.2
($n = 1638$)	Boy	51	50.8	52	52.3	56	55	60	58.2	64	61.9	72	65.6	76	67.9
11	Girl	51	52	54	53.2	58	55.4	62	58.2	67	61.7	74	65.4	79.3	68.1
($n = 1755$)	Boy	52	51.9	54	53.6	57	56.6	62	60.2	68	64.1	75	67.9	80	70.4
12	Girl	53	53.6	56	54.8	60	57.1	65	60	70	63.5	78	67.3	82	70.5
($n = 2116$)	Boy	53	53.1	56	55	59	58.4	64	62.3	70	66.4	79	70.4	83.4	72.9
13	Girl	52	55.2	57	56.4	61	58.7	66	61.7	72	65.3	78	69.1	82	71.8
($n = 1939$)	Boy	53	54.8	56	56.9	61	60.4	65	64.6	71.2	69	80	73.1	86	75.7
14	Girl	57	56.5	60	57.8	63	60.2	68	63.2	73	66.8	79.2	70.6	83	73.2
($n = 2246$)	Boy	57	56.9	60	59.2	63	62.6	68	67	74	71.6	81	76.1	88	78.9
15	Girl	57	57.6	59.3	58.9	63	61.3	68	64.4	73	67.9	80	71.7	85	74.3
($n = 2131$)	Boy	54	59	59	61.1	64	64.8	69	69.3	75	74.2	82.6	79	89	82
16	Girl	57	58.4	60	59.8	64	62.2	68	65.3	73	68.8	80	72.6	83	75.1
($n = 2036$)	Boy	57	61.2	61	63.3	66	67	71	71.6	77	76.7	84	81.8	89.9	85.2
17	Girl	58	NA	60	NA	64	NA	69	NA	74	NA	80	NA	83	NA
($n = 1410$)	Boy	57	NA	61	NA	66	NA	71	NA	78	NA	86	NA	92	NA
18	Girl	60	NA	61	NA	64	NA	70	NA	76.25	NA	83	NA	85.9	NA
($n = 747$)	Boy	52	NA	60	NA	66	NA	72	NA	79	NA	85	NA	91	NA

the level corresponding to the age- and gender-specific 95th percentile, as well as HDL-C lower than age- and gender-specific 5th percentile (Lipid Research Clinics 1980). FBS levels equal or more than 100 mg/dL were considered high (Genuth et al. 2003). Elevated BP was defined as the mean SBP or DBP above the 90th percentile for that age and gender, after adjusting for weight and height (Task Force 1996).

79.2.6 Statistical Analysis

After editing, we transferred the data by the Stat Transfer 7 software to the SPSS version 13.0 software (SPSS, Inc., Chicago, IL).

Smoothed age- and gender-specific percentiles were constructed by the LMS Chart Marker software package (version 2.0, 2005, UK). The LMS method assumes that the data can be normalized by using power transformation. The percentile curves are the result of smoothing the age-specific curves: L for skewness, M for median, and S for coefficient of variation. In order to compare the mean values of the anthropometric measures in different age groups, the subjects were categorized to three age groups (6–9.99, 10–13.99, and 14–18 years) and by using univariate analysis, the mean values of BMI, WC, HiC, and WHR of both genders were compared between the age groups studied, and their living area (urban/rural). Partial correlation was used to examine the correlations between the age-adjusted anthropometric measures.

In order to determine the best anthropometric index associated with CVD risk factors, two statistical methods were used. First, receiver operating characteristic (ROC) curve analyses were used to calculate the area under ROC curves between each CVD risk factor and anthropometric index. Each value of an anthropometric index was used as a cutoff value to calculate its sensitivity and specificity in classifying a CVD risk factor. The ROC curve is a plot of the sensitivity against specificity for each cutoff value, and the area under curve (AUC) is an indicator of how well the anthropometric indices can distinguish a positive test outcome. AUC ranges from 0 to 1, with 0.5 (diagonal line) indicating that the anthropometric index has no predictive power and 1 indicating perfect power. After determining which the best anthropometric index was, the optimal cutoff value was denoted by the value that had the largest sum of sensitivity and specificity. In addition, partial correlation analysis was performed between CVD risk factors and anthropometric indices. The statistical significance was set at $p < 0.05$.

79.3 Findings

Figure 79.1 shows the smoothed reference curves of BMI, WC, HiC, and WHR for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile in both genders. The BMI percentile curves of girls had a sharp increase from 8 to 15 years of age, and then began to plateau; but, among boys, these curves had a persistent increase until the age of 18 years. For girls, the 50th–95th percentile curves for WC had a sharp increase from 8 to 13 years of age, and began to plateau after that, whereas, for boys, these curves had a persistent and less sharp increase with age until the age of 18 years. In girls, the 50th to 95th reference curves for HiC had a sharp increase, similar to that observed for WC curves, but at a later age, for example, 11–15 years, and began to plateau after that age. In boys, these curves had a persistent increase with age and ran nearly parallel to the WC percentile curves. The WHR curves of girls decreased with age until 15 years and began to plateau thereafter, whereas, for boys,

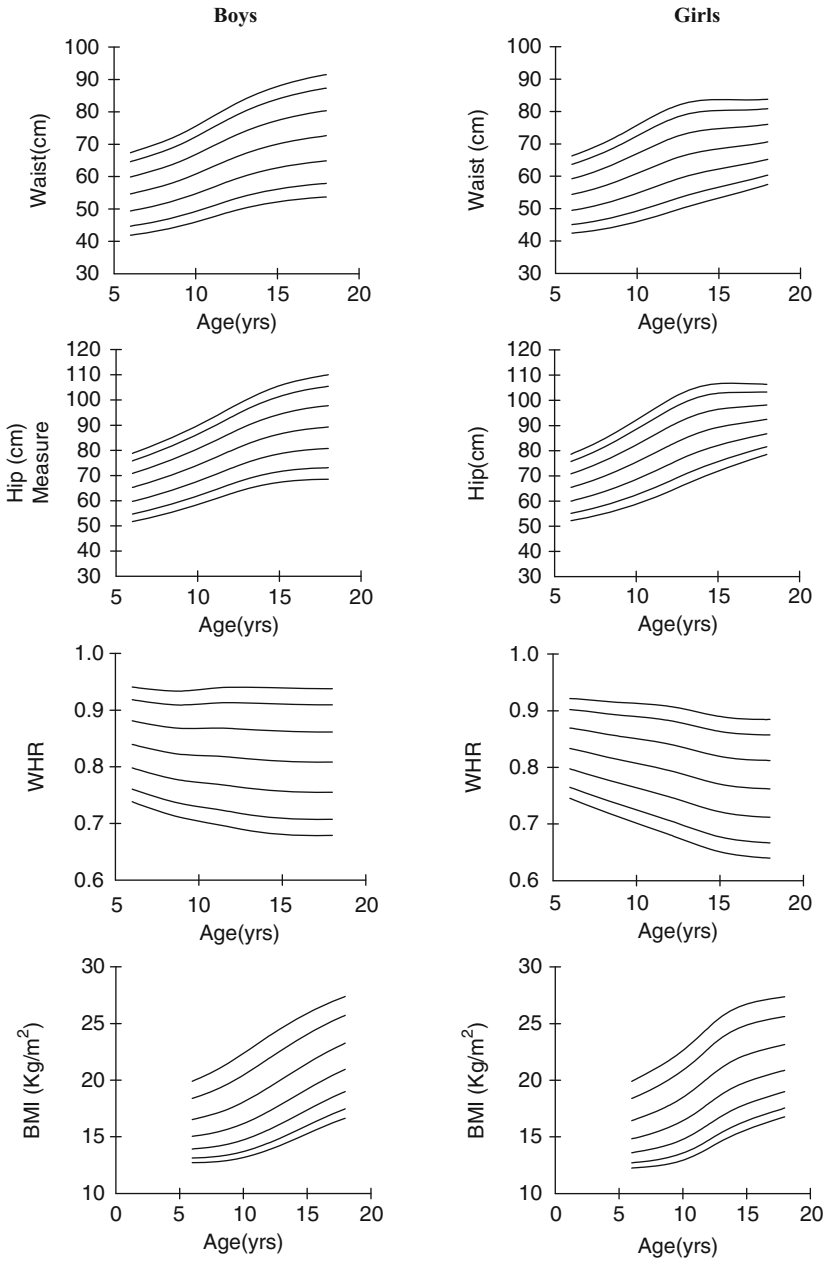

Fig. 79.1 Age- and gender-specific smoothed reference curves of waist and hip circumferences, waist-to-hip ratio (WHR), and body mass index (BMI) of a national sample ($n = 21{,}111$) of Iranian children aged 6–18 years: CASPIAN Study

the 25th–95th percentile curves for WHR had a plateau pattern and the 5th and the 10th percentile curves decreased slowly until 15 years of age.

The age-adjusted correlation between the anthropometric indices was significant in both genders. BMI and WC had the highest correlation ($r = 0.77$, $p < 0.0001$ in boys, and $r = 0.82$, $p < 0.0001$ in girls). The weakest correlation was found between BMI and WSR ($r = 0.56$, $p < 0.0001$ in boys, and $r = 0.63$, $p < 0.0001$ in girls).

ROC analysis showed that, among boys, the AUC of all anthropometric indices was the largest for 2 of the 8 risk factors in 6–9.9 year-old students. The AUC for WC was the largest for 5 of the 8 risk factors in subjects aged 10–13.9 years, and that for BMI was the largest for 6 of the 8 risk factors in the 14–18-year age group (Table 79.2).

Among girls, BMI and WSR were the best in distinguishing an abnormality in 3 of the 8 CVD risk factors in subjects aged 6–9.9 years. The largest AUC was found for WC and WSR (for 3 of the 8 risk factors) and for WC (for 6 of the 8 risk factors) in the 14–18-year age group (Table 79.3).

The ROC curves of the four anthropometric indices in relation to one or more risk factors according to gender and age group are depicted in Fig. 79.2.

Tables 79.4 and 79.5, respectively, present the optimal cutoff values, as well as the sensitivity and the specificity of the anthropometric indices in relation to each CVD risk factor in boys and girls, according to age group. Overall, the cutoff values in boys ranged from 13.91 to 22.04 for BMI, from 45.5 to 79.5 for WC, from 0.75 to 0.92 for WHR, and from 0.39 to 0.46 for WSR. Among girls, they ranged from 15.53 to 21.49 for BMI, from 48.5 to 76.5 for WC, from 0.75 to 0.86 for WHR, and from 0.40 to 0.48 for WSR.

Table 79.6 shows the partial correlation coefficients between anthropometric indices and CVD risk factors according to gender and age group. In boys, BMI had the highest coefficient in 5 of 8 risk factors among 6–9.9-year-old subjects; in the 10–13.9-year age group, BMI and WC had the highest coefficient (4 of 8), and in 14–18-year-old subjects, WC and WSR had the highest coefficient (3 of 8).

In girls, BMI had the highest coefficient in 4 of 8 risk factors in subjects aged 6–9.9 years; in the 10–13.9-year age group, WC and WSR had the highest coefficient (3 of 8), and in the 14–18-year-old subjects, BMI had the highest coefficient (4 of 8).

79.4 Correlations of Anthropometric Indices with Cardiovascular Disease Risk Factors

In the present study, the correlations between the anthropometric indices including BMI, WC, WHR, and WSR were strong in both genders, the highest correlation being between BMI and WC and the lowest between BMI and WSR. Contrary to studies among adults that determined a single anthropometric parameter as the best predictive index for CVD risk factors, in our study, this index varied well according to gender and the age group. Among boys, in subjects aged 6–9.9 years, all anthropometric indices had similar predictive value, whereas, in the 10–13.9-year- and the 14–18-year-age groups, respectively, WC and BMI were the best predictive factors. Among girls, respectively, in the 6–9.9-year age group, BMI and WSR; in the 10–13.9-year age group, WC and WSR; and, in the 14–18-year age group, WC were the best in distinguishing CVD risk factors. Although the best anthropometric indices were identified, it should be noted that the differences for the anthropometric indices were often small, with overlapping confidence intervals.

Most previous studies have determined the correlation of different anthropometric indices with CVD risk factors among adults. Some studies performed in South Asian adult population found WSR as the best anthropometric parameter. For instance, the study of Pua et al. (2005) among Singaporean women and the study of Ho and colleagues (Ho 2003) in Hong Kong Chinese found that WSR might be the best anthropometric index in relation to CVD risk factors. A study in Japan showed that WSR is more sensitive than BMI or WC to evaluate clustering of coronary risk factors among non-obese men and women (Hsieh 2005). However, some studies in Western countries found that other anthropometric parameters have better correlation with CVD risk factors than WSR has. The study of Ledoux et al. among Canadians revealed that WC and BMI correlate most closely with

Table 79.2 Area under the receiver operating characteristic (ROC) curve (95% CI) for anthropometric indices as a predictor of cardiovascular risk factors in boys: CASPIAN Study

Age groups	Risk factors	BMI	WC	WHR	WSR
6–9.9 years	High TC	0.683(0.570,0.795)**	0.680(0.574,0.786)**	0.613(0.507,0.718)*	0.672(0.566,0.779)**
	High LDL-C	0.585(0.516,0.654)*	0.609(0.538,0.680)**	0.599(0.529,0.670)**	0.597(0.527,0.668)**
	Low HDL-C	0.486(0.445,0.526)	0.573(0.532,0.613)**	0.603(0.562,0.644)**	0.573(0.533,0.613)**
	High TG	0.570(0.519,0.622)**	0.571(0.521,0.621)**	0.544(0.496,0.591)	0.616(0.569,0.662)**
	High FBS	0.307(0.150,0.468)*	0.385(0.251,0.518)	0.393(0.280,0.507)	0.453(0.316,0.591)
	High SBP	0.669(0.595,0.742)**	0.627(0.545,0.710)**	0.670(0.596,0.743)**	0.589(0.506,0.671)*
	High DBP	0.565(0.490,0.640)	0.613(0.533,0.693)**	0.573(0.495,0.651)	0.543(0.463,0.622)
	High SBP/DBP	0.613(0.549,0.677)**	0.614(0.544,0.684)**	0.619(0.553,0.684)**	0.561(0.492,0.630)
10–13.9 years	High TC	**0.683(0.589,0.776)****	0.607(0.499,0.714)*	0.552(0.458,0.647)	0.636(0.534,0.738)**
	High LDL-C	0.515(0.430,0.601)	0.541(0.457,0.625)	0.568(0.492,0.645)	**0.575(0.493,0.656)**
	Low HDL-C	.0481(0.430,0.533)	**0.534(0.485,0.584)**	0.532(0.482,0.582)	0.518(0.469,0.567)
	High TG	**0.667(0.622,0.732)****	0.585(0.521,0.659)**	0.515(0.454,0.575)	0.568(0.5046,0.31)*
	High FBS	0.621(0.464,0.777)	0.690(0.587,0.792)*	0.687(0.591,0.738)*	0.622(0.500,0.745)
	High SBP	0.757(0.647,0.866)**	**0.819(0.743,0.896)****	0.593(0.464,0.722)	0.734(0.628,0.841)**
	High DBP	0.648(0.413,0.882)	**0.714(0.514,0.914)***	0.639(0.391,0.888)	0.670(0.438,0.902)
	High SBP/DBP	0.703(0.589,0.817)**	**0.770(0.683,0.856)****	0.581(0.457,0.705)	0.690(0.580,0.800)**
14–18 years	High TC	**0.670(0.562,0.779)****	0.622(0.500,0.744)*	0.533(0.416,0.650)	0.642(0.532,0.752)*
	High LDL-C	**0.689(0.596,0.783)****	0.662(0.561,0.763)**	0.526(0.428,0.625)	0.651(0.551,0.751)**
	Low HDL-C	0.523(0.474,0.572)	0.590(0.543,0.637)**	0.537(0.492,0.582)	0.534(0.487,0.581)
	High TG	**0.650(0.591,0.708)****	0.600(0.537,0.664)**	0.573(0.508,0.639)*	0.637(0.574,0.699)**
	High FBS	**0.647(0.338,0.956)**	0.475(0.228,0.722)	0.439(0.005,0.873)	0.462(0.102,0.823)
	High SBP	0.664(0.588,0.739)**	**0.710(0.633,0.787)****	0.610(0.531,0.688)**	0.644(0.561,0.727)**
	High DBP	**0.710(0.643,0.777)****	0.653(0.575,0.731)**	0.685(0.618,0.751)**	0.649(0.576,0.723)**
	High SBP/DBP	**0.685(0.627,0.742)****	0.653(0.589,0.716)**	0.636(0.576,0.695)**	0.625(0.562,0.688)**

Best indices for each risk factor in bold.

BMI: body mass index (kg/m$^{2)}$, WC: waist circumference (cm), WHR: waist-to-hip ratio,

WSR waist-to-stature ratio; *High TC* total cholesterol ≥ 95th age and gender-specific percentile; *High LDL-C*: low-density cholesterol ≥ 95th age and gender-specific percentile; *Low HDL-C* high-density cholesterol ≤ 5th age and gender-specific percentile; *High TG*: triglyceride ≥ 95th age and gender-specific percentile; *High FBS*: fasting blood sugar > 110 mg/dL; *High SBP* systolic blood pressure ≥ 90th age and gender-specific percentile; *High DBP* diastolic blood pressure ≥ 90th age and gender-specific percentile; *High SBP/DBP* systolic/diastolic blood pressure ≥ 90th age and gender-specific percentile

*Significant at p 0 < 0.05

**Significant at p 0 < 0.01

Table 79.3 Area under the ROC curve (95% CI) for anthropometric indices as a predictor of cardiovascular risk factors in girls: CASPIAN Study

Age groups	Risk factors	BMI	WC	WHR	WSR
6–9.9 years	High TC	0.650(0.571,0.729)**	0.643(0.563,0.724)**	0.645(0.577,0.714)**	**0.681(0.610,0.753)****
	High LDL-C	0.600(0.541,0.660)**	0.620(0.561,0.678)**	0.633(0.581,0.686)**	**0.657(0.604,0.711)****
	Low HDL-C	0.550(0.511,0.588)*	0.620(0.583,0.656)**	0.626(0.589,0.662)**	**0.635(0.599,0.671)****
	High TG	0.608(0.563,0.653)**	0.586(0.540,0.631)**	0.561(0.518,0.604)**	**0.592(0.548,0.636)****
	High FBS	0.500(0.274,0.727)	0.416(0.239,0.594)	0.625(0.448,0.801)	**0.476(0.338,0.614)**
	High SBP	0.687(0.581,0.793)**	0.688(0.587,0.790)**	0.597(0.482,0.713)*	**0.623(0.510,0.736)***
	High DBP	0.610(0.522,0.698)**	0.583(0.497,0.668)*	0.450(0.497,0.668)	**0.555(0.471,0.638)**
	High SBP/DBP	0.650(0.570,0.730)**	0.628(0.550,0.707)**	0.496(0.410,0.582)	**0.590(0.511,0.670)***
10–13.9 years	High TC	0.532(0.444,0.620)	0.567(0.475,0.660)	0.611(0.517,0.705)*	**0.613(0.521,0.704)***
	High LDL-C	0.533(0.460,0.605)	0.564(0.489,0.640)	**0.616(0.546,0.686)****	0.607(0.535,0.679)**
	Low HDL-C	0.506(0.467,0.548)	0.562(0.521,0.603)**	0.540(0.500,0.581)	**0.577(0.536,0.617)****
	High TG	**0.628(0.582,0.674)****	0.599(0.551,0.647)**	0.523(0.475,0.572)	0.612(0.565,0.659)**
	High FBS	0.560(0.309,0.811)	0.599(0.386,0.812)	0.665(0.522,0.809)	**0.699(0.534,0.864)**
	High SBP	0.627(0.497,0.757)	**0.694(0.573,0.815)****	0.633(0.507,0.759)*	0.637(0.501,0.773)*
	High DBP	**0.610(0.489,0.731)**	**0.610(0.473,0.747)**	0.565(0.431,0.698)	0.598(0.461,0.734)
	High SBP/DBP	0.610(0.508,0.713)*	**0.634(0.528,0.739)***	0.580(0.477,0.682)	0.610(0.501,0.719)*
14–18 years	High TC	**0.600(0.504,0.696)***	**0.600(0.506,0.694)***	0.518(0.418,0.618)	0.590(0.496,0.684)
	High LDL-C	**0.632(0.538,0.725)****	0.598(0.504,0.692)*	0.526(0.427,0.626)	0.575(0.479,0.672)
	Low HDL-C	0.559(0.505,0.613)*	0.549(0.496,0.602)	**0.591(0.541,0.641)****	0.562(0.509,0.615)*
	High TG	0.621(0.564,0.677)**	**0.645(0.589,0.700)****	0.585(0.530,0.640)**	0.637(0.583,0.690)**
	High FBS	0.518(0.281,0.756)	**0.577(0.376,0.778)**	0.515(0.387,0.643)	0.515(0.181,0.848)
	High SBP	0.689(0.585,0.793)**	**0.776(0.678,0.873)****	0.653(0.538,0.767)*	0.662(0.540,0.784)*
	High DBP	0.546(0.315,0.777)	**0.608(0.408,0.808)**	0.493(0.279,0.708)	0.602(0.426,0.778)
	High SBP/DBP	0.630(0.526,0.735)*	**0.720(0.622,0.818)****	0.603(0.494,0.712)	0.629(0.523,0.736*

Best indices for each risk factor in bold.

BMI body mass index(kg/m^2); *WC* waist circumference(cm); *WHR* waist-to-hip ratio; *WSR* waist-to-stature ratio; *High TC*: total cholesterol ≥ 95th age and gender-specific percentile; *High LDL-C*: low-density cholesterol ≥ 95th age and gender-specific percentile; *Low HDL-C*: high-density cholesterol ≤ 5th age and gender-specific percentile; *High TG* triglyceride ≥ 95th age and gender-specific percentile; *High FBS* fasting blood sugar > 110 mg/dL; *High SBP* systolic blood pressure ≥ 90th age and gender-specific percentile; *High DBP* diastolic blood pressure ≥ 90th age and gender-specific percentile; *High SBP/DBP* systolic/diastolic blood pressure ≥ 90th age and gender-specific percentile

*Significant at p 0 < 0.05

**Significant at p 0 < 0.01

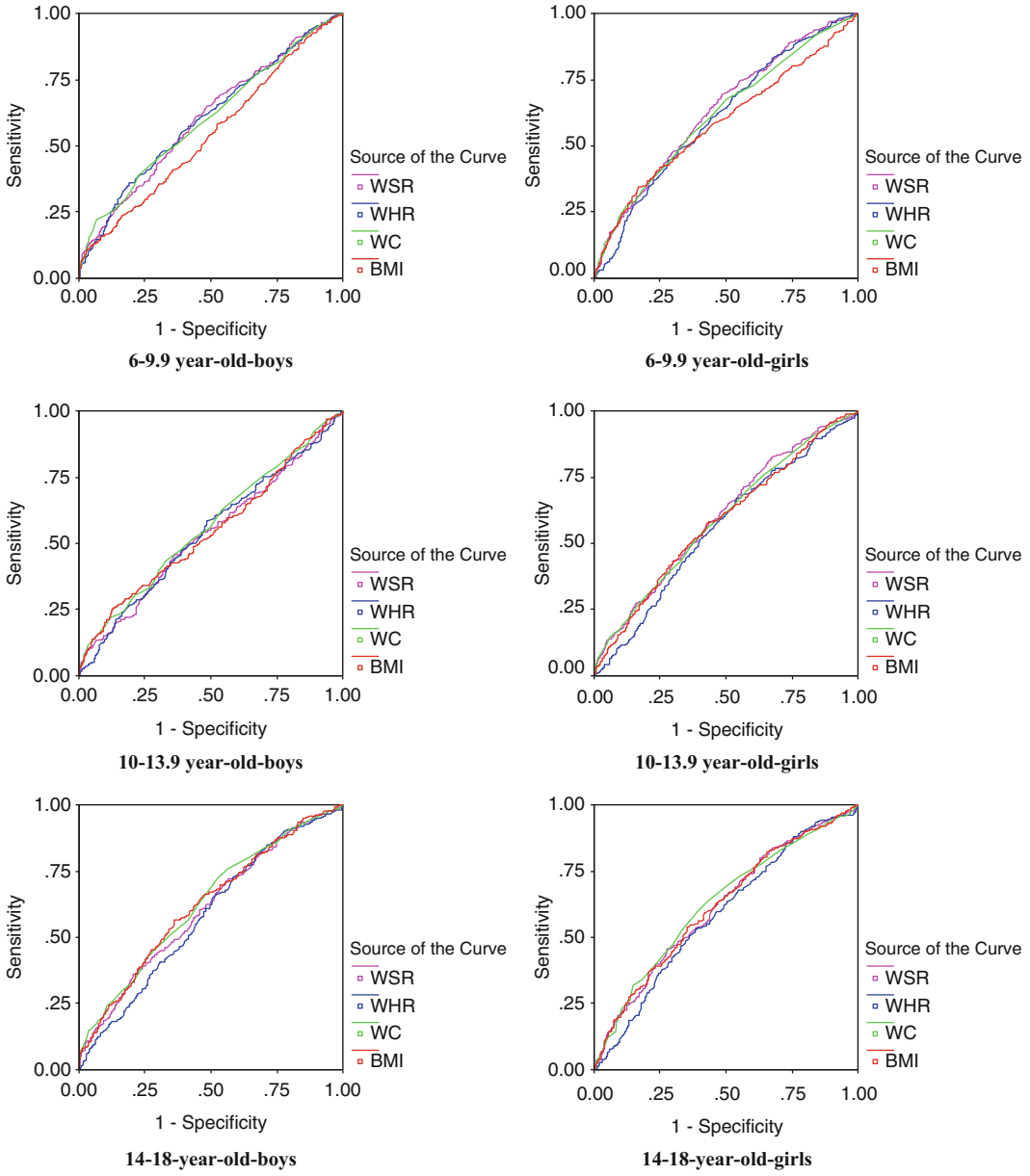

Fig. 79.2 Receiver operating characteristic (ROC) curves for one or more risk factors according to gender and school level: CASPIAN Study

BP and plasma lipids (Ledoux et al. 1997). In the study of Zhu et al. among Americans of three race–ethnicity groups, WC was more sensitive than BMI in predicting CVD risk (Zhu et al. 2005).

Population-based studies concerning the correlation of anthropometric indices and CVD risk factors in children and adolescents are limited, and comprise different age groups, making the comparisons difficult. The recent study of Kahn et al. among a population drawn from the third National Health and Nutrition Examination Survey (NHANES III) in USA showed that WHR is a simpler anthropometric index than sex- and age-specific BMI percentiles, and better identifies youth with adverse CVD risk factors (Kahn 2005).

Table 79.4 Optimal cutoff values,[a] sensitivity (Se), and specificity (Sp) of anthropometric indices for cardiovascular risk factors in boys:CASPIAN Study

		BMI[1]			WC[2]			WHR			WSR		
School level	Risk factors	Cutoff	Se	Sp	Cutoff	Se	Sp	Cutoff	Se	Sp	Cutoff	Se	Sp
6–9.9 years	High LDL-C[6]	**16.75**	0.44	0.70	**60.50**	0.48	0.70	**0.87**	0.41	0.76	**0.44**	0.60	0.56
	Low HDL-C[7]	**13.91**	0.91	0.13	**55.50**	0.73	0.39	**0.82**	0.65	0.50	**0.44**	0.65	0.51
	High TC[5]	**19.41**	0.50	0.88	**65.50**	0.50	0.86	**0.86**	0.47	0.73	**0.48**	0.44	0.85
	High SBP/DBP[12]	**16.06**	0.63	0.57	**62.50**	0.45	0.78	**0.86**	0.53	0.71	**0.44**	0.63	0.52
	High SBP[10]	**16.06**	0.71	0.57	**66.50**	0.39	0.88	**0.86**	0.61	0.70	**0.49**	0.32	0.88
	High DBP[11]	**16.06**	0.57	0.56	**64.50**	0.40	0.84	**0.87**	0.40	0.76	**0.44**	0.64	0.52
	High TG[8]	**18.37**	0.33	0.85	**60.50**	0.43	0.72	**0.82**	0.61	0.48	**0.43**	0.78	0.38
	High FBS[9]	**12.39**	1.00	0.02	**45.50**	1.00	0.01	**0.76**	1.00	0.11	**0.40**	0.93	0.15
10–13.9 years	High LDL-C[6]	**21.43**	0.26	0.85	**72.50**	0.33	0.76	**0.79**	0.76	0.45	**0.43**	0.65	0.54
	Low HDL-C[7]	**21.26**	0.21	0.84	**62.50**	0.74	0.34	**0.80**	0.63	0.47	**0.39**	0.87	0.20
	High TC[5]	**21.07**	0.51	0.84	**66.50**	0.69	0.54	**0.79**	0.75	0.40	**0.44**	0.75	0.59
	High SBP/DBP[12]	**18.76**	0.74	0.64	**69.50**	0.78	0.67	**0.88**	0.37	0.86	**0.44**	0.78	0.59
	High SBP[10]	**19.13**	0.78	0.68	**69.50**	0.87	0.67	**0.88**	0.39	0.86	**0.44**	0.83	0.59
	High DBP[11]	**18.76**	0.75	0.63	**79.50**	0.50	0.90	**0.87**	0.63	0.80	**0.45**	0.75	0.67
	High TG[8]	**19.62**	0.55	0.77	**68.50**	0.56	0.66	**0.83**	0.44	0.63	**0.44**	0.51	0.66
	High FBS[9]	**21.30**	0.50	0.83	**70.50**	0.64	0.70	**0.80**	0.93	0.50	**0.43**	0.79	0.55
14–18 years	High LDL-C[6]	**21.48**	0.59	0.73	**73.50**	0.64	0.64	**0.79**	0.67	0.48	**0.44**	0.59	0.75
	Low HDL-C[7]	**20.07**	0.52	0.57	**69.50**	0.75	0.42	**0.75**	0.92	0.23	**0.39**	0.83	0.29
	High TC[5]	**20.47**	0.69	0.61	**74.50**	0.54	0.68	**0.86**	0.31	0.81	**0.44**	0.58	0.74
	High SBP/DBP[12]	**21.93**	0.48	0.80	**76.50**	0.48	0.78	**0.83**	0.51	0.73	**0.44**	0.45	0.76
	High SBP[10]	**22.04**	0.47	0.79	**76.50**	0.57	0.77	**0.83**	0.50	0.71	**0.46**	0.43	0.84
	High DBP[11]	**20.90**	0.64	0.69	**79.50**	0.44	0.86	**0.83**	0.60	0.72	**0.44**	0.51	0.73
	High TG[8]	**21.48**	0.51	0.75	**73.50**	0.51	0.65	**0.83**	0.45	0.74	**0.44**	0.52	0.73
	High FBS[9]	**21.40**	0.67	0.71	**71.50**	0.75	0.52	**0.92**	0.50	0.94	**0.42**	0.67	0.53

[a]The optimal cutoff value was denoted by the value that had the largest sum of sensitivity and specificity

BMI body mass index (kg/m^2); *WC* waist circumference (cm); *WHR* waist-to-hip ratio, *WSR* waist-to-stature ratio; *High TC* total cholesterol ≥ 95th age and gender-specific percentile; *High LDL-C*: low-density cholesterol ≥ 95th age and gender-specific percentile; *Low HDL-C*: high-density cholesterol ≤ 5th age and gender-specific percentile; *High TG* triglyceride ≥ 95th age and gender-specific percentile; *High FBS* fasting blood sugar > 110 mg/dL; *High SBP* systolic blood pressure ≥ 90th age and gender-specific percentile; *High DBP* diastolic blood pressure ≥ 90th age and gender-specific percentile; *High SBP/DBP* systolic/diastolic blood pressure ≥ 90th age and gender-specific percentile

Table 79.5 Optimal cutoff values,[a] sensitivity (Se), and specificity (Sp) of anthropometric indices for cardiovascular risk factors in girls: CASPIAN Study

		BMI			WC			WHR			WSR		
Age groups	Risk factors	Cut-off	Se	Sp	Cut-off	Se	Sp	Cut-off	Se	Sp	Cut-off	Se	Sp
6–9.9 years	High TC	**17.35**	0.56	0.76	**62.50**	0.48	0.81	**0.83**	0.60	0.64	**0.47**	0.46	0.13
	High LDL-C	**17.46**	0.45	0.78	**59.50**	0.53	0.71	**0.83**	0.58	0.65	**0.44**	0.57	0.32
	Low HDL-C[7]	**15.53**	0.58	0.52	**55.50**	0.68	0.54	**0.79**	0.81	0.41	**0.42**	0.77	0.54
	High TG	**16.67**	0.49	0.72	**62.50**	0.34	0.84	**0.77**	0.86	0.25	**0.46**	0.34	0.15
	High FBS	**18.37**	0.38	0.83	**48.50**	1.00	0.05	**0.84**	0.63	0.72	**0.40**	1.00	0.79
	High SBP[1]	**17.36**	0.64	0.76	**62.50**	0.54	0.81	**0.86**	0.43	0.84	**0.48**	0.37	0.09
	High DBP	**15.81**	0.67	0.55	**59.50**	0.47	0.69	**0.86**	0.28	0.83	**0.42**	0.67	0.55
	High SBP/DBP	**16.98**	0.59	0.72	**63.50**	0.39	0.85	**0.86**	0.31	0.84	**0.47**	0.34	0.16
10–13.9 years	High TC	**16.87**	0.86	0.26	**75.50**	0.29	0.86	**0.83**	0.42	0.82	**0.44**	0.60	0.37
	High LDL-C	**17.90**	0.72	0.40	**62.50**	0.77	0.36	**0.77**	0.82	0.41	**0.43**	0.61	0.41
	Low HDL-C[7]	**21.49**	0.26	0.79	**61.50**	0.78	0.32	**0.77**	0.65	0.47	**0.41**	0.69	0.55
	High TG	**18.51**	1.00	0.00	**72.50**	0.34	0.83	**0.82**	0.35	0.73	**0.43**	0.54	0.35
	High FBS	**25.34**	0.33	0.94	**64.50**	0.83	0.45	**0.77**	1.00	0.42	**0.41**	1.00	0.58
	High SBP[1]	**18.36**	0.80	0.45	**71.50**	0.55	0.78	**0.81**	0.63	0.68	**0.44**	0.65	0.36
	High DBP	**19.18**	0.70	0.55	**68.50**	0.86	0.50	**0.82**	0.45	0.73	**0.47**	0.40	0.16
	High SBP/DBP	**18.35**	0.78	0.45	**71.50**	0.47	0.78	**0.80**	0.52	0.65	**0.44**	0.59	0.37
14–18 years	High TC	**21.09**	0.65	0.58	**72.50**	0.48	0.68	**0.79**	0.43	0.68	**0.43**	0.73	0.50
	High LDL-C	**21.23**	0.66	0.61	**69.50**	0.66	0.54	**0.81**	0.34	0.77	**0.43**	0.68	0.51
	Low HDL-C[7]	**23.18**	0.34	0.77	**68.50**	0.59	0.51	**0.78**	0.59	0.59	**0.45**	0.40	0.29
	High TG	**21.45**	1.00	0.00	**70.50**	0.60	0.63	**0.79**	0.47	0.70	**0.43**	0.63	0.41
	High FBS	**21.22**	0.67	0.59	**65.50**	1.00	0.31	**0.75**	1.00	0.36	**0.45**	0.67	0.33
	High SBP[1]	**20.31**	0.90	0.48	**71.50**	0.85	0.65	**0.76**	0.85	0.45	**0.46**	0.55	0.26
	High DBP	**24.05**	0.43	0.81	**76.50**	0.14	0.81	**0.76**	0.71	0.42	**0.42**	0.86	0.53
	High SBP/DBP	**19.15**	0.92	0.33	**68.50**	0.88	0.50	**0.76**	0.80	0.43	**0.42**	0.80	0.55

[a]The optimal cutoff value was denoted by the value that had the largest sum of sensitivity and specificity

BMI body mass index (kg/m^2); *WC* waist circumference (cm); *WHR* waist-to-hip ratio; *WSR* waist-to-stature ratio; *High TC*: total cholesterol ≥ 95th age and gender-specific percentile; *High LDL-C*: low-density cholesterol ≥ 95th age and gender-specific percentile; *Low HDL-C*: high -density cholesterol ≤ 5th age and gender-specific percentile; *High TG* triglyceride ≥ 95th age and gender-specific percentile; *High FBS* fasting blood sugar > 110 mg/dL; *High SBP* systolic blood pressure ≥ 90th age and gender-specific percentile; *High DBP* diastolic blood pressure ≥ 90th age and gender-specific percentile; *High SBP/DBP* systolic/diastolic blood pressure ≥ 90th age and gender-specific percentile

Table 79.6 Partial Correlation coefficients between cardiovascular risk factors and anthropometric indices according to gender and school level: CASPIAN Study

		Boys				Girls			
Age groups	Risk factors	BMI	WC	WHR	WSR	BMI	WC	WHR	WSR
6–9.9 years	High TC	**0.221****	0.157**	0.061	0.161**	**0.169****	0.130**	0.070*	0.145**
	High LDL-C	**0.149****	0.146**	0.131**	0.147**	**0.143****	0.129**	0.136**	0.189**
	Low HDL-C	**0.045**	–0.097**	–0.197**	–0.099**	**–0.093****	–0.192**	–0.228**	–0.236**
	High TG	**0.245****	0.219**	0.054	0.236**	**0.273****	0.284**	0.089**	0.201**
	High FBS	**0.023**	0.009	–0.056	0.042	**0.053**	0.020	–0.061	–0.097**
	High SBP	**0.260****	0.280**	0.131**	0.136**	**0.340****	0.348**	0.027	0.176**
	High DBP	**0.218****	0.233**	0.070*	0.094**	**0.211****	0.149**	–0.055	0.034
	High SBP/DBP	**0.076***	0.105**	0.032	0.073*	**0.079***	0.054	0.009	0.039
10–13.9 years	High TC	**0.194****	0.120**	0.048	0.147**	0.081*	0.098**	0.085*	**0.153****
	High LDL-C	**0.107****	0.069	0.014	**0.105****	0.058	0.119**	0.094**	**0.166****
	Low HDL-C	–0.036	**–0.069**	–0.033	–0.032	–0.103**	**–0.200****	–0.090*	–0.191**
	High TG	**0.260****	0.180**	0.079*	0.155**	0.211**	0.212**	0.094**	**0.229****
	High FBS	**0.130****	0.095*	0.035	0.066	–0.030	–0.010	0.007	–0.010
	High SBP	0.267**	**0.366****	0.152**	0.180**	**0.257****	0.253**	0.070	0.177**
	High DBP	0.156**	**0.263****	0.228**	0.155**	0.169**	**0.183****	0.037	0.118**
	High SBP/DBP	0.039	**0.054**	–0.007	0.009	0.028	**0.037**	0.032	0.000
14–18 years	High TC	0.145**	0.125**	–0.001	**0.192****	**0.232****	0.182**	0.027	0.165**
	High LDL-C	0.122**	0.124**	–0.036	**0.150****	**0.233****	0.168**	0.044	0.158**
	Low HDL-C	–0.066	**–0.133****	–0.036	–0.039	–0.038	–0.044	**–0.083***	–0.042
	High TG	0.206**	0.232**	0.170**	**0.259****	0.217**	**0.229****	0.090*	0.209**
	High FBS	0.008	0.076*	**0.137****	0.066	0.036	0.031	**–0.083***	0.024
	High SBP	0.271**	**0.308****	0.081*	0.175**	0.133**	**0.194****	0.041	0.065
	High DBP	**0.251****	0.203**	0.131**	0.128**	**0.124****	0.109**	–0.012	0.035
	High SBP/DBP	0.056	**0.116****	0.009	0.083*	**0.032**	0.008	**–0.032**	0.008

Best indices for each risk factor in bold.

BMI body mass index(kg/m^2); *WC* waist circumference (cm); *WHR* waist-to-hip ratio; *WSR* waist-to-stature ratio; *High TC* total cholesterol ≥ 95th age and gender-specific percentile; *High LDL-C*: low-density cholesterol ≥ 95th age and gender-specific percentile; *Low HDL-C*: high-density cholesterol ≤ 5th age and gender-specific percentile; *High TG* triglyceride ≥ 95th age and gender-specific percentile; *High FBS* fasting blood sugar > 110 mg/dL; *High SBP* systolic blood pressure ≥ 90th age and gender-specific percentile; *High DBP* diastolic blood pressure ≥ 90th age and gender-specific percentile; *High SBP/DBP* systolic/diastolic blood pressure ≥ 90th age and gender-specific percentile

*Significant at p 0 < 0.05

**Significant at p 0 < 0.01

In Cyprus, Savva and colleagues found that, in children (with a mean age of 11.4 years), WC and WSR are better predictors of CVD risk factors than BMI (Savva et al. 2000).

The study of Maffeis et al. in Italy showed that WC as well as subscapular and triceps skinfolds could be helpful parameters in identifying prepubertal children with dyslipidemia and high BP (Maffeis 2001).

In Portugal, Teixeira and colleagues showed that, among 159 children with a mean age of 13 years, measures of central adiposity, such as WC and WSR, significantly correlated with serum lipid levels in obese children and adolescents but not in leaner individuals (Teixeira et al. 2001).

Similar to studies performed among adults in Japan, the study of Hara et al. showed that WSR is the best predictor of CVD risk factors in Japanese schoolchildren 9–13 years of age (Hara 2002).The study of Asayama and colleagues among obese Japanese girls confirmed such a correlation, and found that only WSR/Ht showed high-enough sensitivity and specificity to predict CVD risk factors (Asayama 2000).

In the CASPIAN Study, BMI, WC, and WSR were more closely correlated with CVD risk factors. Considering the close correlation between different anthropometric indices studied, and differences in the best predictive index according to age and gender, it may be clinically useful in the pediatric population to routinely measure WC and WSR in addition to BMI as a screening tool to identify high-risk youths.

79.4.1 Applications to Other Areas of Health and Disease

Usually for clinical practice and epidemiological studies, child overweight and obesity are assessed by indicators based on weight and height measurements, such as weight for height or BMI. The present study documented BMI as a predictor of cardiovascular disease risk factors in children and adolescents; this finding is consistent with previous studies confirming the predictive value of BMI for cardiovascular disease risk factors. However, as this index cannot distinguish fat from muscle mass, and cannot represent the fat distribution, some scientific groups stated that, as an overall obesity index, BMI could not be appropriate in predicting chronic diseases.

Different studies have documented that, similar to adults, WC is an indicator of abdominal fat content, and, consequently, is a good predictor of cardiometabolic risk factors among children and adolescents, as well (Weiss 2003). However, there is still no global standard for WC in youth. The cutoff values differ between genders, races, and ethnic groups.

Our findings are in line with the recent study of Janssen and colleagues among the Bogalusa Heart Study population, indicating that BMI and WC did not have independent effects on CVD risk factors in youth aged 5–18 years (Janssen 2005).

In a previous study, we compared the reference curves for anthropometric indices in the 6–11-year age group of the CASPIAN study and a population-based sample of German children (Kelishadi et al. 2008). Comparison of our data with British children (McCarthy 2001) are presented in Table 79.1 and Fig. 79.3, and show that the reference curves for BMI and WC were higher and had a sharper increase in Iranian than in British children.

It is suggested that, in adults, lower cutoff points of BMI should be retained for Asians because the risk factors for CVD at a given BMI are generally higher among Asians compared with Western populations (WHO 2004). Because growth rate and fat patterning vary among different populations (Goran 1997), it is important to develop simple and effective anthropometric indices for the screening of higher metabolic risk subjects in different populations until they reach internationally accepted measures.

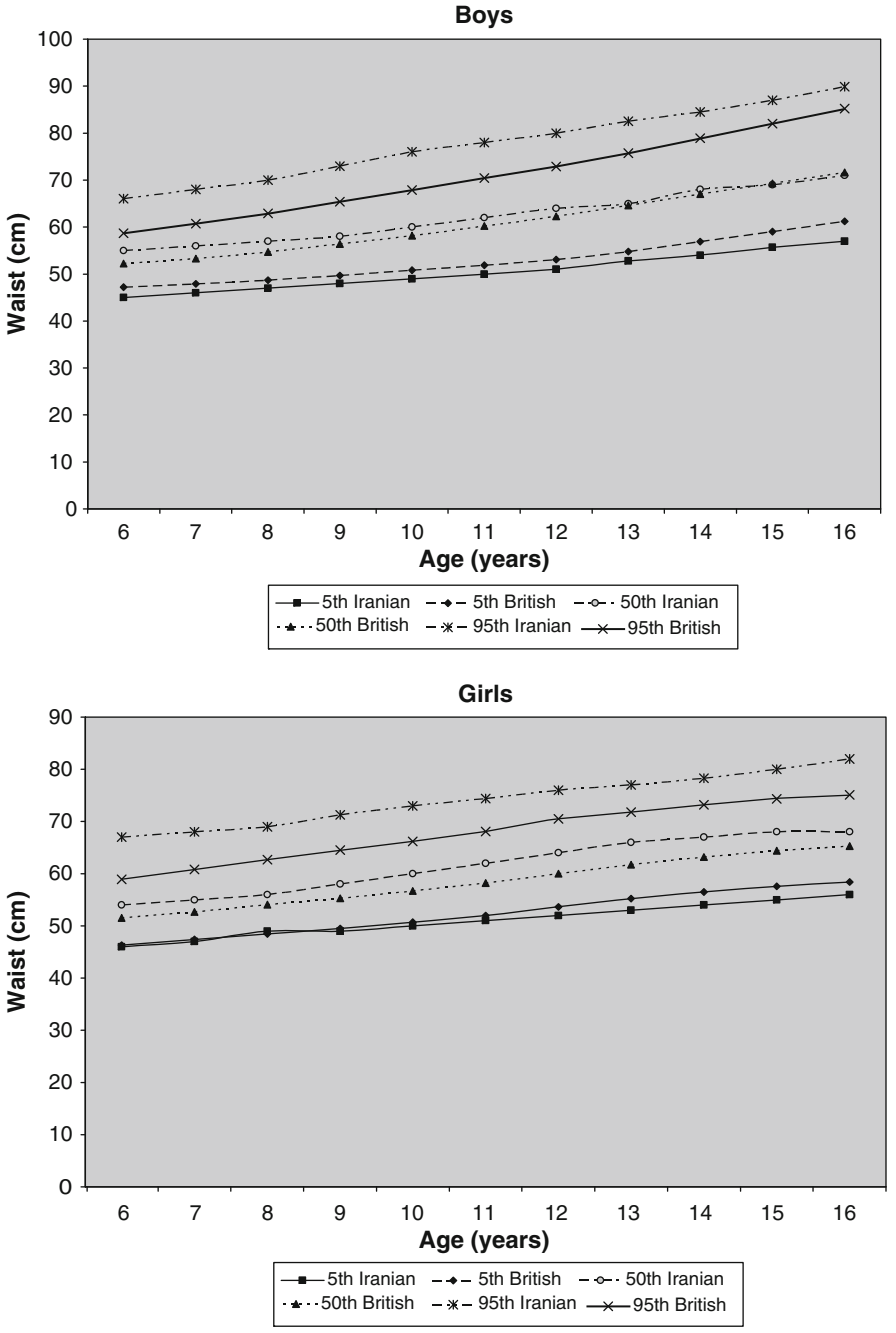

Fig. 79.3 Age- and gender-specific 5th, 50th, and 95th percentile curves of waist circumference (WC) of a national sample of Iranian children and adolescents (2003–2004) in comparison to the British percentiles (McCarthy 2001): CASPIAN Study

79.4.2 Features of the Association of the Anthropometric Indices and Cardiovascular Disease Risk in Children and Adolescents: CASPIAN Study

- It may be clinically useful in the pediatric population to routinely measure WC and WSR, in addition to BMI, as a screening tool to identify youth at risk of future cardiovascular diseases.
- Ethnic differences in anthropometric indices and their association with cardiometabolic risk factors are observed from early life onward.
- Among the children and adolescents examined in the CASPIAN Study, BMI, WC, and waist-to-stature were more closely correlated with cardiovascular disease risk factors.

Summary Points

- Age- and gender-specific reference curves as well as cutoff values should be provided for anthropometric indices of children with different ethnicities.
- Contrary to studies among adults that determined a single anthropometric parameter as the best predictive index for cardiovascular disease risk factors, among Iranian children and adolescents analyzed in the CASPIAN Study, this index varied well according to gender and age groups.
- The CASPIAN Study documented BMI as a predictor of cardiovascular disease risk factors. However, as this index cannot distinguish fat from muscle mass, and cannot represent the fat distribution, it is suggested to measure indices of abdominal obesity in addition to this measure of generalized obesity.
- The 5th and 50th percentile curves for WC obtained in the CASPIAN Study were similar to the British ones, but the obtained 95th percentile curve was higher than the British curves. For girls, the obtained 50th and 95th percentile curves were higher than the British ones.
- Because of smaller size and shorter stature of Asian children and adolescents compared with their Western counterparts, WSR can be considered as an appropriate index for abdominal obesity and associated cardiometabolic risk factors.

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Chapter 80
Secular Trends in the Anthropometry of Adolescents and College Students: Polish Perspective

Boguslaw Antoszewski and Aneta Sitek

Abstract Socio-economic disparities lead to biological consequences manifested in the differences in anthropometric traits as well as in pubertal timing within a population, which is the case not only in Poland, but all over the world. The screening of the development of somatic traits in the Polish population has been conducted for over 100 years. Furthermore, some studies on stratification trends, i.e. intergenerational changes occurring in social groups singled out from the general population, have been conducted. Such analyses allow observing social stratification changes over a given period and determining the intensity of the biological consequences of these disparities.

The analysis of intergenerational changes in respect of body height (stature) of Polish males based on a representative sample of military conscripts shows that the genetically determined growth potential of Poles has not been fully exploited yet, and thus a further increase in mean body height may be anticipated. However, it seems that the increase in adult stature will be in the near future less considerable than the intergenerational changes leading to BMI (Body Mass Index) increase. The continuing presence of social gradients in respect of body height and relative mass reflect the stability of social divisions in Polish living standards. The results of studies on earlier pubertal timing in Polish girls demonstrate that the lowering of age at menarche will continue, as the genetically determined limit has not been achieved yet, either.

Abbreviations

B-v	Body height
BMI	Body Mass Index
°C	Degree centigrade
GH	Growth Hormone
GDP	Gross Domestic Product
ng/mL	Nanogram per milliliter
R	Pearson correlation coefficient
Y	Years

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_80,

80.1 Introduction

The factors that make up the socioeconomic status result in two kinds of variation in the measures of the human biological condition: social gradients and secular trends (Łaska-Mierzejewska and Olszewska 2007).

The term "social gradients" denotes a change in the value of biological parameters and their direction at the rate that reflects the economic situation of the groups studied (Łaska-Mierzejewska and Olszewska 2007). In the description of social disparities, paired groups differing in respect of the "quality" of factors influencing them (such as big cities and villages, and small and large families) are usually contrasted.

A secular trend (the word "secular" derives from the Latin word *seculum*, which means a 100 years old, ancient) means intergenerational, directional changes of morphological, physiological, and motor traits. The elements of time variation occurring in human biological traits include the acceleration of development and earlier puberty timing, modifications in the sequence of certain developmental events (e.g., ossification and dentition) as well as retardation of involutionary processes. The secular trend is considered to result from the progress of civilization, involving socioeconomic changes, leading to improvement in the general living conditions. It is also thought that genetic factors related to an increase in the distance between parental birthplaces due to migrations, which result in the heterosis effect, are crucial in this respect (Malinowski 1977). Moderate heterosis leads to larger sensitivity to external factors. When these factors are favorable, the body develops at increasingly higher levels in respect of the individual norm of reaction in order to exploit its full genetic potential. Short persons' tendencies in perinatal and marital selection (Malinowski 2003) are thought to have certain significance within the genetic determinants of the secular trend. Koh (citation after Malinowski 1977) ascribed the existence of secular changes to the larger effect of the sun's rays on contemporary humans and emphasized the role of ultraviolet radiation in the activation of vitamin D. However, this concept has not been confirmed in the face of, for example, the lower average body height (B-v) in the rural population, which is generally more exposed to the sun's rays as compared with the big-city population (Malinowski 1977). According to a number of researchers, intergenerational changes are related to specific generational factors, which influence the determinative and regulatory functions of the genes responsible for body size. These may include various vaccinations, antibiotics, and biological and chemical substances used in breeding animals to accelerate their growth and body mass as well as chemicals used to improve crops in growing plants. Consequently, meat products and animal-based foods, such as milk or butter, as well as some plant-based foods, represent a potential capacity to stimulate and modify the functioning of the endocrine system, primarily in respect of the secretion of the human growth hormone (GH).

The study of intergenerational changes with respect to social gradients sheds some light on changes in living standards over time and the degree of social stratification. Secular changes are usually more distinct in the least developed social groups and populations. Thus, this process is very intensive, particularly in a number of developing countries as well as in groups with the lowest social status. As regards the affluent social groups in Western Europe, body height in successive generations is not subject to significant variation. The differences between social strata are also declining. The disappearance of environmental differences results primarily from a larger rate of somatic trait gains in the groups of children from poor families with a lower economic status. Intergenerational transformations are usually more distinct in males than in females, which results from the different threshold sensitivity of boys and girls in terms of the influence of environmental variables (Bielicki and Charzewski 1977). However, a number of studies reveal the opposite direction of sex differences in respect of the extent of morphological intergenerational changes (Ignasiak and Sławińska 1993).

This is probably the effect of the difference in the above-mentioned biological sensitivity of males and females. Boys, who are more eco-sensitive, react to changes in their living conditions more promptly and approach the upper limit of their genetic capabilities earlier, which results in the decline of the rate of their secular trend. Girls, who are less eco-sensitive, react to the stimuli later; therefore, when favorable environmental conditions persist, they achieve the upper limit of their genetic capabilities later, and thus their process of intergenerational changes also stops later.

As numerous studies reveal, the Polish population is highly homogeneous and, consequently, no distinctive genetic differences are found (Bielicki et al. 2000). Such a population provides excellent material for observing intergenerational changes, as any differences in the biological development primarily reflect a large diversification in terms of family living conditions, social strata, and local populations.

80.2 Acceleration of Body-Height Increase

Body height represents a typical example of a continuous trait whose variation develops under the influence of genotype as well as the environmental characteristics of the places where the individuals are raised. Studies show that the final body height of individuals is determined genetically, in about 60%, and after taking into account the additional influence of uterine environmental factors during fetal development as well as cultural factors, this figure amounts to 71% (Byard et al. 1993). The environmental variables directly affecting B-v throughout an individual's development include nutritional habits (food quantity and quality) in proportion to energy expenditures of the body as well as the degree of disease impact on the progressive stage of ontogenesis (Bielicki et al. 2005). The environmental factors listed earlier are strictly connected with family living standards, which largely result from the country's economic situation.

Body height has been recorded in a number of European countries since 1750. Recently, this trait has been commonly used to describe the economic development of different countries. Komlos (1994) analyzed economic fluctuations in a number of countries, using the state of nutrition and health, and economic status of social strata and groups based on body-height changes over 205 years. In his opinion, data on body height may replace information on gross national product per capita, which was previously used in the evaluation of affluence of social strata and groups.

80.3 Secular Trend in Body Height of Polish Conscripts

In Poland, studies involving 19-year-old conscripts provide the most extensive and representative data for the assessment of intergenerational changes with respect to body height. Pursuant to the Polish law, every year, all 19-year-old males are involved in conscription procedures, regardless of whether they are to be subsequently enlisted. Based on the data gathered in this manner and prepared at the beginning of the twentieth century by Mydlarski (1933), and subsequently by Bielicki et al. (2000, 2005), it is possible to state that, over 74 years (1927–2001), the mean body height of Polish males increased by 11.3 cm (Table 80.1). The increase in body height over this period, perceived as an increasingly fuller exploitation of the genetic growth potential, was caused by the improvement in living and development conditions of children and adolescents. During these years, Poland suffered from economic crises resulting from World War II and an economic downturn in the 1980s,

Table 80.1 Secular trend in body height of Polish conscripts in the years 1927–2001

Year of study	*n*	$\overline{x}$	SD	*v* (%)	Gain per decade (cm/decade)	Author
1927	–	166.1	6.3	3.79	–	Mydlarski (1933)
1928	–	166.1	6.3	3.79	–	Mydlarski (1933)
1929	–	166.3	6.2	3.73	–	Mydlarski (1933)
1930	–	166.6	6.1	3.66	–	Mydlarski (1933)
1965	21,155	170.5	5.9	3.46	–	Bielicki et al. (2000)
1976	12,711	173.2	6.3	3.64	2.4	Bielicki et al. (2000)
1986	29,275	175.3	6.2	3.54	2.1	Bielicki et al. (2000)
1995	30,940	176.9	6.4	3.62	1.8	Bielicki et al. (2000)
2001	30,850	177.4	6.7	3.78	0.8	Bielicki et al. (2005)

The table shows the height increase in Polish conscripts in the years 1927–2001 including height gains in particular decades

n number of conscripts examined; $\overline{x}$ average body height of conscripts in a given year; SD standard deviation of body height; *v* (%) coefficient of variation ((SD/ $\overline{x}$)100%). 8

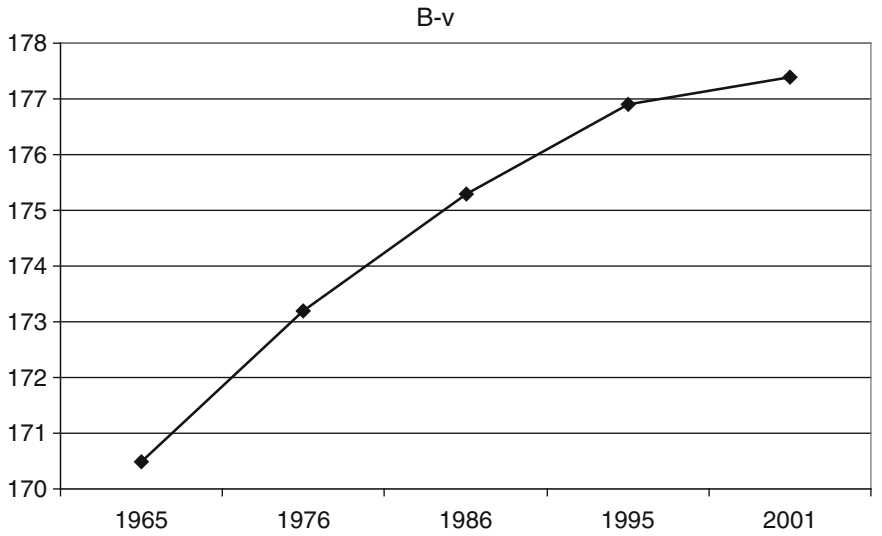

Fig. 80.1 Secular trend in body height (B-v) of Polish conscripts in the years 1965–2001 (Bielicki et al. 2000, 2005). Arithmetic mean values of body height demonstrate a height increase in Polish conscripts in the years 1965–2001 (Based on, Bielicki et al. 2000, 2005, by permission)

and underwent a socioeconomic transformation in the 1990s. A precise estimation of body-height gains per decade was possible, as the studies were repeated in approximately 10-year time intervals. Such results calculated per decade on the basis of data from, for example, a 35-year period, would lead to excessive averaging of the values of these changes, which are not a monotonic phenomenon. Thus, the data gathered allow for the precise determination of the rate of height increase of Polish males only over the past 4 decades. A gradual slowdown in the rate of increase in the mean body height among conscripts was observed in this period, as it fell from 2.4 cm/decade in the years 1965–1976 to 0.8 cm/decade in the years 1995–2001 (Table 80.1, Fig. 80.1). There are two hypotheses as regards the reasons for the slowdown, which has been observed since 1986: the so-called "crisis hypothesis" and the "genetic limit hypothesis" (Bielicki et al. 2005). The cohort studied in 2001 was affected by both the economic crisis (1980s) in their childhood and "the shock" caused by the transformation (1990s) during their puberty (Bielicki et al. 2003). It should be noted, however,

Table 80.2 Body height of Polish conscripts by degree of urbanization of their place of residence (Reprinted from Bielicki et al. 2005, by permission)

	1965		1986		1995		2001	
Type of settlement	$\bar{x}$	SD	$\bar{x}$ (cm)	SD	$\bar{x}$ (cm)	SD	$\bar{x}$ (cm)	SD
Cities over 500,000	172.7	6.0	176.9	6.5	178.0	6.7	178.8	6.8
Cities 100–500,000	171.3	5.9	175.6	6.3	177.4	6.7	178.2	6.7
Cities 25–100,000	171.0	6.0	175.9	6.4	177.3	6.4	177.8	6.6
Towns under 25,000	170.8	5.9	175.5	6.4	177.0	6.5	177.5	6.6
Rural areas	169.8	5.8	174.0	6.1	175.7	6.3	176.4	6.5

The table shows height increase in Polish conscripts by the size of their place of residence. Throughout the study period (1965–2001), the mean body height of males manifests a distinct gradation by the size of the place of their residence

$\bar{x}$ means body height of conscripts in a given year; SD standard deviation of body height

that despite food rationing and a drop in consumption resulting from the shortages of products, a marginal GDP increase was still observed in the 1980s. Moreover, the rapid educational advancement of the conscripts' parents continued and the percentage of mothers with secondary and university education in the cohort of conscripts in 2001 doubled as compared with 1986; mother's education is considered to have a particularly strong influence on family living standards (Bielicki et al. 2005). Consequently, these factors may have provided protection against the influence of the economic crisis on height increase in the young generation of Poles. The "genetic limit" hypothesis assumes that every individual represents a genetically determined upper value of the trait, which may theoretically be achieved provided an individual's development is not disturbed by any environmental deficits. It seems that in the event that the secular trend in the body height of Poles is inhibited, both hypotheses concerning the reasons for this phenomenon are probable and do not exclude each other.

The analysis of intergenerational changes in the groups singled out with respect to the degree of urbanization of their place of residence reveals a gradual increase in the mean body height in all cohorts. At the same time, a distinctive social gradient of body height is noticeable and represents the same direction throughout the period analyzed. The mean body height of conscripts increases along with the increase in the size of the place of residence, and the difference between extreme groups isolated with respect to the urbanization factor (big cities and villages) over 35 years generally remained unchanged (2.9 cm in 1965 and 2.4 cm in 2001). This proves the lasting living standard diversification (consumption, health, and parents' education) in cities and villages (Table 80.2, Fig. 80.2).

The secular trend in body height in the groups singled out with respect to father's socio-professional status showed that, in all cohorts, average body height increased along with social advancement. Furthermore, intergroup disparities did not undergo major changes over 36 years (1965–2001). Conscripts from big-city, well-educated families are the only exception, as height increase was not observed in them between 1995 and 2001 and, thus, in 2001, their mean body height was not different from big-city conscripts whose fathers had secondary education. A similar situation was observed in 1986 following the rapid body-height increase trend in the sons of fathers with secondary education from big cities (Fig. 80.3). Body-height stabilization in the conscripts from big-city, well-educated families, distinct particularly after 1995, might show that the group achieved its "genetic limit" in terms of body height, if it were not for the fact that, in 2001, they were surpassed by a new social group – entrepreneurs. The presence of social gradients without tendencies for bridging the disparities between the elites and social groups with a lower economic status, as well as the appearance of a new elite, demonstrates that the Polish population still represents considerable "genetic reserves," which can enable a further increase in average body height. Consequently, the deceleration of body-height increase, which has recently been observed, most likely results from a series of socioeconomic crises, which is emphasized by Bielicki et al. (2005).

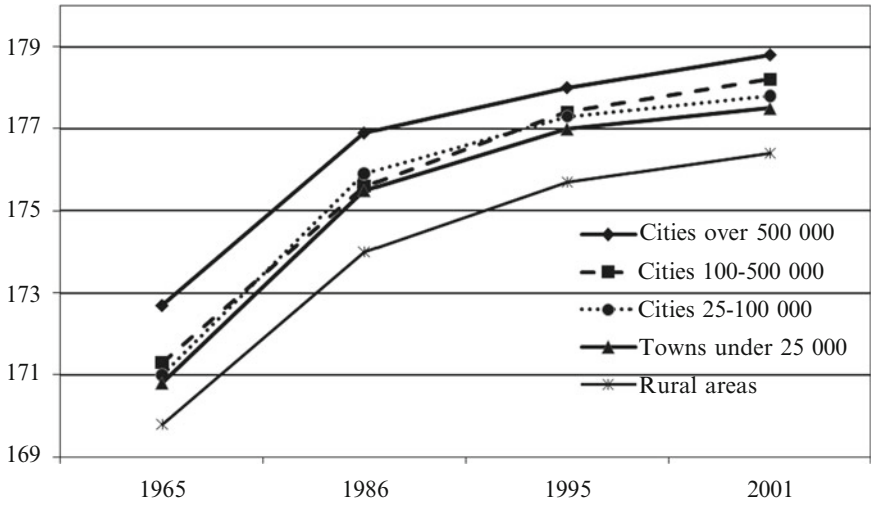

Fig. 80.2 Body height of Polish conscripts in the years 1965–2001 by size of their place of residence. Height increase of Polish conscripts in the years 1965–2001 occurred regardless of the degree of urbanization of the place of residence. However, throughout the study period, distinct environmental differences with respect to the size of the place of residence persisted. (Reprinted from Bielicki et al. 2005, by permission)

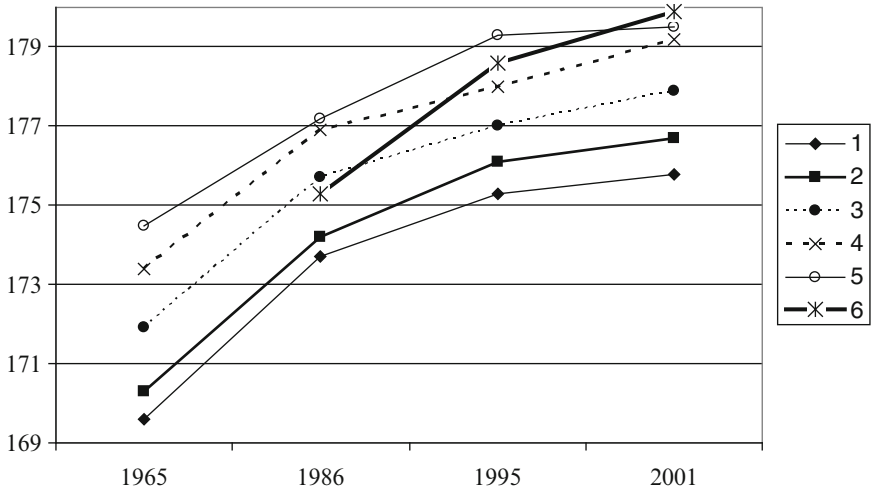

Fig. 80.3 Body height of conscripts by degree of urbanization of their place of residence and social status of father. In the years 1965–2001, the mean body height of Polish conscripts increased, which demonstrates socio-environmental disparities determined by father's education and the degree of urbanization of the place of residence. Entrepreneurs constituted a new social stratum, which was first recorded in 1986. In 2001, their sons were found to be taller than the tallest conscripts from big-city families whose fathers had university or secondary education. This demonstrates the continuing presence of "genetic reserves," which, in favorable conditions, will result in further height increase of the Polish people. (*1*) Village, father – farmer, primary education; (*2*) village, father – farmer, secondary education; (*3*) city over 100,000, father – skilled worker, vocational education; (*4*) city over 100,000, father – technician, secondary education; (*5*) city over 100,000, father – specialist, university education; (*6*) city over 100,000, father – entrepreneur, university or secondary education. (Reprinted from Bielicki et al. 2005, by permission)

80.4 Secular Trend in Body Height of Polish Students

The comparison of body heights of Polish conscripts and students of the Medical University of Poznań provides another confirmation that social gradients do exist. Throughout the study period, students of the Medical University were, on average, much taller than Polish conscripts, which shows that there is a positive selection, as students presumably come from well-educated families with a good economic situation and high living standards. The slowdown of the upward body-height trend observed in 1988 as compared with the data from 1976 demonstrates that living conditions deteriorated to a certain extent during the development of this cohort (Table 80.3, Fig. 80.4). This is a surprising phenomenon, as, at the same time, a continuing body-height increase in Polish conscripts was observed. It seems that this results from the relatively small size of the sample of students examined in 1988 (92 persons).

Table 80.3 Secular trend in body height of students of the Medical University of Pozna in the years 1965–1994

Year of study	*n*	$\overline{x}$	SD	*v* (%)	Gain per decade (cm/decade)	Author
1966	134	176.0	4.4	2.5	–	Malinowski and Strzałko (1970)
1977	126	177.4	5.9	3.3	1.3	Drozdowski et al. (1980)
1988	92	177.8	6.1	3.4	0.4	Deckert (2000)
1993	132	178.3	5.4	3.0	1.0	Deckert (2000)

The table shows height increase in the students of the Medical University of Pozna
n number of students examined; $\overline{x}$ mean body height of students in a given year; SD standard deviation of body height; *v* (%) coefficient of variation, ((SD/ $\overline{x}$). 100%) together with body-height gains per decade

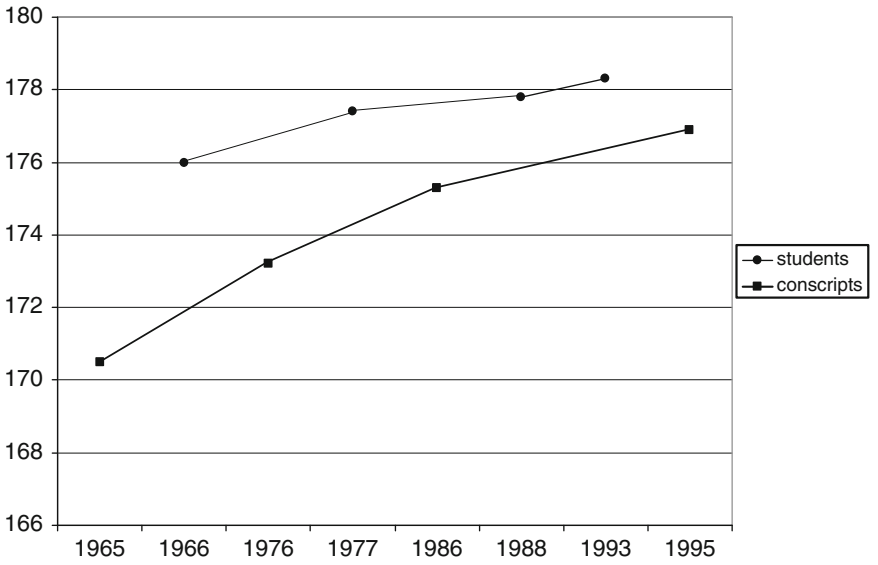

Fig. 80.4 Secular trend in body height in students against intergenerational changes in conscripts in the years 1965–1995. The diagram shows stature increase in the students of the Medical University of Pozna and the population of Polish conscripts. As regards body height, distinct differences prove the existence of a discrepancy with respect to socioeconomic conditions in both groups. The figure shows mean body-height values. (Based on data from Malinowski and Strzałko 1970; Drozdowski et al. 1980; Deckert 2000; Bielicki et al. 2000, 2005)

80.5 Acceleration of Relative Body Mass (BMI) Increase

Body mass is strongly correlated with body height and, usually, demonstrates secular variability as well. The examination of body mass as an absolute trait significantly impedes the interpretation of the results; hence, analysis of the secular trends of this trait was based on BMI, which reflects its relative value. Studies show that BMI is less genetically determined than body height and, consequently, is more influenced by environmental conditions. The heritability of relative body mass is estimated at 30%. The index demonstrates exceptional lability, which means it rapidly reacts to even short-time changes in the environmental factors, such as nutrition, physical activity, or diseases. Its major advantage is that it carries significant information value for the assessment of the organism's health, as it correlates with different measures of body fat and obesity.

80.6 Secular Trend in the Body Mass Index (BMI) in Polish Conscripts

The mean value of BMI in the population of conscripts throughout the 36-year study period increased by 0.53 units and represented the values as follows: 0.12 units/decade in the years 1965–1986, zero in the decade 1986–1995 (political and socioeconomic transformation period), and as much as 0.48 units in 1995–2001 as expressed per 10 years. The upward trend as regards the mean value of BMI shows a distinctive improvement in the living conditions, particularly over the recent years (1995–2001) (Table 80.4, Fig. 80.5.). This is confirmed by economic data, which reveal that, in the years 1995–1997, a rapid economic growth of 6–7% GDP was observed, which resulted in an increase in the population'sincomes, albeit unequal in particular professional groups. It should be noted that, at the same time, the upward trend in height was small, which demonstrates the considerable stability of this trait, which is in fact an irreversible reaction to the cumulative influence of factors operating throughout the period of growth of an individual. BMI depends considerably on absolute body mass and reflects much sooner the effects of an even short influence of environmental factors. Throughout the study period, mean values of BMI in 19-year-old males decreased relative to city size, where the biggest cities with the population of 100,000–500,000 were at the top as regards BMI, small towns with the population below 25,000 in the middle, and medium-sized towns with the population between 25,000 and 100,000 at the bottom. In 1965, conscripts from villages (food producers) represented the highest BMI value, whereas, after 25 years, they were caught up with by big-city

Table 80.4 Intergenerational changes in the body mass index (BMI) in Polish conscripts in the years 1965–2001 (Reprinted from Bielicki et al. 2005)

Year of study	n	$\overline{x}$ (kg/m^2)	SD	v (%)	Gain per decade
1965	21,145	21.73	1.98	9.10	–
1986	26,440	21.98	2.40	10.90	0.12
1995	26,245	21.97	2.76	12.58	–0.01
2001	26,528	22.26	3.09	13.86	0.48

The table shows intergenerational BMI increase in Polish conscripts in the years 1965–2001, including the rate of increase per decade. The mean values show that the trend came to a standstill during the period of political and economic transformation of Poland (1986–1995)

n number of conscripts examined; $\overline{x}$ BMI mean value for conscripts in a given year; SD standard deviation of BMI; v (%) coefficient of variation $\overline{x}$

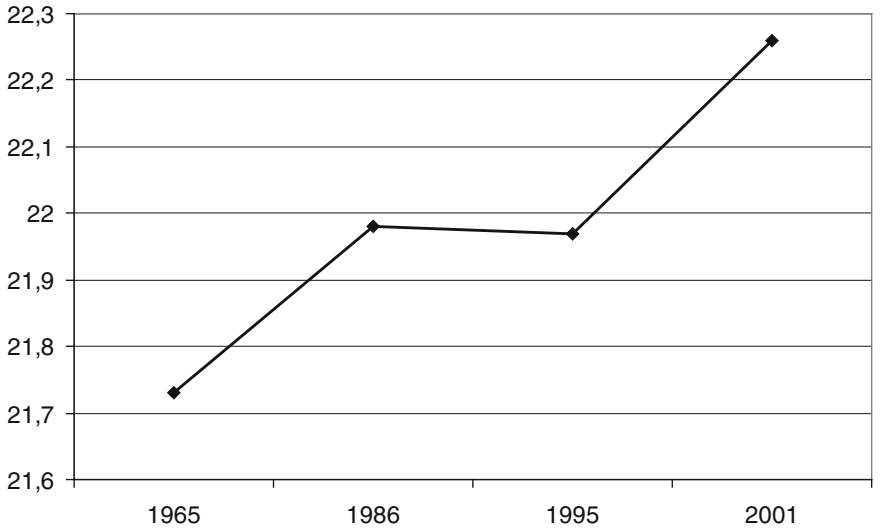

Fig. 80.5 Changes in BMI mean value in Polish conscripts in the years 1965–2001. The diagram shows body-weight increase in proportion to body height in Polish conscripts in the years 1965–2001, with a distinct standstill in the years of the political and economic transformation (1986–1995). The above relationship confirms the socioeconomic conditions of this secular trend. (Reprinted from Bielicki et al. 2005, by permission)

Table 80.5 Relative body mass of Polish conscripts by degree of urbanization of the place of residence (Reprinted from Bielicki et al. 2005, by permission)

	1965		1986		1995		2001	
Type of settlement	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Cities over 500,000	21.58	2.58	22.05	2.65	22.25	3.00	22.39	3.24
Cities 100,000–500,000	21.73	2.06	21.97	2.48	21.97	2.93	22.30	3.09
Cities 25,000–100,000	21.54	2.00	21.90	2.51	21.78	2.85	22.10	3.15
Towns under 25,000	21.69	2.00	21.94	2.43	21.86	2.74	22.17	3.15
Rural areas	21.82	1.89	22.04	2.25	22.05	2.65	22.28	2.99

In the years 1965–1986, a strong increase in the BMI value was observed in conscripts from big cities (over 500,000). These conscripts have consistently represented the highest value of this index since 1995. High BMI values in conscripts from rural areas (food producers) demonstrate that, unlike body height, absolute body mass is more sensitive to the influence of environmental factors. Throughout the study period, the dispersion of the index values (SD) increased markedly

(500,000+) conscripts, who represented a rapid increase in the index value in the years 1965–1986. In subsequent years, big-city conscripts represented the highest BMI values. Data from 1995 show a distinctive deceleration in respect of the relative body mass in almost all social groups, which is undoubtedly the result of deterioration of living conditions caused by the transformation in the 1990s. Big-city conscripts provide an interesting exception with respect to BMI values, which, instead of decelerating or regressing, gradually increased. The trend demonstrated a noticeable revival in all examined urban categories except for big cities in the years 1995–2001 (Table 80.5, Fig. 80.6). It seems that the changes in nutritional behaviors toward a diet with a large content of fats and carbohydrates, coupled with a decrease in physical activity in favor of more time spent in front of a computer or television set, account for a rapid increase in BMI mean values.

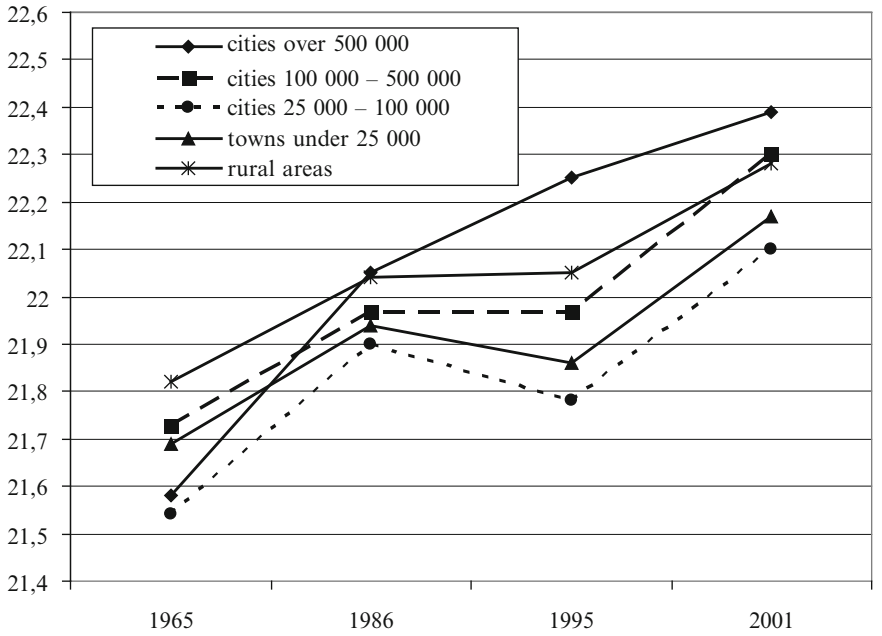

Fig. 80.6 Changes in the body mass index (BMI) in Polish conscripts in the years 1965–2001 by degree of urbanization of their place of residence. Regardless of the degree of urbanization of the place of residence, conscripts represented an upward BMI trend. In the years 1986–1995 (during the economic transformation in Poland), a deceleration of relative body mass was observed in the majority of males, except for big-city dwellers (500,000+). Renewed BMI acceleration was observed in the years 1995–2001, which reflected the changes in nutritional behaviors toward a diet with a large content of fats and carbohydrates coupled with a decrease in physical activity. (Reprinted from Bielicki et al. 2005, by permission)

80.7 Secular Trend in the Body Mass Index (BMI) in Polish Students

A comparison of the relative body mass trend in the Polish population of conscripts and students of the Medical University of Pozna reveals that the students' BMI mean value was on the decline until the late 1980s and then demonstrated a rapid increase (1.88 units as calculated per decade in the years 1988–1993). Interestingly, the increase occurs during the period of the socioeconomic transformation in Poland, which led to a regression in the increase of the BMI value in conscripts (Tables 80.4, 80.6, Fig. 80.7). It should be noted that substantial BMI values may be caused not only by excessive body fat but also by a muscular, mesomorphic body build. It is possible that individuals' intentional care about their physical appearance accounts for the above-mentioned differences in respect of relative body mass between students and conscripts. As men intend to keep a muscular body build, they may consequently do appropriate physical exercises and select food products appropriate in terms of quantity and quality. However, it seems that study results for the cohort of students in 1988 are not fully representative on account of their limited number, which was mentioned earlier. To sum up, BMI values seem to have been on the decline in 1966–1988, but the decrease was not considerable; hence, the change in the trend after 1988 was not rapid, either. However, this hypothesis requires more extensive analysis, which would in particular take into account the socioeconomic status of students. However, this is impossible due to the nature of the source, which provided data on the male students.

While assessing the stabilized value of changes in body height and relative body mass between successive cohorts of conscripts, it is easy to notice that males examined in 1986 were different from their peers 21 years earlier more in terms of height than the BMI value. This difference declined over

Table 80.6 Secular increase in the relative body mass in students of the Medical University of Poznań (Own calculations based on data from Malinowski and Strzałko 1970; Drozdowski et al. 1980; Deckert 2000)

Year of study	*n*	BMI*	Gain per decade
1966	134	22.38	–
1977	126	22.11	–0.24
1988	92	21.61	–0.46
1993	132	22.55	1.88

The table shows BMI deceleration in students of the Medical University of Poznań in the years 1966–1988, followed by a rapid increase in their relative body mass. BMI changes per decade are also provided

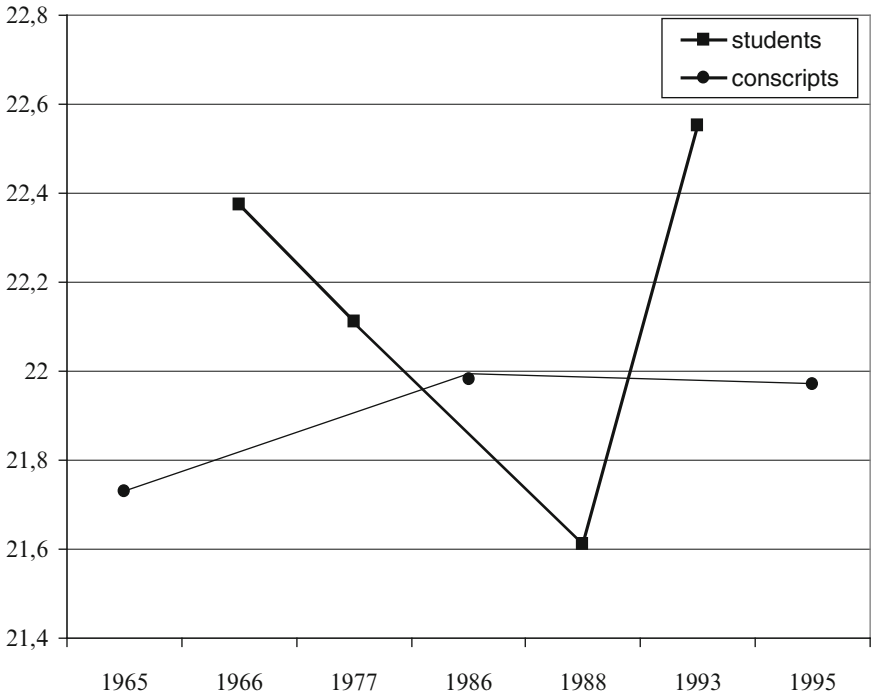

Fig. 80.7 Secular increase in the body mass index (BMI) in students against intergenerational changes in conscripts in the years 1965–1995. Except for the students examined in 1988, throughout the study period, students invariably represented a higher BMI than conscripts, although the representativeness of the 1988 sample may raise doubts on account of its small size ($n = 92$). (Based on Deckert 2000; Bielicki et al. 2005)

the subsequent 9 years, but, in 2001, the conscripts outdistanced their peers examined 21 years earlier in respect of both traits to a similar degree (Fig. 80.8). This demonstrates a gradual decline in the body-height increase trend in favor of an increase in the relative body mass of successive generations.

80.8 Intergenerational Changes in Other Somatometric Traits

Scientific literature describes secular trends more frequently on the basis of body height than body mass. Other somatic traits are analyzed extremely rarely. Current studies reveal that acceleration does not concern all traits to the same degree. The literature reveals that diversification in respect of

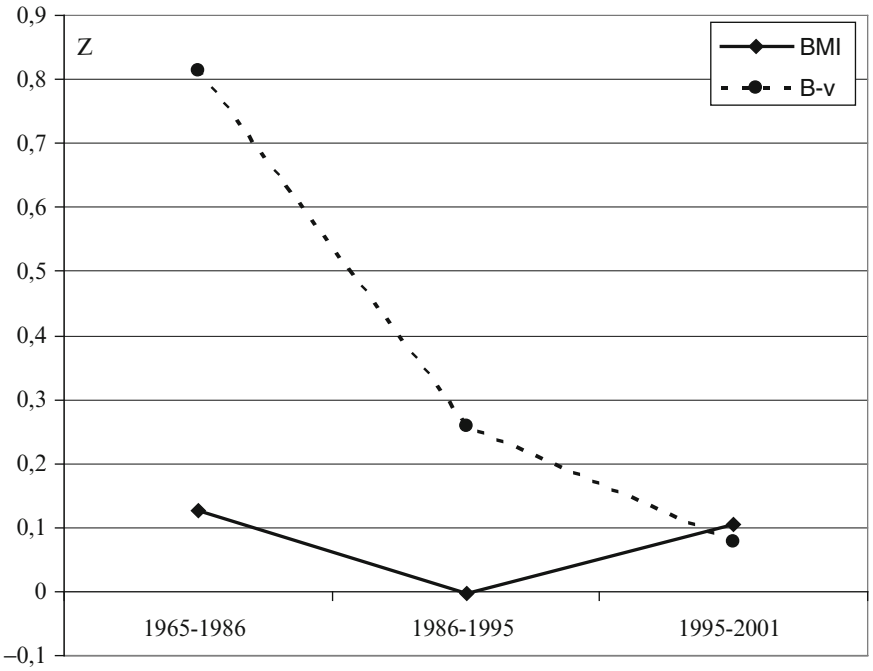

Fig. 80.8 Normalized values of gains of body height and the body mass index (BMI) in conscripts in successive time intervals. Normalized values of body height and BMI in Polish conscripts manifest deceleration of body-height increase and an upward relative body mass trend in successive generations. Mean value of trait/index from 1986 was normalized for mean and standard deviation of trait/index from 1965, etc. (Based on Bielicki et al. 2005)

acceleration in the development of body height and mass leads to a more slender average body build (Szczotkowa 1970; Malinowski 1978; Ignasiak and Sławińska 1993). Acceleration is also thought not to concern trunk length (Szczotkowa 1970, Malinowski 1978) and chest depth (Malinowski 1978). Conversely, the broadening of shoulders (Szczotkowa 1970; Malinowski 1978; Sitek et al. 2007), chest broadening, as well as the narrowing of the hips have been observed over a number of years (Szczotkowa 1970; Malinowski 1978). The change in the proportions of limb length caused by the lengthening of lower limbs is noticeable as well (Szczotkowa 1970).

80.9 Conditionings of Acceleration of Menarche

On average, menarche occurs a year after pubertal growth spurt. This is the most characteristic and critical moment in female puberty. The occurrence of menarche manifests their ability to reproduce, with a balanced development of external sex characteristics, and depends largely on the functioning of the hormonal system. Biologically, menarche means the commencement of hypothalamus control of the gonadotrophic activity of the pituitary gland as well as the cyclic activity of ovaries. The age when menarche occurs is affected by genetic and environmental factors. It is widely thought that age at menarche is a very sensitive indicator of the socioeconomic situation of the population, a kind of a litmus paper reacting to the slightest changes in living conditions. The socioeconomic factors are found to have a more considerable impact on pubertal timing in children than chemical and physical pollution of water, soil, and air (Hulanicka et al. 1994). It is girls who are well nourished, raised in good living conditions, and have parents with larger incomes, who attain the ability to reproduce earlier (Hulanicka et al. 1994;

Wolański 2006). Conversely, early reproductive ability is also related to difficult psychosocial situations related to parental conflicts, divorce, absence of the biological father, step parents, or lack of affection and attention on the part of the mother or father (Cichocka and Żarów 2002). Early reproductive ability was also found in girls with vision or hearing disorders (Umławska 2006) as well as in the daughters of parents who smoked (Umławska and Kolasa 2002). Hulanicka (1986) proposed the following model of relationship between pubertal timing and psychological stimuli: "Lack of psychological stimuli inhibits puberty. A large intensity of stimuli and frequent stressful situations accelerate puberty, but when stressful situations become excessively frequent and stimuli excessively strong puberty is inhibited." Given the above, Hulanicka et al. (1994) present the opinion that early puberty should not be perceived a priori as a symptom of good biological condition of individuals or the population.

Pubertal timing is also related to the climate. The earliest onset of puberty is observed in moderate climate areas, that is, with the average annual temperature ranging between 5°C and 10°C (e.g., Mediterranean countries), whereas the latest onset of puberty is observed in the areas with a low average temperature (e.g., Inuit and Sami people) (Wolański 2006).

Age at menarche is related to the body build as well (Łaska-Mierzejewska and Łuczak 1996). Girls with a very slender body build menstruate 1.8–2.58 years later than their peers with an extremely stout body build (Łaska-Mierzejewska and Łuczak 1996). In the 1970s, Frisch and Revelle declared that menarche may be initiated when the so-called critical body mass is attained or the metabolism rate declines. Over many years, this hypothesis was revised and criticized by numerous authors (e.g., Billewicz et al. 1976). At the same time, some papers that confirmed the decisive role of adipose tissue in initiating the first menstruation were published. It is currently thought that conversion of androgens to estrogens in adipose tissue is the reason for earlier menarche in obese girls. An intermediary factor in the interaction between the body build and age at menarche is leptin, which represents a positive correlation with the quantity of adipose tissue ($r = 0.81$) and an inverse correlation with the pubertal age. Studies revealed that a body-fat increase by 1 kg accelerates menarche by 13 days and an increase in leptin concentration by 1 ng/mL accelerates menarche by 1 month (Matkowic et. al. 1997).

Physical exercise is another factor related to age at menarche. Studies demonstrate that excessive physical load caused by sport training delays menarche (Malina 1983; Skierska 1998). There are different hypotheses concerning the reason for this phenomenon. Physical load is frequently thought to be a direct factor that delays menarche (Malina 1983), which would be plausible only in the event of girls who exercised intensively prior to menarche. However, this correlation also concerns girls who commenced practicing sports after their first menstruation. Consequently, the most probable hypothesis seems to be the one suggesting selection for sports in terms of body build. As it is widely known, a slender body build is necessary in sports, such as gymnastics or long-distance running, and it is those girls practicing these sports who are characterized by the latest menarche (Malina 1983; Skierska 1998). It was even found that the better sport results girls achieve, the more delayed their puberty timing is (Skierska 1998).

A secular trend in the form of earlier pubertal timing in successive generations has been observed for over 100 years (Cichocka and Żarów 2002; Łaska-Mierzejewska and Olszewska 2007). Over the past 150 years, the onset of puberty has been globally lowered by 3 years, which is 0.2 year/decade. It should be noted that this phenomenon significantly varies among different parts of the world (Wolański 2006). A noticeable drop in age at menarche in successive generations is thought to result from improvement in living conditions, hygiene, increasing consumption of animal protein, and the lifestyle change triggered by urbanization (Bielicki 1999; Wolański 2006). According to other authors, the factor which accounts for menarche acceleration is the right body size, which girls now attain earlier, including critical body mass (i.e., weight and characteristic composition of the body, which is necessary to menstruate) (Frisch and Revelle 1970). Along with frequent acceleration of puberty, an inverse process, that is, its regression or deceleration, is observed as well.

80.10 Acceleration of Menarche in Polish Girls

Age fluctuations with respect to menarche occurrence in Polish girls, observed after World War II, clearly reflect political and economic changes that Poland experienced in this period. Postwar Poland was in the possession of modest capital, social, and cultural resources and suffered from civilizational backwardness, which led to delayed industrialization. The rapid development of industry and an increase in employment have been observed since the 1950s, which has led to the improvement of living conditions, particularly in large urban areas. The emphasis on industry hampered the development of other economic sectors, and, in particular, agriculture. This is reflected in the acceleration of puberty in girls, which was primarily noticeable in big cities (0.51 years; 6.12 months). The most beneficial in economic terms was the period 1971–1975, when, due to mechanization and widespread use of fertilizers, agriculture represented a considerable rate of development. Age at menarche, being an exceptionally eco-sensitive measure of living conditions, illustrated this advantageous situation for Polish villages, as it demonstrated the most considerable decrease (0.48 year – 5.76 months). Small towns also saw a substantial acceleration of menarche (0.43 year – 5.16 months). Subsequent years (1977–1989) witnessed a severe economic crisis, including the rationing of food, as well as of a number of non-food products. This was reflected in pubertal timing in girls, which manifested delayed age at menarche in three social groups. Except for the above-mentioned period, this phenomenon was not observed in any anthropological studies conducted in Poland after World War II. The largest delay of age at menarche affected girls living in small towns (0.25 years – 3 months) and those living in big urban areas (0.12 years – 1.44 months). Deceleration of puberty timing in girls living in villages was negligible (0.06 years – 0.72 month), which seems to be obvious as food rationing must have hardly affected its producers. The years 1987–2001 witnessed a political and economic transformation related to the change in the system of ownership (privatization of state-run enterprises). Numerous industrial enterprises were liquidated and unemployment increased considerably, which had a greater effect on villages than cities on account of the liquidation of state-run farms. These changes led to a huge increase in social disparities, as impoverishment of a considerable part of the society was accompanied by an increase in the affluence of a relatively small group of the population. The results of studies conducted in 1997 and 2001 demonstrate a further acceleration of puberty timing in girls as compared with the 1980s (0.20 years – 2.4 months/decade for big cities and 0.24 years – 2.88 months/decade for villages), which demonstrates that political and economic transformation was more favorable for the development and puberty of girls than the period of the economic crisis at the turn of the 1980s (Table 80.7, Figs. 80.9 and 80.10).

The economic situation of the country had a varied impact not only on young generations living in environments with different degrees of urbanization but also on children and adolescents living in the same environments but coming from families with different socioeconomic status. This is confirmed by studies on age at menarche in Polish girls living in the countryside

Table 80.7 Secular trend in age at menarche in Poland by degree of urbanization of the place of residence (Based on Hulanicka and Waliszko 1991; Charzewski et al. 1998; Łaska-Mierzejewska and Olszewska 2007)

Type of settlement	1955	1966	1978	1988	1997	2001
Big cities of over 500,000	13.41	12.90	12.84	12.96	12.76	–
Small towns of about 10,000	13.94	13.58	13.15	13.40	–	–
Rural areas	14.28	13.95	13.47	13.53	–	13.22

Arithmetic mean values for the age at menarche demonstrate acceleration of age at menarche in all environments under analysis

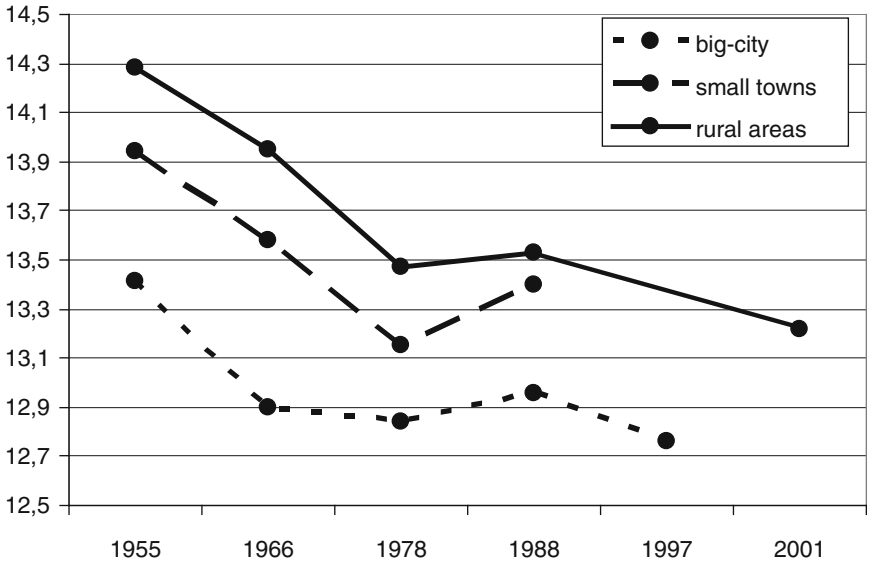

Fig. 80.9 Changes in age at menarche in girls, Poland 1955–2001. Throughout the period under analysis, lowering of age at menarche was observed along with increased degree of urbanization of the place of residence. (Based on Hulanicka and Waliszko 1991; Charzewski et al. 1998; Łaska-Mierzejewska and Olszewska 2007)

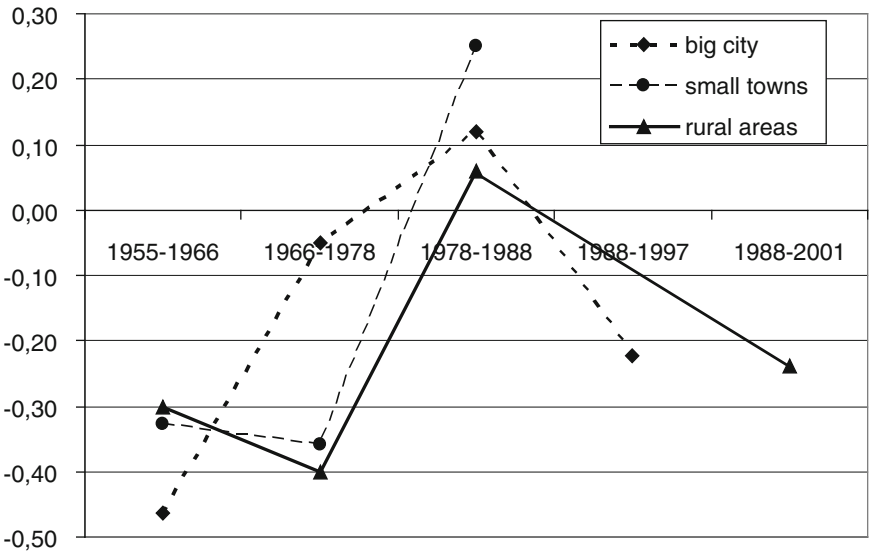

Fig. 80.10 Changes in age at menarche in Polish girls in the years 1955–2001 by degree of urbanization of the place of residence. In 1966, big cities saw the largest acceleration of age at menarche, which was the consequence of industrial development and higher employment resulting in living conditions improvement. The subsequent decade saw rapid agricultural development, which resulted in acceleration of age at menarche in villages and small towns; the years 1977–1989 witnessed an economic crisis resulting in the deceleration of age at menarche in all social environments. Lowering of the age at menarche in Polish girls was observed in subsequent years, despite the political and economic transformations. (Based on Hulanicka and Waliszko 1991; Charzewski et al. 1998; Łaska-Mierzejewska and Olszewska 2007)

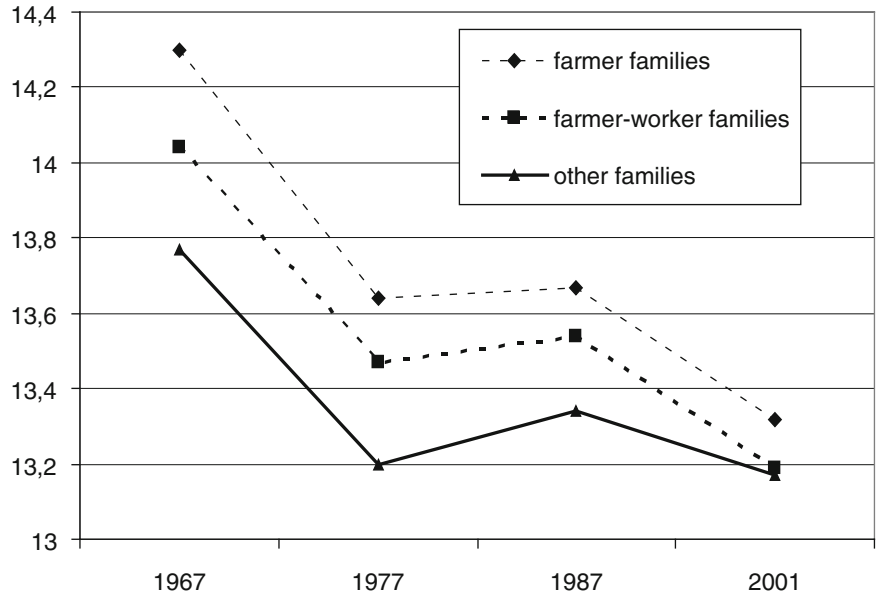

Fig. 80.11 Age at menarche in girls from Polish villages by socio-professional groups. Poland's economic situation has an unequal impact on children and adolescents living in the same environment but in families of different socio-professional status. Throughout the period under study, the latest onset of puberty was observed in the daughters of farmers, whereas girls in rural families possessing no land menstruated earliest. The above gradients demonstrate the bad economic situation of Polish farmers in the study period. (Reprinted from Łaska-Mierzejewska and Olszewska 2007, by permission)

(Łaska-Mierzejewska and Olszewska 2007). Throughout the study period (1967–2001), the daughters of villagers who were not landowners attained the ability to reproduce earlier than girls from families consisting of both farmers and workers, whereas the daughters of farmers were the last to become sexually mature. In 1967, the average pubertal age was 14.3 years for the farmer group, 14.04 years for the farmer–worker group, and 13.77 for the non-agricultural group. The difference between extreme groups amounted to 0.53 years. In the decade of prosperity purchased with bank loans, a rapid acceleration of puberty was observed in all the three socio-professional groups, although the largest drop in age at menarche was noted in girls from farming families (0.66 year), whereas, in the other two groups, it amounted to 0.57 years. The villagers, who were not landowners, were the most severely affected during the period of economic crisis and food rationing. The rate of deceleration of age at menarche in girls from this group amounted to 0.14 in the decade 1977–1987, whereas, in girls from farmer–worker families, it was 0.07, and, in the group of food producers (which was then most privileged), only 0.03. Although this diversification with respect to the deceleration of age at menarche reduced the gradient between these socio-professional groups, which amounted to 0.33 in 1987, the disparities still persisted and had the same direction. The studies repeated by Łaska-Mierzejewska and Olszewska in 2001 involved only four out of eight Polish rural areas studied previously. The results confirmed continuing diversification with respect to age at menarche in girls from different social groups, although the difference between extreme groups decreased to 0.15 years (Fig. 80.11).

The presented changes, in respect of menarche timing, demonstrate the continuing lowering of pubertal age in Polish girls, regardless of the degree of urbanization of their place of residence or social background. However, disparities between different social groups and areas still persist. Considerable differences in terms of age at menarche between big-city-, small-town-, and village

dwellers as well as between girls from different social strata within the same environment with respect to the degree of urbanization are the biological manifestation of disparities in living conditions and undoubtedly demonstrate poor living conditions of Polish villagers, and farmers in particular. The results demonstrate that Polish girls do not fully exploit their genetic potential as regards the age when they attain the ability to reproduce. This age will continue to decrease along with improvement in the socioeconomic conditions in Poland.

80.11 Conclusions

Over a period of 74 years (1927–2001), the mean body height of Polish males increased by 11.3 cm, of which as much as 61% (6.9 cm) occurred over the past 36 years. During the same time (36 years), the BMI mean value increased by 0.53 units. This trend demonstrates a fuller exploitation of the growth potential in the Polish population, which reflects the continuing improvement in the socioeconomic conditions of the society. The slowdown with respect to body-height increase in the Polish population, which has been noted in the past 9 years, results from the slower rate of improvement in the living standards of a number of social groups and from the attainment of the "genetic limit" of body height. It seems that, in the nearest future, the trend of increasing relative body mass will surpass body-height increase. In the years 1955–1988, age at menarche in Polish girls was lowered by 0.45 years (big cities), 0.54 years (small towns), and as much as 0.75 years (villages). The acceleration of age at menarche is still in progress, as, in this respect, the female population has not exhausted its genetic possibilities yet. The social gradients of body height, relative body mass, and age at menarche, persisting in the period studied, demonstrate a lasting diversification of the living standards of Poles.

Table 80.8 Key features of secular trend

1. In successive generations, a number of human biological traits are subject to adaptation-based, non-evolutionary changes called a secular trend.
2. These changes cause intergenerational phenotype variability of morphological–functional traits affected by civilizational development.
3. The changes include the following:
   - Acceleration of development and earlier puberty timing
   - Change in the sequence of a number of development stages (e.g., secondary dentition sequence), and
   - Retardation of involutionary processes – delay in aging processes
4. Developmental acceleration, which is the best-known component of the secular trend, consists of the acceleration of biological development and earlier puberty timing, which entails earlier completion of particular development stages and a larger body size.
5. Acceleration affects primarily the traits representing weaker genetic determination, which means that this phenomenon is primarily caused by changes in external factors.
6. It is thought that secular changes manifest the determination of the body to fully exploit its genetic potential in view of environmental conditions improvement.
7. The consequences of the secular trend are generally positive and include improvement of physical development and skills in children and deceleration of aging, whereas its negative consequences include divergence between biological age, calendar age, and social maturity, temporary disharmonies in the development of internal systems and organs, for example, the size of heart during the so-called pubertal growth spurt, increased incidence of faulty postures, and lower age of occurrence of a number of diseases (e.g., diabetes).

The table lists the key facts concerning the secular trend, including its reasons and consequences

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Chapter 81
Vitamin D, Exercise, and Body Composition in Young Children and Adolescents

Leng Huat Foo

Abstract Vitamin D is now more correctly categorized as a seco-steroid prohormone, rather than as a nutrient or a vitamin. The primary function of vitamin D is thought to be the maintenance of calcium and phosphate homeostasis and skeletal integrity throughout life. Although persistent severe vitamin D deficiency results in the bone disease rickets in children and osteomalacia in adults, low vitamin D status can influence musculoskeletal health at any age. Numerous epidemiological studies suggest that vitamin D deficiency and/or insufficiency are global problems for growing children and adolescents. An adequate vitamin D status in children and adolescents is associated with higher levels of lean body mass and muscle strength levels. On the contrary, vitamin D deficiency in children and adolescents is associated with elevation of PTH level, increased bone remodelling rates and a reduction in bone mass. Thus, avoiding vitamin D deficiency by ensuring an adequate supply throughout childhood and adolescence might enhance physical growth and bone mass accretion, which ultimately could reduce the risk of osteoporotic fracture later in life. Furthermore, in recent years, the positive association of vitamin D status with many non-skeletal metabolic processes such as antiproliferative, differentiation, and immunosuppressive effects, has been related a decreased risk of chronic diseases such as cardiovascular diseases, various types of cancers and type-I diabetes. However, this review will be focused on the importance of vitamin D status on body composition and bone growth in children and adolescents.

Abbreviations

25(OH)D	25-Hydroxyvitamin D
1,25(OH)D	1,25-Dihydroxyvitamin D
aBMD	Areal bone mineral density
AI	Adequate intake
ANZBMS	Australia and New Zealand Bone and Mineral Society
BA	Bone area
BMC	Bone mineral content

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_81,

BMI	Body mass index
DRI	Dietary reference intakes
DXA	Dual-photon energy *X*-ray absorptiometry
EAR	Estimated average requirements
FBM	Fat body mass
LBM	Lean body mass
LS	Lumbar spine
MED	Minimal erythemal dose
PA	Physical activity
PTH	Parathyroid hormone
UV	Ultraviolet light

81.1 Introduction

Vitamin D is chemically a seco-steroid, which acts biologically as a prohormone and requires two hydroxylation processes, first in the liver and then in the kidney, before becoming active. Either vitamin D is obtained through photosynthesis in the skin upon exposure to sunlight or it may be obtained from food. Vitamin D in the blood is taken up by the liver, and its metabolite, 25-hydroxyvitamin D [25(OH)D], is further metabolized by the kidney to the biologically active metabolite, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. This metabolite functions in calcium homeostasis by acting on the intestinal mucosal cells to increase the capacity for calcium absorption. It also has a role in decreasing renal calcium excretion and in mobilizing calcium from bone in conjunction with the actions of parathyroid hormone (PTH) and probably calcitonin to maintain extracellular ion calcium concentration within a narrow range (Fraser 1995). Other, more general functions include maintenance of skeletal integrity by influencing bone mineralization and growth in children and adolescents (Outila et al. 2001; Lehtonen-Veromaa et al. 2002a; Foo et al 2009a) and diminishing the loss of bone and of osteoporotic facture risk in postmenopausal women and the elderly (Dawson-Hughes et al. 1997; Lips 2001) by stimulating osteoblast function and promotion of mineralization of the osteoid, the unmineralized matrix. Furthermore, 1,25$(OH)_2$D also plays an important role in modulating the synthesis and secretion of PTH (Lips 2001).

81.2 Vitamin D Metabolism and Functions

Vitamin D is now more correctly categorized as a prohormone, rather than a nutrient or a vitamin. The most important source of vitamin D is that derived from the synthesis in the skin through the exposure of 7-dehydrocholesterol in the epidermis to ultraviolet radiation. This precursor undergoes photochemical isomerization to precholecalciferol (previtamin D) upon exposure to ultraviolet B radiation in the wavelength range of 300–320 nm. Precholecalciferol is thermodynamically unstable and undergoes thermal isomerization to form the more stable cholecalciferol or vitamin D_3 (Fig. 81.1). After vitamin D_3 is formed in the skin, it is transported by the vitamin D-binding protein, an α_2-globulin, in blood to the liver where vitamin D 25-hydroxylase introduces a hydroxyl group at carbon 25 to form 25$(OH)D_3$, which is the major circulating form of vitamin D; its concentration in blood gives a good indication of vitamin D status (Hollis 1996). There may also be some vitamin D in adipose tissue and muscle tissue, which may contribute substrate for the functional metabolism of vitamin D.

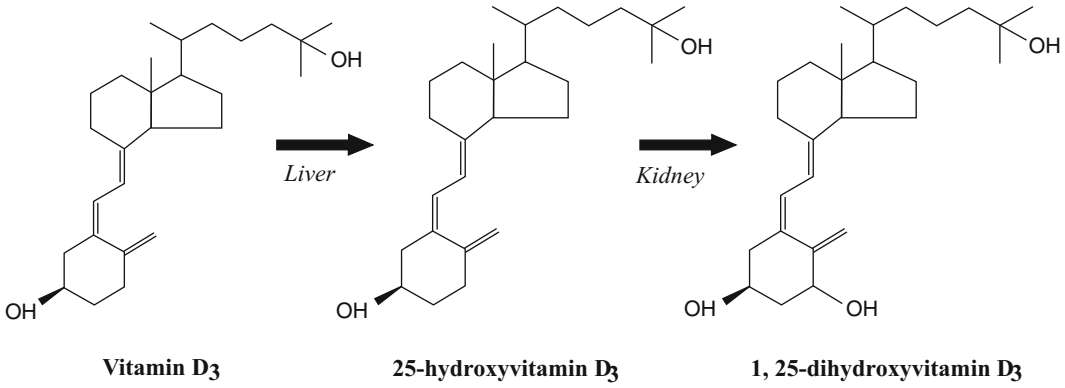

Fig. 81.1 Biosynthesis of vitamin D_3 in human body. This figure illustrates the bioconversion of vitamin D_3 to the biologically active metabolite, $1,25(OH)_3$, through two hydroxylation processes in the liver and the kidney, respectively

In order to become physiologically active, 25(OH)D is further metabolized in the mitochondria of the proximal renal tubules in the kidney, where 1α hydroxylation of 25(OH)D by 25(OH)D 1α-hydroxylase yields 1,25 $(OH)_2D_3$ (Fraser and Kodicek 1970). The renal hydroxylation to $1,25(OH)_2D$ is closely regulated by PTH, hypocalcemia, and hypophosphatemia. The compound $1,25(OH)_2D$ regulates gene transcription through a nuclear, high-affinity, vitamin D receptor (VDR) and initiation of rapid cellular response, including the synthesis of a calcium-binding protein through an interaction of $1,25(OH)_2D$ with VDR. The VDR has been found in cells of the intestine, colon, kidney, bone, brain, skin, prostate, and parathyroid, as well as other cells (lymphocytes, osteoblasts, β-islet cells, and mononuclear cells) (Holick 2004).

The biologically active form of vitamin D is now considered as a hormone because its production is at a site distant from the targets of hormone action, and it is carried to its target tissues by the blood. The conversion of 25(OH)D to 1,25(OH)D in the kidney is tightly controlled, and, except in vitamin D deficiency, is mainly independent of the supply of 25(OH)D (Fraser 1995).

The parent vitamin D is either vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol), with identical chemical structure of three double bonds, at carbons 5, 7, and 10. The differences between vitamin D_2 and vitamin D_3 are in the side chain where vitamin D_2 has an additional double bond at carbon 22 and a methyl group at carbon 24. Both vitamins D_2 and D_3 undergo the same metabolic activation process by 25-hydroxylation in the liver, followed by 1α-hydroxylation in the kidney, to make the biological active compounds, $1,25(OH)_2D_2$ and $1,25(OH)_2D_3$, respectively. The biological activity of vitamins D_2 and D_3 are often considered to be equal in humans (Jones et al. 1998). However, it is also suggested that they may have different pharmacokinetics and that vitamin D_2 may have less biological activity than vitamin D_3 (Armas et al. 2004).

Historically, the role of vitamin D has been recognized in terms of the deficiency disease of rickets in children and osteomalacia in adults. However, it is now apparent that its physiological function is also related to bone mineral homeostasis. The primary function of vitamin D is thought to be the maintenance of calcium and phosphate homeostasis and skeletal integrity throughout life (Fraser 1995). In children, the regulation of calcium homeostasis is important to ensure an adequate growth and development of bone mass (Lehtonen-Veromaa 2002a; Heaney et al. 2000). Vitamin D may also play a crucial role in prevention of chronic diseases, in which deficiency in vitamin D has been implicated, as in the development of cardiovascular diseases, autoimmune diseases, certain types of cancer, and type-I diabetes (Holick 2004).

81.3 Vitamin D Deficiency and Its Health Consequences in Children and Adolescents

It is generally agreed that persistent, severe vitamin D deficiency results in the development of rickets in children and osteomalacia in adults. Unlike deficiencies of water-soluble micronutrients, vitamin D deficiency takes many weeks to develop and can be asymptomatic. Therefore, in the past two decades, research has focused on the influence of mild vitamin D deficiency on bone health. It is suggested that a low 25(OH)D concentration, also known as hypovitaminosis D, is not only a biochemical abnormality, but also associated with physiological, pathological, and clinical signs of vitamin D deficiency, along with secondary hyperparathyroidism, and increased bone remodeling. In elderly people, such deficiency may exacerbate age-related bone loss and the risk of osteoporotic fractures (Dawson-Hughes et al. 1997; Lips 2001). Vitamin D deficiency might arise from either an inadequate supply, impaired utilization, or enhanced excretion of vitamin D.

Elderly and postmenopausal women are susceptible to vitamin D deficiency and insufficiency, but vitamin D deficiency is also being found among apparently healthy growing children and adolescents (Docia et al. 1998; Du et al. 2001; Foo et al. 2009b; Guillemant et al. 1995, 1999; Lehtonen-Veromaa et al. 2002b; Looker et al. 2002; Gordon et al. 2004). Recent surveys indicate that rickets is reappearing in developed countries (Weisberg et al. 2004) and that the prevalence of hypovitaminosis D was also increasing in developed and developing countries (Chapuy et al. 1997; Looker et al. 2002; Fraser 2004). Surprisingly, hypovitaminosis D has been found in sunny countries at tropical latitudes where cutaneous production of vitamin D can occur throughout the year (Gannage-Yared et al. 2000; El-Hajj Fuleihan et al. 2001; Hatun et al. 2005).

Severe vitamin D deficiency is associated with increased PTH levels in blood. Persistent vitamin D deficiency results in a net loss of bone, and, in children, in the development of rickets. By contrast, little is known about the effects on body composition and bone health in children and adolescents with low vitamin D status without clinical signs of rickets. Nevertheless, several studies have found that vitamin D deficiency and insufficiency in children and adolescents resulted in secondary increases in serum PTH (Guillemant et al. 1999; Foo et al. 2009b; El-Hajj Fuleihan et al. 2001; Outila et al. 2001; Gordon et al. 2004), increased bone turnover (Lehtonen-Veromaa et al. 2002a; Cheng et al. 2003; Foo et al. 2009a), and a decrease in the rate of bone mass accumulation (Jones and Dwyer 1998; Lehtonen-Veromaa et al. 2002a; Foo et al. 2009a). These studies indicated a significant inverse relationship between serum 25(OH)D and PTH concentrations. Additionally, an increase in bone turnover and in secretion of PTH due to vitamin D deficiency may increase the rate of skeletal remodeling during periods of bone growth, thus resulting in reduced bone accumulation (Slemenda et al. 1997).

81.4 Prevalence of Vitamin D Deficiency in Children and Adolescents

The definition of vitamin D deficiency based on the serum 25(OH)D concentration varies among studies. When vitamin D deficiency is defined as a serum 25(OH)D concentration of <25 nmol/L, the prevalence of deficiency ranges from 2.4% to 72%, depending on the age groups, the latitude of the population assessed, and the season of the year (Table 81.1). When deficiency was defined at the higher threshold concentration value of <50 nmol/L, the prevalence rates increased upward to range about 10–91% for young children and adolescents. Even 11–10% of apparently healthy children at 6–24 months of age living in Alaska and New Zealand had serum 25(OH)D concentrations of <37 nmol/L

Table 81.1 Key Features of Vitamin D

1. Vitamin D acts biologically as a prohormone, in which it requires two hydroxylation processes that occur in the liver and the kidney, respectively, before becoming active as 1,25-dihydroxyvitamin D [1,25(OH)D].
2. Vitamin D is obtained either through photosynthesis in the skin through exposure to the sunlight or from food.
3. Main functions of vitamin D is involvement in calcium homeostasis by regulating the intestinal calcium absorption, renal calcium excretion and mobilization of calcium from bone in conjunction with the actions of parathyroid hormone (PTH) and probably calcitonin to maintain extracellular ion calcium concentration in the body.
4. A persistent severe vitamin D deficiency is associated with the bone abnormalities of rickets in children and osteomalacia in adults.
5. Suboptimal vitamin D deficiency in the elderly and in postmenopausal women is associated with rapid age-related bone loss and increase in the risk of osteoporotic fractures.
6. Vitamin D deficiency in growing children and adolescents is associated with an increase in PTH concentration in blood, increase rate of bone turnover, and a decreased rate of bone mass accumulation.
7. Preventive strategies should be implemented to maintain optimum vitamin D status by promoting the production of adequate cutaneous vitamin D through sunlight exposure and intake of vitamin D-rich foods, such as milk, or foods fortified with vitamin D.

This table lists the key facts of vitamin D including the biosynthesis of vitamin D, function of the vitamin in the body, health consequences of vitamin D deficiency, and recommended preventive strategies to maintain adequate vitamin D status

(Gessner et al. 2003) or <27.5 nmol/L (Grant et al. 2009), thus indicating that vitamin D deficiency can occur early in life. The prevalence rates of deficiency were found to be higher among adolescents from various regions of the world (Du et al. 2001; Foo et al. 2009b; Hatun et al. 2005; Gordon et al. 2004) compared to younger children (Grant et al. 2009; Stein et al. 2006).

It is generally agreed that higher rates of vitamin D deficiency or/and insufficiency are found in children and adolescents living at far northern or far southern latitudes compared to those in more equatorial regions. Such deficiency is seen particularly in the winter months because of the seasonal decrease in intensity of UV light (see details in Sect. 81.5). In equatorial countries, a high prevalence of hypovitaminosis D was also found among adolescent girls and women who wore full-length covered dresses (El-Hajj Fuleihan et al. 2001; Ganage-Yared et al. 2000; Hatun et al. 2005). Thus, such epidemiological evidence suggests that vitamin D deficiency and/or insufficiency are global problems for growing children and adolescents.

81.5 Factors Contributing to Vitamin D Deficiency in Children and Adolescents

Vitamin D deficiency in children can be associated with clinical signs, such as retarded growth and motor development, failure to thrive, short stature, bone deformities including tibial bowing and splaying of the anterior ribs, tetany, seizures, and dental enamel defects. Several factors, such as exclusive breastfeeding of infants, lack of sunlight exposure, darker skin pigmentation, living at temperate latitudes, and low intake of vitamin D and calcium as well as higher body adiposity levels, have been shown to contribute to vitamin D deficiency and the disease of rickets (Table 81.2). When the vitamin D status of pregnant women is low, their infants have a high risk of vitamin D deficiency in the neonatal period. In addition, limited exposure to sunlight due to religious, cultural, and lifestyles practices may also play a part in the etiology of vitamin D deficiency. It is reported that about 52% of Lebanese schoolchildren aged between 10 and 16 years, who wore full-length clothes, had vitamin D insufficiency (El-Hajj Fuleihan et al. 2001). Additionally, in apparently healthy Caucasian adolescent boys aged from 16 to 18 years, there was a significant association between sports-related

Table 81.2 Prevalence of vitamin D deficiency in children and adolescents worldwide

Study reference	Participant characteristics	Age (year)	Location and latitude	25(OH)D assessed method	Mean 25(OH)D levels (nmol/L)	Vitamin D (%)	
						Insufficiency	Deficiency
Young children							
Grant et al. (2009)	353 young urban children	6 months–2	Auckland, New Zealand and 36°S	RIA	55 (42–70)		$10^{27.5}$
Stein et al. (2006)	168 white and black girls	4–8	Georgia, US and 34°N	RIA	93.8 ± 28.1	2.4^{50}	
Docio et al. (1998)	51 children	8 ± 2	Cantabria, Spain and 43°N	CPB	38.5 ± 13.5	80^{50}	31^{30}
Jones et al. (1999)	201 Caucasian boys and girls	7.8 ± 0.4	Tasmania, Australia and 42°S	RIA	79.0 ± 29.5		10^{50}
Cheng et al. (2003)	193 girls	10–12	Jyväskylä, Finland and 62°N	RIA		46^{40}	32^{25}
Adolescents							
Lehtonen-Veromaa et al. (1999)	191 Caucasian girls	9–15	Turku, Finland and 60°N	CPB	33.9 ± 13.9	$67.7^{37.5}$	13.4^{20}
El-Hajj Fuleihan et al. (2001)	169 Lebanese girls	10–16	Beirut, Lebanon and 33.5°N	CPB	42.5 ± 20	44^{50}	21^{25}
Guillemant et al. (2001)	54 Caucasian boys	13–16	Paris, France and 49°N	CPB	20.4 ± 6.9		72^{25}
Foo et al. (2009a)	323 Chinese girls	15 ± 0.4	Beijing, China and 42°N	RIA	34		89.2^{50}
Outila et al. (2001)	178 Caucasian girls	14–16	Helsinki, Finland and 45°N	RIA	39.0 ± 14.0	61.8^{40}	13.5^{25}
Hatun et al. (2005)	89 Turkish girls	13–17	Kocaeli, Turkey and 40°N	RIA		43.8^{50}	21.3^{25}
Jones et al. (2005)	136 Caucasian boys	16.7 ± 0.8	Tasmania, Australia and 41°S	RIA	43.6 ± 15.3	68^{50}	
Gordon et al. (2004)	307 US boys and girls	11–18	Boston, US and 42°N	CPB		42^{50}	$24.1^{37.5}$
Looker et al. (2002)	NHANES III	12–19	Southern regions of the US and 25–41°N with median: 32°N	RIA	Boys: 78.6		13^{50}
	625 Boys and 699 girls				Girls: 64.9		29^{50}
Children and adolescents							
Rockell et al. (2005)	456 Maori	5–14	New Zealand, 35–46°S	RIA	43 (38–49)	$41^{37.5}$	$5^{17.5}$
	646 Pacific				36 (31–42)	59	8
	483 Caucasians and others				53 (47–59)	25	3
Lapatsanis et al. (2005)	178 boys and girls	3–18	North West, Greece &	CPB	3–10: 46.3		3-10: 14^{25}
					11–14: 52.5		11–14: 13^{25}
					15–18: 31.8		15–18: 47^{25}
Puri et al. (2008)	404 Indian boys and girls	6–18	New Delhi. India and 28.4°N	RIA	31.9 ± 15.4		91^{50}
							35^{25}
Weng et al. (2007)	382 US boys and girls	6–21	Philadelphia, US and 40°N	RIA	Median: 70 (47.5; 87.5)		68^{30}
							51 (Whites)
							94 (Blacks)

25(OH)D 25-hydroxyvitamin D; *RIA* radioimmunoassay; *CPB* Competitive protein-binding assay

This table shows the percentage of persons at risk of vitamin D deficiency or vitamin D insufficiency, as measured by the 25(OH)D in the blood of different age groups in children and adolescents living in countries of various latitudes throughout the world

sun exposure and serum 25(OH)D concentrations, indicating that adequate sunlight exposure in summer is important for optimal vitamin D status (Jones et al. 2005). Similarly, a study of Chinese adolescent girls aged 15 years also found that lifestyle factors, such as participation in organized sports and the time spent in physical exercise, both at school and in leisure time, showed significant independent positive association with 25(OH)D concentration (Foo et al. 2009b). In the multivariate analysis of this cohort, adolescent girls, who participated in organized sports, had a higher vitamin D status than those who did not engage in any sport. It is possible that the higher vitamin D status of those with greater exercise could a result of an increased exposure to sunlight. Conversely, there is an awareness of the hazards of ultraviolet-B light exposure in childhood and the subsequent risk of development of skin cancer in adulthood. This problem may cause difficulties for public health policy in advocating exposure to sunlight of children and adolescents, when there is a risk of skin cancer. However, only a small amount of ultraviolet exposure is needed to maintain vitamin D status, and this would have a low risk of development of skin cancer.

It is generally agreed that the dietary sources of vitamin D in most natural foods are very limited, being only present in significant amounts in oily fish and the yolks of eggs of domestic chickens provided with vitamin-D-fortified food (Gannage-Yared et al. 2000). Several studies have shown that low intake of vitamin D was significantly associated with decreased vitamin D status in children, adolescents, and adults (Weng et al. 2007; Ilich et al. 1997). Furthermore, low dietary calcium intake or reduced dietary calcium availability may also lead to rickets by inducing vitamin D deficiency. In animal studies, dietary calcium deprivation appears to affect the efficiency of vitamin D utilization. Low intakes of dietary calcium or diets high in phytate induce mild hyperparathyroidism and elevation of $1,25(OH)_2D$ concentrations, which enhances the catabolism (metabolic destruction) of 25(OH)D and decreases its half-life in the circulation (Clements et al. 1987a). The increased catabolism of 25(OH)D is mediated through elevated levels of $1,25(OH)_2D$, which have been shown to correlate inversely with the half-life of 25(OH)D (Clements et al. 1987b) with a resultant reduction in vitamin D status. It is thus likely that diets low in calcium content and high in calcium absorption inhibitors, such as phytate, might exacerbate vitamin D deficiency, leading to the development of rickets. Such a mechanism has been proposed as a factor in the high prevalence of rickets among the Asian community in the United Kingdom (Clements 1989).

People in temperate regions also show seasonal variations in vitamin D status as the angle of sunlight reaching earth's surface changes. Exposure to sun for part of winter is of no use in improving vitamin D status because the intensity of UV light drops, even though the visible light may be very bright. In addition, the seasonal variation in UV light is greater at higher latitudes than at lower ones. Apart from these factors associated with limited sunlight exposure and dietary practices, the role of body composition may also affect vitamin D status in children and adolescents (see details in Sect. 81.6).

Therefore, a decline in levels of serum 25(OH)D in children and adolescents from summer to winter has been well documented by several studies, in which the prevalence of vitamin D deficiency (low vitamin D status) is increased during winter in China (Du et al. 2001; Foo et al. 2009b), Finland (Lehtonen-Veromaa et al. 1999; Outila et al. 2001), France (Guillemant et al. 1995), Spain (Docia et al. 1998), and New Zealand (Rockell et al. 2005). Regardless of the definition of hypovitaminosis D, a high proportion of subjects had deficient levels of 25(OH)D during winter compared to summer because of low or no ultraviolet-B light of sufficient intensity to activate the conversion of 7-dehydrocholesterol to previtamin D in skin (Webb et al. 1988). Low vitamin D status in winter may increase PTH secretion and thus may decrease bone mass accumulation. The optimal concentration of 25(OH)D required for bone health in children and adolescents is unclear; however, optimal vitamin D status during childhood and adolescence is considered to be important for long-term benefits to musculoskeletal health.

81.6 Relationship of Vitamin D Status and Body Composition and Muscular Strength in Young Children and Adolescents

Although it is well established that obesity, expressed as excess body fat, has an adverse effect on vitamin D status in adults (Wortsman et al. 2000), there is limited data on the relationship of vitamin D status to body composition in growing children and adolescents. An understanding of any such relationships would be particularly crucial, given that the epidemic of childhood obesity is increasing worldwide. Two studies in Caucasian children and adolescents found an inverse relationship between vitamin D status and body mass index (BMI) (Gordon et al. 2004; Rockell et al. 2005). However, a significant positive independent association has been reported between vitamin D status and BMI in adolescent Chinese girls (Foo et al. 2009b). This positive association between 25(OH)D levels and BMI is contrary to the common view that vitamin D status declines as BMI increases (Gordon et al. 2004; Rockell et al. 2005). In the studies of Gordon et al. (2004) and Rockell et al. (2005), obesity was defined only by a high BMI rather than by using a direct estimate of body fat mass. The use of BMI to assess the degree of body fatness in children and adolescents is of limited value (Wells et al. 2002) compared to adults because, during growth, an increase in BMI in childhood and adolescence may also be related to an increase in the fat-free lean body mass (LBM), instead of body fat mass (Wells et al. 2002; Maynard et al. 2001). Hence, higher vitamin D status is found in children with a higher proportion of LBM. This is complicated further by variation in growth rates and maturity levels (Daniels et al. 1997).

Until recently, the mechanism by which vitamin D status impacts on body composition is not well elucidated. The relationship between vitamin D status and body composition has been examined in a representative population-based study of adolescent girls of Chinese-origin aged 15 years, by direct measurement with dual-energy X-ray absorptiometry (DXA). A significant positive association was found between 25(OH)D concentration and LBM, whereas there was no significant association between the percentage of body fat and vitamin D status, as indicated in Figs. 81.2 and 81.3, even after adjustment for other possible confounding factors (Foo et al. 2009b). When different body components, such as LBM and body fat mass, were compared according to vitamin D status groups, adolescent girls in the vitamin D sufficient group (>50 nmol/L) had significantly higher LBM than those who were vitamin D deficient (<25 nmol/L). By contrast, there was no association between vitamin D status and body fat mass, after adjusting for other confounding lifestyle and dietary factors. Thus, in these adolescent girls, the relationship of adiposity to vitamin D status was less pronounced than that between LBM and vitamin D status (Foo et al. 2009b). It is suggested that changes in BMI are related not just to changes in adipose tissue mass, but also to changes in the proportion of LBM during this stage of growth. This seems to be the first study to examine any relationship between differences in body composition profiles and vitamin D status in children and adolescents. Furthermore, this study also suggests that BMI is not as good an indicator of mild obesity in children and adolescents as it is in adults. By contrast, a recent study of 90 postpubertal Hispanic and Caucasian females aged 16–22 years with a mean BMI of 25.7 kg/m^2 showed a significant negative association between 25(OH)D levels and regional body composition of visceral and subcutaneous fat measured by computed tomography (CT) and also total body fat mass determined by DXA (Kremer et al. 2009). In the sub-analyses of vitamin D status groups, females who were vitamin D insufficient, as defined by 25(OH)D concentrations of ≤72.5 nmol/L (29 ng/mL), were found to have a significantly higher body weight and BMI, but were shorter than females, who were vitamin D sufficient with serum 25(OH)D levels more than or equal to 75 nmol/L. This indicated that females with 25(OH)D in the vitamin D insufficient range tend to be shorter and heavier (Kremer et al. 2009). Additionally, there was a surprisingly significant positive association between serum 25(OH)D levels and height in these populations (Kremer et al. 2009). This observation was in line with a previous study in adolescent girls aged 13–17 years that also found a significantly lower height in girls with low vitamin D status

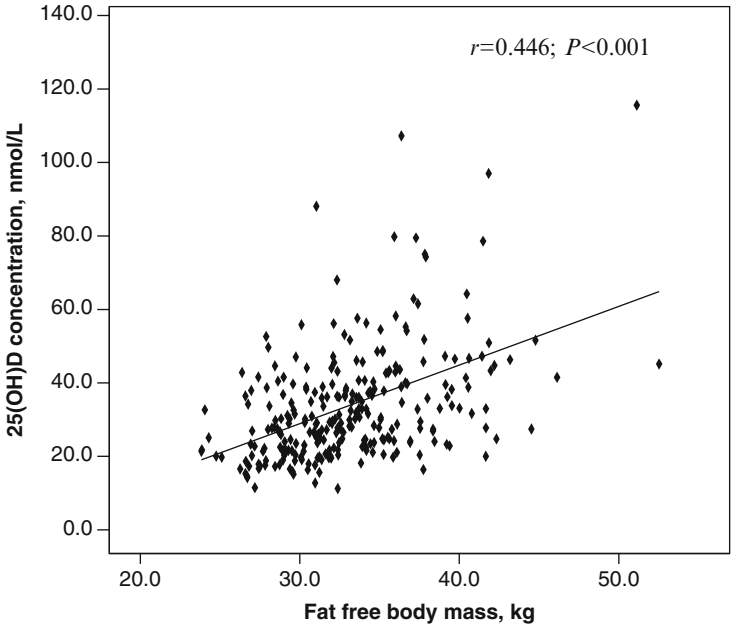

Fig. 81.2 Relationship between plasma 25(OH)D (nmol/L) and fat-free body mass (kg). Relationship between vitamin D status as measured by 25(OH)D levels in the blood and total body lean body mass (Reprinted from Foo et al. (2009b). With permission. 25(OH)D: 25-hydroxyvitamin D)

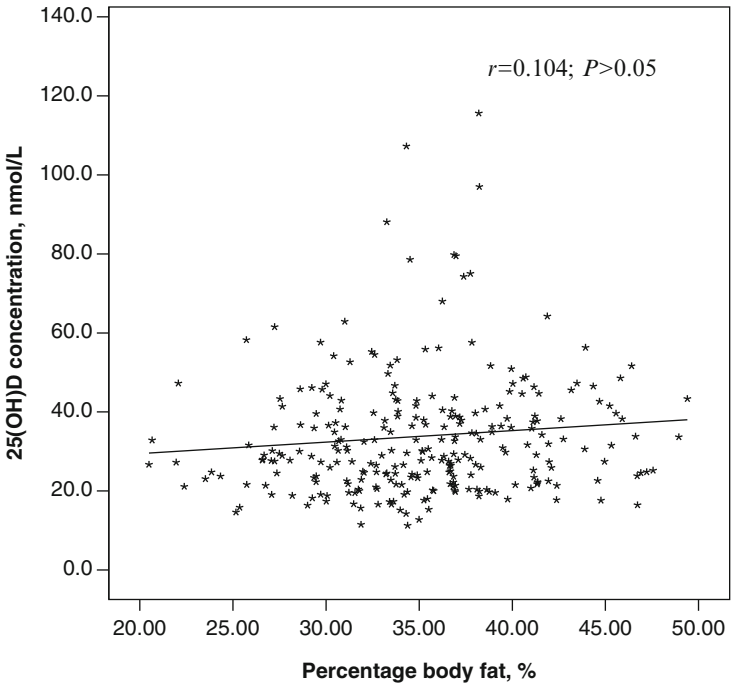

Fig. 81.3 Relationship between plasma 25(OH)D (nmol/L) and percentage body fat (%). Relationship between vitamin D status measured by 25(OH)D levels in the blood and percentage of body fat (Reprinted from Foo et al. (2009b). With permission. 25(OH)D: 25-hydroxyvitamin D)

compared to those with higher vitamin D status (Hatun et al. 2005). These positive relationships between vitamin D status and height warrant further population-based longitudinal studies to determine the possible mechanism by which vitamin D status affects longitudinal bone growth.

It is still uncertain whether (1) a higher vitamin D status is caused by increased LBM or (2) a higher vitamin D status leads to an increase in LBM. In a recent randomized clinical trial of vitamin D supplementation in healthy school-aged Lebanese girls, a significant beneficial effect on LBM was found in premenarcheal girls. By contrast, there were no such effects in postmenarcheal girls (El-Hajj Fuheihan et al. 2006), and it was postulated that any beneficial effect during the postmenarcheal period may be confounded by the powerful effects of pubertal growth. Several mechanisms have been proposed to explain why obesity is associated with lower vitamin D status. One theory is that low vitamin D status might diminish leptin secretion into the circulation, which, in turn, may contribute to the increase in adipose tissue mass (Menendez et al. 2001). Another possible mechanism is attributed to greater mass of adipose tissue may trap vitamin D so that it becomes unavailable for functional conversion to 25(OH)D (Wortsman et al. 2000). More longitudinal population studies in growing children and adolescents are needed to explain how changes in body composition during growth might be related to vitamin D status. A more comprehensive understanding of the mechanisms relating vitamin D deficiency and/or insufficiency and adipose tissue mass is required because obesity later in life is associated with serious health problems, such as osteoporosis, diabetes, cardiovascular diseases, cancer, and multiple sclerosis (Holick 2004).

Although it is well documented that long-term severe vitamin D deficiency can cause rickets, which is characterized as a failure of mineralization of the organic matrix of bone, particularly at the epiphyseal growth plate, with deformities of the skeleton, enlargement of the joints of the long bones and rib cage, curvature of the spine and thighs, muscle spasms, weakness, and atrophy in children. There is, however, little information about the effects of less severe vitamin D deficiency and/or insufficiency on muscle function in children and adolescents. A study in Chinese postpubertal adolescent girls aged 15 years found that subjects with 25(OH)D levels ≥50 nmol/L showed significantly greater handgrip muscle strength compared with those of lower vitamin D status (Fig. 81.4). This relationship was independent of pubertal growth parameter, body size, level of physical activity (PA), and dietary calcium and vitamin D intakes (Foo et al. 2009a). This finding is further supported by another study of 99 post-menarcheal girls, aged 12–14 years, where a significant positive association was found between serum 25(OH)D concentration and muscle strength in the lower limb, measured by jumping velocity, height and power, Esslinger Fitness Index, and maximum voluntary force (Ward et al. 2009). This suggested that muscle contractility is affected by vitamin D status. Adolescent girls with low 25(OH)D concentrations generated less muscle power, and, hence, jump height and velocity were lower compared to those with higher vitamin D status (Ward et al. 2009). These findings in adolescents are comparable to those in elderly subjects in whom higher serum 25(OH)D levels were significantly associated with increased muscle strength and improved lower extremity function (Bischoff et al. 2003; Dawson-Hughes et al. 1995). In the elderly, this improved muscular function and strength may lower the risk of falls and consequent osteoporotic fractures.

The mechanism responsible for the greater muscle strength, force, and power in subjects with better vitamin D status was not explored in these two studies. One possible mechanism may involve a direct role of vitamin D (either as $1,25(OH)_2D$ or 25(OH)D) in muscle action. Although such an effect has not been shown, there has been much research on the molecular action of vitamin D in muscle, in which 1,25(OH)D stimulates the growth and proliferation of muscle cells and regulates intracellular calcium in muscle cells (Boland 1986; Boland et al. 1995). It may be that vitamin D either has a role in modifying the transport of calcium in muscle cells or may have a role quite independent of that. For instance, low vitamin D status may result in fatigue and diminished muscle oxygenation, and, consequently, may affect muscle strength and function, and give rise to muscle weakness

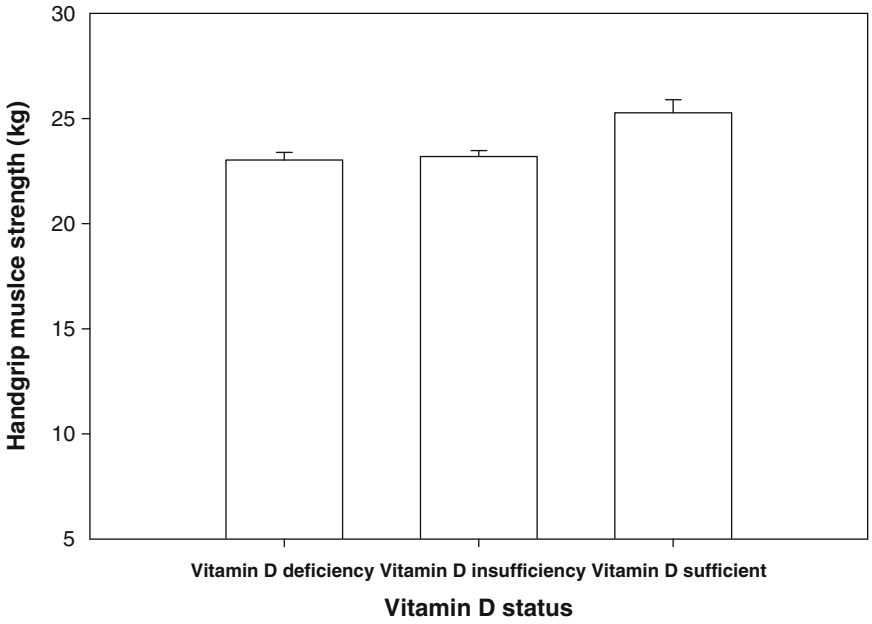

Fig. 81.4 Vitamin D status and handgrip muscle strength. Association between the stages of vitamin D status measured by 25(OH)D levels in the blood and muscle strength at the handgrip in Chinese adolescent girls aged 15 years after adjusting for body size, Tanner pubertal stage, dietary intakes of calcium, vitamin D and milk, organized sports participation status and total PA levels. Results are expressed as mean ± SEM. 25(OH)D: 25-hydroxyvitamin D

(Boland 1986). Conversely, a separate observation that 25(OH)D is apparently stored in muscle in newborn rats may indicate a special role of muscle in vitamin D homeostasis, which is quite independent of any role of vitamin D in muscle function (Clements and Fraser 1988). Therefore, more studies are required to identify the mechanisms for these interactions. Such information is much needed because the development of optimum muscle strength has an important influence on bone mass accrual as well as for the maintenance of bone mass integrity during this critical period of growth. For instance, several studies in children and adolescents found that increases in muscular strength were significantly associated with both changes in bone mass (Foo et al. 1998) and changes in bone geometry, and, hence, the structural properties of bone, independent of the bone mass properties (Haapasalo et al. 1998). This is compatible with the functional model of bone development, described as the mechanostat hypothesis, in which muscle and bone together form a functional unit, so that greater muscle strength leads to increased bone strength and mass (Frost and Schonau 2000).

81.7 Relationship Between Vitamin D Status and Bone Composition Growth in Young Children and Adolescents

It is well recognized that persistent severe vitamin D deficiency is associated with the bone abnormalities of rickets in growing children. There is now a growing body of evidence which suggests that mild vitamin D deficiency in children and adolescents may also be deleterious to bone health in this population. Achieving adequate vitamin D status is important for skeletal health because of a vitamin D role in calcium homeostasis and bone cells. Numerous studies in growing children and

adolescents have found that a persistently low vitamin D status with prolonged elevation of PTH and a subsequent increase in bone remodeling leads to suboptimal bone mass accretion. However, studies investigating the influence of vitamin D status on bone mass accretion in healthy growing children and adolescents have yielded inconsistent results, especially with adolescents at the time of pubertal growth development. In Caucasian adolescent girls, a positive association has been found in some studies between vitamin D status and bone mass measurements (Lehtonen-Veromaa et al. 2002a; Outila et al. 2001; Cheng et al. 2003). However, this association was not found in other studies (Kristinsson et al. 1998; Willett 2005). In a cross-sectional survey of adolescent girls aged 14–16 years, a positive association was found between serum 25(OH)D concentrations and forearm areal bone mineral density (aBMD), but only in subjects who had a 25(OH)D concentration of less than 40 nmol/L (Outila et al. 2001). Similarly, in a 3-year longitudinal investigation of bone development in Finnish adolescent girls aged 9–15 years, Lehtonen-Veromaa et al. (2002a) found a positive association between changes of serum 25(OH)D levels from baseline as well as the baseline 25(OH)D levels themselves on lumbar spine (LS) aBMD. Both studies used areal BMD as their bone outcome variable, but, in growing children and adolescents, this is now regarded as an inaccurate measure of bone mass accretion because it depends on bone size and body growth factors (Prentice et al. 1994). The increase in aBMD reported in these studies may have been related to differences in bone size between individuals rather than to vitamin D status. Hence, there is still uncertainty about the importance of vitamin D deficiency during childhood and adolescence on final bone mass at maturity.

Limited data exist about the influence of vitamin D status on bone growth in children and adolescents in non-Caucasian children and adolescents. In a population-based study of Chinese adolescent girls aged 15 years, adequate vitamin D status (≥50 nmol/L) was found to be associated with a significant increase in size-adjusted BMC of the total body, and distal and proximal forearm compared to those with poor vitamin D status (Foo et al. 2009a). These relationships persisted after adjusting for stage of pubertal development, dietary intake of calcium and vitamin D, and total time spent in PA, thus demonstrating that these variables did not influence the changes in bone measurements in relation to vitamin D status. By contrast, there were no significant differences in bone area (BA) as an indicator of bone size at the skeletal sites measured between the three groups of vitamin D status. Similar findings were also reported by Kristinsson et al. (1998) where Icelandic adolescent girls aged 16–20 years showed a significant positive association between 25(OH)D concentration and total forearm BMD and BMC. These findings are in line with the two recent intervention studies of vitamin D supplementation on bone growth in growing adolescents (Viljakainen et al. 2006; El-Hajj Fuleihan et al. 2006). In the study of 212 Finnish prepubertal adolescent girls aged between 11 and 12 years, who were randomly given different doses of vitamin D supplements of either 200 IU or 400 IU daily for a year, it was found that bone mineral augmentation of the proximal femur was 14% and 17% significantly greater in participants who received 200 IU and 400 IU of vitamin D per day, respectively, compared to control subjects (Viljakainen et al. 2006). Another investigation in Lebanese premenarcheal adolescent girls aged 10–17 years, supplemented with either 1,400 IU/week or 14,000 IU/week vitamin D_3 for 1 year had significantly increased bone mineral content (BMC) and BA of the total hip as compared to the controls (El-Hajj Fuleihan et al. 2006).

Most of the published reports investigating the influence of vitamin D status on bone mass in children and adolescents focused on BMC and/ or areal BMD, assessed by DXA as the endpoint bone variable. This assessment method does not measure bone geometry and structural properties of the skeleton and only provides a two-dimensional rather than a more complex three-dimensional analysis of the bones measured. There are two reports of investigations into the association between vitamin D status and bone geometry. One of these studied Caucasian prepubertal girls aged 10–12 years (Cheng et al. 2003) and the other examined Hispanic and Caucasian postpubertal females aged 16–22 years (Kremer et al. 2009). The study by Cheng et al. (2003) using peripheral quantitative computed tomography (pQCT) found that girls with vitamin D deficiency, defined as 25(OH)D levels

≤25 nmol/L, had significantly lower cortical volumetric BMD (vBMD) in the distal radius compared with subjects with higher vitamin D status. By contrast, however, no significant differences were found between vitamin D status and any BMC or BMD measurements for the total body, femur, and LS, measured by DXA (Cheng et al. 2003). The authors concluded that, when only DXA was used to determine the influence of vitamin D status on bone mass, there could be a misinterpretation of the role of vitamin D on bone mass accretion. When pQCT was used to measure volumetric bone density, vitamin D status was found to influence the results (Cheng et al. 2003). Conversely, no significant association was found between the adequacy of vitamin D status and bone growth, as measured by either computed tomography (CT) or DXA methods (Kremer et al. 2009).

Although it is well established that low vitamin D status in postmenopausal and elderly women is considered as a major risk factor associated with increased risk of rapid bone loss and osteoporotic fractures (Lips 2001; Dawson-Hughes et al. 2005), on the contrary, the precise beneficial effects of vitamin D status on bone mass growth and development in growing children and adolescents are still inconclusive. Interpretation of the effects of vitamin D status and bone mass accretion in growing children and adolescents is complicated and confounded by various biological growth factors, such as sexual maturation and changes in the rate of linear growth. The interaction between these variables is complex during this rapid growth period (Heaney et al. 2000; Saggese et al. 2001). For instance, there is a strong confounding effect of puberty on skeletal modeling and remodeling, where plasma calcium and phosphate concentrations may be affected by factors other than vitamin D status (Kristinsson et al. 1998; Saggese et al. 2001). This suggests that these biological variations may confound the independent influence of vitamin D on bone mass accretion. In a study of Chinese girls, the significant association between vitamin D status and bone mass remained unchanged, even after adjusting for pubertal stage (Foo et al. 2009a). This is not surprising as most of the subjects were at a postpubertal stage of development, where changes in sex hormones are less pronounced compared to those in subjects at an earlier stage of puberty (Saggese et al. 2001). This finding is strengthened by the homogeneity in age and sex of the population studied, which was similar to that of Kristinsson et al. (1998), where analysis was stratified according to individual age. Other explanations for inconsistency in the findings of studies in Caucasians and those of other ethnicities may be differences in study design, subject characteristics, their sexual maturity, data interpretation and/or baseline vitamin D status defined as deficient, the techniques used for bone measurements, and the skeletal sites measured.

The mechanism by which adequate vitamin D status leads to higher bone mass in healthy growing children and adolescents is not understood. However, current evidence suggests that the increased bone mass with adequate vitamin D status may be, in part, a consequence of lower secretion of PTH, followed by a decrease in the rates of bone remodeling, as indicated by the biochemical markers for bone formation and resorption (Outila et al. 2001; Foo et al. 2009a). Therefore, adequate vitamin D status is important and may contribute to attaining optimal peak bone mass in growing children and adolescents. Further longitudinal population studies are needed to evaluate what the optimal serum 25(OH)D concentration might be for maximal bone accretion during the time of rapid growth and also to identify the optimal levels of vitamin D intake in relation to greater bone mineralization and physical growth in children and adolescents.

81.8 Recommended Daily Intake of Vitamin D for Children and Adolescents

The US Dietary Reference Intakes (DRI) panel for calcium, phosphorus, magnesium, vitamin D, and fluoride was established in 1997 (Institute of Medicine 1997). Adequate intakes (AIs) for all nutrients except for vitamin D were set from the estimated average requirements (EARs), which are based on

Table 81.3 Factors contributing to low vitamin D status in children and adolescents

Low sunlight exposure
- Little time spent in outdoor activity
- Clothing due to religious and cultural practices that prevents skin exposure to sunlight
- Increased urbanization with more atmosphere pollution that absorbs ultraviolet light

Decrease in dietary intake of vitamin D and calcium
- Decreased consumption of dietary vitamin D and/or food fortified with vitamin D
- Low calcium diets

Higher levels of body fat mass or obesity
- Decreased bioavailability of vitamin D in the body

This table lists the lifestyle, dietary, and body composition factors that contributing to lower vitamin D status in children and adolescents

nutrient demands for accretion and obligatory losses through absorption, or are the intakes required for maximum retention (Weaver and Fleet 2004). However, this approach seems to be inappropriate for vitamin D, which is metabolized like a hormone and which is mainly acquired by solar irradiation of skin. Furthermore, EARs are difficult to set for vitamin D because inputs from sunlight and food are difficult to assess. Therefore, AI was used instead of EAR for vitamin D. This is defined as the intake necessary to achieve the normal range of serum 25(OH)D concentration. The current vitamin D intake recommendation established by the Food and Nutrition Board of The Institute of Medicine in 1997 for various age groups of populations is given in Table 81.3. The current recommendation of vitamin D intake for infants, young children, and adolescents, regardless of sunlight exposure, age, degree of skin pigmentation, geographic region, and gender, is 200 IU (5 μg)/day, and the upper limit levels were set at 2,000 IU/day (50 μg/day). The upper level was set to prevent hypervitaminosis D when serum 25(OH)D concentrations are in excess of 400 nmol/L. Since 1997, there has been debate about whether the AI level for vitamin D is really "adequate" and ideal for optimal bone health (Dawson Hughes et al. 2005; Vieth 1999). Since then, progress has been made toward determining the optimal vitamin D intake needed to produce changes in serum 25(OH)D concentration. Two direct functional measures for vitamin D adequacy were used, namely calcium absorption (Heaney et al. 2003; Vieth 1999) or bone resorption (Chapuy et al. 1992; Dawson-Hughes et al. 1997). Revised recommended AI of vitamin D for populations were proposed in 2004 (Table 81.3). As expected, the recommended AI for vitamin D for growing girls and for women are higher, and are approximately five times higher than the recommended levels set in 1997 to achieve and maintain a concentration of 25(OH)D at or above 80 nmol/L, a level found to prevent elevation of PTH concentration in various age groups (Chapuy et al. 1997; Dawson-Hughes et al. 1997). A recent estimate is that a daily oral cholecalciferol intake of ~12.5 μg/day (500 IU/day) would be required to maintain and prevent the winter fall in serum 25(OH)D level (Heaney 2005).

81.9 Dietary Sources of Vitamin D

Food sources of vitamin D are extremely limited. Vitamin D is not present naturally in most foods. The only food sources relatively rich in vitamin D are some oily fish, fish liver oils, and egg yolk. In developed countries, foods such as breakfast cereals, fruit juices, margarine, and some dairy products may be fortified with vitamin D. Dietary supplements containing vitamin D in amounts that will increase vitamin D status are also consumed (Table 81.4).

Table 81.4 Dietary reference intake (DRI) for vitamin D for populations based on 1997 and 2004

	US	
	1997[a]	2004[b]
Male		
0–11 years	5	NA
12–19 years	5	2
20–39 years	5	16
Female		
0–11 years	5	NA
12–19 years	5	22
20–39 years	5	25

This table lists the recommended amount for dietary vitamin D intake required, according to different age groups of children and adolescents in 1997 and 2004.
Conversion factor: 1 μg cholecalciferol (vitamin D_3) = 40 IU; *NA* not available
[a]The Institute of Medicine (1997)
[b]Proposed by Weaver and Fleet (2004)

81.10 Conclusions

Vitamin D deficiency and insufficiency occur in a high proportion of growing children and adolescents worldwide, regardless of what 25(OH)D level is used to define vitamin D deficiency. Poor vitamin D status should be regarded as of universal concern. Low vitamin D status is not only a biochemical abnormality, but also associated with physiological, pathological, and clinical signs of vitamin D deficiency, along with secondary hyperparathyroidism and increased bone remodeling, which could have long-term detrimental effects on physical growth and skeletal development and mineralization. Vitamin D has also been found to impair optimal muscle function and action on the skeleton. These conditions would therefore compromise bone mass accretion and muscular strength and function during the growing years. Hence, an adequate nutritional vitamin D status during growth is particularly crucial for optimal musculoskeletal health.

It is strongly recommended that children and adolescent participate in intervention programs to combat vitamin D deficiency. Several preventive strategies to maintain optimum nutritional vitamin D status, such as promoting the production of cutaneous vitamin D through exposure to sunlight and intake of vitamin D rich foods, such as milk, or foods fortified with vitamin D, have been developed. Although there is some debate on the adverse effects of exposure to highly intense ultraviolet-B light and the risk of skin cancer, only a small amount of ultraviolet exposure is needed to maintain vitamin D status. For instance, exposure of hands, face, and arms to approximately one-third of a minimal erythemal dose (MED) of sunlight most days before 10 am and after 3 pm during the summer months is sufficient to enable adequate cutaneous synthesis of vitamin D (Working Group of the ANZBMS, Endocrine Society of Australia and Osteoporosis Australia 2005). This approach is very important, as natural dietary sources of vitamin D are limited. In addition, innovative health and nutrition education programs focused on vitamin D, PA, and dietary modification as well as skeletal health should be included in the school health-education curriculum, as most children and adolescents can be reached through schools.

Emerging evidence showing a significant positive effect of adequate vitamin D status on maintaining non-skeleton health, such as diminishing the risk of diabetes, obesity, some cancers, and other long-latency disease processes warrants further investigation in healthy growing children and adolescents.

Summary Points

- The main function of vitamin D is associated with calcium and phosphate homeostasis and skeletal integrity throughout life.
- Vitamin D status should be regarded as of universal concern.
- Vitamin D deficiency and insufficiency occur in a high proportion of growing children and adolescents worldwide.
- Risk factors attributed to vitamin D deficiency are prolonged exclusive breastfeeding of infants, lack of sunlight exposure, low intake of vitamin D and calcium, darker skin pigmentation, and living at temperate latitudes.
- Persistent severe vitamin D deficiency results in the bone disease, rickets, in children and in osteomalacia in adults.
- Adequate vitamin D status is associated with higher LBM and muscle strength levels in children and adolescents.
- Adequate vitamin D status throughout childhood and adolescence might enhance lean body physical growth and bone mass accretion, and consequently reduce the risk of osteoporotic fracture later in life.
- The beneficial effects of vitamin D status regarding many non-skeletal metabolic processes in the prevention of chronic diseases are being increasingly recognized.

Acknowledgments Sincere appreciation and gratitude are extended to Professor Dr. David Fraser, for his excellent mentorship and his sharing of critical comments and intellectual thoughts throughout the preparation of this chapter.

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Chapter 82
Anthropometry of Adolescents: Brazilian Perspectives

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Abstract Health status of Brazilian adolescents is directly affected by huge inequalities, considering the social and economic conditions they are submitted to. According to a national survey, 10% of adolescents present height-for-age deficit. The analysis of the secular trend of the nutritional profile of the group under discussion emphasizes the drop in height deficit for 30 years, although the prevalence observed is still considerable. On the other hand, there is increased prevalence of excess weight and obesity. Adolescents are in full transformation and the chronological age not always means similarity among peers. Hence, in some studies of female adolescents, the methodology includes a 1-year period after menarche to have a homogeneous sample and assure that the typical changes of adolescence influence less in the results. This methodology also enables adolescents assessed by non-medical professionals to have more specific orientations according to their sexual maturation stage. Despite the fact this methodology assesses sexual maturation close to real situation, it is known that there are limitations, mainly in males and in females who had no menarche yet.

Abbreviations

BMI	Body mass index
BSF	Bicipital skinfold
CFM	Central fat mass
CI	Conicity index
ENDEF	National Study on Family Expenses [*Estudo Nacional sobre Despesas Familiares*]
F kg	Fat in kg
FBMI	Fat body mass index
HC	Hip circumference
HOMA-IR	Homeostasis Model Assessment - Insulin Resistance
IBGE	Brazilian Institute of Geography and Statistics [*Instituto Brasileiro de Geografia e Estatística*]
LBMI	lean body mass index
LL	Leg length
MUAC	Mid upper arm circumference

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_82,

NCEP-ATP	National Cholesterol Education Program's Adult Treatment – Panel III
PFM	Peripheral fat mass
PNSN	National Health and Nutrition Survey [*Pesquisa Nacional de Saúde e Nutrição*]
POF	Familiar Budget Survey [*Pesquisa de Orçamento Familiar*]
PPV	National Survey on Standard of Living [*Pesquisa Nacional sobre Padrões de Vida*]
SISF	Suprailiac skinfold
SSF	Subscapular skinfold
TCH	Trunk-cephalic height
TSF	Tricipital skinfold
UmC	Umbilical circumference
WC	Waist circumference
WHO	World Health Organization
WHR	Waist to hip ratio
WTR	Waist to thigh ratio

82.1 Introduction

Adolescence is defined by the World Health Organization (WHO 2005) as the age group 10–19 years. It is a transition period between childhood and adulthood when many adult characteristics or lifestyle habits are acquired and/or consolidated.

It is characterized by intense growth and development and many morphologic and physiologic changes (WHO 2005). Among the biological alterations that better describe puberty, growth spurt, sexual maturation, and changes in body composition stand out.

In this phase, the individuals reach their peak of growth velocity, and there is no age specific for all adolescents. This stage depends on sexual maturation, and those who mature early or late achieve the velocity peak before or after the average population, respectively (Colli 1991). During adolescence, the individuals acquire approximately 25% of their final height and 50% of their definite weight (Colli 1991; Carvalho et al. 2001).

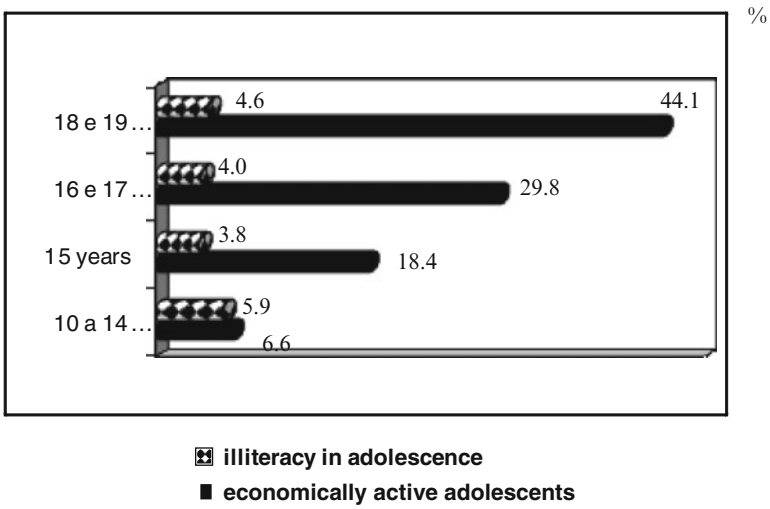
Some relevant aspects to be considered include anthropometric modifications and body composition. In both sexes, there is gain of fat and lean mass. Males, unlike females, gain more lean mass than fat tissue (Siervogel et al. 2000).

82.1.1 Brazilian Adolescents

Brazil is a country of large inequalities that influence the health status of its adolescents, who are directly affected by social and economic conditions they are submitted to.

According to the last demographic census data (IBGE 2000), 20.7% of the Brazilian population (n = 35,302,972) is aged between 10 and 20 years, of which 10,516,531 adolescents (29.7%) are economically active. Among the adolescents who have already performed any paid activity, 25% are aged under 15 years (Fig. 82.1) and 31.6% of them work over 40 h/week (IBGE 2000).

The Laws no. 8069 and 8242 guarantee the right to education of adolescents, aiming at their full development, preparing them to exercise citizenship and qualification for work, and prohibit any work for those aged under 14 years, except as apprentices (Brasil 1990, 1991).



Source: IBGE, 2000.

Fig. 82.1 Economically active and illiterate adolescents, per age group. This table list the key facts of inequalities that impact on the health status of its adolescents, who are directly affected by educational level and socioeconomic conditions (Source: IBGE 2000)

The repercussions of work in the development of adolescents may have consequences for their health. When dealing with child and adolescent work, family socioeconomic level has been repeatedly shown as the determining factor in entry into the job market. Poor families more frequently pressurize the younger members to enter the job market aiming to add to their income (Priore 1997).

The illiteracy rate is also relevant and it has been proved to influence health status. Approximately 6% of adolescents aged 10–14 years have never attended school (IBGE 2000).

There is a high prevalence (21%) of pregnancy in adolescence, according to the National Liveborn System. The Ministry of Health indicates that, regardless of information given about this issue, 45–60% of Brazilian adolescents initiate their sexual life without using any contraceptive methods (Gama et al. 2002; Brasil 2006).

82.2 Nutritional Profile

Three studies were conducted in the Brazilian population: the National Study on Family Expenses [*Estudo Nacional sobre Despesas Familiares*] – ENDEF, 1974/1975; the National Health and Nutrition Survey [*Pesquisa Nacional de Saúde e Nutrição*], at the end of the 1980s – PNSN 1989; and the Familiar Budget Survey [*Pesquisa de Orçamento Familiar*] – POF, 2002/2003 (POF 2003). These studies obtained the anthropometric indices for all age groups.

The National Health and Nutrition Survey – PNSN 1989 – demonstrated that Brazilian babies are born with height equal to or greater than Americans, but, before the age of 6 months, there is an inversion in this pattern. In 1996/1997, the National Survey on Standard of Living [*Pesquisa Nacional sobre Padrões de Vida*] – PPV, 1996/1997, carried out in two regions of the country – Northeastern (most deprived) and Southeastern (most developed) – also provided data on the nutritional status of

Table 82.1 Anthropometric indicators of Brazilian adolescents, per sex %

Anthropometric indicators of adolescents aged 10–19 years per sex (%)					
Male			Female		
	Household			Household	
Total	Urban	Rural	Total	Urban	Rural
Height deficit					
11.3	9.6	18	8.3	7.4	12.6
Deficit of BMI					
2.8	2.7	3.0	4.6	4.7	4.3
Weight excess					
17.9	19.5	11.4	15.4	15.9	12.9
Obesity					
1.8	2.0	0.8	2.9	3.1	1.9

Source: POF (2003)
This table lists the key facts of nutritional assessment through anthropometric indicators such as height deficit, body mass index, weight excess, and obesity and shows its distribution in rural areas and urban areas in Brazil

Table 82.2 Anthropometric indicators, per sex, per monthly per capita family income

	Anthropometric indicators of adolescents, per sex (%)			
Income (minimum wage)	Height deficit	Low BMI for age	Weight excess	Obesity
Male				
Up to ¼	22.1	3.6	8.5	0.4
1–2	8.5	2.1	20.2	2.2
Over 5	5.9	1.4	28.2	4.1
Female				
Up to ¼	17.5	5.8	8.9	1.4
1–2	6.1	4.8	15.7	3.2
Over 5	4.2	4.6	18.4	3.1

Source: POF (2003)
Minimum wage is similar – U$282
This table lists the key facts of low income in the nutritional status of adolescents and its distribution according to location of residence

the Brazilian population. Overweight in adolescents was more prevalent among females. In the Southeastern region, the prevalence of overweight ($p < 0.05$) and obesity in early adolescence ($p < 0.01$) and mean adolescence ($p < 0.05$) was also higher (POF 2003).

The most recent data on the nutritional status of the Brazilian population are described in Table 82.1.

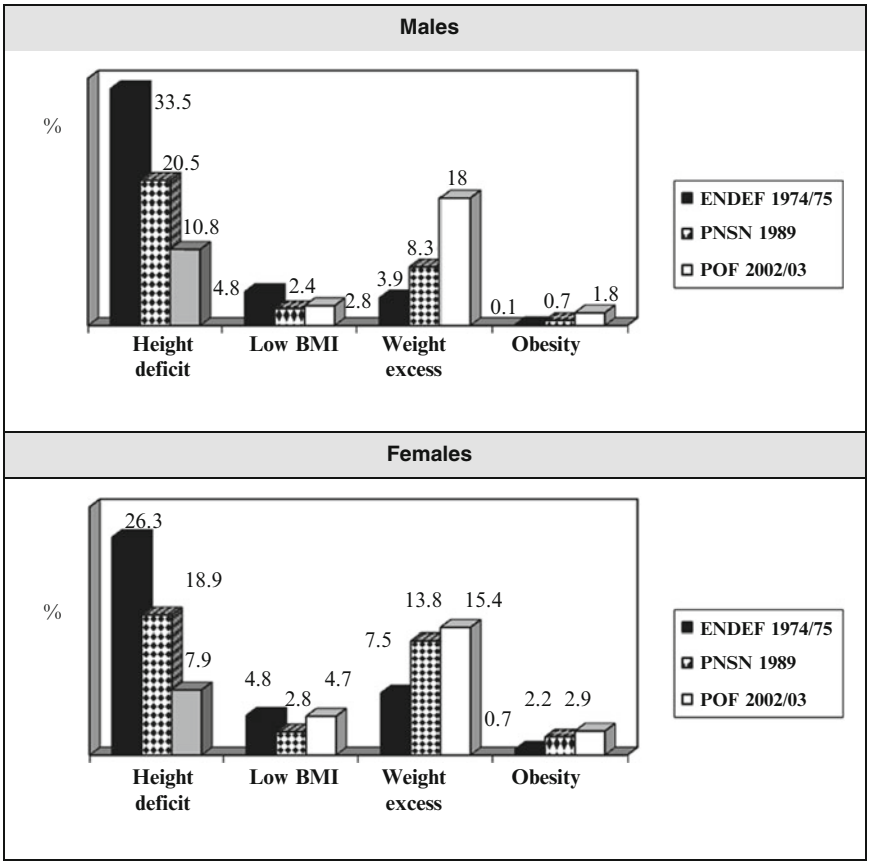
According to Table 82.1, approximately 10% of Brazilian adolescents present deficit of height for age. The frequency of height deficits is roughly threefold higher in regions with worse living conditions. Obesity among adolescents is more prevalent among females and in urban areas (POF 2003).

Table 82.2 demonstrates the influence of economic status on anthropometric indicators.

82.2.1 Secular Trend of Adolescent Nutritional Status

The secular trend of nutritional status of Brazilian adolescents is presented in Fig. 82.2.

The evolution of height-for-age deficit is characterized by a drop throughout the three Brazilian studies, although the prevalence is still higher than expected. The frequency of low-weight



Source: POF, 2003

Fig. 82.2 Secular trend of adolescent nutritional status. This figure shows, by sex, the secular trend in BMI of Brazilian adolescents, according to the three national studies that assessed the nutritional status of the group in question: Studies of Household Spending (1974/1975), National Survey of Health and Nutrition (PNSN 1989), and the Household Budget Survey (2002/2003) (Source: POF 2003)

adolescents, shown by the BMI for age, is below the expected 5%, in accordance with the cutoff point used to calculate the nutritional status, varying from 2.4% to 4.8%, regardless of sex; however, there is a different situation between the sexes – in males, the decline remains throughout 30 years (between studies), whereas, in females, the situation in 2000 is basically the same as in the 1970s. The increased prevalence of weight excess and obesity in this group is remarkable.

82.3 Application to Other Health and Disease Areas

82.3.1 Consequences of Weight Excess

The problems related to insufficient food intake are still relevant in Brazil, but health conditions resulting from weight excess deserve attention.

The scientific literature describes individuals with adequate BMI and excess fat tissue as metabolically obese normal weight (MONW). These individuals present a BMI within normal values, but have an increased risk to develop metabolic alterations, such as insulin resistance and hypercholesterolemia, indicating the important role played by fat tissue in the individual nutritional profile (Serrano 2008).

Due to increased overweight/obesity, adolescents already show metabolic alterations, such as hyperglycemia, dyslipidemia, and arterial hypertension, which are risk factors for coronary artery disease that were found only in adults in the past (Oliveira et al. 2004).

- *ARTERIAL HYPERTENSION*: It increases with aging, but the prevalence in adolescents is not negligible (Kuschnir and Mendonça 2007). In Brazil, the prevalence observed was 2.7% in children and adolescents in the State of Sao Paulo (Romaldini et al. 2004) and 6.6% in adolescents in the State of Rio Grande do Sul, which presented levels above the 95th percentile for diastolic pressure and 12.9% for systolic pressure (Barros and Victora 1999). Rosa and Ribeiro (1999) revised studies about arterial hypertension in adolescence and found evidence indicating that arterial hypertension (AH), which is more characteristic of adults, may initiate in childhood and adolescence. The authors reported that the prevalence of AH among children and adolescents is 2–3% and that increased arterial blood pressure levels in childhood and adolescence seem to be the most potent predictor of arterial hypertension in adults.
- *DIABETES MELLITUS*: The prevalence of diabetes in adolescents was lower, mainly of type 2 diabetes mellitus (DM), but, in the past two decades, there has been an increase of this disease in this age group, and the characteristics are similar to those found in adults (Gabbay et al. 2003). In Brazil, a study of adolescents aged 10–19 years found a prevalence of insulin resistance of 10.9%, in 23% of those overweight and in 43.5% of those obese (Silva et al. 2005).
- *DYSLIPIDEMIAS*: The association of obesity and dyslipidemia observed in adults has also been reported in children and adolescents. Faria et al. (2006) studied adolescents from a Brazilian city examined by the Adolescent Healthcare Program, and found that the lipid profile was inadequate in 63% and the highest percentage was for total cholesterol (47.4%); females presented higher and significant total cholesterol levels ($p = 0.009$), LDL ($p = 0.02$), and lower HDL levels ($p = 0.0009$). A study conducted by Giuliano et al. (2004) in another city in Brazil demonstrated cholesterol levels above the desired values in 28%, hypertriglyceridemia in 22%, LDL above the desirable levels in 14%, and low HDL in 5% of adolescents.
- *METABOLIC SYNDROME*: Its prevalence in childhood and adolescence varies according to the diagnostic criterion used as well as the definition adopted for cutoff points (Jessup and Harrell 2005).

In Brazil, Silva et al. (2005) studied the prevalence of metabolic syndrome and insulin resistance in adolescents. They adopted the BMI curves and arterial pressure levels adjusted to the Brazilian population; they considered as obese those with BMI > 97th percentile and as hypertensive those with systolic or diastolic blood pressure > 95th percentile. The metabolic alterations analyzed were triacylglycerols > 130 mg/dl, HDL ≤ 35 mg/dl, decreased glucose tolerance, abnormal fasting glucose, or type 2 diabetes according to the American Diabetes Association. They also included the criterion of presence of insulin resistance by the HOMA-IR (Homeostasis Model Assessment-Insulin Resistance), that is, [(fasting insulin (μU/ml) × fasting glucose [mmol/l])/22.5] > 2.5). The prevalence of metabolic syndrome according to the NCEP-ATP III (2001) was 6% in the total group of adolescents and 26.1% in the obese. Adolescents with normal BMI or overweight presented the necessary number of factors to diagnose this syndrome. Faria (2007) analyzed several criteria to classify metabolic syndrome in female adolescents who have already had menarche, and found a

prevalence of the syndrome ranging from 1% to 28%, depending on the criteria and cutoff points chosen. The WHO criterion (1998) adjusted to age group had a positive predictive value and a prevalence of metabolic syndrome of 16%.

82.3.2 Consequences in the Long Run

The major consequence of above-average nutritional status of adolescents is excess weight, which tends to persist in adult life, significantly contributing to morbidity and mortality.

According to Lamounier et al. (2000), about 50% of children who are obese at 6 months of age, and 80% of those at 5 years, will be always obese.

Aiming to investigate the influence of nutritional status in adolescence in the current nutritional situation of individuals when adults, Oliveira et al. (2009) carried out a study in Brazil with males, in three stages of life: at birth, at the end of adolescence (18 and 19 years), and at the beginning of adulthood. The BMI in adolescence related positively to weight and BMI in adulthood ($r = 0.634$; $p < 0.001$; $r = 0.678$; $p < 0.001$; respectively). The adults with metabolic syndrome presented, in adolescence, higher values for weight, waist circumference, and BMI, emphasizing the observed increased prevalence of overweight/obesity in adolescence, which corresponds to the observed rise in prevalence of metabolic syndrome in adulthood. It was concluded that adolescence, mainly at its end, seems to be very important in determining future nutritional status and health problems.

82.4 Anthropometric Indices in Post-Menarche Adolescents

With the development of secondary sexual characteristics, females have their first menstruation, called menarche (Colli 1991). It interferes with their social and psychic behavior and is biologically important. It is a landmark in the reproductive process of humans and a marker of growth. The first menstruation usually occurs between the maturation stages M3 and M4 (breasts) (Colli 1991), when adolescents continue to gain height, but growth velocity slows down, that is, when they are close to the end of spurt.

The assessment of infant–pubertal growth and development, observation of secondary sexual characteristics, and age at menarche are recommended in periodical growth evaluation (Zerwes 1993). Menarche is one of the sexual maturation indicators more often used in clinical and population practice by healthcare professionals, since it is a noninvasive method that requires no clinical examination and any professional is able to obtain this piece of information, which will help choosing the specific management (Horta 1991). Menarche has genetic and socioeconomic influences. It is found in the same group of adolescents at the same age, but with different maturation processes, demonstrating that chronological age of adolescents is not the main biologic indicator of health and nutritional status.

The variability of data regarding the first menses involves genetic characteristics and environmental influence, with complex interactions (Sedenho 1984). The literature indicates that, generally, menarche occurs between 12 and 13 years of chronological age (Crespin 1999). Data from the National Health and Nutrition Survey (PNSN 1989), a study with national representation, showed that the mean age of menarche in Brazil was 13.02 (±0.09) years (Picanço 1995).

The 1-year period after menarche as the inclusion criterion in population studies has been used to make the studied population homogeneous and to assure that hormone alterations and body composition characteristic of adolescence are not confounding variables in investigations. Moreover, adolescents who already had menarche are considered (in studies) because physicians specialized in adolescence are not always available to evaluate sexual maturation; and obtaining data based on self-assessment may have important biases. Hence, information on menarche is more reliable, enabling to have a more homogeneous population, even if it presents some differences, such as chronological age. The disadvantage is that studies are limited to females and those who are in more advanced stages of sexual maturation.

Weight and height are utilized to calculate the body mass index (BMI), waist circumference (WC), hip circumference (HC), and skinfolds, among other measurements. The anthropometric and body composition indices used in Brazilian studies on adolescents 1 year after a menarche are described in Chart 82.1.

Table 82.3 briefly describes some Brazilian studies on adolescents and 1-year period after a menarche.

Chart 82.1 Measures and body composition or anthropometric indices

Measurements and body composition or anthropometric indices	Description
Mid-arm circumference (MUAC)	Midway between the tip of the acromion process of the scapula and olecranon process of the ulna in the right arm
Umbilical circumference (UmC)	Measured under the navel
Leg length (LL)	Measured with the adolescent seating on a bench previously measured. The LL is the difference between the total height and the trunk-cephalic height (TCH).
Sagittal abdominal diameter	It corresponds to the distance between the back and the abdomen.
Coronal diameter	It corresponds to the distance between the iliac crests.
Trunk–cephalic height (TCH)	Height of a seated adolescent, in a bench previously measured. The bench height is then subtracted.
Central (CFM) and peripheral (PFM) fat mass	CFM: sum of central skinfolds (SSF + PSC) PFM: sum of peripheral skinfolds (TSF + BSF)
Central skinfold/fourfold sum ratio – ∑4P (CFM/∑4P)	It is calculated by adding up the central skinfolds (SSF + PSC) and dividing by the sum of four folds (SSF + SISF + BSF + TSF).
Central skinfold/peripheral skinfold ratio (CFM/PFM)	It is calculated by adding up the central skinfolds (SSF + PSC) and dividing by the sum of peripheral folds (TSF + BSF).
Conicity index (CI)	It is calculated using the formula: $CI = \frac{\text{umbilical circumference}}{(0.09)\sqrt{\text{weight / height}}}$
Fat body mass index (FBMI)	Ratio between body fat and squared height
Lean body mass index (LBMI)	Ratio between lean mass (LM) and squared height
Waist-to-hip ratio (WHR)	Ratio between WC and HC measurements
Waist-to-thigh ratio (WTR)	Ratio between UmC and thigh circumference (measured 3 cm above the patella)
Trunk cephalic height to height ratio (TCH/height)	It is calculated by dividing the TCH by height.

This table list the key facts used to assess the nutritional status of adolescents
MUAC mid upper-arm circumference; *LL* leg length; *UmC* umbilical circumference; *TCH* trunk–cephalic height; *CFM* central fat mass; *CI* conicity index; *FBMI* fat body mass index; *LBMI* lean body mass index; *BSF* bicipital skinfold; *SSF* subscapular skinfold; *SISF* suprailiac skinfold; *TSF* tricipital skinfold; *PFM* peripheral fat mass; *WTR* waist-to-thigh ratio; *WHR* waist-to-hip ratio

Table 82.3 Description of Brazilian studies using the 1-year period after menarche as inclusion criterion to investigate adolescents

References	Site	Sample	Objective	Results
Vieira et al. (2003a)	Viçosa-MG	*120 adolescents* One year after menarche *Study group (CFM)*: 60 adolescents with normal BMI (percentile 5–85) and with body fat percentage >25% *Comparison group*: 60 adolescents with normal BMI (percentile 5–85) and with normal body fat percentage	To study sociocultural nutritional variables and lifestyle habits of adolescents with elevated body fat	The study group presented higher weight, WC, HC, F in kg and BMI values It demonstrated the importance of assessing detailed body composition of adolescents with normal BMI and not only the BMI
Vieira et al. (2003b)	Viçosa-MG	*80 adolescents* One year after menarche *Study group (CFM)*: 40 adolescents with height deficit < percentile 5 *Comparison group*: 40 adolescents with normal height ≥ percentile 50	To identify the factors associated to low height in adolescents	The low height group presented lower HC ($p < 0.05$). No results indicated that CFM presented weight excess or central body fat
Faria et al. (2007)	Viçosa-MG	*100 adolescents* One year after menarche	To study the criteria for diagnosis of metabolic syndrome in adolescents	6% of adolescents presented BMI > percentile 85, 61% had high body fat percentage The prevalence of the syndrome varied from 1% to 28%, depending on criteria and cutoff points used

Referência	Local	Casuística	Objetivo	Resultados
Pereira et al. (2008)	Viçosa-MG	113 adolescents One year after menarche *Study group (CFM)*: 38 adolescents with normal BMI (percentile 5–85) and high body fat percentage (>25%) *Comparison group 1 (GC1)*: 40 adolescents with normal BMI (percentile 5–85) and normal percentage of body fat *Comparison group 2 (GC2)*: 35 adolescents with BMI > percentile 95 and percentage of body fat >25%	To verify the association of body fat measurement sites and cardiovascular risk factors in adolescents	Results demonstrated the relevance of body fat measurement sites in adolescence; among them, waist circumference and waist-to-height ratio were the best predictors of the risk of diseases in the population studied.

(continued)

Table 82.3 (continued)

Referência	Local	Casuística	Objetivo	Resultados
Serrano et al. (2008)	Viçosa-MG	113 adolescents One year after menarche *Study group (CFM)*: 38 adolescents with normal BMI (percentile 5–85) and high body fat percentage (>25%) *Comparison group 1 (GC1)*: 40 adolescents with normal BMI (percentile 5–85) and normal percentage of body fat *Comparison group 2 (GC2)*: 35 adolescents with BMI > percentile 95 and percentage of body fat >25%	To study the interference of body fat with risk factors for cardiovascular diseases in female adolescents	The group of adolescents with adequate BMI and high adiposity presented blood pressure, HDL fraction, and glucose levels similar to adolescents with BMI > percentile 95
Carvalho et al. (2008)	Viçosa-MG	113 adolescents One year after menarche *Study group (CFM)*: 38 adolescents of normal BMI (percentile 5–85) and high body fat percentage (>25%) *Comparison group 1 (GC1)*: 40 adolescents with normal BMI (percentile 5–85) and normal percentage of body fat *Comparison group 2 (GC2)*: 35 adolescents with BMI > percentile 95 and percentage of body fat >25%	To assess the metabolic profile of adolescents with overweight, "weight normal metabolically obese" and of adolescents with overweight resistant to insulin	Adolescents metabolically obese and with normal weight presented metabolic and inflammatory profile and body composition similar to those overweight.

This table lists the key facts of nutritional assessment of adolescents according to 1 year or more of menarche
WC circumference of the waist; *HC* circumference of the hip; *Gor kg* gordura in kg; BMI body mass index

82.5 Final Considerations

Evaluating adolescents demands a broad-range knowledge since they are in a stage of total transformation. It is important to search for more detailed information to understand the biopsychosocial aspects of this group since chronological age is not the most relevant indicator to make up a homogeneous sample. To assess females who already had menarche enables homogenization, but it is not possible to extrapolate such data to male or adolescents who presented no menarche.

Summary Points

- *Introduction: Brazilian adolescents*: Adolescence is defined by the World Health Organization (WHO) (2005) as the age group 10–19 years. It is a transition period between childhood and adulthood when many adult characteristics or lifestyle habits are acquired and/or consolidated.
- *Nutritional profile: secular trend of nutritional status of adolescents*: Brazil is a country with large inequalities that impact on the health status of its adolescents, who are directly affected by social and economic conditions.
- *Application to other health and disease areas: consequences of weight excess*: The problems related to insufficient food intake are still relevant in Brazil, but health conditions resulting from weight excess deserve attention.
- *Age of menarche in adolescents*: Data from the National Health and Nutrition Survey (PNSN 1989), a study with national representation, showed the mean age of menarche in Brazil was 13.02 (±0.09) years, and
- *National Health and Nutrition Examination Survey*: The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in USA. The survey is unique in that it combines interviews and physical examinations.
- *Studies that used in their methodologies adolescents 1 year after menarche. Final considerations*: Evaluation of adolescents demands a broad-range knowledge because they are in a stage of total transformation. It is important to search for more detailed information to understand the biopsychosocial aspects of this group to measure their nutritional status.
- *Trunk-cephalicheight*: To implement this measure, an individual should be seated with the trunk at an angle of 90° with the legs. The height is then measured, of the outcome subtracting this result the height of the seat.

Key Points

Figure 82.1 – Key features of adolescents who have already performed any paid activity and educational level.

1. According to the last demographic census data, 20.7% of the Brazilian population ($n = 35{,}302{,}972$) is aged 10–20 years, of which 10,516,531 adolescents (29.7%) are economically active. Among the adolescents who have already performed any paid activity, 25% are aged under 15 years, and 31.6% of them work over 40 h/week.
2. Approximately 6% of adolescents aged 10–14 years have never attended school.

Table 82.1 – Key features of nutritional assessment using anthropometric indicators such as: height deficit, body mass index, weight excess, and obesity and its distribution in rural areas and urban areas in Brazil.

1. Use of indicators according to sex, to assess its distribution in rural areas and urban areas.
2. Body mass index (BMI) is a measurement of the relative percentages of fat and muscle mass in the human body, in which weight in kilograms is divided by height in meters and the result used as an index of obesity.

Table 82.2 Key features of influence of income on the nutritional status of adolescents.

1. The poverty threshold, or poverty line, is the minimum level of income deemed necessary to achieve an adequate standard of living in a given country.
2. It is a situation where the per capita income is equivalent to less than 1 international dollar per day
3. The use of index height/age was used to classify the adolescents with height deficit.

Chart 82.1 – Key features of measures of body composition and anthropometric indices to assess nutritional status in adolescents.

1. There are several measurements and body composition or anthropometric indices used to assess nutritional status in adolescents.

Table 82.3 – Key features of three studies using the 1-year period after menarche as inclusion criterion to investigate adolescents.

1. Results of six studies developed with adolescents in Viçosa, Minas Gerais state.

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Chapter 83
Anthropometric Indices for Obesity and Hypertension in Indian Affluent Adolescents

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Abstract Childhood obesity and its health consequences have been attracting more attention in view of the increasing prevalence worldwide and the long term effects of obesity in adults. Earlier, anthropometric indices of obesity were recommended based on their correlation with body fat percent. However, in view of the fact that increasing body fatness is positively associated with blood pressure and other cardiovascular disease risk factors in adolescents, the choice of a cut off for anthropometric indicator should be based on health related criteria. Review of childhood obesity indicates that criteria used for assessing obesity in adolescents varied greatly. Nevertheless, it indicates that despite potential problems with body mass index (BMI), it still remains to be a popular indicator for estimating obesity in adolescents. One of the major limitations of BMI is however, that it does not perform well as a surrogate major of adiposity among thinner children thus affecting its validity in populations where prior undernutrition exists. The need for anthropometric indices for assessing total body fat or its distribution in large population studies is even more, in view of the fact that the existing equipment like Dual X-ray Absorptiometry (DXA) are not affordable and have limited ability outside the research setting. The chapter therefore describes benefits and limitations of different skinfolds and circumferences with the help of the data collected on urban affluent adolescents from Pune, India. It is worthwhile to mention that there is no uniform definition of assessment of overweight and obesity in adolescents and that any index will not fully characterize the impact of body fat patterning on metabolism. In fact, there are recently no guidelines for the classification of obesity related health risks among adolescents. The chapter thus highlights the need for examining the concordance between various indicators used for assessing obesity in adolescents, need for using national BMI reference data and developing cut offs anchored to metabolic risks and validating such indicators across different populations.

Abbreviations

BIA Bioelectrical impedance analysis
BMI Body mass index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_83,

CHD	Coronary heat disease
CVD	Cardiovascular disease
DXA	Dual X-ray absorptiometry
FM	Fat mass
HDBP	High diastolic blood pressure
HDL	High density lipoprotein
HSBP	High systolic blood pressure
HSE	High socio economic
IOV	Inter observer variability
LDL	Low density lipoprotein
LSE	Low socio economic
MRI	Magnetic Resonance imaging
ROC	Receiver operating characteristics
WC	Waist circumference
WHR	Waist hip ratio

83.1 Introduction

Obesity in adolescents is a major public health problem in developed countries and in some parts of developing countries too. It is a growing nutritional concern in countries that are witnessing nutritional transition (Popkin et al. 2001). Obesity's persistence into adulthood, its resistance to treatment, and its health consequences make it critical to understand adiposity in adolescents.

Obesity in adults is known to be a major risk factor for many noncommunicable diseases and especially for cardiovascular disorders. Childhood obesity too has important health consequences for adolescents and is a major antecedent of adult obesity (Popkin and Udry 1998). Persistence of childhood obesity into adulthood has been shown by several studies (Woelk 1994; Bao et al. 1995). Guo et al. (1994) have shown that overweight during childhood, especially beyond 8 years, is an important risk factor for overweight at the age of 35 years. Second, childhood obesity carries important health and social implications. Several epidemiological studies support the hypothesis that the relationship between adiposity and risk of disease begins early in life (Owens et al. 1998; Goran and Gower 1999).

Association between obesity and hypertension in adolescents has been reported in numerous studies among a variety of ethnic and racial groups with virtually all studies finding higher BP and/or higher prevalence of hypertension in obese compared with lean children (Sorof and Daniels 2002). Bogalusa Heart Study revealed that the prevalence of clinically diagnosed hypertension was significantly higher in adult subjects whose childhood BP was in the top quintile. These studies provide ample evidence for the fact that hypertension in adults has its onset in childhood which has caused growing concern with monitoring arterial blood pressure in adolescents in the last few decades. Understanding predictors of BP in adolescents is therefore important because childhood BP has been shown to track in adulthood. Further, obesity in adolescents not only is associated with hypertension and abnormal lipid profile but also shows clustering of risk factors for cardiovascular disease (Chu et al. 1998). Therefore, its prevention in childhood may help in preventing severe disease conditions in later years. This chapter attempts to discuss relative importance of various anthropometric indicators used for assessing adiposity, their limitations, caution in their interpretation, and their association with risk of hypertension in young Indian adolescents (place for key features).

83.2 Assessment of Obesity in Adolescents

The increasing prevalence of childhood obesity and its concomitant health risks justify widespread efforts toward its prevention. Reported studies show large variation in criteria used to assess obesity in adolescents (Dietz and Bellizzi 1999). There is no uniform definition and an indicator for assessment of overweight or obesity in children (Mast et al. 2002). Although DXA or other techniques such as densitometry, magnetic resonance imaging (MRI), and total body water offer reasonably accurate estimates of adiposity, they have limitations to research setting because of their complexity. Various researchers have proposed several anthropometric parameters but ideal measures of body fat in populations should be reliable and should correlate well with body fat in both sexes and across all ages and ethnic groups.

83.2.1 Body Mass Index (BMI)

Knowledge of the characteristic of adolescents who become obese is a matter of public health importance because it may aid both in identifying high-risk adolescents and in targeting primary preventive strategy. Because of lack of simple and accurate methods for assessing body fat directly, anthropometric indices are often used as surrogates for body compositions. BMI defined as a ratio of weight (kg) to height^2 (mt) offers a reasonable measure of fatness in children and adolescents and is widely used because of relative ease and accuracy of basic measurements. For assessing prevalence of 'at risk of overweight' adolescents, the conventional cut off for BMI (age and sex specific) above the 85th percentile (Must et al. 1991) can be used while that for 'obese' above the 95th percentile is considered. Similarly, age-sex specific cut-offs for BMI developed by Cole et al. (2000) are also used to define overweight/obese adolescents. However, these cut-offs are linked with adult cut-offs and extrapolated to childhood as proposed at the International Obesity Task Force (IOTF) meeting in 1997.

83.2.1.1 Limitations of BMI

Although BMI is used as a surrogate measure of adiposity, it is a measure of excess weight relative to height rather than excess body fat and is not without limitations. The foremost among these is the fact that almost all reported data pertain to adolescents from Europe or North America and therefore validation studies in other populations are needed (Dietz and Bellizzi 1999). There is need for an indicator that has acceptability across broad range of populations, because ethnic variation in relative subcutaneous fat distribution and in relative proportion of the trunk and the lower extremities to height are potential confounding factors in use of BMI as an index of adiposity.

Second, interpretation of BMI among adolescents is complicated by the changes that occur in weight, height, and body composition during growth, especially timing and tempo of adolescent growth spurt and sexual maturation may be an additional concern in the interpretation of BMI (Malina and Katzmarzyk 1999). The limitations of BMI as a measure of adiposity in the pediatric population are therefore believed to be larger than those in adult population. Further, it has been shown that it does not perform well as a surrogate measure among thinner adolescents, thus affecting the validity of BMI in populations where prior undernutrition exist (Freedman et al. 2005). Additional studies in undernourished populations are therefore required to show whether increase in weight for height is attributable to increase in body fat. Limitations of BMI are further underscored by the fact that it has high specificity and variable sensitivity in adolescents. Ideally, when designing an obesity screening program the choice

of cut-off should be based on health-related criteria. (Sardinha et al. 1999), because, in Indian adolescents, cut-offs for health risks especially that for high blood pressure are observed to be much lower than the conventional ones used for defining overweight (Rao et al. 2007). Recommendations such as IOTF are made despite the fact that the reference has not been thoroughly evaluated in terms of screening ability and relation to morbidity and mortality (Neovius et al. 2004).

83.2.2 Body Fat (%)

Excess body fat is the hallmark of obesity. DXA has the advantage of direct measurement of fat and lean tissue mass and the ability to evaluate the differences in fat deposition by region (Danials et al. 1999). However, such accurate methods used to assess total body fat and body fat distribution (computed tomography and magnetic resonance imaging) in humans are not suitable for large population studies because of cost, radiation exposure, and limited availability outside the research setting. Equipments based on the principle of bioelectrical impedance analysis (BIA) are often used for assessment of fat mass (FM) in field studies. However, the equations it uses for estimating FM are population specific and therefore may not be valid for other populations. In fact, it has been reported that different prediction formulas suffer from systematic over- or underestimations of %FM in adolescents and, therefore, development of a specific algorithm derived within the study population and validated against a so-called 'gold-standard' (i.e., densitometry) is preferable (Mast et al. 2002). The conventional cut-off as defined by Williams et al. (1992) for estimating prevalence of overweight in adolescents, using body fat (%), is above 25% for boys and above 30% for girls.

83.3 Body Fat Distribution

Skinfolds: In view of the lack of simple, accurate methods for assessing body fat directly, anthropometric indices are often used as surrogates for body composition. Simple skinfold measurement at various sites are often preferred as an alternative to sophisticated equipments for estimating body fat distribution, in field studies. Measurement of subcutaneous layer of fat, namely skinfold, is an easy method of assessing % body fat in adolescents. Conventionally, skinfolds are measured at four (biceps, triceps, subscapular, and suprailliac) to seven different places (additionally at chest, abdomen, and thigh) in humans and are used in isolation or in combination. Prediction of body fat % from skinfold thickness is an acceptable method for assessment of body composition in children and adolescents.

One of the limitations of these measures is that the measurements are subject to large between and within variabilities due to observer bias and, therefore, inter-observer variability (IOV) assessment studies are essential. Further, although skinfolds are shown to be correlated well with body density, the correlation is low in younger adolescents (Deurenberg et al. 1990). Due to changing subcutaneous tissue distribution during maturation, the relations between skinfolds and body density (and hence body fat) could be dependent on biological age, which could hamper assumptions of % body fat by skinfolds.

83.3.1 Skinfold at Triceps

It is reasonably well correlated with body fat and offers best results for assessing and screening obesity in adolescents regardless of disproportionate distribution of adipose tissue in various part of the

Table 83.1 Concordance between various indicators of assessing overweight in urban affluent Indian adolescents (Source: Rao and Apte 2008)

Indicator	No. of adolescents overweight	Adolescents who were also overweight by			
		BMI > 85th percentile *n* (%)	BMI (IOTF) *n* (%)	TSFT > 85th percentile *n* (%)	Body fat%© *n* (%)
Boys					
BMI > 85th Kappa value	315	–	283(89.8) 0.928**	126(40.0) 0.475**	305(97.1) 0.461**
BMI (IOTF) Kappa value	283	283(100.0)	–	124(43.8) 0.518**	277(98.2) 0.423**
TSFT > 85th Kappa value	134	126(94.0)	124(92.5)	–	132(98.5) 0.198**
Body fat%	615	305(49.6)	277(45.0)	132(21.5)	–
Girls					
BMI > 85th Kappa value	220	–	217(98.6) 0.978**	69(31.4) 0.392**	203(92.3) 0.719**
BMI (IOTF) Kappa value	221	217(98.2)	–	70(31.7) 0.396**	207(93.7) 0.739**
TSFT > 85th Kappa value	79	69(87.3)	70(88.6)	–	77(97.5) 0.327**
Body fat%	294	203(69.0)	207(70.4)	77(26.2)	–

This table examines concordance between four different indicators (BMI, IOTF, TSFT, and body fat) used for assessing overweight in adolescents, gives Kappa values indicating the strength of concordance and its statistical significance. There is a good concordance between the indicators BMI, IOTF cut–off, and body fat, while TSFT shows poor concordance with these indicators

BMI Body mass index, *TSFT* Skinfold thickness at tricep, *IOTF* International obesity task force cut-off

**$p < 0.000$, © Using CDC cutoffs – by McCarthy (2006)

body (Kapoor et al. 1991), but has large variability in measuring fatter subjects (Dietz and Bellizzi 1999). The cut-off used for skinfold at triceps for defining overweight is often same as that of BMI, that is, above the 85th percentile given by Must et al. (1991). Observation shows that combination of BMI and skinfold at triceps would also be important to assess the pattern of adipose tissue in adolescents (Sarria et al. 1998). However, it may be mentioned here that in the case of Indian adolescents the prevalence of overweight was highest using body fat percent cut-offs and was lowest based on triceps cut-off (Rao and Apte 2008) and triceps showed the poorest concordance with conventional indicators of assessing adiposity (Table 83.1). Similar observations are reported by Malina and Katzmarzyk (1999) for data from six different study groups.

83.3.2 Subscapular Skinfold

The other important measure is subscapular skinfold and is considered to represent centrally located body fat. However, unlike triceps skinfold, there are no cut-offs or standards defined for subscapular and other skinfolds that can be used for assessing obesity. Nevertheless, researchers have used the combinations of skinfolds and have also used them in combination with BMI to study the associations with adiposity and health risks in adolescents.

The observations from Bogalusa Heart Study show that centrally located body fat (subscapular skinfold) is independently correlated with blood pressure even after controlling for triceps skinfold. As subscapular skinfold increased, mean SBP increased, and the difference in mean SBP among adolescents in its lowest and highest quartile was of 8.5 mmHg (Shear et al. 1987). By contrast, no independent association was observed between peripheral fat (as measured by triceps skinfold) and blood pressure. The relationship was stronger in younger subjects and in males. More accurate measurement of trunkal fat recorded in this study using DXA (four regions considered for measurement were subscapular, waist, hip, and thigh) have shown positive association with triglycerides and negative with

Table 83.2 Correlation of skinfolds and circumferences with indicators of adiposity and SBP in urban affluent Indian adolescent boys

Indicators	BMI	Body fat†	Systolic BP
BMI	–	0.714**	0.145**
Triceps	0.754**	0.717**	0.191**
Biceps	0.708**	0.701**	0.167**
Subscapular	0.808**	0.650**	0.228**
Suprailiac	0.785**	0.629**	0.193**
Sum of all skinfolds	0.836**	0.721**	0.216**
Peripheral adiposity (triceps + biceps)	0.763**	0.735**	0.188**
Central adiposity (Suprailiac+subscapular)	0.825**	0.663**	0.218**
Waist circumference	0.903**	0.603**	0.359**
Hip circumference	0.857**	0.435**	0.386**
Waist to Hip ratio	0.250**	0.404**	0.031

This table illustrates correlation of BMI and body fat with different skinfolds, circumferences, and waist–hip ratio. Correlations of all the skinfolds were high and significant with conventional indicators of adiposity, that is, BMI and body fat and all these indicators also show significant correlations with systolic blood pressure

BMI Body mass index, *BP* Blood pressure

†Body fat estimated using OMRAN-HBF-300

**$p < 0.01$

high-density lipoprotein (HDL) cholesterol levels, indicating that relative preponderance of fat in the upper body including abdominal fat is an important determinant of cardiovascular risk factor status in adolescents (Daniels et al. 1999). It is, however, worthwhile to mention that methods used to estimate fat distribution (skinfolds and DXA) do not specifically measure the visceral fat depot.

Combinations of skinfolds as sum of two, defining central adiposity (subscapular and suprailiac) versus peripheral adiposity (triceps and biceps) or sum of all four and their different combinations have also been considered. In our study on urban affluent adolescents from Pune, India, it was observed that all the skinfolds are well correlated with adiposity indicators, that is, BMI and body fat percent (Table 83.2), yet the prevalence estimates of overweight based on them differ significantly from those based on either BMI or body fat (Table 83.1). Thus, the skinfolds represent mainly fat distribution, which is known to differ greatly for a given BMI. Further, all these indicators have lower correlations with health risks, for example, systolic blood pressure.

83.4 Circumferences

Recent studies in adolescents showed that a greater deposition of central fat is correlated with less favorable patterns of serum lipoprotein concentrations and blood pressure. Although early identification of adolescents with high central adiposity is important, studies on efficacy of anthropometric techniques for this purpose are scarce (Fox et al. 1993; Goran et al. 1998).

83.4.1 Waist Circumference (WC)

Whereas BMI is thought to be an indicator of overall adiposity, WC has been advocated as an indicator of abdominal fat content. Among the different circumferences considered in our study on urban affluent adolescents, WC correlated well with body fat and BMI (Table 83.2). However, there is a

Table 83.3 Age-specific WC percentile values reported for adolescent boys from various countries in comparison to urban affluent Indian adolescent boys

	Present study							
Age (year)	No of adolescents	85th percentile	90th percentile	Canada 90th	US[b] 90th	Turkey[c] 90th	UK[d] 90th	Hong Kong[e] 90th
9+	149	65.00	67.70	–	78.0	67.3	63.2	68.5
10+	326	68.49	71.00	–	80.0	69.9	65.6	70.6
11+	344	71.32	74.20	76.0	84.2	72.5	67.9	72.5
12+	300	75.28	78.10	76.7	85.9	74.9	70.5	74.0
13+	239	76.08	78.00	78.3	90.0	77.3	73.1	75.3
14+	238	78.04	80.01	81.0	96.0	79.5	76.1	76.3
15+	146	77.19	79.26	85.2	95.9	81.1	79.0	79.6

Source: [a]Katzmarzyk (2004); [b]Li et al. (2006); [c]Nihal et al. (2008); [d]McCarthy et al. (2001); [e]Sung et al. (2008)
This table compares 90th percentile values for waist circumference of affluent adolescents from India with those reported for Canada, US, Turkey, UK, and Hong Kong population. Although BMI for Indian adolescents is known to be lower compared to those from developed countries, it is interesting to note that the 90th percentile values for WC are in fact higher. WC- Waist circumference

dearth of information on the clinical utility of WC in addressing obesity-related health risk among adolescents and no guidelines are available for the classification of obesity-related health risks using WC. Despite increasing interest in the measurement of regional fat distribution, commonly accepted cut-offs for classifying subjects with high central adiposity do not yet exist with any assessment method (Taylor et al. 2000). Nevertheless, studies have examined the risk cut-offs for WC using receiver operating characteristic (ROC) analysis. ROC analysis is a way of evaluating the accuracy of a diagnostic test by summarizing the potential of the test to discriminate between the absence and presence of a health condition. In the case of 10–14-year-old adolescents from Cyprus, WC cut-off of 'above the 75th percentile' predicted high blood pressure, high cholesterol, high LDL (low-density lipoprotein) cholesterol, and high triglycerides (Katzmarzyk et al. 2004), while the cut-off for clustering of risk factors in adolescents was observed to be above the 90th percentile (Maffeis et al. 2001).

Clearly, studies are required to determine whether WC also performs well as an index of central adiposity in adolescents from different populations. Despite large differences in BMI and body fat percent in populations of developed and developing countries, it is interesting to note that 90th percentile values for WC observed in urban affluent Indian adolescents are closer to those reported for Canadian adolescents and in fact higher compared to UK adolescents (Table 83.3). The prevalence of overweight based on triceps skinfold is lowest and that based on body fat percent is highest in Indian adolescents indicates that, for a given BMI, adolescents have relatively higher body fat, not deposited at triceps but perhaps at abdomen, the observation well documented in the case of Indian adolescents. The relatively higher 90th percentile values of WC in urban Indian adolescents support this postulation. Far less is known about the combined influence of BMI and WC on health outcomes among adolescents. BMI and WC change during normal growth and maturation, at times rapidly; therefore, age-specific cut-off points are needed to classify adiposity status among adolescents (Janssen et al. 2005).

Use of other circumferences (abdomen, hip, thigh, etc.) have been reported in literature but in our study hip circumference showed low correlation with body fat (Table 83.2). Therefore, ratios based on them such as waist–hip ratio (WHR) or waist-to-height ratio are also considered for identifying central obesity or health risks but evidence is scarce. Among these, WHR has been explored to some extent but it can be seen that its correlation with BMI and body fat percent was lowest compared to WC (Table 83.2). It is therefore felt that ratios may not be appropriate because they are highly age dependent (Power et al. 1997) and may obscure stronger relations that may be present with separate circumference measurements.

83.5 Hypertension in Adolescents

Childhood blood pressure is related to adult levels and together with changes in BMI is a significant predictor of adult blood pressure. As the pathological process of atherosclerosis and essential hypertension begins in childhood and as obesity is related to both blood pressure and lipid levels in adolescents, the setting of cardiovascular disease (CVD) in adults is possibly accelerated with the mature obesity and fat deposition in adolescents (Shear et al. 1987).

Comparative data on blood pressure among adolescents from different populations indicate that South Asian adolescents have higher body mass adjusted blood pressure levels than white adolescents in US. Ethnic differences in blood pressure trajectories persisted after adjusting for socioeconomic status or growth or adiposity in both males and females (Dekkers et al. 2002). Therefore, targeting intervention in adolescents may be a critical opportunity for preventing ethnic differences in BP in later life.

Blood pressure variation is so closely associated with growth that these factors must be taken into account when assessing blood pressure in childhood and adolescents. The more recent update from Task Force on Hypertension Control in Children and Adolescents has provided population-based percentiles for blood pressure values in children adjusted for age, sex, and height. Values that exceed the 90th and 95th percentiles are defined as 'high normal' blood pressure and 'hypertension', respectively. Thus, identification of blood pressure threshold for hypertension in a child first requires determination of height percentile followed by interpretation of a dense table of blood pressure values with a separate threshold for each combination of gender, age, and height percentile (Update on the 1987 Task Force Report, National High Blood Pressure Education Program 1996).

83.5.1 Adiposity Indicators and Risk of Hypertension

Several epidemiological studies support the hypothesis that the relationship between adiposity and risk of disease begins early in life. Therefore, it is necessary that the choice of cut-off for obesity screening indicator should be based on health-related criteria. One of the criteria suggested (Kraemer et al. 1990) for choosing a measure of adiposity is a clinical validity, that is, ability to predict morbidity. The data on Indian urban affluent adolescents show that higher adiposity using any indicator is associated with higher systolic blood pressure (Fig. 83.1). It can be seen that the prevalence of high systolic blood pressure (HSBP) is almost similar when skinfolds are used either individually or as sum of two or four skinfolds. Similarly, the prevalence of HSBP and high diastolic blood pressure (HDBP) when examined (Fig. 83.2) in relation to percentiles of WC (age adjusted) show sudden increase in the prevalence beyond the 85th percentile, indicating that WC can also predict the risk of high blood pressure. It is however beyond doubt that the different indicators need to be compared for their potential to discriminate the health risks (i.e., HSBP) associated with adiposity. The correlations of different skinfolds and their combinations with systolic blood pressure were identical but were higher in younger age groups. It has been attributed to a greater detrimental effect of adipocyte hyperplasia, which occurs during youth versus adipocyte hypertrophy that occurs later in life (Hirsch et al. 1966).

In view of the fact that correlation analysis is blind to systematic bias and cannot describe the nature and magnitude of mis-classification, sensitivity and specificity of these indicators using ROC analysis have been studied by few researchers (Sardinha et al. 1999; Rao and Apte 2008). These studies have indicated that conventional cut-offs (IOTF, WHO, etc.) are highly specific but

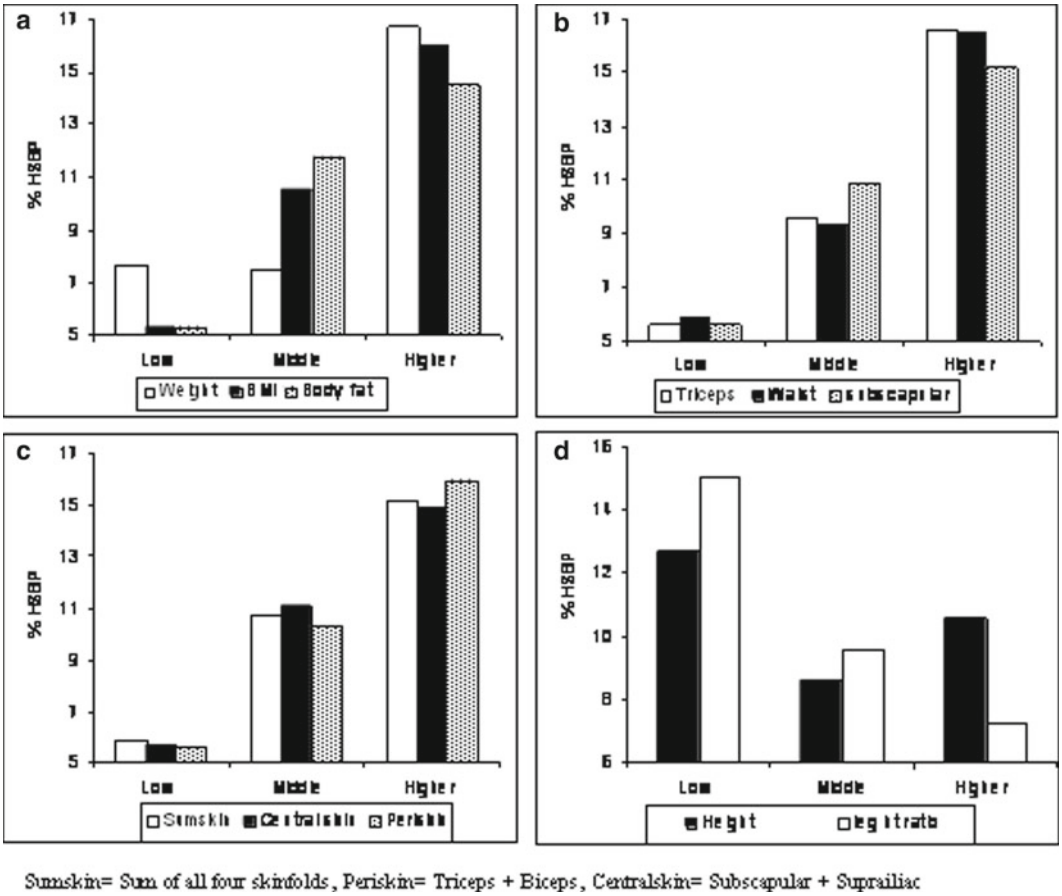

Fig. 83.1 Prevalence (%) of HSBP among urban affluent Indian adolescent boys according to (**a**) tertiles of Weight, BMI and body fat or (**b**) tertiles of triceps, subscapular and waist circumference or (**c**) tertiles of sumskin, central skin and periskin or (**d**) tertiles of height and leg height ratio. The prevalence of HSBP is almost similar when skinfolds are used either individually or as sum of two or four skinfolds. The adiposity thus showed positive association while leg height ratio showed inverse association with higher systolic blood pressure. *Sumskin* Sum of all four skinfolds, *Periskin* Triceps + Biceps; *Centralskin* Subscapular + Suprailiac

have low sensitivity. In the case of Indian adolescents, the ROC cut-offs for BMI improved the sensitivity of the indicators but they were much lower compared to conventional cut-offs and highlight ethnic variations in body composition (Table 83.4). Clearly, diagnostic demands intended for a clinical practice are different from those needed for public health use or monitoring. The implication is that there is a need for population-specific customized classification systems for assessing obesity in view of the probable population differences in relative risks of noncommunicable adult diseases.

83.5.2 Poor Skeletal Growth and Risk of Hypertension

Although adiposity is a major factor that confers risk for increased blood pressure in adolescents, there is a growing interest in investigating developmental origins for hypertension. One

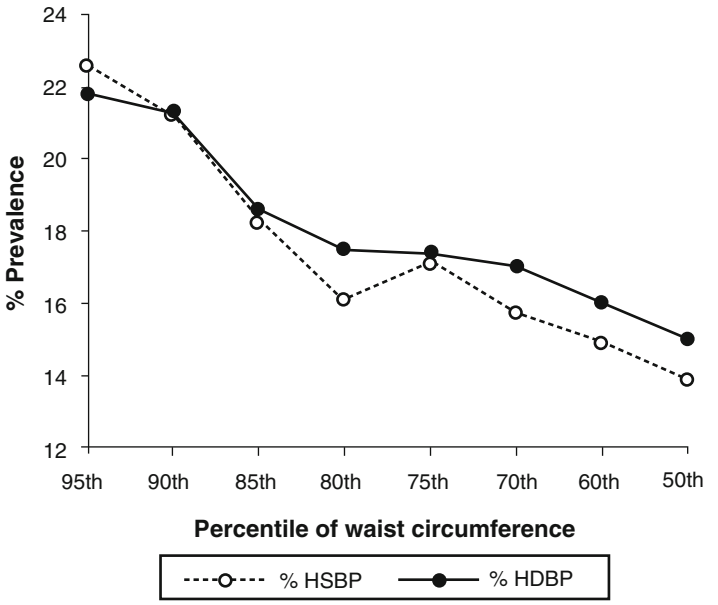

Fig. 83.2 Prevalence (%) of HSBP/HDBP above different percentiles for waist circumference. Prevalence of both HSBP and HDBP increased significantly 85th percentile among urban affluent Indian adolescents. *HSBP* high systolic blood pressure; *HDBP* high diastolic blood pressure

HSBP -high systolic blood pressure, HDBP - high diastolic blood pressure

Table 83.4 Predictive features for risk of high SBP for various indicators using conventional cut-offs as well as ROC cut-offs for urban affluent Indian adolescents

	Conventional			ROC		
Variable	Cutoff	Sensitivity (%)	Specificity (%)	Cutoff	Sensitivity (%)	Specificity (%)
Boys						
BMI	>85th 21.0	58.3	76.1	19.7	74.2	65.1
	(IOTF) 21.4	55.8	79.0			
TSFT	>85th 17.1	30.8	90.6	10.1	67.5	64.9
Body fat	>85th 22.4	73.3	48.6	23.8	66.9	60.1
Girls						
BMI	>85th 22.5	64.4	83.4	21.2	75.3	74.6
	(IOTF) 22.7	64.4	83.3			
TSFT	>85th 21.7	31.7	95.0	14.5	71.3	68.8
Body fat	>85th 29.2	72.1	76.4	28.4	74.0	72.6

This table gives the sensitivity and specificity of conventional cut offs of BMI, TSFT and body fat for predicting risk of high systolic blood pressure. Further it shows that the cut offs for these indicators obtained by the ROC technique had higher sensitivity and that they were lower than the conventional cut offs in case of Indian adolescents
BMI Body mass index, *TSFT* Skinfold thickness at tricep, *ROC* Receiver operating characteristics

of the potential areas that needs attention is the early life growth retardation. It is interesting to note that though South East Asian children were shorter and weighed less than Blacks and Whites, they had greater mean systolic blood pressure than Blacks and Whites across all weight strata (Munger et al. 1991). Similarly, high diastolic blood pressure has been reported in the case of adolescents from India, Pakistan, and Bangladesh by several researchers (Agyemang et al. 2004; Harding et al. 2006; Rao and Apte 2009). It is believed that poor childhood height growth may be associated with adult systolic blood pressure through socially patterned factors such as early nutrition, infection, or stress (Hardy et al. 2004). Further, these factors may,

Table 83.5 Odds Ratio (OR) for HSBP and HDBP by tertiles of various components of height among urban affluent Indian adolescent girls

		LSE				HSE			
		HSBP		HDBP		HSBP		HDBP	
		Adjusted for[a]		Adjusted for[a]		Adjusted for[a]		Adjusted for[a]	
Variable	Tertile	BMI	BF	BMI	BF	BMI	BF	BMI	BF
Leg Ht	L	2.05	2.59	1.43	1.56	1.77	1.94	2.62	2.85
	M	1.18	1.24	1.33	1.39	0.86	0.88	2.26	2.33
	H	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Leg Ht	L	1.38	2.11	2.00**	2.28**	2.05**	2.27**	2.10	2.23
Ht	M	1.18	1.70	1.52	1.61*	1.35	1.42	1.73	1.71
	H	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

This table gives odds ratios for risk of HSBP and HDBP for adolescents by tertiles of leg height and leg height to height ratio considering higher tertile as a reference category. These ORs are computed after adjusting for BMI/body fat. It shows that rather than absolute leg height, it is the ratio of leg height to height which was able to predict risk for HDBP among girls from LSE class and risk for HSBP among girls from HSE class

BMI Body mass index, *BF* Body fat, *Ht* Height, *LSE* Low socioeconomic class, *HSE* High socioeconomic class, *HSBP* High systolic blood pressure, *HDBP* High diastolic blood pressure, *L* Lower tertile, *M* Middle tertile, *H* Higher tertile

*$p < 0.05$; **$p < 0.01$

[a]All odds ratios are obtained after adjusting for height in addition to BMI or BF

through endocrine control, simultaneously influence growth of the arteries and of the bones at specific hormonally controlled phases of development, leading to both short height and high blood pressure in adult life (Leeson et al. 2001).

Slower growth in childhood may result from adversity extending into adult life and accumulated risks associated with this disadvantage may influence blood pressure. Differentials in blood pressure widen over life, possibly amplifying the effect of exposures in early life. Environmental exposures during periods of rapid growth are likely to be of particular importance in influencing subsequent blood pressure. Slow growth is a marker of vulnerability to stress. It is an indicator of exposures that also influences BP control mechanisms (Montgomery et al. 2000).

Short stature, limb height as well as altered skeletal proportions that may reflect interrupted early growth are associated with several metabolic disorders (Han et al. 1997). It has been recently reported that associations between components of height and coronary heart disease were largely unchanged in models controlling for parental height, indicating that genetic factors may not underlie the observed height–risk associations (Gunnell et al. 2003; Lawlor et al. 2004). Leg height is considered a better marker for the diversity of exposure which affects the childhood growth than the measures of childhood socioeconomic status themselves (Gunnell et al. 1998). Therefore, in populations where prior undernutrition may affect validity of body mass index, examining associations of simple measurements such as height or components of height with metabolic risks appears to be a promising alternative.

In Indian urban affluent adolescent boys, the prevalence of HSBP was highest (Fig. 83.1) in lowest tertile of height (age adjusted) but showed a stronger association with leg height to height ratio. The comparison of adolescent girls from high socioeconomic (HSE) and low socioeconomic (LSE) class further revealed that while HSBP was more prevalent in the HSE class (9.7% vs. 4.4%), HDBP was more prevalent in the LSE class (15.3% vs. 2.7%). However, it is essential to mention that leg height to height ratio showed (Table 83.5) significantly high odds ratio (OR) for HDBP in the case of girls from the LSE class and for HSBP in the case of girls from HSE class (Rao and Kanade 2007). This indicates that leg height to height ratio has predictive capability for respective risks across the two social classes. Since stunting is a major problem in many Asian countries, it is necessary to

examine whether somatic disproportions have the same predictive power for CVD risk across different populations.

In conclusion, assessing obesity in adolescents is highly essential in view of the global trends indicating increasing CVD risks in young adults. Clearly, there are several anthropometric indicators used for assessing adiposity in adolescents but concordance between them and their validity in different populations remains to be a major area for future research. Second, international reference standard is a compromise to obtain acceptable, comparable prevalence estimates at the global level. However, the rush to use an apparently universal definition of childhood obesity is premature and probably clinically detrimental. Defining pediatric obesity using national BMI reference data provides a safe, practical, and evidence-based approach. Further, due to probable population differences in relative risk, such customized classification systems derived from national data are likely to be more efficient. Finally, in view of the fact that evidence for screening obesity in relation to morbidity is scarce, developing cut-offs anchored to metabolic risk appears to be the prominent challenge for researchers.

Summary Points

- BMI is widely used as a surrogate measure of fatness in adolescents. It has high specificity but variable sensitivity and needs to be validated across broad range of populations.
- Body fat distribution is relatively more important than total body fat for assessing health risks associated with obesity.
- Skinfolds are well correlated with adiposity indicators, that is, BMI and body fat percent, yet the prevalence estimates of overweight based on them differ significantly from those based on either BMI or body fat.
- Waist circumference as an indicator of adiposity appears promising but needs to be tested for its clinical utility.

Key Features

Key features about Indian adolescents

1. India is one of the largest Asian countries which is passing through nutritional transition that is drastically affecting both the food basket and the lifestyle
2. Obesity among children (below 9 years) and among adolescents (9–16 years) is on the rise, mainly in big cities of India. In view of the increasing prevalence of cardiovascular disease risks in India and that adolescent obesity tracks into adulthood, investigations on adolescent obesity are highly essential
3. Our study covered adolescents from extremes of social classes. For example, low social class (LSE) was characterized by lower education of parents, low unskilled jobs of parents, less proportions having ownership of the house, higher number of persons per room, poor income, and no possession of economic assets such as four wheelers as compared to those from high socioeconomic class (HSE) which are referred to as affluent adolescents

This table gives key facts of affluent adolescents, their age group, and social factors that discriminated from lower social class

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Chapter 84
Anthropometry in Relation to Sexual Maturation

Silvia Diez Castilho and Antonio de Azevedo Barros-Filho

Abstract The wide variability in timing, sequence, duration and magnitude of pubertal events determines the need for assessing adolescents in relation to sexual maturation instead of age. During the maturation process there is a growth spurt, characterized by acceleration on growth velocity with an increase in weight, height and body mass index, change in body proportions and diameters and increase in muscle and fat tissue, which will determine the phenotype of each sex. Acknowledging this process, allows the correct understanding and assessment of anthropometric changes that may pose risks to an adolescent's current and future health. During the spurt, they gain ~20% of final height and ~50% of final weight. While muscle mass doubles in boys, it increases only 50% in girls, who in turn accumulate more adipose tissue, reaching ~25% of relative body fat (%BF), while boys reach ~15% in adulthood. Therefore, during maturation, girls gain fat-free mass index and fat mass index while boys gain fat-free mass index and lose fat mass index. Proportionally girls gain fat and lose fat-free mass, while boys present a large increment of fat-free mass and lose fat mass. These findings appoint toward the need to assess body composition of adolescents for a correct nutritional diagnosis.

Abbreviations

B	Breast stage
BFMI	Body fat mass index
BMI	Body mass index
%BF	Relative body fat
FM	Fat mass
FFM	Fat-free mass
FFMI	Fat-free mass index
G	Genitalia stage
NCHS	National Center for Health Statistics

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_84,

NHANES III	Third National Health and Nutrition Examination Survey
P	Pubic hair stage
PHV	Peak height velocity
SKF	Skinfold
WHO	World Health Organization

84.1 Introduction

Anthropometry is a tool for measuring body dimensions. It not only describes the nutritional conditions of individuals or groups, but also assesses them throughout time. The peculiarity of anthropometry during adolescence derives from the change-related factors that influence the understanding of these measurements during the period, and which should be acknowledged in order to correctly assess pathological findings, nutritional risks, or future diseases.

Adolescence has been defined as the transition between childhood and adulthood, during which biopsychosocial transformations occur. Puberty represents the biological component (physical) of adolescence and stands out among the anatomical and functional changes that are responsible for growth and development, aiming at maturation and the ability to procreate. Puberty encompasses variations in the velocity of skeletal growth, development of gonads and secondary sexual features, development of other viscera, and changes in body composition. Thus, an increase in measurements and a variation of body proportions during this phase are expected.

This chapter will discuss how each measurement, accessed through anthropometry, behaves during puberty.

84.2 Anthropometry During the Sexual Maturation Process of Well-Nourished Children

84.2.1 Growth

Growth refers to increase in the physical size of individuals. Weight and height, projected on charts, provide support for nutritional assessment, taking into account the fact that health hazards and/or environmental factors are reflected in growth and, consequently, in these charts.

Growth charts are normally plotted in terms of distance, that is, height and weight, in relation to age. Data of each individual are plotted over a reference curve based on longitudinal, cross-sectional, or mixed studies, carried out on a population at a good socioeconomic level.

Reference curves provide indispensable data for monitoring growth; however, it is necessary to interpret data correctly.

Charts from cross-sectional studies are based on population surveys, in which a large number of individuals were measured once, providing mean values and normal ranges for the population studied. These curves allow the assessment of health and growth, by showing where each subject stands within the wide normal range for sex and age.

The current curves recommended by the World Health Organization (WHO) for assessing adolescents are the "WHO Growth Reference 2007 for boys and girls, 5–19 years," which encompass weight-, height-, and body-mass-index-for-age curves from 5 to 10 years, and height- and body-mass-index-for-age curves from 5 to 19 years of age. These curves derive from the rebuilding of the

NCHS/WHO 1977 curves (a cross-sectional study for this age group), using the original sample (5–19 years, nonobese sample with expected height) supplemented by the WHO Child Growth Standards 2006 data, to facilitate a smooth transition at 5 years of age (Onis et al. 2007).

During adolescence, any deviation from the norm (percentile) should be interpreted carefully because charts built with cross-sectional data do not represent individual curves correctly, especially for adolescents who mature faster or slower than average.

Most of the knowledge that we have today on pubertal phenomena is based on longitudinal studies, in which a group of children is followed up and measured repeatedly during growth. The difficulty in this type of study lies in the high cost and high dropout rate, which makes it difficult to standardize normal limits, as the number of individuals followed up is insufficient at the end (of the study). This type of follow-up, however, allows calculating the increments of height in units of centimeter per year (cm/year) that occur in relation to age, associating them to the body changes that accompany the maturation process.

The first growth velocity curve was published in 1942 by D'Arcy Thompson in *On Growth and Form.* Thompson calculated the increments in measurements made by Philibert Montbeillard, who recorded his son's height from birth to age 18 years (between 1759 and 1777). These data were initially published as tables by Buffon (1777). Exactly 150 years later (1927), Scammon converted these measurements into the metric system and placed them on a height-for-age chart. According to Thompson's publication, growth velocity decreases from birth to 6 or 8 years, when there is a mid-growth spurt (more evident in boys), then continues to decrease until the beginning of the adolescent growth spurt. During this phase, there is an intense acceleration for ~2 years, followed by deceleration, and the end of growth. Since the first edition of Growth at Adolescence (1955), when Tanner combined the height-for-age- and height-growth velocity curves, they have been considered the best illustration of human growth (Tanner 1962).

In view of the great variability regarding the beginning and duration of pubertal events, the acceleration and deceleration of growth have a stronger correlation with sexual maturation stages than with age, which makes growth velocity useful in puberty evaluation.

In order to calculate growth velocity, we use the formula: growth velocity = (current height – previous height)/(# of months between measurements/12). Tanner, however, recommended using the time interval in decimal places instead of in months, to make it easier to calculate velocity. According to this system, the year is divided into ten parts and not into 12.

84.2.2 Growth in Height

Growth is the product of continuous and complex interactions between hereditary and environmental factors.

When a child grows in favorable conditions, the final height strongly correlates with the height of parents, manifesting the child's genetic inheritance.

From birth to 2 years, height reflects conditions of life inside the uterus. As of this age and throughout childhood, the correlation between the height of the child and that of their parents is moderate ($r = 0.5$), decreasing afterward during adolescence due to the great variability in relation to the onset of puberty. When one wants to estimate the final height of a boy, 13 cm should be added to the mean height of parents. For girls, 13 cm should be subtracted, according to the formula: final height = [(height of father + height of mother)/2] (±) 13 cm. Expected height is the mean of both values after adjustment, and whose value is determined by the difference of height between genders at adult age. Correlation with parents' height increases after the growth spurt, reaching a moderately

Table 84.1 Breast development stages in girls, genitalia development stages in boys, and pubic hair stages (P) in girls and boys according to Tanner (1962) (Does not require copyright permission)

Stages	Secondary sex characteristics (Tanner stages)
	Breast in girls
B1	Infantile stage that persists from birth until the changes of puberty begin.
B2	The bud stage; breast and papilla are elevated as a small mound and there is an increase of the areolar diameter.
B3	The breast and areola are enlarged with no separation of contours.
B4	The areola and papilla enlarge to form a secondary contour of the remaining breast.
B5	Adult breast; projection of papilla only; the secondary mound present in B4 disappears.
	Genitalia in boys
G1	Infantile stage that persists from birth until the changes of puberty begin.
G2	Enlargement of testes and scrotum, with changes in color (red) and texture of the scrotal skin.
G3	Enlargement of penis in length and to a lesser extent in breadth. Further growth of testes and scrotum.
G4	Enlargement of penis in length and in breadth. Further growth of testes and scrotum, with darkening in color of scrotal skin.
G5	Adult genitalia in size and shape.
	Pubic hair in girls and boys
P1	The vellus over the pubes is similar to that over the abdominal wall.
P2	Sparse growth of long, slightly pigmented and curled hair along the labia or at the base of the penis.
P3	Darker, coarser, and curled hair spreads over pubis.
P4	Pubic hair resembles adult type but covers a smaller area than in most adults.
P5	Adult pubic hair distributed in an inverse triangle (horizontal pattern); spread to medial surface of thighs.
P6	The pubic hair spreads up to the linea alba, onto the abdominal wall.

This table describes breast development in girls, genitalia development in boys, and pubic hair development in both genders, during sexual maturation according to Tanner (1962)
B breast stage; *G* genitalia stage; *P* pubic hair stage

high value (0.7) in adult age. Equations that take into account bone age, current height, and age, and for girls, information on the occurrence of menarche, improve accuracy in the prediction of final height (Tanner 1986).

Among the most important environmental factors that interfere with growth are nutrition, diseases, urbanization, physical activity, and stress. These factors are somehow related to the socioeconomic class that the child belongs to.

A prolonged physical injury in the beginning of life may determine delay in growth and eventually cause a height-for-age deficit (stunting). Children, who have had their growth compromised (severely malnourished) for a long period during the initial years of life, do not recover from this "loss," even if the injury ceases. In these cases, the height in adult age will be below the genetic potential. Therefore, the growth spurt does not recover from height losses; it is actually independent from growth in previous phases.

Height increase reflects the increase in fat-free body mass.

In terms of height for age, adolescents grow faster during puberty before reaching their final height. This rate may be identified through the tangent that touches the curve. When the curve of growth velocity is analyzed, an initial acceleration, with posterior deceleration, is observed. Before the growth spurt, during the latent period, a child grows at a rate of 4–6 cm/year.

The adolescent growth spurt is associated with the appearance of secondary sex characteristics that can be evaluated by Tanner stages, as described in Table 84.1. This evaluation may also be done by comparing adolescent sexual characteristics to illustrations.

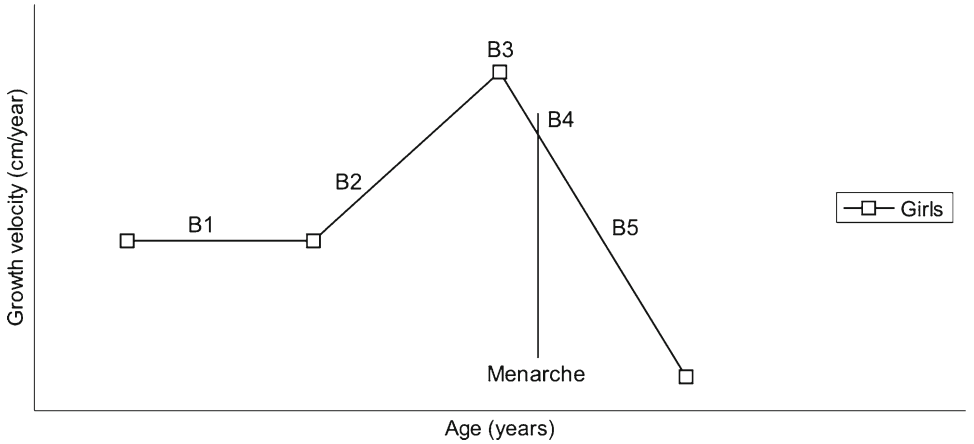

Fig. 84.1 Relation between height growth spurt and Bs (girls). A theoretical diagram of the height growth spurt (acceleration, PHV, and deceleration phases) in relation to Tanner stages in girls. B1–B5 refer to Bs (Diagram made by authors; does not require copyright permission)

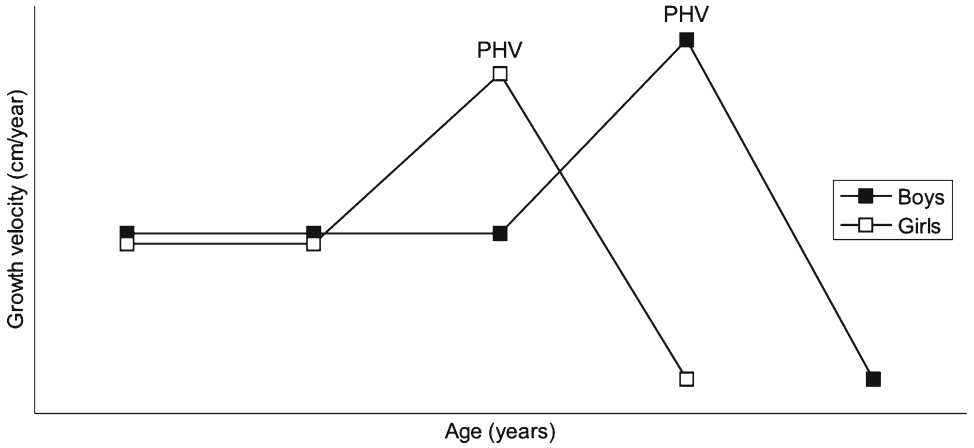

Fig. 84.2 Growth spurt of boys and girls. A theoretical diagram of the height growth spurt (acceleration, PHV, and deceleration phases) of girls and boys, showing that boys usually begin it, on average, 2 years after girls and grow more during the PHV. PHV: peak height velocity (Diagram made by authors; does not require copyright permission)

In girls, the spurt identifies the beginning of puberty and coincides with the appearance of the breast bud – breast stage (B) 2 (Tanner 1962). At this point, they have reached ~80% of their final height. During peak height velocity (PHV), they grow 7–11 cm/year and usually reach the B3 stage (Marshall 1977). Peak timing varies greatly from one population to another. Therefore, girls may reach this point between 10 and 14 years of age, depending on the age at which puberty began. Menarche occurs in the deceleration phase, at B4. By this point, they have ~95% of adult height and will continue to grow for ~4 years (Roche and Davila 1972). The mean duration of the growth spurt is 3 years, two-thirds of which are spent in the acceleration phase (Largo et al. 1978) (Fig. 84.1).

Boys begin to increase growth velocity, on average, 2 years after girls (Fig. 84.2). Thus, girls are temporarily taller than boys, who continue to grow at their preadolescent rate. Growth acceleration in

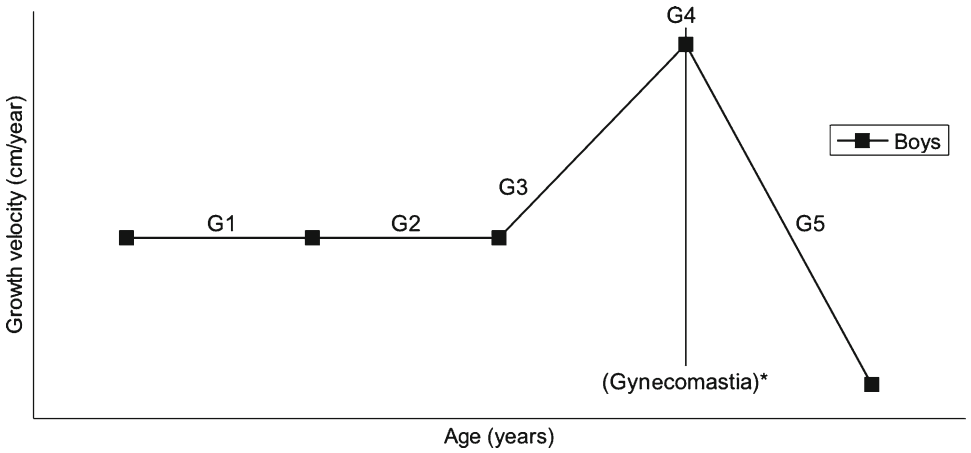

Fig. 84.3 Relation between height growth spurt and Gs (boys). A theoretical diagram of height growth spurt (acceleration, PHV, and deceleration phases) in relation to Tanner stages in boys. G1–G5 refer to Gs. *Gynecomastia may occur in boys, during PHV, when they are at G4 (Diagram made by authors; does not require copyright permission)

boys does not coincide with the beginning of sexual development. Growth velocity only accelerates when they are in genitalia stage (G) 3 (Tanner 1962) (Fig. 84.3). During PHV, boys grow 3 cm more than girls (Largo et al. 1978) and are in stage G4. At this time, they grow by 7–13 cm (~10 cm) (Marshall 1977) and are between 12 and 16 years (~14 years), depending on the age puberty began. The difference in the final height between boys and girls (13 cm) is due to the additional centimeters boys gain during the PHV, and also due to the growth during the 2 extra years before the spurt, a period in which boys grow at a rate of ~5 cm/year. The height growth in boys tends to continue longer after PHV. Men, in general, reach their final height at around 20 years of age. Largo et al. (1978) consider that individuals achieve their final height when increments become smaller than 0.5 cm in 2 years. Meanwhile, Roche and Davila (1972) prefer to define final height as being reached when there are consecutive measurements less than 0.5 cm in the past four semesters.

Children with an earlier PHV (early maturers within normal variability) reach a peak of greater magnitude than those who mature later, but there is no relation between the age in which the peak occurs and an individual's final height. The earlier puberty begins, the greater the magnitude of their PHV, and, afterward, they will grow more and for a longer period until reaching final height. Late maturers gain some centimeters before reaching PHV, which presents a smaller magnitude, and, after the peak, they grow for a shorter time period until reaching adult height (Tanner 1962).

84.2.3 Secular Trend of Growth

In the past 150 years, there has been a trend toward a reduction in the age in which the growth spurt and sexual maturation occur, in addition to an increase in the final height of the population, known as a positive secular trend. This trend has alternated with periods in which height increments tend to slow down, without stopping, whereas maturation may stop or even reverse. These periods correspond to phases in which the population suffered nutritional deprivation. The secular trend has been identified in all social levels, and is more evident in the less privileged classes, mainly in the Third World, when children are offered better life conditions.

84.2.4 Weight Gain

Weight increases as adolescents grow and develop. This increase is reflected in both fat-free mass (largest component) and fat mass, mainly in women.

Weight gain goes through an acceleration phase and posterior deceleration phase during puberty, similar to what occurs in height. In males, the velocity of weight gain practically coincides with the PHV, whereas, in girls, it occurs a few months (~6 months) after the PHV is reached.

84.2.5 Body Proportions

The increase in an adolescent's height results from a nonuniform acceleration in the growth of lower limbs and trunk. There is an initial limb spurt, following a distal–proximal direction, that is, first, feet and hands; ~6 months later, legs and forearms; and, finally, thighs and arms. Although the trunk grows ~6 months after the limbs, it contributes in an expressive manner to the height gain during puberty, increasing the trunk–limbs ratio (Marshall 1977). Hence, at 3 years of age, the upper segment/lower segment ratio is 1.3, and, in puberty, 0.9. These measurements may be estimated through the assessment of the upper segment (sitting height: measured from the distance between the surface where the individual is seated and the vertex) and lower segment or subischial height (difference between stature and sitting height).

There are gender differences in the growth of biacromial (shoulder breadth or scapular waist) and bi-iliac (hip width or pelvic breadth) diameters, in which the former grows more in males, whereas the latter is similar for both genders. These diameters reach maximum growth levels concomitantly with the trunk (Marshall 1977). This leads to the adult phenotype of each gender in which men have broad shoulders (android shape) due to increase in the biacromial/bi-iliac ratio and women broad hips (gynecoid shape), as the biacromial/bi-iliac ratio decreases and fat accumulates in the region of the hips (Loomba-Albrecht and Styne 2009). In females, as the hip grows, the waist-to-hip ratio also decreases, accentuating the curves of the female body. These diameters should be measured using a skeletal anthropometer or caliper (sliding or spreading), and circumferences measured with a non-expandable tape. Waist circumference has usually been measured at the smallest portion of the torso, and hip circumference, preferably, at the level of maximum posterior extension of the buttocks (Heyward and Stolaczyk 1996).

From birth to 18 years, the head circumference grows ~20 cm. Half of this growth occurs up to the ninth month and three-fourths up to the second year. The remaining growth is slow; a small acceleration can be detected during adolescence. In a small proportion, the skull also takes part in the spurt (Marshall 1977). During this growth, the eye globe grows, predominantly in the sagittal plane, which may determine the development or increase in myopia. More marked face changes are observed in males, with growth in the forehead, nose, mandible, and lower jaw, which frequently contribute to dental malocclusion.

84.3 Changes in Body Composition

During adolescence, individuals acquire 20% of their final height and double (50% increase) their body mass (weight). Most sexual differences that occur during this phase and lead to the adult phenotype result from the characteristic growth pattern of each gender, which is molded by the endocrine system. Whereas girls deposit more fat, boys gain more muscle and bone mass. In adult

age, men have 1.5 times the fat-free mass (FFM) of women, who, in turn, have twice as much body fat as men (Loomba-Albrecht and Styne 2009).

Most children go through a repletion phase between 8 and 10 years of age. At this time, both genders gain fat, increasing skinfold (SKF) thickness. In the beginning of the growth spurt, fat gain slows down. The deceleration is concomitant to the increase in bone and muscle tissue and it reaches the lowest point at PHV. The difference between genders consists of the fact that girls always have a higher fat deposit rate than boys. During the deceleration phase, they continue to gain fat, whereas boys lose adipose tissue.

Tanner et al. (1981) studied the behavior of adipose and muscle tissues, having calculated the respective cross-sectional areas in arm X-rays. The figures obtained were grouped around the PHV and not the chronological age, making the analysis of correlations between spurt and growth in these tissues easier, as the dispersion of ages for growth spurt is eliminated. At 9 years of age, both genders have about 15% fat in their bodies. At the time of PHV, the amount is 12% in boys, remaining the same for some years, and 19% in girls, reaching 25% after menarche.

Muscle mass corresponds to 25% of a newborn's weight and 40% of the weight of an adult. The major gain in the muscle tissue of men occurs mainly during the growth spurt and is associated with biochemical changes that are part of the functional differences between both genders (Marshall, 1977). From 11 to 16 years of age, muscle mass doubles in boys, whereas it only increases by 50% in girls. The increase in muscle tissue is concomitant to the acceleration in growth velocity and reaches its maximum at the time of PHV or a few months later. The peak of muscular strength gain, which can be measured by a dynamometer, occurs a few months later, and is higher in boys than in girls due to sexual hormones (Tanner 1962).

84.3.1 Skinfolds

Clinically, adiposity can be assessed by SKF measurements in several body sites. It estimates body density from which relative fat derives and estimates the regional distribution of fat mass (FM). Measurements are preferably made by using a metal caliper, such as the Harpenden or Lange. Approximately 3–9% of the variability of these measurements is due to technical errors. Errors vary according to site, with 8.8% in the abdomen, 7.1% in thigh, 3% in triceps, 3–5% in the subscapular, and 4% in suprailiac SKF sites (Heyward and Stolarczyk 1996). Thus, it is recommended that each SKF be measured at least twice at each site and that new measurements be made in cases where there is a difference greater than 10%.

During the pubertal process, there is a decrease in the fat gain rate in both genders, being less intense in the trunk than in limbs. This explains why the thickness of the subscapular SKF also continues to grow slightly in males, unlike the tricipital SKF. Regarding the latter, a progressive increase in females and a decrease in males are observed (Forbes 1986).

The easy access to subcutaneous fat by measuring SKFs (two or more) has allowed the development of many equations to estimate relative body fat (%BF) considering a variety of sites. Prediction equations developed by Slaughter et al. (1988), using the sum of triceps SKF and subscapular SKF, were aimed at children 8–18 years old. They take into account sex, ethnicity, maturation stage, and chemical changes in body composition (Table 84.2). Relative body fat makes it possible to calculate FM and FFM:

$$\% \text{ BF} = (\text{FM}/\text{weight}) \times 100$$
$$\text{FM} = (\% \text{ BF} \times \text{weight})/100$$
$$\text{FM} = \text{weight} - \text{FFM}$$
$$\text{FFM} = \text{weight} - \text{FM}$$

Table 84.2 Slaughter et al. (1988) SKF equations recommended for predicting %BF in children 8–18 years of age (Does not require copyright permission)

Σ triceps SKF + subscapular SKF < 35 mm			
Sex	Tanner Stage	Ethnicity	Prediction equation
Male	G1 and G2	White	% BF = 1.21 (Σ SKF) – 0.008 (Σ SKF)^2 – 1.7
		Black	% BF = 1.21 (Σ SKF) – 0.008 (Σ SKF)^2 – 3.2
	G3	White	% BF = 1.21 (Σ SKF) – 0.008 (Σ SKF)^2 – 3.4
		Black	% BF = 1.21 (Σ SKF) – 0.008 (Σ SKF)^2 – 5.2
	G4 and G5	White	% BF = 1.21 (Σ SKF) – 0.008 (Σ SKF)^2 – 5.5
		Black	% BF = 1.21 (Σ SKF) – 0.008 (Σ SKF)^2 – 6.8
Female	Independent of stage	All	% BF = 1.33 (Σ SKF) – 0.013 (Σ SKF)^2 – 2.5
Male	Independent of stage	All	% BF = 0.783 (Σ SKF) + 1.6
Female	Independent of stage	All	% BF = 0.546 (Σ SKF) + 9.7

Equations recommended by Slaughter et al. (1988) for predicting %BF
%BF relative body fat; ∑*SKF* sum of skinfolds (mm); *G* genitalia stage

84.3.2 Body Mass Index

Weight for age is inappropriate for monitoring growth beyond childhood due to the inability to distinguish body mass in relation to height (Onis et al. 2007).

The body mass index (BMI) has been used to assess nutritional status mainly in adults given that, at this age, it has a stronger correlation with FM and a weak correlation with height. It is also an appropriate predictor of morbidity and mortality. During adolescence, there are limitations for its use due to certain characteristics of this age group. It does not reflect the changes in body composition and does not correlate with height. Despite these limitations, it has been recommended for monitoring children and adolescents with overweight and obesity, as there is a lack of other cheap, fast, easy, noninvasive methods that could provide immediate results.

The increase in BMI values during adolescence should be interpreted as a marker of organic maturation, expressing the increase in the trunk-to-limb ratio, body mass, height, and changes in body composition. Actually, the index reflects more the increase in weight expected at this stage rather than the excess of fat, making it difficult to interpret data. Sexual differences in maturation rate, such as female precocity, explain the pattern found in the curves. Median BMI/age values for girls are systematically higher than those found for boys between 12 and 20 years of age, present increasingly higher differences up to 15 years of age, and drop afterward, as the sexual maturation stages of boys and girls grow closer. After 20 years of age, the index is higher in males. This is because the muscle tissue that prevails in men is heavier than the adipose tissue that prevails in women.

BMI-for-age curves of the "WHO Growth Reference 2007 for boys and girls, 5–19 years" are currently recommended as a reference for adolescents. The cutoff points for overweight and obesity are respectively +1 SD (25.4 kg/m^2 for boys and 25.0 kg/m^2 for girls), which is the equivalent to the cutoff point for overweight in adults (≥25 kg/m^2), and + 2 SD (29.7 kg/m^2 for both genders), which corresponds roughly to the cutoff point for obesity (≥30 kg/m^2) (Onis et al. 2007).

Table 84.3 Body mass index percentile distribution according to Bs

BMI (kg/m²) – Girls												
Breast stages	*n*	Mean	SD	Min	p5	p15	p25	p50	p75	p85	p95	Max
B1	115	18.0	3.19	12.8	14.1	14.9	15.4	17.0	20.7	21.3	23.8	29.1
B2	143	18.8	3.23	14.2	15.0	15.8	16.2	18.1	20.7	22.1	25.0	30.5
B3	134	19.5	2.74	14.8	16.0	16.8	17.5	19.1	20.8	21.6	24.4	29.4
B4	144	20.4	2.70	16.0	16.8	18.0	18.6	20.1	21.7	22.8	24.9	34.9
B5	120	22.4	3.65	16.0	18.4	19.6	20.0	21.5	23.8	25.5	28.6	39.2

Descriptive statistics of body mass index distribution according to Bs (Tanner 1962) in girls. Body mass index at the 50th percentile increases with maturational stages

BMI body mass index; *B* breast stage; *n* number of subjects; *SD* standard deviation; *min* minimum; *p* percentile; *max* maximum (Reprinted from Castilho et al. 2008. With permission)

Table 84.4 Body mass index percentile distribution according to Gs

BMI (kg/m²) – Boys												
Genitalia stages	*n*	Mean	SD	Min	P5	p15	p25	p50	p75	p85	p95	Max
G1	138	19.7	3.58	13.8	14.9	16.0	16.7	19.1	22.0	23.3	26.7	28.6
G2	133	19.6	3.84	13.8	14.8	15.8	16.6	18.5	22.2	23.9	26.8	30.6
G3	116	19.9	3.38	14.9	15.8	16.8	17.4	18.9	21.8	23.9	27.8	29.0
G4	117	21.2	3.57	15.4	16.7	17.8	18.8	20.4	22.9	24.3	28.3	37.9
G5	115	21.4	3.08	16.3	17.6	18.6	19.1	21.1	22.7	23.8	27.5	33.2

Descriptive statistics of body mass index distribution according to Gs (Tanner 1962) in boys. Body mass index at the 50th percentile is fairly constant from G1 to G3, increasing in G4 and G5

BMI body mass index; *G* genitalia stage; *n* number of subjects; *SD* standard deviation; *min* minimum; *p* percentile; *max* maximum (Reprinted from Castilho et al. 2008. With permission)

The interpretation of BMI values should consider that adolescents of the same sex, with the same weight and height, may go through identical phases of development at different ages, mainly between 10 and 14 years of age. Therefore, there are studies correlating BMI with sexual maturation stages for both genders (Castilho et al. 2008) – Tables 84.3 and 84.4. While the BMI increases when girls advance from B1 to B5, it is fairly constant from G1 to G3 in boys, increasing in G4 and G5. This correlation, similar to when the BMI is assessed in relation to age, is low for males (0.2) and moderate for females (0.4) (Castilho et al. 2008). In order to improve this evaluation, it would be better to correlate BMI with age, and check the variability of the index according to the maturational stage for each age, but there are no data available.

If, in adults, the increase in BMI generally reflects the increase in adiposity, in adolescents, it occurs at the expenses of fat and FFM (muscle, bone, and viscera). This index, however, does not distinguish among these compartments, making it difficult to interpret its value; thus, it is necessary to associate data from SKF measurements or bioimpedance, assessing fat-free mass index (FFMI) and body FM index (BFMI).

Bioimpedance makes clinical assessment easier, as it does not require previous training or the use of prediction equations to access body compartments, given that the equipment is linked to a computer that calculates these values. Leg-to-leg bioimpedance is appropriate, and has been validated for assessing body fat, mainly in field studies. In clinical practice, hand-to-foot bioimpedance is preferable given that the current flow that crosses the whole body provides an indirect estimation of %BF, unlike leg-to-leg bioimpedance where fat accumulated in the lower segment can be privileged.

The assessment of body compartments leads to conclude that girls gain FFMI and BFMI in absolute terms during the sexual maturation process, whereas boys gain FFMI and lose BFMI (Figs. 84.4 and 84.5).

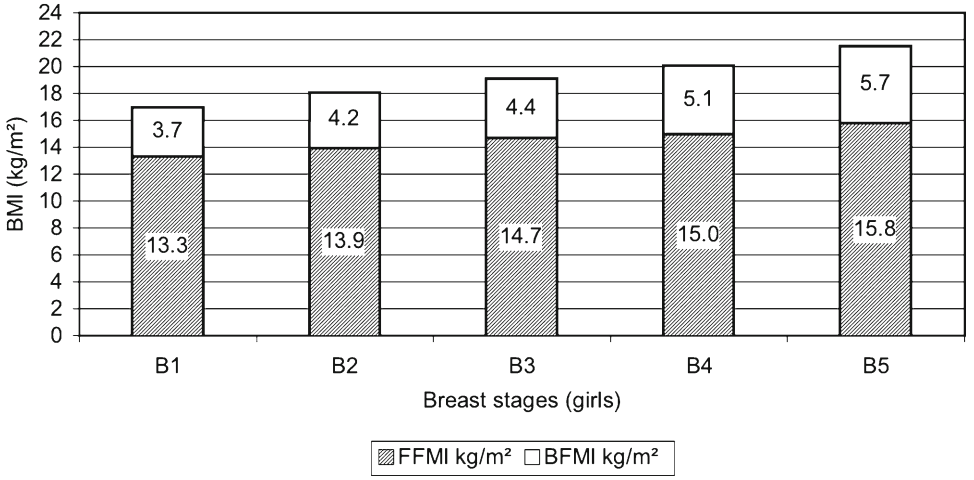

Fig. 84.4 Body mass index, FFM index and BFMI according to Bs. Body mass index increases in relation to sexual maturation stages. Girls gain FFM index and BFMI from the infantile stage to the adult stage. *BMI* body mass index; *FFMI* fat-free mass index; *BFMI* body fat mass index; *B* breast stage; BMI + FFM/height^2 = FM/height^2 = FFMI + BFMI. BMI based on p50 of Table 84.3 (Reprinted from Castilho et al. 2008. With permission)

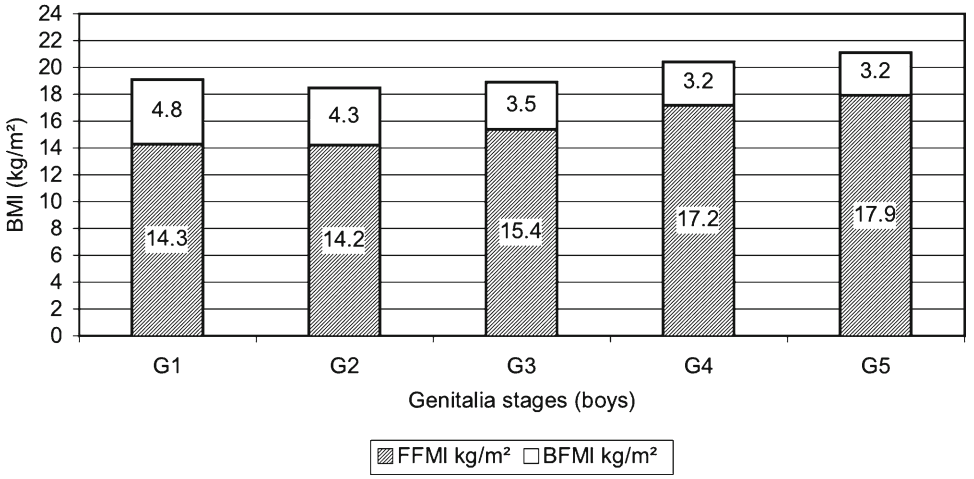

Fig. 84.5 Body mass index, FFM index, and BMI according to Gs. Body mass index is fairly constant from G1 to G3, increasing in G4 and G5. Boys gain FFM index and lose BMI from infantile stage to adult stage. BMI: body mass index, FFMI: fat-free mass index, BFMI: body fat mass index, G: genitalia stage, BMI + FFM/height^2 = FM/height^2 = FFMI + BFMI. BMI based on p50 of Table 84.4 (Reprinted from Castilho et al. 2008. With permission)

In relative terms, girls gain FM, going from 21.3% in B1 to 26.6% in B5 and lose FFM (78.7% in B1 and 73.4% in B5), whereas boys have greater increments of FFM (75.9% in G1 and 84.8% in G5) and lose FM, going from a %BF of 24.1% in G1 to 15.2% in G5 (Figs. 84.6 and 84.7). Not only BMI, but also FFMI and BFMI should be measured to monitor weight gain in adolescents in order to identify overweight and obesity, especially in boys who have not lost FM as they mature (Castilho et al. 2008).

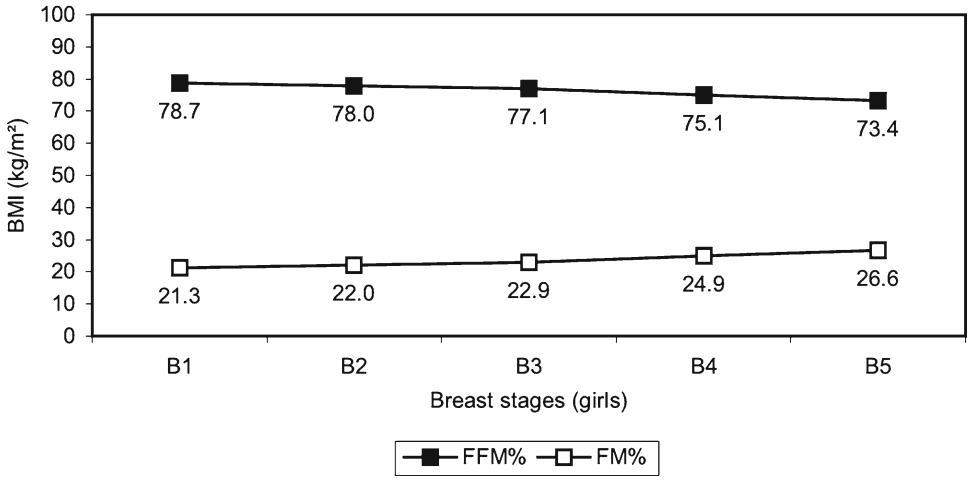

Fig. 84.6 Percentages by which FFM and FM contribute to body mass index increase according to Bs. As girls mature, the proportion of body mass index components changes. They gain FM and lose FFM. *BMI* body mass index; *FFM* fat-free mass; *FM* fat mass; *B* breast stage (Reprinted from Castilho et al. 2008, with permission)

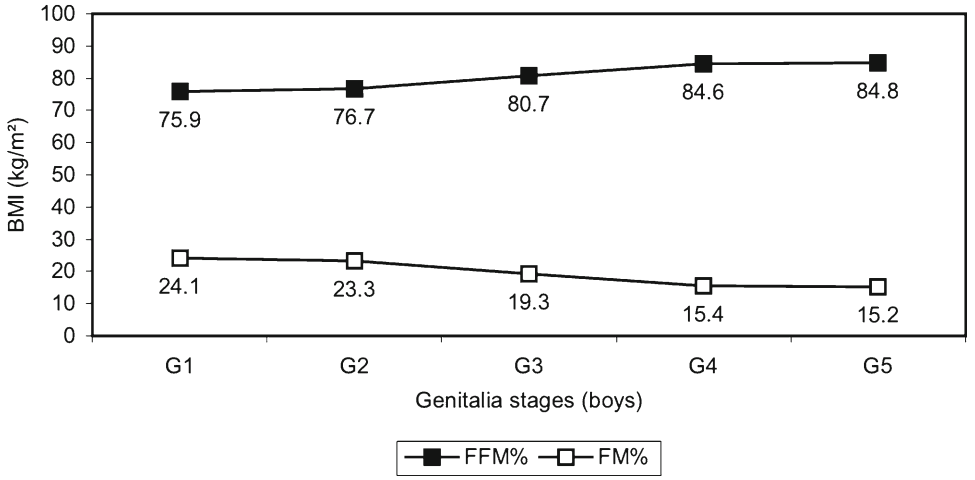

Fig. 84.7 Percentage by which FFM and FM contribute to body mass index increase according to Gs. As boys mature, the proportion of body mass index components changes. They gain FFM and lose FM. *BMI* body mass index; *FFM* fat-free mass; *FM* fat mass; *G* genitalia stage (Reprinted from Castilho et al. 2008. With permission)

84.3.3 Visceral Development

During puberty, the heart, lungs, liver, spleen, kidneys, pancreas, thyroid, adrenals, gonads, and other organs grow in different proportions (Tanner 1962). The central nervous system grows little and only the lymphoid tissue involutes. Several physiological adjustments of the cardiovascular system, pertinent to this phase, contribute to the increase in blood pressure, stabilization of heart rate, expansion of plasma volume, and increase in heart output and peripheral vascular resistance (Marshall 1977).

84.4 Maturation

84.4.1 Sexual Maturation

During puberty, sexual maturation encompasses the development of gonads, reproduction organs, and secondary sexual features. Sexual maturation reflects the adolescents' biological age.

The sequence in which secondary features emerge was classified by Tanner (1962), taking into account the development of breast in females, genitals in males, and pubic hair in both. Variables are classified into five stages that range from the prepubertal stage (infantile body, stage 1) to the adult phase (adult body, stage 5). With regard to pubic hair, the event progresses up to stage 6, when hairs spread toward the umbilical scar. The assessment of breast or genital maturation and pubic hair should be performed separately, as there may be disagreement between the stages (Table 84.1).

84.4.2 Females

In general (85%), girls begin puberty with thelarche (appearance of the breast bud), although pubarche (appearance of pubic hairs) may sometimes precede it (Wheller 1991). As breasts develop, the uterus, tubes, vagina, and vulva undergo anatomical and functional changes. These changes result from estrogen produced by the ovaries. The ovaries, which grow slowly and progressively since birth, begin to grow faster in the months preceding menarche. Axillary hair appears later (~6 months). Menarche is a late event within the pubertal process occurring on average 2 years after the appearance of the breast bud and also after PHV, during the phase of growth deceleration (Wheller 1991). Several factors may influence the onset of menarche (Castilho and Barros Filho, 2000). Usually, girls of a higher socioeconomic level, those living in urban regions, in warmer climates, and at lower altitudes menstruate earlier. The smaller the size of the family, the earlier they menstruate, and the youngest daughter tends to menstruate earlier than her older sisters. The influence exerted by ethnicity is difficult to be quantified, given that nutritional status, culture, and climate may influence the age of menarche. This event has been occurring 3–4 months earlier each decade (Table 84.5).

Frisch and Revelle (1970) proposed a critical weight theory that relates menarche to weight. According to these authors, girls must reach 47.8 ± 0.51 kg in order to menstruate. Afterward, Frisch and McArthur (1974) concluded that a minimum weight for height was necessary to establish the menstrual cycle. This weight would reflect a minimum of 17% stored fat, which would change the metabolism and decrease hypothalamic sensitivity to circulating steroids. Increase in gonadotropins and estrogen would lead to ovarian and uterine maturation, resulting in menarche. Ellison (1982), however, found evidence that growth velocity is a better predictor of menarche than weight and

Table 84.5 Key features of puberty in girls

- Girls generally begin puberty with the appearance of breast buds (thelarche) at B2.
- Pubic hair may sometimes precede thelarche.
- Axillary hair appears ~6 months later.
- Menarche usually occurs 2 years after thelarche and after PHV, during deceleration of growth velocity.
- Girls usually do not ovulate soon after menarche. It takes some time for them to become fertile.

This table lists the key facts of puberty in girls including the sequence of appearance of the secondary sex characteristics

PHV peak height velocity; *B* breast stage

Table 84.6 Key features of puberty in boys

Boys generally begin puberty with scrotum and testes enlargement (4 mL).
Pubic hair usually appears later.
Axillary and facial hair and hair in remaining parts of the body emerge ~2 years later.
Testes reach 12 mL at PHV.
Size of testes usually varies between 12 and 25 mL in adults.
Spermarche usually occurs before PHV, in stage G2 or G3.
Boys are fertile at this time (after spermarche).
Gynecomastia may occur during PHV, when they are at G4.

This table lists the key facts of puberty in boys including the sequence of appearance of the secondary sex characteristics
PHV peak height velocity; *G* genitalia stage

suggested that the event is determined by the rate of maturation and not by the size of the body. More recently, studies on leptin have once again evoked the critical weight theory.

84.4.3 Males

The beginning of testes enlargement indicates the onset of puberty in boys (G2). The volume of the testes can be assessed, by comparison, using the Prader orchidometer that consists of a series of ellipsoid-shaped models mounted on a cord in order of increasing size (from 1 to 25 mL). In prepubertal boys, the volume varies little (1–3 mL). At the beginning of puberty, it reaches 4 mL and rapidly increases its size reaching a mean volume of 12 mL at PHV. In adults, it varies between 12 and 25 mL. The emergence of pubic hairs occurs a few months (~6 months) after the initial increase of the volume of testes, whereas the hair in axillas, face, and remaining parts of the body appears later. The prostate, bulbo-rectal glands, and seminal vesicles have marked growth during puberty. Spermarche is rarely studied, as boys usually do not report it. A study identified that it occurs before PHV, in stage G2 or G3 (Guízar-Vázquez et al. 1992). Voice change subsequent to larynx growth due to androgenic action occurs later. One-third of adolescents may present increase in mammary tissue during puberty. In general, this increase occurs when boys are in stage G4 is restricted to the subareolar mammary tissue, and may be unilateral or bilateral (Tanner 1962). Gynecomastia used to be transient (1–1.5 years). On average, boys take 2 years to reach G2–G4 and 2 more years to reach G5 (Table 84.6).

84.4.4 Bone Maturation

Similar to sexual maturation, bone age also reflects the adolescents' biological age. It shows how far an individual has gone toward adulthood.

Skeletal growth is processed through progressive mineralization of ossification centers (nuclei) of short bones and epiphyses of long bones. Complete ossification of a nucleus or an epiphyseal center (conjugation cartilage) marks the end of the bone growth phase. Skeletal maturation is processed through a predictable sequence of ossification of different nuclei, allowing to rate different bone ages. Despite the great variability of when ossification nuclei emerge, the order of appearance is more constant. Radiographic models were created to assess which bone age corresponds to a qualitative and quantitative pattern of certain nuclei of one or more sites of the skeleton. Population standards

of chronological ages for the emergence of each ossification nucleus (Greulich & Pyle Atlas) or centers associated with a score that represents a certain stage of skeletal maturity (TW2) are the methods of reference for this assessment.

84.4.5 Variability

The physical changes in puberty usually occur in the second decade of life (10–19 years), but timing, sequence, duration, and magnitude of these events tend to vary. Individuals of the same age may present different physical aspects, especially in younger ages, because they are going through different developmental phases. This makes anthropometric assessment difficult, given that available charts and tables relate height, weight, SKFs, and BMI measurements to chronological age.

Genetic inheritance that encompasses ethnic and nutritional factors determines the age at which the body triggers puberty. Thus, adolescents with early or late maturation generally have parents or grandparents who report a similar development. This may be observed in relation to menarche, an event that is generally acknowledged by the family.

The assessment of any precocity or delay in the beginning of puberty, due to great variability and secular trend, should in clinical practice be based on updated references for each population. Therefore, one must only define puberty as precocious or delayed, if initial secondary sexual characteristics appear before or after the normal limits of the standard reference for the population to which the assessed adolescent belongs.

Children, who enter puberty before average, but within expected variability, are considered early or advanced maturers. Late or slow maturers are those who begin the pubertal process after the average, but are within the expected variability for events. Sexual maturation maintains a strong correlation with growth velocity; therefore, both early and late maturers, despite being taller or shorter than their colleagues at initial puberty, will end growth with the same adult height mean.

The timing spent progressing from one maturation stage to another varies. When an adolescent quickly passes from stages 2 to 3, it does not mean that this will happen at the same velocity in the following stages.

Although girls generally present thelarche before pubarche, the order of these events may change, with pubic hairs emerging first. Menarche that normally occurs in stage B4 may also occur in B3, and is less frequent in B5. Although not usual, some boys can present axillary hair concomitantly to pubic hair.

The size of breasts, hips, genitals, distribution of fat, muscle mass, weight, final height, and distribution and amount of hairs are also influenced by genetics. These differences are a matter of concern, especially in this day and age in which beauty references are stricter.

84.5 Anthropometry During the Sexual Maturation Process of Children with Nutritional Problems (Malnourished and Obese)

84.5.1 Nutrition, Growth, and Maturation

Malnourishment, due to low ingestion of calories, proteins, and/or certain nutrients, such as iron or vitamin D, may limit growth (Marshall 1977) and delay skeletal maturation. When the period of food

deprivation is short, there is a deceleration in weight gain that may be fully recovered with the reintroduction of an adequate diet. However, when food deprivation is extended throughout the growth phase, the genetic potential is no longer reached because the deficit in height gain, more evident during the faster growth phase, cannot be recovered, not even during the spurt.

Conversely, the height gain in obese girls has been found to be greater during childhood; therefore, they are taller in the beginning of puberty. Nonetheless, they reach the same final height as nonobese girls, highlighting a smaller gain during the spurt (Villar Villar et al. 2004). Complementing these data, Castilho et al. (2005) observed, by studying a cohort of Brazilian girls, that obesity does not interfere in post-menarcheal growth.

The nutritional status also interferes in the sexual maturation process. The critical weight theory (Frisch and Revelle 1970) suggests both a delay in the menarche of malnourished children and the anticipation of puberty in obese girls. The observation that these girls tend to mature earlier led to the assumption that body fat determines neuroendocrine changes, measured by leptin, triggering puberty (Shalitin and Phillip 2003). Although these findings are well documented in girls (Himes 2006), there is controversy regarding the effects of overweight and obesity on maturation in boys. Wang (2002), analyzing NHANES III data, observed a negative correlation with obesity delaying boys' maturation, whereas Denzer et al. (2007) did not observe any change in the timing for genital development or in the emergence of pubic hair, even though levels of testosterone were low. In the sample studied, these authors identified a slight anticipation in breast development.

Although the secular trend of anticipation of menarche is evident, studies have suggested that the age of menarche in well-nourished children has become stable, reaching its potential with improvement of nutritional conditions. The current positive trend may be due to increase in the prevalence of obesity (Ong et al. 2006).

Adolescence has been considered a critical period for the development of obesity. The risk is higher in girls, mainly when parents are overweight. The growth in obesity and the importance of its consequences for health – in a society where food habits and physical activity are changing – point toward the need to monitor the trend of BMI, FFM, and FM, as well as the changes in fat distribution. BMI increase has not been proportional to height gain (Mészáros et al. 2008). It is occurring at the expense of fat – mainly central fat (Dollman and Olds 2006) – which plays an important role in the development of chronic diseases (diabetes, hypertension, and cardiopathies) compromising adolescents' health.

84.5.2 Difficulties in Taking Measurements

Anthropometry is challenging in individuals in extreme nutritional conditions.

In the obese individuals, measuring SKF thickness may be difficult because the SKF can exceed the maximum opening of calipers and not be separated easily from underlying muscle. Likewise, access to body fat, by measuring SKF in malnourished individuals, may be compromised because they have proportionally more internal fat than subcutaneous fat. In these individuals, internal fat tends to decrease when they gain weight, and their total body fat increases. Equations developed by Slaughter et al. (1988) (suggested as appropriate to assess body composition in this age group) do not take into account maturation stage when the sum of folds is higher than 35 mm. In face of these difficulties, bioimpedance may be helpful.

In order to determine the risk of disease, fat distribution is more important than the estimation of total body fat. The impact of this distribution resides in the fact that visceral fat (located in the

abdominal cavity) increases the risk of morbidity–mortality (Esmaillzadeh et al. 2006). The term android obesity is used when fat prevails in the upper segment, and gynecoid obesity is applied when the fat is located in the lower segment. Android obesity is more typical in males and gynecoid obesity is characteristic of females, even though men and women can be classified in either group. Skinfold measurements should be taken in the trunk (umbilical, suprailiac, and subscapular) in order to estimate fat distribution in these cases. When this is not possible, measurements of waist and hip circumferences and/or the relationship between them are used. As waist circumference is strongly associated with visceral fat, and hip circumference is only influenced by subcutaneous fat, the use of the waist-to-hip ratio is preferred. Aside from the lack of universal standardization of measurement sites, there is also a lack of reference curves for assessing adolescents.

Limitations are also observed in height measurements of obese individuals, given that it is frequently difficult for shoulder blades, buttocks, calves, and heels to touch the vertical plane, generating errors in data.

After the first decade, weight loses importance for nutritional assessment. It should be considered in relation to height by assessing BMI. This index does not distinguish FFM from FM; hence, it is important to assess these components in order not to underestimate the increase in fat.

84.5.3 Difficulties in Assessment of Maturation

Parents of obese boys usually seek pediatricians when their children are teenagers, expressing two concerns: delay in puberty compared to classmates and the size of their penis. What actually happens is that the suprapubic fat deposit makes the genital, usually of normal size, seem small (Lee and Reiter 2002).

Unilateral or bilateral, benign gynecomastia is transient during puberty in boys, causing great distress. In obese individuals, excess of fat may suggest gynecomastia or determine its occurrence in a higher proportion, requiring the correct assessment of mammary tissue (Ma and Geffner 2008).

The same difficulty may be seen in females, mainly when follow-up is not longitudinal. One must avoid confounding the excess of fat with mammary tissue. Thus, breast contour and not size should be valued. Studies that compare maturational self-assessment with the assessment made by a trained professional have highlighted the difficulty in assessing Bs in obese children.

84.6 Applications to Other Areas of Health and Disease

Due to a wide variation in puberty events, it is important to acknowledge the normal onset limits for the population assessed. When puberty begins before or after the expected time, it may reflect endocrine problems that need to be carefully investigated.

Changes in the growth channel (weight/age or height/age percentiles) should draw professionals' attention. They can reflect either the lack of growth hormone or thyroid hormone or an acute process of malnourishment.

The growth spurt does not recover from previous losses of height gain. When children change growth channel to higher percentiles, it is important to assess if this is due to earlier, normal, or pathological puberty or to an actual increase in weight, given that adolescence is a favorable period for the development of obesity.

84.7 Practical Methods and Techniques or Guidelines

Bioimpedance makes the assessment of body composition easier, as it does not demand specific training, unlike SKF measurements. It also does not require using mathematical formulas in order to calculate %BF, FM, and FFM, given that the equipment already provides these data. Due to its practicality, leg-to-leg equipment is used to access body composition in field surveys. Meanwhile, hand-to-foot bioimpedance is restricted to individual assessment because it requires not only the correct placement of electrodes but also that the subjects be lying down. This method also favors the assessment of patients with nutritional problems, as it is difficult to assess SKF in obese patients (due to limitation in the opening of calipers) and in the malnourished (who may have their relative fat underestimated because they generally have more central fat when compared to others).

Summary Points

- During adolescence, boys and girls should be assessed in relation to sexual maturation.
- It is normal to gain weight, height, and body mass index, change body proportions, and increase FFM and FM because these parameters will lead them to acquire the characteristic phenotype of each gender.
- Puberty in boys begins on average 2 years after girls; therefore, girls are temporarily taller.
- The 2 years that boys take to begin their spurt, and the extra centimeters they gain during PHV determine the difference of final height between genders.
- The peak velocity of weight gain in boys coincides with height gain; in girls, this happens ~6 months later.
- Limbs grow before the trunk, although the trunk contributes substantially to height increase.
- Men have wide shoulders due to the increase in the biacromial/bi-iliac ratio diameter, and women have wide hips, due to the decrease in this ratio and fat accumulated in the hip region.
- During adolescence, youngsters achieve 20% of their final height and 50% of their final weight.
- Fat gain decreases during the spurt. This decrease is concomitant to the increment of FFM and reaches minimum velocity during PHV. There is more fat deposit in girls than in boys, and even when the rate of growth decreases, they continue gaining FM, whereas boys may lose FM.
- At 9 years of age, both genders have about 15% of body fat. At the time of PHV, it is 12% in boys and 19% in girls, reaching 25% after menarche.
- The gain of muscle tissue in males occurs mainly during the growth spurt. From 11 to 16 years, muscle mass doubles in boys, whereas it only increases 50% in girls.
- The increase in BMI reflects the weight gain expected in this phase, rather than fat excess; therefore, it is necessary to assess FFMI and BFMI.
- During maturation, girls gain FFMI and BFMI, whereas boys gain FFMI and lose BFMI. In relative terms, girls gain FM and lose FFM, whereas boys have a large increment in FFM and lose FM.
- In girls, the beginning of sexual maturation (B2) coincides with growth acceleration. Boys begin their growth spurt from G2 to G3.
- Nutrition influences sexual maturation. Whereas malnourishment delays puberty in both genders, excess weight in general anticipates puberty in girls and delays it in boys, due to hormonal changes.
- Obesity makes it difficult to take anthropometric measurements and assess sexual maturation in both genders.

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Chapter 85
Reference Curves of Waist Circumference in Children and Adolescents

Peter Schwandt and Gerda-Maria Haas

Abstract The global increase of adiposity in youth necessitates early diagnosis and intervention. Among other anthropometric measures waist circumference assessment has become increasingly important as an easy, non-invasive and inexpensive routine tool since waist circumference is a measure of central adiposity. The waist circumference is essential for a correct definition of abdominal obesity and consequently for a common definition of the metabolic syndrome in childhood and adolescence in order to allow for considerable ethnic variations. Furthermore, central obesity and therefore the waist circumference are predictive for cardiovascular risk.

To compensate for gender- and age-specific variations in development and ethnic origin of children and adolescents percentiles rather than absolute values are used for comparison with adults. This contribution paper has taken over the task of collating equivalent world-wide data as far as they have been published until now (October 2009, PubMed). However, the authors apologize in advance for having possibly missed some important publications.

Abbreviations

BMI	Body mass index
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
F	Female
LMS	Smooth (L) curve, trends observed for the mean (M), an coefficient of variation (S)
M	Male
MRI	Magnetic resonance imaging
PEP	Prevention Education Program
WC	Waist circumference
WHO	World Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_85,

85.1 Introduction

In USA, the prevalence of obesity in children has increased from about 5% in 1963–1970 to 17% in 2003–2004 (Ogden et al. 2008) measured against a stable cutoff point, ≥ 95th percentile body mass index (BMI) for gender and age (Cole et al. 2000). In addition, mean waist circumference among 2–19-year-old youth increased between 1988 and 2004 (Li et al. 2006). Trends in waist circumference (WC) as a highly sensitive and specific measure of central fatness during the past 10–20 years have given more significant results than measures using BMI in Great Britain (McCarthy et al. 2003). For a uniform definition of the metabolic syndrome in children and adolescents, the International Diabetes Federation proposed using the ≥90th percentile as a cutoff for WC for gender and age (Zimmet et al. 2007), but without the ethnicity-specific recommendations as proposed for adults (Alberti et al. 2005). An expert committee has concluded that: "Waist circumference is not recommended for routine use because measurement is difficult and appropriate cut-off values are uncertain, although it may be useful to characterize risks for obese children" (Barlow 2007). Indeed, central obesity is associated with an increased cardiometabolic risk in children and adolescents (Katzmarzyk et al. 2004).

National reference values are urgently needed in order to build global reference curves for waist circumference in children and adolescents similar to those for body mass index (Cole et al. 2000). However, the validity of comparisons between different populations critically depends on the comparability of the survey methods. This has recently been shown by a collaborative study from five European countries (Pigeot et al. 2009). Therefore, this paper collects corresponding data from all over the world and builds subsections as far as possible where comparability is considered to be more important than completeness.

85.2 Practical Methods and Techniques

85.2.1 General Remarks

In adults, normal weight, overweight, and obesity are globally defined as <25 kg/m², 25 to <30 kg/m² and ≥30 kg/m² body mass index (BMI), but waist circumference as an indicator for central adiposity is still waiting for a worldwide-accepted definition by gender and ethnicity (Alberti et al. 2005). This is also the case for children and adolescents for whom age–gender–ethnicity-specific centile values have to be defined for waist circumference, especially because of different rates of growth and development between males and females of different ages and ethnic groups.

85.2.2 Reference Methods

The comparisons with invasive methods in youth are sparse because of ethical and technical concerns. WC has been cross-validated against MRI (Brambilla et al. 2006). Further imaging techniques are computed tomography (CT) and dual X-ray absorptiometry (DXA). Bioimpedance is a rapid and inexpensive method to measure body fat and has been validated against DXA. It was used to construct LMS reference curves for body fat in UK children. (McCarthy et al. 2006).

85.2.3 Sites of Measurement

Sites of measurement is a very critical point, which needs urgent attention because this may cause substantial misleading informations of the lack of comparability of the sites of measurements made results in false reference data and wrong diagnosis, as demonstrated by the following examples. In adults, the prevalence of abdominal obesity (≥102/88 cm) varies between 22.1–33.2% in men and 30.1–55.5% in women, depending on the measurement site (Mason and Katzmarzyk 2009). In 1,140 Japanese subjects, the mean WC values in men/women were 85.2/73.1 cm at the midpoint, 86.8/78.8 cm at the umbilical level, and 87.2/82.5 cm at the iliac crest (Matsushita et al. 2009). The superior border of the iliac crest, midpoint between the iliac crest and the lowest rib, the umbilicus, and minimal waist are the four commonly used anatomic sites for measuring waist circumference. In 111 subjects aged from 7 to 83 years, WC values differed in magnitude depending on gender, but were highly reproducible and were correlated with total body and trunk adiposity. Separate analyses for children were not carried out (Wang et al. 2003). Among Japanese children, two measurement sites were used (maximum waist narrowing and top of the iliac crest) with significantly higher values for the iliac crest; the differences were much larger in girls than in boys (Inokuchi et al. 2007).

85.2.4 Practical Procedure

WC was measured to the nearest 0.1 cm, according to WHO recommendation, at the end of expiration with a nonelastic flexible tape placed directly on the skin horizontally at the midpoint between the lowest rib and the iliac crest and the hip over the major trochanters. Participants were standing erect with the abdomen relaxed. They were balanced on both feet with the feet touching each other and both arms hanging freely, with special attention being paid to ensure that the tape was positioned perpendicular to the longitudinal axis of the body and was parallel to the floor.

Common sites of measurement:

1. Midpoint between lowest rib and iliac crest (natural waist) (WHO 1995)
2. Umbilicus level (Norris and Wilson 1994)
3. Superior border of the iliac crest and
4. Minimal waist

85.3 Global Age–Gender–Ethnicity-Specific Waist Circumference Values

This review is necessarily incomplete because several national surveys are in the process of being published. Furthermore, to provide better comparability, WC percentiles are presented in separate tables, according to their calculation either by the LMS method (Cole et al. 1990) or by other methods. Nevertheless, comparisons between the percentile curves are complicated, as they cover different age ranges without separate classification for children (3–11 years) and adolescents (12–18 years), as proposed by the International Diabetes Federation (Zimmet et al. 2007). Thus, in infancy, gender differences for WC were small, but WC was significantly higher in boys than in girls from the age of 11 years onwards (Fredriks et al. 2005) (Fig. 85.1).

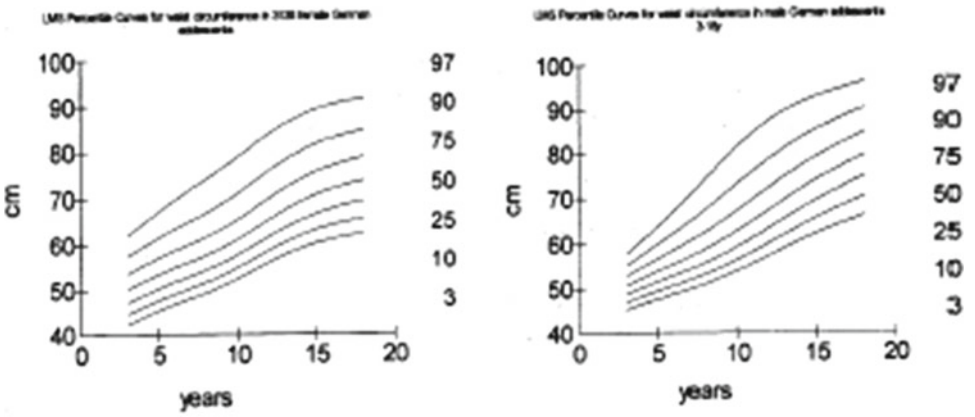

Fig. 85.1 Smoothed reference curves of 3–18-year-old German females (n = 3,136) and males (n = 1,421)

Generally, WC curves increase continuously with age in both genders; males have higher WC than females, especially in adolescence. In Spanish children, WC was higher at late puberty than in early and mid-puberty (Moreno et al. 2007). Compared with adolescents from Spain, the percentiles were higher in USA (Fernandez et al. 2004) and lower in Australia (Eisenmann 2005), Canada (Katzmarzyk 2004), and the UK (McCarthy et al. 2001). The Chinese 50th and 90th percentiles were lower than the curves for Iranian children, but closer to those of British children, except the 90th percentile curve for boys which had higher values (Sung et al. 2008). However, the shapes of the curves are variable, for example, the curves for Japanese boys aged 9–12 years demonstrated a prominent hump to the 97th percentile curves, which significantly differed from that of UK, Dutch and USA youth (Inokuchi et al. 2007). Between 7–8 years and 12–13 years, WC increased more than total adiposity (Garnett et al. 2005). At the 50th percentile, 5–19-year-old Nigerians had lower WC values than American and Spanish children, whereas Nigerian boys up to 9 years and girls up to age 14 years were similar to UK children (Senbanjo et al. 2009). Among 6–18-year-old Bulgarians, WC percentile values were higher than for British and Turkish children, but lower than for US children (Galcheva et al. 2009) (Fig. 85.2a, b).

Although measurement sites and the time of data collection were not too different, the main cause for the differences found might be ethnicity (genetic and environmental). Particularly after the age of 10 years, white males tended to have higher WC thresholds than the other groups (Katzmarzyk et al. 2004). Data from USA representing different ethnicities (Fernandez et al. 2004) pose some concern due to the use of the wide age range of 0–21 years, which means that comparisons between babies and young adults are being made. However, the Bogalusa Heart Study clearly demonstrates that the cutoff percentiles are fairly close in white and black 5–18-year-olds (Table 85.1).

As of now, the debate on appropriate cutoff points will continue so long as no global age-gender-ethnicity-specific cutoff points have been defined. Until then, several options have been proposed: a WC of 71 cm corresponded to a 14 times higher likelihood to have an adverse risk factor profile in prepubertal children aged 4–11 years (Higgins et al. 2001). The 90th or 95th percentiles were provisionally proposed to denote central obesity in Canadian adolescents (Katzmarzyk 2004). The 56th and 57th percentiles were suggested for white and the 50th and 52nd percentiles for black 5–18-year-old US males and females (Katzmarzyk et al. 2004) (Tables 85.1–85.3).

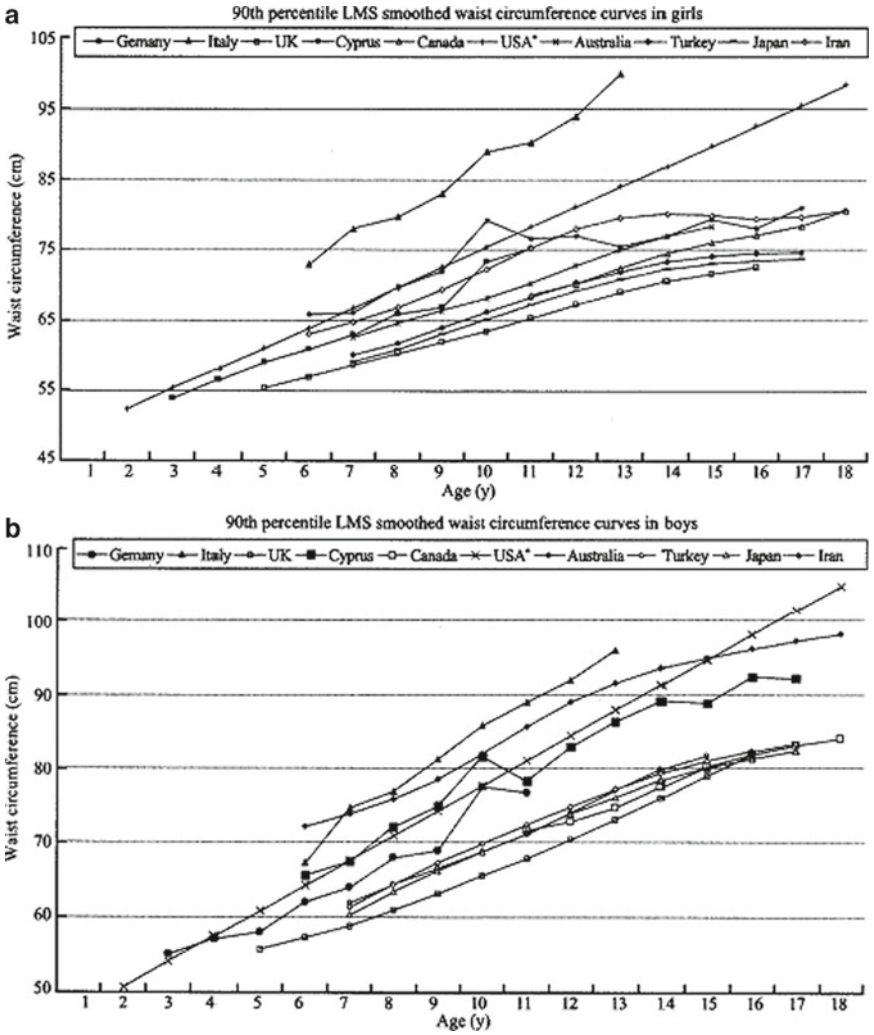

Fig. 85.2 (**a** and **b**) Comparison of the 90th percentile LMS-smoothed WC reference curves of 2–18-year-olds from 10 countries (Schwandt et al. 2008)

Table 85.1 Age- and gender-specific LMS percentiles for waist circumference children and adolescents from 14 countries

Country	Male/female	Age, years	Survey	Site	Cutoff #	Authors
Australia	M 4,277, F 4,162	7–15	1985	II		Eisenmann (2005)
Bulgaria	M 2,952, F 1,758	6–18	2006–2007			Galcheva et al. (2009)
Canada	M 1,540, F 1,524	10.5–18.5	1981	I		Katzmarzyk (2004)
China	M 1,366, F 1,227	6–12	2002–2004	I	85th percentile	Sung et al. (2007)
	M 7,472, F 7,370	6–18	2005–2006	I		Sung et al. (2008)
Germany	M 1,788, F 1,743	3–11	1994–2004	I	90th percentile	Schwandt et al. (2008)
	M 1,633, F 1,391	12–18	1994–2004	I	90th percentile	Haas et al. (2011)
Iran	M 10,253, F 10,858	6–18	2003–2004	I		Kelishadi et al. (2007)
Italy	M 1,440, F 1,418	6–14	n. r.	II	2 SD	Zannolli and Morgese (1996)
	M 443, F 375	3–11	n. r.	I	90th percentile	Maffeis et al. (2001)

(continued)

Table 85.1 (continued)

Country	Male/female	Age, years	Survey	Site	Cutoff [#]	Authors
Japan	M 5,851, F 4,762	6–18	1992–1994	III, IV	97th percentile	Inokuchi et al. (2007)
Mexico	M 415, F 428	6–10	n. r.	I		Gómez-Diaz et al. (2005)
Netherlands	M 7,482, F 7,018	0–21	1996–1997	I	>1.3/>2.3 SD	Fredriks et al. (2005)
New Zealand	M 302, F 278	3–19	n. r.	IV	80th percentile	Taylor et al. (2000)
Spain	M 701, F 659	6–15	1996	I		Moreno et al. (1999)
	140	11			70th percentile	Moreno et al. (2002)
	M 1,109, F 1,051	13–18.5	2000–2002	I		Moreno et al. (2007)
Turkey	M 2,337, F 2,433	7–17	2005	I		Hatipoglu (2008)
UK	M 3,585, F 4770	5–17	1988	I		McCarthy et al. (2001)
USA White	M 742, F 771	5–18	1992–1994	I	M 56th F 57th	Katzmarzyk (2004)
Black	M 510, F 574				M 50th F 52th	

I indicates midpoint between lowest rib and iliac crest (natural waist), *II* umbilicus, *III* superior border of the iliac crest, *IV* minimal waist. *n. r.* indicates not reported

[a]Arbitrary

[b]Black and white

Table 85.2 Age- and gender-specific percentiles by methods other than LMS for waist circumference in children and adolescents

Country	Male/female	Age, y	Survey	Site	Cutoff*	Authors
USA * *	M 4769, F 4944	2–18	1988–1994	III		Fernandez et al. (2004)
Cyprus #	M 1,037, F 950	10–14	1998–1999	II	75th percentile	Savva et al. (2000)
	M 1,214, F 1,258	6–17	1999–2000	II		Savva et al. (2001)

* arbitrary **residents of different ethnicity but living in one country; I indicates midpoint between lowest rib and iliac crest (natural waist), II umbilicus, III superior border of the iliac crest, IV minimal waist; n. r. indicates not reported; # polynomial regression

Table 85.3 Comparison of 90th percentile values for WC (cm) among 6–11-year-old boys and girls from 12 countries

Boys				Girls			
6 years		11 years		6 years		11 years	
Japan	55.0	UK	67.9	Japan	56.0	UK	65.4
UK	57.1	Japan	70.0	UK	57.0	Japan	66.0
China	60.0	Australia	71.3	China	58.0	Turkey	68.4
Turkey	61.3	Canada	71.7	Turkey	60.1	Canada	68.7
Australia	61.9	Turkey	72.5	Germany	61.8	China	69.0
Germany	62.6	China	75.0	Australia	62.7	Australia	70.4
US	64.2	Iran	75.5	Iran	63.5	Germany	74.7
Iran	65.0	Germany	77.1	USA	64.0	Iran	75.0
Cyprus	65.6	Cyprus	78.4	Cyprus	65.9	Mexico	75.2
Italy	67.4	USA	81.1	Mexico	68.0	Cyprus	76.6
Mexico	70.3	Mexico	87.4	Italy	73.0	USA	78.3
		Italy	89.0			Italy	90.3

Summary Points

- Both overweight and obesity in children and adolescents are increasing worldwide.
- Especially central obesity is associated with an increased risk of cardiovascular disease.
- Therefore, early detection of adiposity in children and adolescents is mandatory.

- This should be the basis for simple, exact, reproducible, noninvasive and inexpensive diagnostic tools.
- For central obesity, this is obviously the measurement of waist circumference.
- Contrary to adults, the growing and developing body of children and adolescents requires cutoff values, which can be adapted to accommodate this special situation.
- The first step is the development of age- and gender-specific percentile curves, necessitating identical measurement methods.
- The second step is the determination of cutoff values, which have to be associated with cardiovascular risk factors, for example, by receiver operating characteristic (ROC) curves.
- The third step is the consideration of ethnic and national influences, which take into account the worldwide epidemic of adiposity in children and adolescents and which should result in national age–gender–ethnicity-specific percentile curves.
- The final step is developing a globally accepted definition of WC, as has been done for BMI.

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Part XIV
Anthropometry of Middle-Aged and Aged in Health and Disease

Chapter 86
Anthropometric Aspects and Common Health Problems in Older Adults

Prasert Assantachai

Abstract The fast-growing numbers of older people worldwide and their health needs is coming under greater scrutiny, especially in developing countries where the rate of such growth is in the highest range. When compared to other age groups, nutritional problems are the most prevalent within older age group. Anthropometry is one of the ideal tools for nutritional assessment, either for under- and over-nutrition since it is cheap, easy to use and practical even in remote communities, comparable and requires no need for any sophisticated laboratory test or staff training. Although the traditional body mass index is commonly used for nutritional assessment both in clinical and research practices, its denominator, height, decreases rapidly in older age giving rise to a falsely high value in older people especially those who suffer from kyphoscoliosis. An alternative set of anthropometric measurements, namely, demiquet for older men and mindex for older women, is developed to compensate for this fault. Apart from nutritional assessment, more studies recently also highlight the potentials of anthropometry in assessing some other common health risks in older people such as atherosclerosis-related disorders, cognitive decline, osteoporosis, poor activity of daily living and all-cause mortality. However, in view of the physiologic aging changes and other confounding factors, the information found in younger age groups cannot be projected to and used directly in older adults. Some alternative anthropometric measurements and their interpretation must be recognized and developed.

Abbreviations

ADL	Activity of daily living
BMI	Body mass index
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
MMSE	Mini-Mental State Examination
MJ	Megajoule
OSTA	Osteoporosis Self-Assessment Screening Tool for Asians
TPP	Thiamin pyrophosphate

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_86,

WC Waist circumference
WHR Waist–hip ratio
WHO World Health Organization

86.1 Introduction

The fast-growing number of older people worldwide and its health needs are highlighted by every related discipline of medicine. When compared to other age groups, nutritional problems are the most prevalent among older people due to underlying factors, such as physiologic aging changes, chronic illness, as well as socioeconomic changes (Scrimshaw 1989). Although many advanced techniques to assess nutritional status have been developed over the last decade, anthropometry is an easy-to-use, unsophisticated, cheap, as well as practical tool, even when applied in the community, when compared to body composition analysis. However, many anthropometric parameters are subject to aging changes, for example, redistribution of fat in older women (Perissinotto et al. 2002). Moreover, gender difference, underlying global health status, urban versus rural community setting, and community dwelling versus institutionalized setting also influence the normative data in each particular group (Oguntona et al. 2000; Shatenstein et al. 2001). Therefore, the extrapolation of anthropometric standards derived from a younger age group is not appropriate for application directly in older people. The development of specific reference data collected from a large sampling population of older people is needed in almost every country (Chumlea et al. 1993).

To date, anthropometry has been studied in older people in various settings in terms of physiologic aging changes, alternative anthropometric measurements, and nutritional assessment and its associations with other health problems. Some common health problems prevalent among older adults, which relate to anthropometry, namely malnutrition (both undernutrition and overnutrition), hypertension, diabetes mellitus, cardiovascular disorders, cognitive dysfunction, osteoporosis, functional decline, and all-cause mortality, will be addressed in this chapter. Understanding all these topics is essential in applying anthropometric measurement in both clinical practice and epidemiologic studies for older people.

86.2 Physiologic Aging Changes of Anthropometric Measurements

86.2.1 Weight

Body weight is one of the most important and useful indicators of nutritional status, especially if it is followed up over time. If it is not intentionally lost, weight loss of 5% or more over the preceding 3 months indicates undernutrition. Weight declines longitudinally both in community-dwelling older people (Barbosa et al. 2005) and in the institutionalized setting (Shatenstein et al. 2001), in both Asian (Woo et al. 2001) and European people (Perissinotto et al. 2002). Although the prevalence of overweight increases with increasing age in developed countries for both men and women (to a greater degree in women), longitudinal body weight measurements taken 10 years apart tend to indicate weight loss in those aged 55 years or more (Williamson 1993).

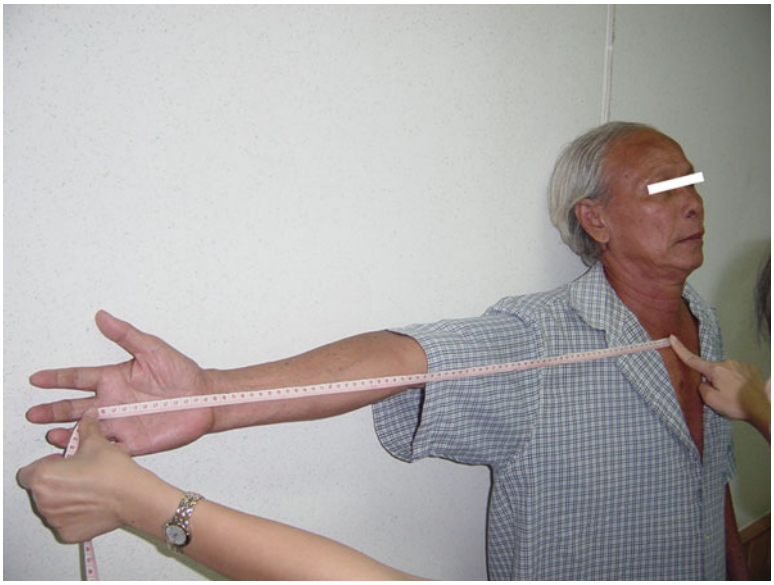

Fig. 86.1 Demispan measurement: the length between the center of suprasternal notch and the metacarpophalangeal joint between the third and fourth fingers while the subject stands against a flat wall, with the arm extended laterally and kept at shoulder height

86.2.2 Height

Height is the most widely used measure of skeletal size, which also decreases 1–2 cm/decade, but more rapidly at older ages due to associated vertebral compression, disk change, and postural changes. Therefore, careful measurement and interpretation of height in older people with kyphoscoliosis should be done.

86.2.3 Body Mass Index

Similar to body weight change, body mass index (BMI) declines with age, and it tends to be higher in women than in men. This reflects decline in weight to a greater extent than in height, as height also decreases. The turning point of BMI was observed at the age of 75 years in Europeans (Perissinotto et al. 2002). Although BMI has been widely used to reflect global nutritional status in the general population, some age-related changes make the use of the standard classification system for BMI less reliable in older people. First, the loss of height with age due to age-related osteoporosis, kyphoscoliosis and degenerative disk changes, and, second, the increase in fat-to-lean ratio in older people are the two main causes. There is, however, a set of alternative indices using demispan (the length between the center of suprasternal notch and the metacarpophalangeal joint between the third and fourth fingers while the subject stands against a flat wall, with the arm extended laterally and kept at shoulder height) to replace height in the calculation formula, giving rise to two alternative indices, namely mindex and demiquet. Figure 86.1 demonstrates the correct way to measure demispan. The relationship between arm span and body weight remains constant in older people with normal morphology.

86.2.4 Mindex and Demiquet

Mindex (mindex = body weight divided by demispan) is for use in women, whereas demiquet (demiquet = body weight divided by demispan squared) is for use in men. This is based on the study by Lehmann (1991) that weight increases proportionately with arm span in women and arm span squared in men. There are some studies indicating the usefulness of both of these Quetelet indices in predicting undernutrition in older people.(Donkin et al. 1998; Murphy et al. 2000) It is easier to measure demispan in older people than height, using a small-sized, convenient-to-carry, measuring tape, even in the sick elderly who cannot stand up.

86.2.5 Upper-Arm Anthropometric Circumference

The circumference of the mid part of the upper arm (mid-arm circumference or MAC), is a useful alternative to body weight, if the subject cannot be weighed as in the case of sick or frail older people. Two other indices reflecting lean body mass, mid-arm muscle circumference (MAMC) and mid-arm muscle area, can be calculated from MAC, as shown below. Again, all these three parameters also show significant decline with increasing age in both genders (Falciglia et al. 1988; Izawa et al. 2009).

$$\text{MAMC} = \text{MAC} - (\pi \times \text{triceps skinfold})$$

$$\text{Mid-arm muscle area} = (\text{MAMC})^2 / 4\pi$$

86.2.6 Skinfold Thickness

Skinfold thickness is the most widely used direct measure of body fat mass. It is proposed that the amount of subcutaneous fat stored in four favorite sites, that is, triceps skinfold, biceps skinfold, subscapular skinfold, and suprailiac skinfold can represent total body fat (Durnin and Womersley 1974). However, as there is age-related fat redistribution, with subcutaneous fat on the limbs tending to decrease but intra-abdominal fat tending to increase, which is especially more pronounced in older women, skinfold thickness cannot be used to assess changes in body fat mass in older people (Hughes et al. 2004).

86.2.7 Waist Circumference

Although fat redistribution occurs with aging, waist circumference (WC) decreases longitudinally in both genders (Barbosa et al. 2005). In men, both WC and waist–hip ratio were higher for the youngest age group than for the oldest age group. Meanwhile, in women, waist–hip ratio was higher in the oldest age group, indicating marked visceral fat redistribution within older women (Perissinotto et al. 2002).

86.3 Anthropometric Measurements and Malnutrition in Older Adults

As there is a limitation in using BMI to assess nutritional status in older people, the two alternative indices have been proposed, as mentioned earlier. Using the normative data of height and demispan from 2,324 older Thai people aged 60 years or more, who were randomly recruited from each region of Thailand and the cutoff points of BMI denoting underweight, overweight, and obesity proposed by the Steering Committee of the Regional Office for the Western Pacific Region of WHO, the International Association for the Study of Obesity, and the International Obesity Task Force (Anuurad et al. 2003), the cutoff points of mindex and demiquet indicating global nutritional status (Table 86.1) have been created by simple arithmetic equations as shown below (Assantachai et al. 2006a):

$$\text{BMI} = \text{body weight} / (\text{height})^2 \text{ and}$$

$$\text{body weight} = \text{BMI} \times (\text{height})^2$$

$$\text{while, demiquet} = \text{body weight} / (\text{demispan})^2 \text{ and}$$

$$\text{body weight} = \text{demiquet} \times (\text{demispan})^2;$$

$$\text{therefore, body weight} = \text{BMI} \times (\text{height})^2 = \text{demiquet} \times (\text{demispan})^2 \text{ and}$$

$$\text{demiquet} = \text{BMI} \times (\text{height})^2 / (\text{demispan})^2$$

From normative data of 2,324 older Thai people aged 60 years or more:

$$(\text{height})^2 / (\text{demispan})^2 = 4.0863 \ (\text{men}) \text{and}$$

$$(\text{height})^2 / (\text{demispan}) = 3.0241 \ (\text{women})$$

As the cutoff point of BMI denoting undernutrition = <18.5, the cutoff point of demiquet denoting undernutrition in older men

$$= < 18.5 \times 4.0863$$

$$= < 75.60 \text{ kg.} / \text{m.}^2$$

Table 86.1 The corresponding values of three Quetelet indices for each category of nutritional status, based on the Steering Committee of the Regional Office for the Western Pacific Region of WHO, the International Association for the Study of Obesity, and the International Obesity Task Force

	BMI (kg/m^2)	Mindex (kg/m)	Demiquet (kg/m^2)
Underweight	<18.5	<55.95	<75.60
Normal range	18.5–22.9	55.95–69.25	75.60–93.58
Overweight at risk	23–24.9	69.55–75.30	93.98–101.75
Obese I	25–29.9	75.60–90.42	102.16–122.18
Obese II	≥30	≥90.72	≥122.59

Table 86.2 Characteristics of three Quetelet indices of Asian and Caucasian older adults in terms of mean (standard deviation), 50th percentile and their correlation coefficients to each relevant parameter (Asian (Assantachai et al. 2006a): 644 men, 1,013 women and Caucasian (Smith et al. 1995): 182 men, 212 women)

	Mean (SD)		50th percentile		Pearson correlation coefficient (r)			
	Asian	Caucasian	Asian	Caucasian	Asian		Caucasian	
					mindex	demiquet	mindex	demiquet
BMI: men	21.5(4.0)	26.0(3.1)	21.4	25.9	n/a	0.88	n/a	0.89
BMI: women	22.8(4.5)	25.9(4.3)	22.8	25.6	0.93	n/a	0.96	n/a
mindex	68.3(15.5)	88.6(14.7)	69.3	86.6	n/a	n/a	n/a	n/a
demiquet	86.7(20.2)	121.1(15.6)	88.1	120.0	n/a	n/a	n/a	n/a

and the cutoff point of mindex denoting undernutrition in older women

$$= < 18.5 \times 3.0241$$

$$= < 55.95 \text{ kg./ m}$$

The Pearson correlation coefficients between BMI and mindex and demiquet in older people are satisfactorily very high, with the r-value of 0.93–0.96 for mindex and 0.88–0.89 for demiquet (Smith et al. 1995; Assantachai et al. 2006a). Comparisons of the normative data between various Quetelet indices of Caucasian older adults (data from Canada reported by Smith et al. 1995) and Asian older adults (data from Thailand) are shown in Table 86.2. It is quite obvious that the normative data between these two ethnics are markedly different. Any universal cutoff points of these Quetelet indices proposed to indicate a similar health parameter in the future should be invalid. This situation has been proven by the current effort of health authorities trying to set a population-specific cutoff point for BMI (WHO expert consultation 2004).

Comparing the correlations between these three Quetelet indices and other nutritional parameters based on Thai older people, body fat mass achieves the highest r-value of 0.94 for BMI in females; the other r-values are 0.93 for mindex, 0.83 for BMI in males, and 0.74 for demiquet (Table 86.3). Likewise, MAC, as an alternative to body weight, also achieves the second highest r-value of 0.87 for mindex and the others are 0.86 for BMI in females, 0.85 for BMI in males, and 0.76 for demiquet. Subcutaneous fat, in line with fat mass, also correlates satisfactorily with these Quetelet indices, especially when the subscapular skinfold thickness reaches the highest r-value of 0.74 for BMI in males and mindex, followed by the suprailiac skinfold thickness, whereas the biceps skinfold thickness has the poorest correlation with all these three Quetelet indices. This pattern is also seen in a study in USA, which concluded that BMI is positively correlated with subscapular and triceps skinfold thickness to a higher degree than with suprailiac skinfold (Yearick 1978).

Based on the national survey among Thai older people, the correlations between two alternative Quetelet indices (demiquet and mindex) and other anthropometric measurements and body composition analysis are demonstrated in Figs. 86.2–86.5 (Assantachai and Lekhakula 2000). When the r-values of each pair of Quetelet index and other nutritional parameters are compared for any statistical significance, there is no difference between the degree of correlations of MAC and skinfold thickness with mindex and BMI, whereas, for demiquet, this is not so. Therefore, mindex is a better index of obesity, in parallel with BMI, than demiquet (White et al. 1991; Assantachai et al. 2006a).

Regarding the correlations with both hematological and biochemical parameters in older people, lymphocyte count acquires the highest r-value of correlation with demiquet (0.37), followed by mindex (0.35), BMI in females (0.31), and BMI in males (0.25). Blood total cholesterol and low-density lipoprotein are among the blood chemistry parameters that correlate better with all these three Quetelet indices, in both men and women. Interestingly, serum albumin, a non-specific nutritional

Table 86.3 Pearson correlation coefficients of BMI, mindex, and demiquet with various anthropometric measurements and other nutritional parameters ((Assantachai et al. 2006a): 644 men, 1,013 women and (Yearick 1978): 25 men, 75 women: only for skinfold thickness data)

	BMI			
	Men	Women	Demiquet	Mindex
1. Anthropometry				
Mid-arm circumference*	0.85	0.86	0.76	0.87
Subscapular skinfold*	0.74–0.75	0.63–0.72	0.69	0.74
Triceps skinfold*	0.65–0.70	0.57–0.71	0.59	0.69
Suprailiac skinfold	0.48**–0.70*	0.55*–0.72*	0.59*	0.73*
2. Hematological and biochemical measurements				
Hemoglobin	0.12**	0.23*	0.18*	0.28*
Lymphocyte count*	0.25	0.31	0.37	0.35
Total cholesterol*	0.27	0.27	0.37	0.31
Triglyceride*	0.27	0.14	0.21	0.15
Low-density lipoprotein*	0.25	0.24	0.37	0.29
High-density lipoprotein*	–0.22	–0.09	–0.23	–0.13
Albumin*	0.27	0.19	0.42	0.27
3. Body composition analysis				
Fat weight*	0.83	0.94	0.74	0.93
Lean weight*	0.65	0.77	0.69	0.87
4. Vitamin status				
Thiamin pyrophosphate effect**	–0.09	–0.10	–0.22	–0.16
Vitamin A	–0.08	–0.10**	–0.20**	–0.18**
α-Tocopherol	0.03	–0.08**	–0.10**	–0.15**

*$p < 0.001$, **$p < 0.05$

parameter commonly used in daily clinical practice, also correlates satisfactorily with demiquet, mindex, BMI in males, and BMI in females, with *r*-values of 0.42, 0.27, 0.27, and 0.19, respectively. Furthermore, their degree of correlations with demiquet and mindex is higher, with statistical significance, than with BMI. In summary, although mindex and demiquet do not correlate with fat parameters, that is, body fat mass, MAC, and skinfold thickness as well as BMI, they perform better than BMI as general nutrition and metabolic indices, such as, lymphocyte count, serum albumin, and lean body mass.

Compared to other nutritional parameters, many kinds of vitamins obviously show little or no relationship with all three Quetelet indices, based on data of Asian older adults ($r < 0.25$). The majority of them even show inverse relationships, especially in older women (Assantachai et al. 2006a). In Caucasian older adults, there was also no association between low micronutrient status (vitamin B12, erythrocyte folate, vitamin C, and vitamin D) and having BMI, mindex, demiquet or MAC in the lowest third of these measurements (McNeill et al. 2002). However, within Thai older adults, the thiamin pyrophosphate effect (TPP effect) acquires the highest *r*-value of –0.22 ($p < 0.05$) for demiquet and –0.16 ($p < 0.05$) for mindex, whereas cyanocobalamin level has the least relationship with mindex ($r = 0.02$, $p > 0.05$) Interestingly, the correlation coefficient of demiquet and the TPP effect ($r = –0.22$) is significantly higher than those for BMI and the TPP effect ($r = –0.09$), with a p-value of 0.025. It seems that demiquet may be superior to BMI in indicating thiamin level. When using multiple logistic regression analysis to explore independent factors determining various vitamin deficiencies, thiamin is found to be the only vitamin with which the anthropometric variable, BMI, is significantly associated with the case with adjusted OR = 0.959 (95% CI: 0.938–0.981) (Assantachai et al. 2007). As the main sources of thiamin for the Thai people are rice and legumes, which are also

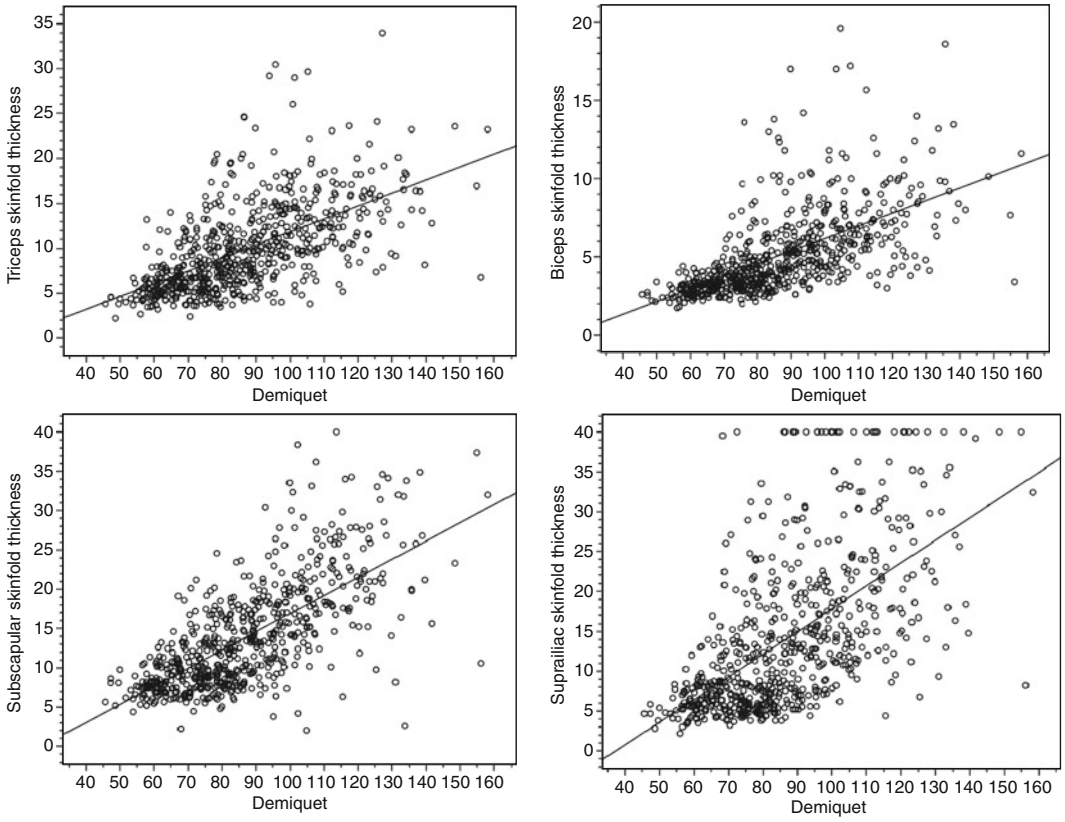

Fig. 86.2 Correlations with regression lines between demiquet and four common sites of measured skinfold thickness among older men

the main ingredients in daily Thai food, those who cannot consume these traditional dishes, therefore, suffer from both thiamin deficiency and global undernutrition, which the Quetelet index can also predict. The discordance of the relationships between all three Quetelet indices, and protein–energy nutritional parameters, and vitamin levels, except thiamin, may be explained by the different food sources rich in each specific nutrient and the inability of older adults to consume a heterogeneous daily diet. In conclusion, anthropometry can suggest vitamin deficiency, but only the one which is closely related to protein–energy malnutrition, that is, Quetelet indices and thiamin deficiency. Demiquet seems to be better than BMI regarding this specific condition.

86.3.1 Epidemiology of Malnutrition in Older Adults Based on Anthropometry

86.3.1.1 Undernutrition

With the use of BMI < 18.5 kg/m^2 to indicate undernutrition, as recommended by WHO, epidemiological data reveal the high prevalence of undernutrition in older adults ranging from less than 5% in

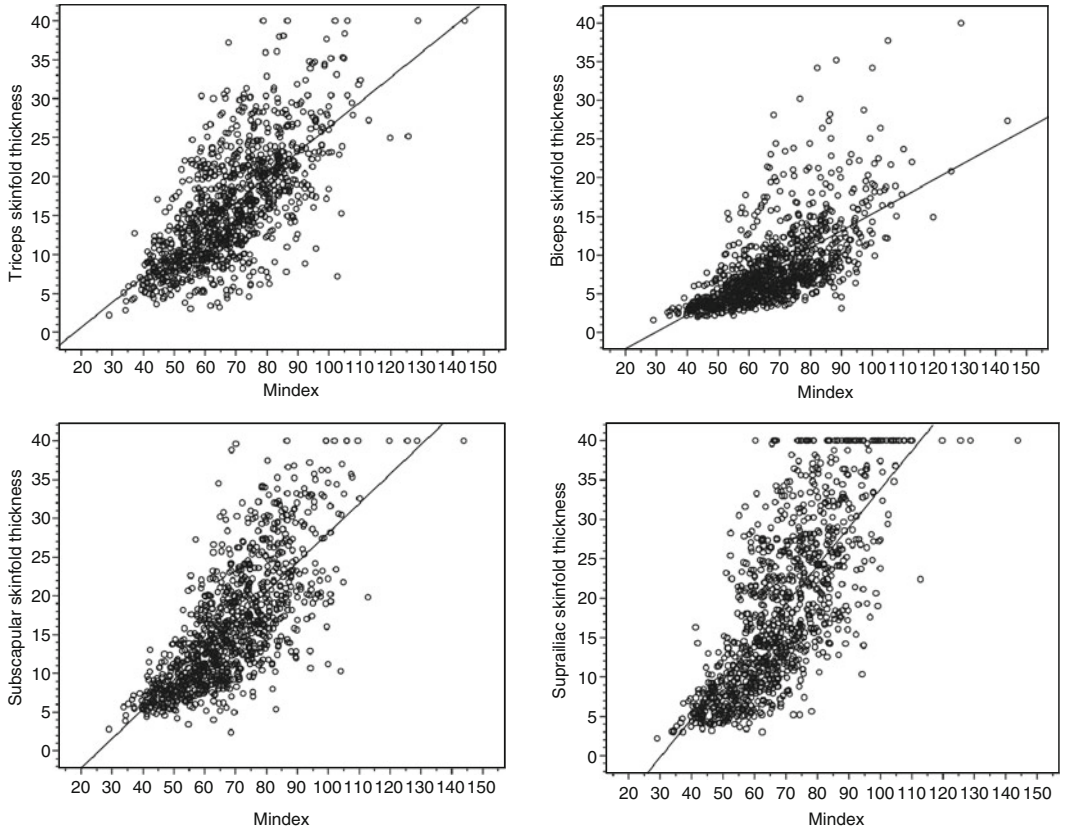

Fig. 86.3 Correlations with regression lines between mindex and four common sites of measured skinfold thickness among older women

Italy to 7.8–8.4% in Brazil and 33.3% in Uganda (Tavares et al. 1999; Perissinotto et al. 2002; Kikafunda et al. 2005). Although BMI in older women tends to be higher than in older men, the last study reveals the prevalence of malnutrition of up to 68% in women, whereas it is only 32.4% in men. As such, there are some factors which can affect the prevalence of undernutrition, as detected by anthropometry, and they need to be highlighted as follows.

Age Group

The proportion of older adults with BMI < 20 kg/m^2 increased with age in a study involving 19 geographically and ethnically varied populations. The prevalence of underweight in women aged 80 years or more was 1.5 times higher in Brazil and 6.0 times higher in Italy than those aged 60–69 years old (Launer et al. 1996). In a cross-sectional study involving Thai older adults living in a rural area, BMI and mindex started to decline significantly at the age of 70 years or more in women, but there was no BMI and demiquet difference between age groups in older men (Assantachai and Lekhakula 2000). This may be the result of early death of older men who have lower BMI, and only those who have higher BMI are able to survive up to the oldest age group. Therefore, careful interpretation of a cross-sectional study regarding the age-specific Quetelet indices should be undertaken.

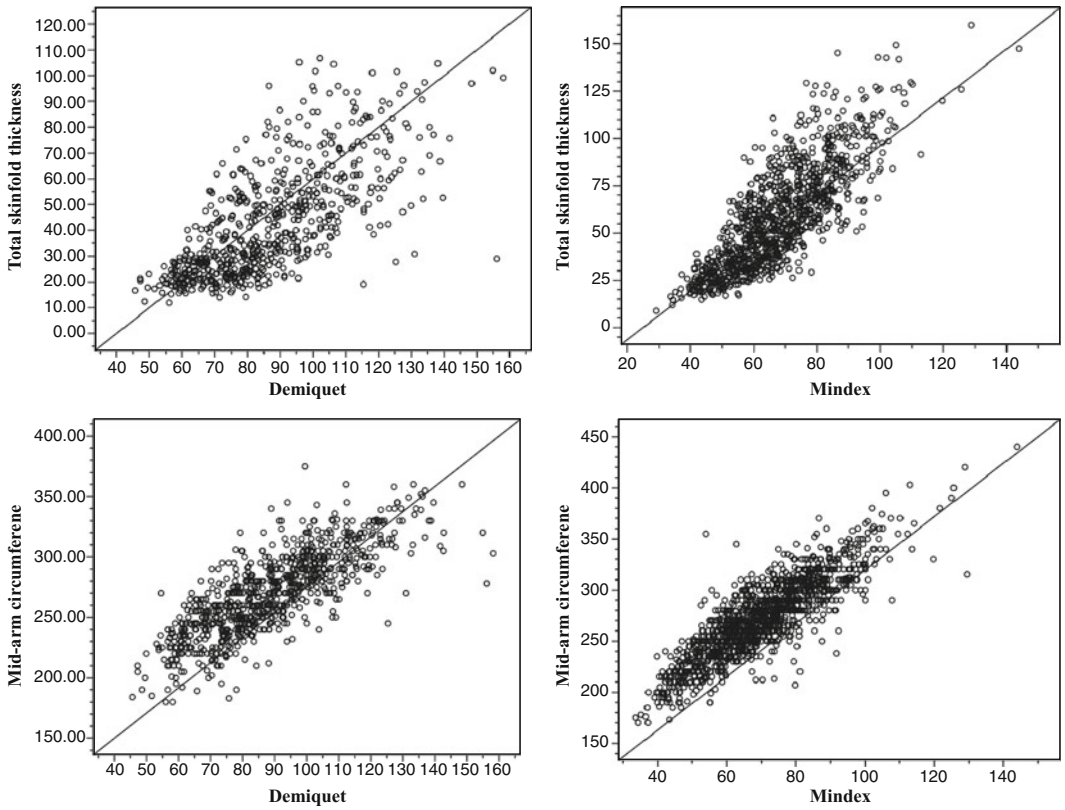

Fig. 86.4 Correlations with regression lines between Quetelet indices (demiquet and mindex) and other anthropometric parameters (MAC and total skinfold thickness: biceps, triceps, and subscapular and suprailiac skinfold thickness)

In conjunction with the longitudinal study in Hong Kong, which found that lower anthropometric indices were associated with higher mortality though waist–hip ratio was not, this point also highlights the greater importance of undernutrition over weight gain in older adults (Woo et al. 2001).

Gender

Although the majority of studies reveal that BMI is significantly higher in older women than in men, the study in Uganda shows the opposite direction (Kikafunda et al. 2005). This indicates the interaction between gender and other factors, for example, sociocultural issues, which can influence the nutritional status of older people in an unexpected direction.

Institutionalized Setting

The prevalence of protein energy malnutrition is comparatively high, up to 45–85%, in older people living in institutions. The prevalence of underweight (body weight less than 80% of ideal), lower triceps skinfold, and MAMC less than 90% or more of standard is 12%, 21%, and 55%, respectively

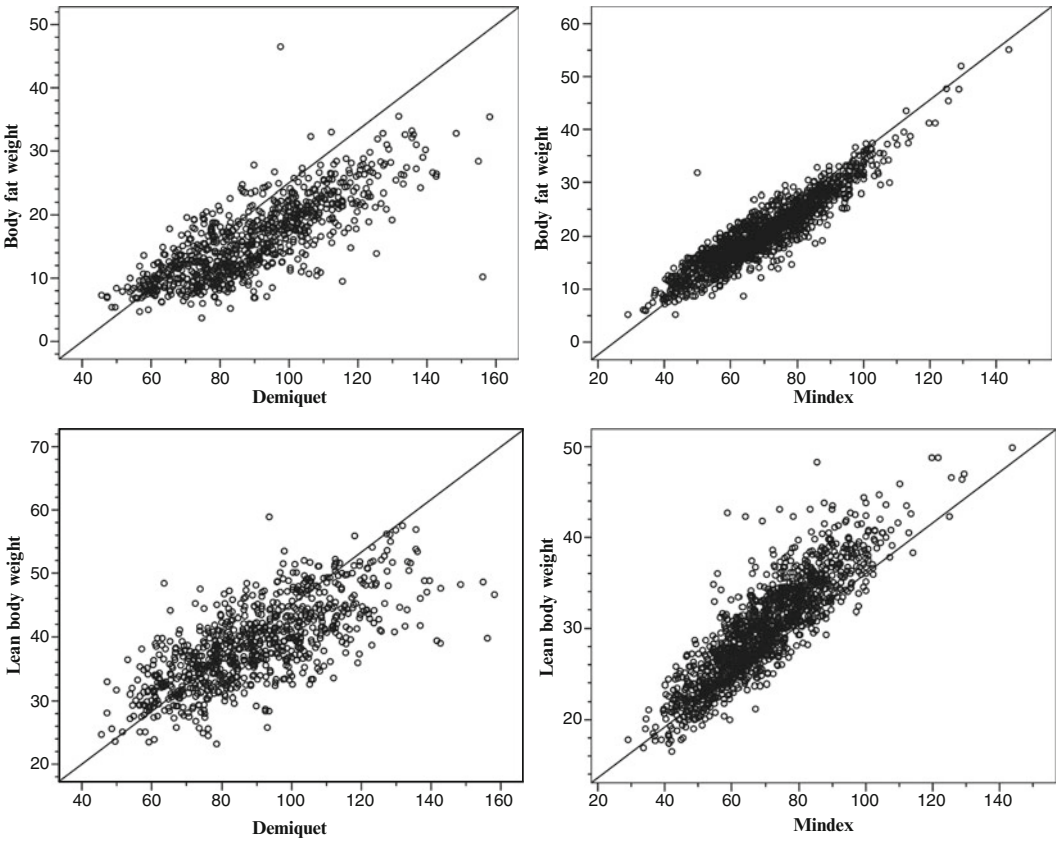

Fig. 86.5 Correlations with regression lines between Quetelet indices (demiquet and mindex) and body composition parameters (body fat weight and lean body weight)

(Abbasi 1995). In a 5-year longitudinal comparative study, height declined by an average of 2 cm in institutionalized subjects, which was significantly more than their counterparts, who lived in the community and lost height by an average of 1.4 cm (Shatenstein et al. 2001). The common causes of decreased food intake among nursing home populations include advanced age, higher degree of functional decline, higher prevalence of chronic diseases and their associated poor physical and mental health as well as polypharmacy, monotonous food, and, lastly, unmet need for assistance.

Community Setting

Available studies from three continents indicate that the prevalence of underweight found in rural areas is persistently higher than those found in urban settings (Side et al. 1991; Tavares et al. 1999; Oguntona et al. 2000). Waist circumference, hip circumference, and MAC in older women living in rural areas of Nigeria are also lower than for those in urban areas (Table 86.4). The study from China revealed that both older men and women in rural areas consumed lower amounts of protein, fat, calcium, iron, retinol, thiamin, riboflavin, and nicotinic acid than those from urban areas. Meanwhile, the study from Nigeria also showed that the daily food intake in rural subjects was 4.23 MJ, significantly lower than the amount consumed by urban subjects (5.86 MJ). The waist–hip ratio in older

Table 86.4 Comparisons of the means of anthropometric indices between gender and community differences using data from China (Side et al. 1991) and Nigeria (Oguntona et al. 2000)

	Rural				Urban				*p* value*			
	China		Nigeria		China		Nigeria		China		Nigeria	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Body weight	53.8	46.8	54.5	52.6	65.9	54.4	59.9	56.5	yes	yes	yes	yes
Height	1.63	1.51	1.72	1.61	1.67	1.54	1.75	1.64	yes	yes	no	no
Body mass Index	20.4	20.6	18.9	20.1	23.2	23.0	19.7	21.2	yes	yes	no	no
Waist circumference	77.6	75.5	70.1	68.2	88.3	84.9	71.8	77.5	yes	yes	no	yes
Hip circumference	86.4	87.2	87.5	84.2	99.9	98.4	88.7	92.3	yes	yes	no	yes
Mid-arm circumference	23.8	23.3	22.6	20.2	28.1	26.3	24.8	24.0	yes	yes	no	yes

*p value of comparisons between area difference in each country: yes – $p < 0.05$; no – $p > 0.05$

women correlates best with 24-h dietary recall, in both rural and urban settings, with *r*-values of 0.34 and 0.39, respectively. Waist circumference in older men appears to be correlated best with dietary recall in rural and urban settings, with *r*-values of 0.26 and 0.31, respectively. The underlying causes of lower food intake in the rural environment relate to low income, low educational level achieved, and poor access to a variety of food.

86.3.1.2 Overweight and Obesity

Although BMI is the anthropometric variable suggested by WHO to identify overweight or obesity in the general population, application of its original cutoff point of ≥25 kg/m^2 suggesting overweight to non-Caucasian population, especially for those whose body builds are much smaller, is controversial (Anuurad et al. 2003). In the year 2004, WHO expert consultation had published their consensus, which not only agreed with the different associations between BMI, percentage of body fat, and health risks of Asian and European populations, but also identified further potential public health action cutoff points of 23.0, 27.5, 32.5, and 37.5 kg/m^2 along the BMI continuum (WHO expert consultation 2004). The result of a national survey in Mexico showed that use of the current BMI thresholds to identify being overweight may lead to an overestimation of the number of overweight elderly (Sánchez-García et al. 2007).

An important longitudinal study involving subjects aged ≥75 years (n = 14,833) in the UK found that current BMI-based health-risk categories used to define the burden of disease related to adult overweight and obesity are not valid for older people aged ≥75 years. In this same situation, waist–hip ratio is suggested to be used, as it has a positive relation with risk of death at the cutoff points of >0.99 for nonsmoking men and >0.90 for nonsmoking women (Price et al. 2006). Whether these cutoff points can also be applied to non-Caucasian older people needs further longitudinal study recruiting a large population sample. However, in a study using anthropometry to predict abdominal visceral fat in older people, WC was found to be the best overall predictor, with areas under the ROC curves of 0.88–0.92, higher than BMI and waisthip ratio (WHR) did (Rankinen et al. 1999). The better performance of WC compared to the waist–hip ratio in predicting mortality was supported by a study, which revealed that, in men aged 55 years or more, a large WC was a better predictor of higher 5-year mortality than waist–hip ratio or BMI (Visscher et al. 1999). Theoretically, the waist–hip ratio is subject to other confounding factors leading to hip muscle wasting, which is much more pronounced in older people, resulting in more difficult interpretation of this anthropometric parameter in older people. As such, WC reflecting abdominal obesity performs as a better anthropometric indicator than BMI or, probably, waist–hip ratio, in predicting obesity-related health risk in older adults.

86.4 Applications to Other Areas of Health and Common Diseases in Older Adults

86.4.1 Functional Decline

The relationship of anthropometry and functional decline in older adults can be seen in both directions of nutritional status indicated by its parameters.

86.4.1.1 Undernutrition

In a longitudinal study involving community-dwelling frail elderly, the decline of BMI and MAC over 2 years of follow-up associates with the loss of activity of daily living (ADL) (Izawa et al. 2009). Low BMI (<18.5 kg/m^2) is also found to be one of the independent factors predicting hospital admission over the last 1 year in community-dwelling older adults (Assantachai and Maranetra 2005). Regarding details of ADL affected by anthropometry, impaired mobility, incontinence, and difficulty in feeding were significantly associated with BMI (Kikafunda et al. 2005).

86.4.1.2 Overnutrition

Higher BMI, either current or from past record, has been associated with increase in self-reported functional decline in older people. BMI was also found to be negatively related with some physical performance tests, for example, get-up-and-go test, walking speed, chair stands, and reach test in a study involving 705 older Japanese women in Hawaii (Jensen 2005). Information from a large cross-sectional study (56,510 women aged 45–71 years) revealed a significant dose-response relationship between increasing levels of BMI and increased function limitations (Coakley et al. 1998). Likewise, data from a large prospective cohort study (6,632 women aged ≥65 years) also showed that obesity was one of the modifiable predictors of self-reported functional decline over a 4-year period (Sarkisian et al. 2000).

86.4.2 Cognitive Dysfunction

There were two longitudinal studies that evaluated the effects of BMI and body weight upon cognitive function, two longitudinal studies that examined the effects of regional adiposity, whereas another study examined the relationships of both BMI and regional adiposity upon cognitive function simultaneously. The association of anthropometry and cognitive dysfunction in older adults is subject to gender-specific difference. Higher BMI at baseline was found to be associated with cognitive decline in men alone (Elias et al. 2003; Kanaya et al. 2009). In older women, it had a protective effect against cognitive decline (Kanaya et al. 2009) and those who lost the most weight suffered from the worst cognitive function (Bagger et al. 2004).

As far as the regional adiposity is concerned, there were three prospective cohort studies in which anthropometric measurements were used to assess the relationship between regional adiposity and cognitive decline. A total of 1,814 subjects were followed up in the Framingham Offspring Study; of these, those who had the uppermost quartile of waist–hip ratio performed executive function and visuomotor skills testing (Trails B, Visual Reproductions–Immediate and Delayed Recall) significantly poorer after 12 years of follow-up (Wolf et al. 2007). In another interesting study, where 6,583 members of Kaiser Permanente were followed up for an average of 36 years, those in the uppermost quintile regarding sagittal abdominal diameter had a threefold increase in risk of dementia independently of BMI and other cardiovascular risk factors (Whitmer et al. 2008). However, the study reported by Kanaya et al., as mentioned earlier, also examined the relationship between the modified version of Mini-Mental State Examination (MMSE) and regional adiposity measured by both anthropometry and abdominal computed tomography (CT) scan. Interestingly, the anthropometric measures of visceral fat (WC and abdominal sagittal diameter) had a better relationship with cognitive decline than visceral fat measured directly by CT scan in men alone (Kanaya et al. 2009).

When anthropometry is used to assess nutritional status in demented and non-demented older people, body weight, BMI, skinfold thickness, and MAC were significantly lower among patients with dementia, especially those hospitalized, than normally cognitive older adults. This was not the result of low nutritional intake among patients with dementia, as all dementia patients had higher intake of energy, protein, vitamins, and minerals than control subjects (Burns et al. 1989).

86.4.3 All-Cause Mortality

The relationship between mortality and BMI in the general population is U-shaped, with a tendency for mortality to increase at both extremes of the range, that is, very low or very high BMI. However, because of fat redistribution toward more abdominal visceral fat in older adults and reduced lipolysis in the visceral fat of older people (this being less harmful as compared to young adults), high BMI has a less pronounced relationship with mortality in older than in younger populations.

Conversely, low BMI and weight loss in the older adults are persistently strong predictors of mortality. As mentioned in the section discussing the epidemiology of malnutrition, undernutrition carries a greater risk for mortality than does overweight in older people. Common consequences of undernutrition in older people involve a wider range of adverse outcomes, namely, alteration in immune function and its associated infections, cognitive decline, pressure ulcer, delayed wound healing, functional decline, poor quality of life, and, ultimately, death (Table 86.5). In a nutritional survey in a 200-bed nursing home, triceps skinfold and MAC were two anthropometric variables identified by univariate analysis as significant predictors of death (Abbasi 1995).

86.4.4 Hypertension

According to The Bangkok Longitudinal Study by Siriraj Hospital for the Older Men and Women (BLOSSOM) Study, in 2,201 community-dwelling older adults who were initially normotensive and followed up for 3 years, high BMI was found persistently as a significant risk factor predicting the emerging of hypertension, with RR = 1.074 (95% CI: 1.043–1.107) and RR = 1.049 (95% CI: 1.018–1.081) at the second year and third year of follow-up, respectively (Assantachai et al. 2008). Likewise, a nationwide cross-sectional study in Thailand (n = 2,336) also revealed that body weight, BMI, demiquet, mindex, MAC, all four sites of skinfold thickness, and waist–hip ratio of older adults who had hypertension were significantly higher than in those who were normotensive, except for height and MAMC (Assantachai and Lekhakula 2000). However, hypertension was associated with obesity based on BMI (OR = 1.98) to a greater degree than with overweight (OR = 1.42), high-WC (OR = 1.62), and tertile 3 of the conicity index (OR = 1.53) (Sánchez-Viveros et al. 2008).

In the Framingham Heart Study where 1,814 subjects were followed up for 12 years, those who had hypertension or were receiving anti-hypertensive treatment performed executive function and visuomotor skills (Trails B, Visual Reproductions–Immediate and Delayed Recall) significantly poorer than those who did not suffer from hypertension. Meanwhile, when hypertension and regional adiposity were combined, the hypertensive cases, who had waist–hip ratio in the uppermost quartile, had poorer neurocognitive performance than their counterparts, whereas those who had a waist–hip ratio in the range of the first to the third quartiles did not show this relationship (Wolf et al. 2007). Nevertheless, there were positive correlations between systolic blood pressure and the waist–hip ratio for both older men and women (Side et al. 1991).

Table 86.5 Adverse outcomes of abnormal anthropometric measurements among older people, apart from the direct effect of malnutrition

Adverse outcome	Anthropometric measurement	Study		
		Setting	Outcome	Author
Functional decline	↓ BMI, ↓ MAC	Community, frail	ADL loss	Izawa et al. (2009)
	↓ BMI	Community	Hospital admission	Assantachai (2005)
	↓ BMI	Community	Mobility, incontinence, and feeding	Kikafunda (2005)
	↑ BMI, WC	Community, prospective	Mobility, physical function	Bannerman (2002)
	↑ BMI	Community	Physical performance test	Jensen (2005)
	↑ BMI	Community women	Physical functioning	Coakley (1998)
	↑ BMI (obesity)	Community women	Self-reported ADL decline	Sarkisian (2000)
Cognitive decline	↑ BMI, ↑ WC, and ↑ sagittal abdominal diameter	Community, prospective	↓ MMSE only in men but inverse relationship in women	Kanaya (2009)
	↑ BMI	Community, prospective, men	↓ Cognitive performance in men	Elias (2003)
	↓ Weight	Community, prospective, women	↓ Short Blessed test in women	Bagger (2004)
	↑ WHR	Community, prospective	↓ Executive function	Wolf (2007)
	↑ Sagittal abdominal diameter	Community, prospective	↑ Dementia	Whitmer (2008)
Fall	↓ Height	Community, cross-sectional	↑ Fall over past 6 months	Assantachai (2003)
Hypertension	↑ BMI	Community, prospective	New case of hypertension	Assantachai (2008)
	↑ Weight, BMI, demiquet, mindex, MAC, skinfold, and WHR	Community, cross-sectional	Case comparison	Assantachai (2000)
	↑ BMI (obesity)	Community, cross-sectional	Case comparison	Sánchez-Viveros (2008)
	↑ WHR + hypertension	Community, prospective	Executive function and visuomotor skill	Wolf (2007)
	WHR	Community, cross-sectional	Correlation with systolic blood pressure	Side (1991)
Diabetes mellitus	↑ Weight, BMI, and demiquet, mindex, MAC, and skinfold	Community, cross-sectional	Case comparison	Assantachai (2000)
	↑ Weight, BMI, triceps skinfold, and WC	Community, cross-sectional	Case comparison	Kubena (1991) and Onisto (2009)
	Relative weight	Community, cross-sectional	Correlation with serum glucose	Yearick (1978)
	↑ WC better than ↑ BMI	Community, cross-sectional	Case comparison	Sánchez-Viveros (2008)
Osteoporosis	Height	Institution, cross-sectional	Predict calcaneal bone mineral density	Assantachai (2006b)
	Weight	Community, cross-sectional	Screening for osteoporosis	Koh (2001)
	Weight	Hospital, cross-sectional	Screening for osteoporosis	Adler (2003)
All-cause mortality	Triceps skinfold and MAC	Institution, cross-sectional	Case comparison	Abbasi (1995)

WC waist circumference; *MAC* mid-arm circumference; *WHR* waist–hip ratio

86.4.5 Diabetes Mellitus

The nationwide cross-sectional study in Thailand (n = 2,336) showed that those who suffered from diabetes mellitus had significantly higher levels of the majority of anthropometric indices, namely, body weight, BMI, mindex, demiquet, subscapular skinfold, suprailiac skinfold, biceps skinfold, and MAC, except for triceps skinfold, height, and MAMC, than those who were not diabetic (Assantachai and Lekhakula 2000). The other two studies done in Caucasian older women reported that, those who had type-2 diabetes had statistically significantly higher body weight, BMI, triceps skinfold thickness, and WC than nondiabetic women (Kubena et al. 1991; Onisto et al. 2009). Relative weight (observed body weight expressed as a percentage of the suggested weight for adult men or women of similar height and medium frame) also correlated with serum glucose level in nondiabetic women with the r-value of 0.44 ($p < 0.01$) (Yearick1978).

Comparing among anthropometric parameters, WC was associated with type-2 diabetes to a higher degree than overweight and obesity (Sánchez-Viveros et al. 2008). Central adiposity measured by anthropometry is also employed by the International Diabetic Federation (IDF) using WC at the cutoff points of ≥90 cm in Asian men (≥94 cm in Caucasian men) and ≥80 cm in women as a prerequisite for diagnosis of metabolic syndrome.

86.4.6 Fall

The older adults who had a history of falls over the previous 6 months had lower height (152.6 ± 8.1 cm) than non-fallers (154.9 ± 7.9), with statistical significance ($p < 0.001$) (Assantachai et al. 2003).

86.4.7 Osteoporosis

Height is found to be one of the five factors, which can predict the calcaneal bone mineral density measured by peripheral dual energy X-ray absorptiometry in institutionalized older people with the regression coefficient of 0.003 for every 1 cm of height change ($p < 0.001$) (Assantachai et al. 2006b).

As body weight and increasing age are two strong risk factors of osteoporosis, a screening tool for osteoporosis based on these two factors was originally developed for postmenopausal Asian women and named the Osteoporosis Self-Assessment Screening Tool for Asians (OSTA) (Koh et al. 2001). The risk index can be calculated with the equation shown below:

$$\text{Risk score} = [\text{body weight in kg.} - \text{age in year}] \times 0.2, \text{ truncated to an integer}$$

Based on defining osteoporosis as a T score of -2.5 or less of bone mineral density at the vertebrae, total hip, or femoral neck, a cutoff point of OSTA at –1 provided a sensitivity of 70–90% and a specificity of 70%. When this tool (at the cutoff point of 3) was applied to American older men at a veterans hospital, the sensitivity and specificity were 93% and 66%, respectively (Adler et al. 2003).

Summary Points

- More studies involving the application of population-specific alternative Quetelet indices are needed for nutritional assessment as well as for health promotion and nutrition-related disease prevention in older adults.
- Mid-arm circumference is a good alternative nutritional parameter to body weight, if the patient cannot be weighed; subscapular skinfold thickness is the best site to assess subcutaneous fat in older adults.
- Although mindex is a better index of obesity, parallel with BMI, than demiquet, both mindex and demiquet reflect general nutritional status more accurately than BMI. While WC is better than BMI in predicting the adverse outcome of obesity, mindex and demiquet are better than BMI in predicting the occurrence of undernutrition in older adults.
- Nutritional assessment in older adults requires comprehensive coverage of various nutritional parameters including protein and energy intake as well as micronutrients, due to their inability to consume various types of food resulted from edentulism, physiologic aging changes, associated chronic illness, and socioeconomic changes. As anthropometry correlates poorly with micronutrient status, it should be accompanied by other aspects of nutritional assessment, such as, dietary recall, body composition analysis, and biochemical tests.
- Although there exists the U-shaped relationship between BMI and mortality in the general population, undernutrition in older adults, as identified by anthropometry, should be of greater concern compared to overweight, as it associates with higher mortality.
- Functional decline in older adults can be affected by either under- or overnutrition, as suggested by BMI and other related indices.
- Apart from nutritional assessment, anthropometry can be used to assess other common health problems in the older adults, for example, functional decline, cognitive decline, hypertension, diabetes mellitus, fall, osteoporosis, and all-cause mortality.

Acknowledgment The author would like to thank Dr. William M. Honsa, Jr. BS. PhD. for his attention in checking the whole manuscript for language and grammar.

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Chapter 87
Anthropometrical Changes in Older Taiwanese and Diet and Exercise

Alan C. Tsai

Abstract The aging process involves changes in weight, height, body mass index (BMI), muscle mass, and a redistribution of body fat. These anthropometrical measures are closely related to nutrition, functional ability and health. However, most studies conducted on aging-associated anthropometrical changes so far involve Western populations. Knowledge on population-specific changes is necessary for understanding the population-related differences. This article aims to review anthropometrical changes important to geriatric nutritional assessment including weight, height, BMI, and mid arm (MAC) and calf circumferences (CC) in older Taiwanese. BMI is probably the most widely studied anthropometrical indicator but mid arm and CC have also received increasing attention in recent years. The pattern of age-associated anthropometrical changes in Taiwanese generally parallels the Western populations. BMI, an indicator of body weight relative to height, is often considered an indicator of body fatness. Currently, the World Health Organization (WHO) sets a uniform standard of BMI 25–29.9 kg/m^2 for overweight and ≥30 for obesity. However, there is evidence that these thresholds may underestimate the prevalence of overweight and obesity in Taiwanese. The Department of Health of Taiwan has adopted modified thresholds of BMI 24–26.9 kg/m^2 for overweight and ≥27 for obesity for Taiwanese. Similarly, because of stature differences, elderly Taiwanese appear to have different cut-points of MAC (22.5/21 cm for Taiwanese men/women vs. 21/21 cm for Western men/women) and CC (28/25 cm for Taiwanese men/women vs. 31/31 cm for Western men/women) for undernutrition. Several social, lifestyle and dietary factors have been observed to impact these indicators in older Taiwanese. Age has the strongest impact on BMI, MAC and CC. Routine physical exercise is associated with higher BMI, MAC and CC. Cigarette-smoking is associated with lower BMI and CC but not MAC. Consumption of dairy products is associated with lower BMI and MAC but not CC. Consumption of fruit is associated with greater BMI and CC but not MAC whereas consumption of tea is associated with greater BMI, MAC and CC. These anthropometrical indicators are useful nutritional and health indicators for old persons or hospitalized patients and are included in many major geriatric nutritional assessment tools. MAC and especially CC, in addition to reflecting general nutritional status, also reflect body muscle mass or the

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_87,

functional status in frail elderly. Understanding these aging-associated changes and the implication of these indicators as they relate to health is important to health care and support to elderly individuals.

Abbreviations

BMI	Body mass index
CC	Calf circumference
MAC	Mid arm circumference
MNA	Mini Nutritional Assessment
MUST	Malnutrition Universal Screening Tool
SHLSET	Survey of Health and Living Status of the Elderly in Taiwan
WHO	World Health Organization

87.1 Introduction

The aging process involves physiological and nutritional changes that are highlighted by height, weight, and muscle mass losses, and body fat redistribution. Age-associated changes in body size, body composition, and body shape occur throughout various life stages. In older adults, body shape and composition can change even without change in body weight. Changes in body composition differ in men and women at different life stages. Different anthropometric indicators are used at different life stages to evaluate them. Certain body measurements can reflect over- or undernutrition status and can be indicative of specific health conditions. Excessive body weight or obesity has been shown to be associated with a number of chronic health conditions in various age groups (Seidell and Flegal 1997). Thus, there has been a strong interest in finding an anthropometrical indicator that best reflects obesity. In older adults, body mass index (BMI) is probably the most widely used or most thoroughly studied anthropometrical indicator. It is calculated from two easily accessible indicators, height and weight, using the simple equation of kg/m^2. There are also other indicators, such as waist circumference, hip to waist ratio, and waist to height ratio, that have been shown to reflect body fatness well.

In older adults, circumferences of extremities, such as arm and calf, are particularly useful. Mid-arm circumference (MAC) and calf circumference (CC) both reflect subcutaneous fat and therefore are at least, to some extent, similar to BMI, indicative of overall body fatness. However, MAC and CC are also indicative of body muscle mass. Thus, MAC and CC reflect both body fatness and physical functional ability. A severe decrease in CC can result from severe illness or the aging-related functional decline and greatly limits mobility, whereas a severe decrease in MAC often occurs during the final stage of functional decline. Aging-related mobility impairment often limits the activities of daily living and that can have an impact on nutritional status (Mason et al. 2008).

Most studies conducted on aging-related anthropometric measurements to date involve subjects of Western populations and are heavily concentrated on the BMI–body fatness–health relationship. Relatively few studies have been conducted in Asian populations, especially related to MAC and CC. Anthropometrical variations among populations, especially between the Western and the Asian populations, are well recognized (Chumlea 2006; Wen et al. 2008). Data derived from Western populations may not be directly applicable to Eastern populations. Therefore, the objective of this chapter is to examine the recent findings on the aging-associated changes in anthropometrical parameters, especially BMI (or weight and height), MAC, and CC in the Chinese population in Taiwan. This information will be valuable for providing better care and support to an increasing number of elderly persons.

87.2 Age-Associated Changes in Anthropometrical Parameters

87.2.1 Aging-Related Anthropometrical Changes

Aging in later life is associated with decreases in both height and weight but the starting point and the rate of decline differ between men and women. Age-related anthropometrical changes in Taiwanese have so far received only limited attention. Recently, Chiu et al. (2000) examined the age-related weight, height, and BMI changes in a cross-sectional sample of elderly Taiwanese, 65 years or older, whereas Tsai et al. (2007b) analyzed age-related changes in mid-arm and CC, in addition to height, weight, and BMI in another cross-sectional sample of Taiwanese, 53 years or older. Tsai et al. (2007b) also analyzed the association of diet and lifestyle with anthropometrical measures. These two studies found that the patterns of the age-associated changes in weight, height, and BMI in older Taiwanese are quite comparable to those observed in Western populations.

Taiwanese women generally start losing height earlier and more severely than their male counterparts. Height loss starts roughly around the late sixth decade of life for women, but in the early seventh decade of life for men. During the period from the age of 60–80 years, average height loss was approximately 1.5 cm and 1 cm/decade for Taiwanese women/men, respectively (Fig. 87.1). Contrary to height changes, body weight peaks during the late 50s in men, but early in the 60s in women (Tsai et al. 2007b). During the period from the age of 60 to 80 years, the average total weight loss is about 5.6 kg (8%) for men and 6.4 kg (12%) for women. Although both height and weight decrease during old age, the magnitude of weight loss is greater than height loss. As a result, BMI generally also decreases during this stage. In the groups surveyed/measured for this study, Taiwanese men reach a peak BMI of 24.0 kg/m^2 in their late 50s, whereas the females reach a peak BMI of 24.4 kg/m^2 in their early 60s (Tsai et al. 2007b). During the period from the age of 60 to 80 years, the average BMI decrease is about 1.5 kg/m^2 in men and 1.9 kg/m^2 in women (Fig. 87.1).

In addition to weight, height, and BMI changes, aging is also associated with a decrease in body muscle mass and that presumably is due to aging-related physiological changes in thyroid hormone, human growth hormone, and testosterone concentrations, and decreased physical activity. Aging-associated body muscle loss is evident in the changes in mid-arm and CC. These changes have not yet been extensively studied in older Taiwanese until our recent attempt to develop a nutrition assessment, the Mini Nutritional Assessment (MNA), for this population. Our analysis of the cross-sectional data indicates that both MAC and CC also decrease during aging. MAC seems to decrease rather slowly (0.71 cm for men and 0.65 cm for women) from the age of 60–75 years, but seems to decrease rather sharply afterward, especially for women (decrease 1.09 cm for men and 1.42 for women in the next 5 years) (Fig. 87.2). The aging-associated decrease in CC appears more gradual, roughly about 0.5 cm/5 years before the age of 75 years and more than 1 cm/5 years afterward (especially for women). Women seem to have more severe MAC and CC losses compared to men after the age of 80 years.

In older Taiwanese, MAC reaches an average peak size of 29.5 cm for men in their late 50s and 28.6 cm for women in their early 60s. From the age of 60–80 years, the proportion of elderly with small MAC (arbitrarily defined as <25 cm) increases from approximately 6.9% to 21.9% in men and from 11.1% to 34.8% in women (Fig. 87.3). The average MAC decreases to 27.0 cm in men and 26.5 cm in women, 80–84 years old (Tsai et al. 2007b). In a 3-year longitudinal study, Woo et al. (2001) observed an average loss of MAC approximately 0.2 cm for Hong Kong Chinese men and 0.6 cm for women. The losses were greater (0.24 and 0.8 cm, respectively) for those who had disease at baseline.

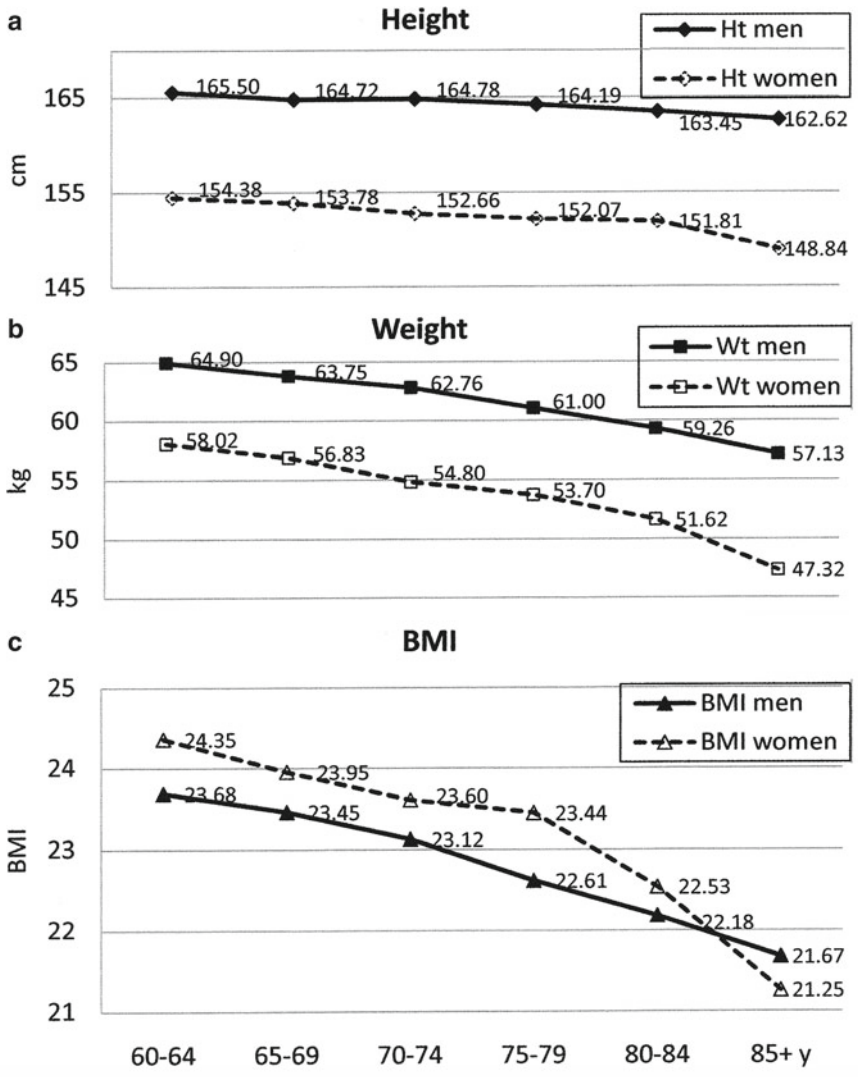

Fig. 87.1 Age-associated changes in height, weight, and BMI in Taiwanese 60 years or older. Mean height, weight, and BMI stratified by gender and 5-year age ranges of men and women, 60 years or older, in Taiwan. n = 315, 284, 640, 385, 165, and 90 for men and 316, 244, 435, 335, 162, and 94 for women, for the respective age groups. Significant ($p < 0.05$) age effects were observed in weight, height, and BMI in both men and women on the basis of one-way ANOVA

The average CC peaks at around 36 cm in the late sixth decade of life and reaches a low of roughly 32.7 cm in the early ninth decade of life. Women start losing CC earlier than men (at around the mid-50s vs. the early 60s for men). As a result, from the age of 60 to 80 years, the proportion of elderly having small CC (arbitrarily defined as <30 cm) increases from 3.6% to 16.5% for men and from 8.9% to 41.9% for women (Fig. 87.3). Significantly greater proportions of elderly women than men have small MAC or CC ($p < 0.05$). These results suggest that, during advanced aging, increasingly larger proportions of the elderly have more severe body muscle mass loss and are therefore encountering an ever-increasing risk of mobility impairment.

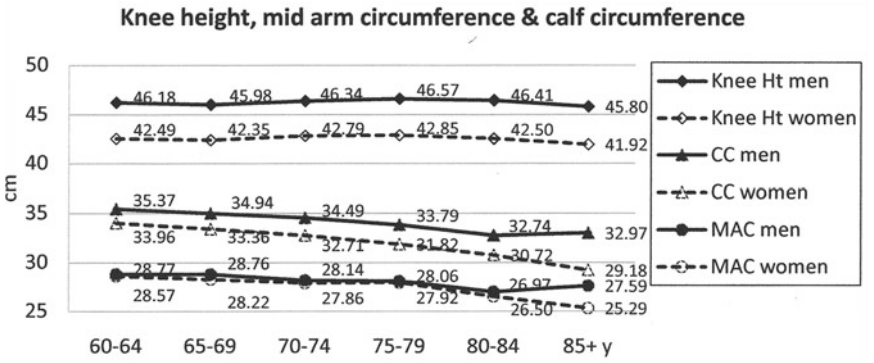

Fig. 87.2 Age-associated changes in knee height, mid-arm circumference (MAC), and calf circumference in Taiwanese 60 years or older. Mean knee height, MAC, and calf circumference (CC) stratified by gender and 5-year age ranges of men and women, 60 years or older, in Taiwan. n = 315, 284, 640, 385, 165, and 90 for men and 316, 244, 435, 335, 162, and 94 for women, for the respective age groups. Significant ($p < 0.05$) age effects were observed in MAC and CC in both men and women on the basis of one-way ANOVA

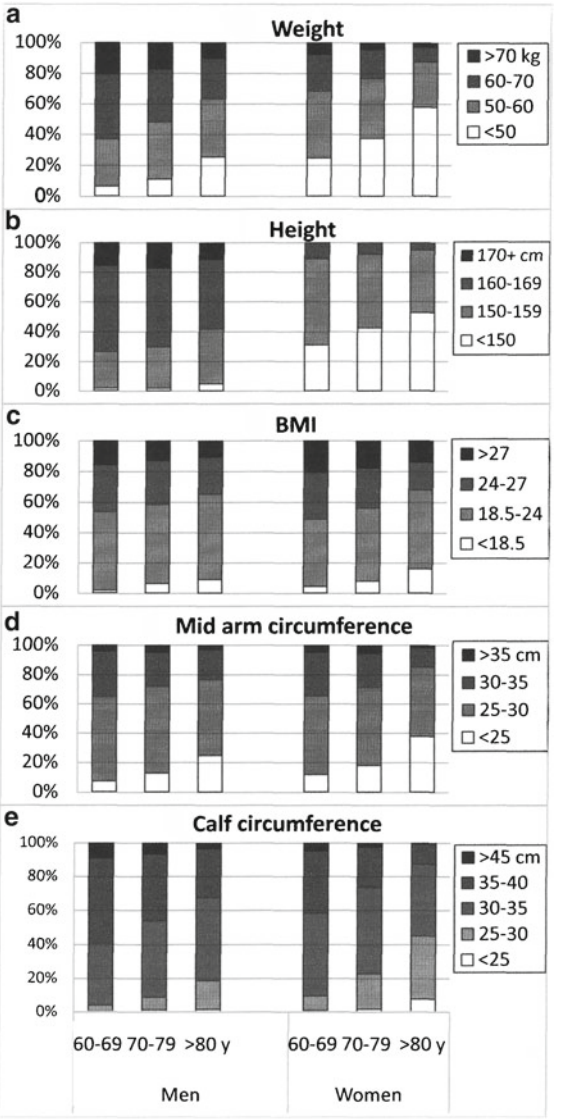

Fig. 87.3 Age-associated changes in the distribution of weight, height, BMI, MAC, and CC in Taiwanese 60 years or older. Cumulative distribution (%) of (**a**) body weight, (**b**) corrected standing height, (**c**) corrected BMI, (**d**) MAC, and (**e**) CC stratified by gender and 10-year age ranges in men and women, 60 years or older, in Taiwan. n = 1879 men and 1586 women. Significant ($p < 0.05$) age effects were observed in all three parameters in both men and women on the basis of one-way ANOVA

Knee heights are relatively constant throughout all age ranges, approximately 46.0–46.5 cm for men and 42.0–42.5 cm for women (Fig. 87.3).

The aging-associated height and weight losses observed in older Taiwanese are comparable to those observed in Western populations (Sorkin et al. 1999). Weight and height losses have also been confirmed in a 3-year longitudinal study in Hong Kong Chinese 70 years or older, with or without disease at baseline (Woo et al. 2001). Aging-associated height and weight losses have been observed in both cross-sectional (Davison et al. 2002) and longitudinal studies in Western populations (Sorkin et al. 1999). The rate of decrease in height has been reported to be between 0.5 and 1.5 cm/decade in Western populations, estimated from trends or slopes of regressions on age using cross-sectional data.

87.2.2 Age-Related Anthropometrical Changes in Distribution

As a result of these changes, the proportions of heavier men and women have decreased and proportions of lighter men and women have increased ($p < 0.05$) (Fig. 87.3). The change in the distribution of height appears less drastic in men than in women. Aging also affects BMI distributions. The proportions of underweight (BMI < 18.5 kg/cm^2) men and women are relatively small, 1.8% and 4.4%, respectively, in 60–64-year-old elderly but increase rather drastically after the age of 70 years. After the age of 80 years, 8.8% of elderly men and 16% of elderly women are underweight, according to the Taiwanese definition (BMI < 18.5 kg/cm^2). The proportions of overweight (BMI = 24.0–26.9 kg/cm^2) men and women decrease drastically after the age of 80 years. A greater proportion of women than men are obese (BMI ≥ 27 kg/cm^2) throughout all age ranges studied.

87.3 Factors Associated with Anthropometrical Changes

Because of the important health implication of the anthropometrical measures, there is a strong interest in delineating the factors that are associated with or can impact these changes. The factors associated with BMI changes, especially in areas related to weight control and obesity treatment in younger age groups, have been well studied in both Western and Eastern populations. However, for older adults, the main concern is weight loss (and its impact on functional ability, morbidity, and mortality), and not weight gain or overweight (Adams et al. 2006). The prevention of excessive weight loss, especially body muscle mass, is a major issue in geriatric nutrition.

87.3.1 Sociodemographic Factors

Associations of the sociodemographic, lifestyle, and dietary factors with BMI, MAC, and CC in subjects who were 60 years or older of the Survey of Health and Living Status of the Elderly in Taiwan (SHLSET) were analyzed and are presented in Table 87.1. Gender has a significant impact on all three measures. The female gender is associated with higher BMI but lower MAC and especially CC. Physiologically, females have a higher percentage of body fat and (as discussed earlier) their body weight peaks later than men but have earlier and more severe height loss than men.

Table 87.1 Multivariate linear regression analysis of the association of sociodemographic, lifestyle, and dietary factors with BMI, MAC and CC in Taiwanese men and women, 53 years or older ($N = 4176$)

	BMI		MAC		CC	
Variable[a]	Beta	t	Beta	t	Beta	t
Sex	0.044	2.12*	–0.053	–2.54*	–0.184	–9.47***
Age	–0.168	–10.15***	–0.150	–8.99***	–0.244	–15.59***
Education	–0.020	–1.03	–0.003	–0.14	0.051	2.84**
Routine exercise	0.059	3.57***	0.040	2.43*	0.106	6.75***
Smoking	–0.083	–4.65***	–0.014	–0.78	–0.057	–3.38***
Alcohol-drinking	0.004	0.25	–0.013	–0.78	0.023	1.40
Meat/poultry	0.043	2.39*	–0.008	–0.43	0.022	1.30
Fish	0.025	1.42	0.060	3.37***	0.014	0.84
Seafood	–0.004	–0.22	–0.007	–0.40	–0.011	–0.71
Egg	–0.022	–1.30	–0.033	–1.93	0.016	1.01
Dairy	–0.056	–3.39***	–0.037	–2.21*	–0.018	–1.16
Legumes	–0.032	–1.96*	–0.041	–2.50*	0.007	0.47
Vegetable	0.021	1.25	0.026	1.55	0.027	1.69
Fruits	0.050	2.82**	0.032	1.80	0.033	1.98*
Grain	0.020	1.19	0.025	1.48	0.032	2.00*
Tea	0.098	5.85***	0.051	2.99*	0.079	4.96***

The level of the associations of sociodemographic, lifestyle, and dietary factors with BMI, MAC and CC in Taiwanese men and women, 53 years or older

For gender, male was the reference. "Beta" = standardized coefficient and "t" = the level of significance of the associations. *, ** and *** designate $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively. Adjusted R^2 values are 0.060, 0.042, and 0.159 for BMI, MAC, and CC, respectively

[a]All variables except gender were treated as continuous numbers

Women generally have smaller MAC and CC than men, perhaps due to stature differences and physiological differences in muscle mass.

Old age is strongly associated with lower BMI, MAC, and CC. Among all factors examined, age has the strongest impact on the three anthropometrical measures. The decreases in BMI, MAC, and CC are, in general, the result of the overall aging-associated physiological decline. Aging impairs metabolic capacity, appetite, and immune competency, resulting in an overall functional decline and an increase in the susceptibility to infections and chronic diseases. In older Taiwanese, socioeconomical status (indicated by years of formal education) is not significantly associated with BMI or MAC, although it is positively associated with CC. The exact reason for the association of higher socioeconomic status with higher CC warrants further investigation.

87.3.2 Lifestyle Factors

Among the lifestyle factors, routine exercise is positively associated with all three anthropometrical factors, but the association is much stronger with CC than with BMI or MAC. This may be because CC is a better indicator of mobility ability than BMI or MAC. The association is bidirectional, as those who exercise routinely can maintain or strengthen CC, whereas those who have good CC are able to maintain physical activity or functional ability. Lower-extremity muscle mass is an important determinant of physical performance among functionally limited elders (Reid et al. 2008). Cigarette

smoking is negatively associated with BMI and CC but not MAC and cessation of smoking is known to result in weight gain. Munafo et al. (2009) have shown that never-smokers and ex-smokers differ in BMI from current smokers by an average of 1.6 kg/m^2 and smoking cessation is associated with a corresponding average increase of 1.6 kg/m^2. It is possible that cigarette smoking affects appetite regulation and therefore reduces energy intake. The negative association between smoking and CC is probably multifactorial. In addition to the dietary factors, smoking has been shown to impair muscle protein synthesis and increase the expression of genes associated with impaired muscle maintenance (Petersen et al. 2007; Stavropoulos-Kalinoglou et al. 2008). Smoking, therefore, is likely to increase the risk of sarcopenia. It is not known whether it is mediated through a direct impact on tissue protein synthesis or through a change in lifestyle pattern, such as less routine physical activity. Alcohol drinking is not significantly associated with the anthropometric indicators.

87.3.3 Dietary Factors

Dietary factors have also been shown to be associated with BMI, MAC, and CC of the elderly. The consumption of meat/poultry is positively associated with BMI but not MAC or CC, whereas the consumption of fish shows a strongly positive association with MAC but not with BMI or CC. It is of interest to note that meat/poultry and fish have different associations with the anthropometrical parameters. Although both are considered protein-rich foods, meat/poultry generally has a higher fat content than most fish. Frequent fish eaters are also generally considered to be more conscientious about health. The consumption of dairy is negatively associated with both BMI and MAC, but not with CC. In Taiwan, most of the current older adults do not habitually drink milk or consume dairy products, mainly due to the unavailability of these products in early years and also due to relatively high prevalence of lactose intolerance. Dairy products have not been widely available or affordable until recent decades in Taiwan. Generally, older adults supplemented their diet with formulated or fortified dairy products only during general weakness or illness. Thus, the negative association is at least in part a result of this negative connection that people consume dairy products when they are considered malnourished or during illness. Conversely, there are reports that dairy consumption is associated with lighter body weight in Western populations and the mechanism is thought to be mediated through its calcium content (Zemel et al. 2004; Zemel 2005). However, this observation remains to be confirmed with more robust studies. Consumption of legume food (mainly soy products) is also negatively associated with BMI and MAC but not with CC. While the exact explanation is not known, it might be related to the fact that legume consumption is related to vegetarianism. A wide variety of soy products, such as tofu and soy milk, is the staple food of most vegetarians in Taiwan. Vegetarians are generally considered to pay greater attention to diet and lifestyle and more closely watch their weight. There is also a notion that soy foods may contribute to weight loss. However, the currently available evidence is still controversial (St Once et al. 2007; Cope et al. 2008). The intake of vegetable is not associated with any of the three parameters, but the intake of fruits is positively associated with BMI and CC but did not reach a statistical significance with MAC. The intake of grain, mainly rice and wheat products in Taiwan, is positively associated with CC but not with BMI or MAC. It is of interest to note that tea (*Camellia*) drinking is associated with greater BMI, MAC, and CC. A possible explanation for this association is that, usually, only people who are relatively healthy will drink tea. People who are weak, on medication, or have sleep disorders do not drink tea, for fear of causing further sleep difficulty.

87.4 Applications to Other Areas of Health and Disease

87.4.1 BMI as an Indicator of Body Fatness

BMI, defined in terms of kg/m^2, is a measure of relative weight to height. Although the indicator does not directly reflect the level of body fat, it is often used to indicate body fatness because people usually gain fat when they gain weight. The WHO defines BMI < 18.5 kg/m^2 as underweight, 18.5–24.9 as normal weight, 25–29.9 as overweight, and ≥30 as obesity. However, there is evidence that the same definition cannot be uniformly applied to all world populations. Studies have shown that, at a given BMI, Asians (Taiwanese, for example) have a higher percentage of body fat than their Western counterparts. On the other hand, at a given level of body fatness, Asians have lower BMI (by about two BMI units). Thus, the WHO definition of overweight and obesity normally under-reflects the prevalence of many obesity-related chronic diseases in Asians. Asians have a higher risk of chronic diseases, such as hypertension and dyslipidemia, at lower BMI (Wen et al. 2008). To correct for these differences, the Department of Health of Taiwan has proposed a set of body fatness definitions for the Taiwanese: BMI < 18.5 kg/m^2 as underweight, 18.5–23.9 as normal weight, 24–26.9 as overweight, and ≥27 as obese. Using these criteria, 13.6% of Taiwanese elderly men and 18.2% of women are obese, instead of 2.8% of men and 5.8% of women based on the WHO definition (Table 87.2).

87.4.2 Accessibility of BMI in Frail Elderly

BMI is a useful indicator because both body weight and height are relatively accessible and easy to measure for most people. However, this indicator may not be very practical for frail or old individuals. As mentioned earlier, both weight and height decrease starting around the seventh decade of life. BMI can change without actually changing body weight. Accuracy of measurements could also be an issue in frail or old individuals. Thus, for old persons, BMI may not be as accessible as it seems. Another drawback about BMI is that it reflects mainly body fatness and not so much functional ability.

Table 87.2 Prevalence rates of overweight and obesity of elderly Taiwanese according to the WHO and the Taiwanese definitions

	WHO definition		Taiwan definition	
Study	Overweight BMI 25–29.9	Obesity BMI ≥ 30	Overweight BMI 24.0–26.9	Obesity BMI ≥ 27.0
1999 SHLSET[a] (%)				
Men	28.3	2.8	29.5	13.6
Women	27.8	5.8	27.2	18.2
1989–1991 Geriatric survey[b] (%)				
Men	27.3	3.2	NA	NA
Women	34.9	6.3		

The percentage of subjects classified overweight or obesity according to two definitions: World Health Organization (WHO) definition or the Taiwan definition

[a]From Tsai et al. (2007b): Subjects were 2,205 men and 1,933 women, 53 years or older

[b]From Chiu et al. (2000): Subjects were 1,322 men and 1,278 women, 65 years or older

Table 87.3 Spearmen's correlations among BMI, MAC and CC of Taiwanese elderly under various living settings

	1999 national sample[a]		Community living[b]		Care center-living[c]		Nursing home-living[c]	
Parameter	MAC	CC	MAC	CC	MAC	CC	MAC	CC
BMI	0.631***	0.602***	0.775***	0.643***	0.711***	0.739***	0.740***	0.712***
MAC		0.555***		0.647***		0.710***		0.703***

Spearman's correlation coefficients (r) showing the strength of relations, ***significant correlation at $p < 0.001$
[a]Tsai et al. (2007b) for the national sample study
[b]Tsai et al. (2009b) for community-living study, and
[c]Tsai et al. (2009c) for the care-center- and nursing-home studies

87.4.3 Applicability of Mid-Arm and Calf Circumferences in Nutritional Assessment

BMI reflects mainly body weight or body fatness, whereas MAC and CC reflect subcutaneous fat (or body fatness) and local muscle mass (functional ability). Thus, weight loss in older adults will be reflected in reduced MAC and CC, in addition to BMI. In fact, there is a relatively high degree of correlation among the three indicators. In Taiwanese elderly, the correlation coefficients (r) among the three variables generally run in the range of 0.6–0.8 (Table 87.3).

Because MAC and CC reflect body muscle mass and, thus, functional ability, in addition to body fatness, MAC and/or CC may offer an advantage over BMI in serving as a component in a nutrition/health assessment tool. For older individuals, good functional ability is important in maintaining good nutritional status. A small CC will suggest poor nutritional state and failing functional ability. Impaired functional ability can impact the ability to shop, prepare foods, or even self-feed. Thus, CC and MAC, in addition to BMI, are increasingly being included in nutritional and health assessment tools (Donini et al. 2007). A very good example is the MNA, a popular geriatric nutrition assessment tool (Guigoz et al. 2002).

87.4.4 Anthropometrics in Nutritional Assessment

Geriatric assessment is essential for quality geriatric care, and nutritional assessment is an essential component of geriatric assessment. Anthropometrical indicators play key roles in geriatric nutritional assessment and one good example is the MNA, one of the most widely used geriatric nutritional assessment tools. The tool was developed in the 1990s in Europe based on clinical data of Western populations. It has a long form (18 questions) for assessment and a short form (including the first six questions of the long form) for screening. The long-form MNA includes four anthropometrical indicators (recent weight loss, BMI, MAC, and CC) and accounts for 8 of the 30 total points, whereas the short form includes two anthropometrical items (recent weight loss and BMI) and accounts for 6 of the total 14 points in the screen. The tool does not involve any invasive indicator and is simple and effective, and thus has gained wide acceptance as a geriatric nutrition assessment tool. Malnutrition Universal Screening Tool (MUST) (Scott 2008) is another popular tool and it relies solely on two anthropometrical indicators (BMI and unplanned weight loss) for grading nutritional risk. However, in both tools, the thresholds for determining undernutrition are based on clinical data of Western populations. Because of the differences in stature, lifestyle, and healthcare systems, it has been cautioned that population-specific modifications should be carried out before applying these tools to populations other than those that the tools are intended for (Chumlea 2006). Given the well-recognized

Table 87.4 Pearson's correlation coefficients (r) of the nutritional status (scores) assessed with the Mini Nutritional Assessment (MNA) using BMI, MAC, and CC in elderly Taiwanese under various settings

Parameters	National sample[a] (N = 2,429)	Community living[a] (N = 501)	Care center[a] (N = 109)	Nursing home[a] (N = 103)
BMI	0.190	0.277***	0.29**	0.518***
MAC	0.244	0.271***	0.31**	0.418***
CC	0.341	0.320***	0.54***	0.564***

Pearson's correlation coefficients (r) showing the strength of correlations between BMI (body mass index), MAC (mid-arm circumference), and CC (calf circumference), with the nutritional status represented by the score of the MNA of older Taiwanese under various healthcare settings. ***significant correlation at $p<0.001$

[a]To avoid the condition that an independent variable is a component of the dependent variable, the testing anthropometric variable was removed from the total MNA score (the independent variable). Data for these analyses were from Tsai et al. (2007b) for the national sample study, from Tsai et al. (2009b) for the community living study, and from Tsai et al. (2009c) for the care center and nursing home studies

differences in body size and composition between the Caucasian and the Asian populations, it would be necessary to adopt the population-specific anthropometrical thresholds in order to maintain the content equivalence of the tool. Thus, Tsai et al. (2008a) have derived Taiwanese-specific BMI, MAC, and CC thresholds for undernutrition from a nationally representative sample of elderly Taiwanese. The minimum threshold for BMI is 17 kg/m^2, instead of 19 kg/m^2 for Caucasians. The threshold for MAC is 22.5 cm for elderly Taiwanese men and 21 cm for women, instead of 21 cm for both Caucasian men and women, and the threshold for CC is 28 cm for elderly Taiwanese men and 25 cm for Taiwanese women, instead of 31 cm for both Caucasian men and women (Tsai et al. 2006) A series of studies by Tsai and his coworkers have demonstrated that the adoption of these population-specific anthropometrical thresholds indeed improves the predictive ability of the MNA (Tsai et al. 2008a, 2007a, 2008b, 2009a, b, 2010a, b; Tsai and Ku 2007).

It should be mentioned that, although MAC and CC are useful nutritional and functional status indicators, only relatively few nutrition assessment tools have included these two indicators. Theoretically, there are advantages in including MAC and CC in addition to BMI or recent weight loss in a nutritional assessment tool. As mentioned earlier, MAC and CC, in addition to reflecting the overall nutritional status, also reflect muscle mass or the functional ability of the upper and lower extremities, respectively. Thus, nutritional tools that include MAC and CC can also reflect mobility ability. However, compared to calf circumference, MAC is not as good an indicator of body muscle mass because movement of the arms in daily living activities occurs until the very late stages of functional decline, which helps to maintain arm muscle mass. Thus, calf circumference is a better indicator of overall muscle mass. The legs contain over half of the muscle mass of the body, and a reduction in calf circumference can happen rather quickly during wasting, severe undernutrition, functional decline, illness, or frailty (Chumlea 2006).

In elderly persons, malnutrition is often accompanied by functional decline. Thus, an anthropometrical indicator that can reflect functional decline in addition to undernutrition would presumably be better than one that can reflect merely undernutrition. We have recently tested such a hypothesis by substituting CC and MAC for BMI in the long-form MNA, or CC for BMI in short-form MNA or MUST and confirmed that CC (and MAC in the case of long-form MNA) not only can substitute for BMI, but also improve the overall predictive ability of the short-form MNA and the MUST in Taiwanese elderly under various living settings (Tsai et al. 2009a). CC is most strongly associated with the overall nutritional scores assessed with the MNA in the elderly under various settings (Table 87.4). These results support the findings observed in hospitalized patients by Coelho et al. (2006) that CC is a stronger indicator of undernutrition than BMI and is a useful noninvasive and economical indicator of nutritional status.

Key Features

Table 87.5 Key facts of anthropometrical changes in older Taiwanese

1. The pattern of changes in weight, height, BMI, and MAC and CC of the Taiwanese elderly is comparable to what is observed in Western populations.
2. The thresholds for undernutrition for BMI, MAC, and CC for older Asians (Taiwanese) are different those for from their Western counterparts.
3. Because Taiwanese have a higher percentage of body fat-to-BMI relationship relative to Western populations, the WHO overweight/obesity definition based on BMI will underestimate the prevalence of overweight/obesity of Taiwanese.
4. BMI is mainly an indicator of relative body weight or body fatness, whereas MAC and, especially, CC reflect body muscle mass or functional ability, in addition to body fatness. Thus, BMI is a useful indicator for overnutrition, whereas MAC and, especially, CC are useful indicators of undernutrition and functional decline.
5. Because of the well-recognized population differences in anthropometrical measures, care should be taken in applying a uniform standard for classifying body fatness or undernutrition in countries where population-specific anthropometrical cut-points are not yet available.

This table lists the key facts of anthropometrical changes in older Taiwanese 60 years or older
BMI body mass index; *MAC* mid-arm circumference; *CC* calf circumference; *WHO* World Health Organization

87.5 Further Studies

To meet the need of increasing geriatric population in most societies and the demand for better quality of care on the one hand, and the increasing workload of caregivers on the other, the development of a simpler and more efficient tool for routine monitoring of the health and nutritional status of frail elderly or hospitalized persons is urgently needed. The anthropometrical measures should probably be a basic component in the construction of such a tool because these indicators are accessible, easy to measure, noninvasive, and, most importantly, indicative of one's nutritional status and functional ability. However, because of the cultural and anthropometrical differences, and the variation in healthcare systems, further effort should be made to develop population-specific tools. The population-specific aging-associated changes in MAC, CC, and other key anthropometrical indicators and their modification by diet, lifestyle, living environment, and health condition or diseases also need to be more extensively explored.

Summary Points

- Body mass index (BMI, calculated from weight (kg)/height (m^2)) and mid-arm and CC are simple anthropometrical measures that reflect the nutritional state of elderly persons.
- Weight, height, and mid-arm and CC are easily accessible, simple to measure, and non-invasive indicators.
- BMI, MAC, and calf circumference decrease during advanced aging.
- The patterns of these changes in Taiwanese are similar to those observed in the Western populations, but the magnitude of changes varies.
- The WHO definition of overweight (BMI 25–29.9) and obesity (BMI > 30) based on BMI values may underestimate the prevalence of overweight and obesity in the Taiwanese. Thresholds of BMI 24–26.9 for overweight and BMI > 27 for obesity have been adopted for Taiwanese by the Department of Health of Taiwan.

- In addition to age, lifestyle factors and diet are associated with the BMI and mid-arm and CC. Routine physical activity is positively associated with these indicators. However, cigarette smoking is negatively associated with BMI and calf circumference.
- Consumption of meat/poultry is associated with higher BMI but not mid-arm or CC.
- Consumption of dairy and legume foods is negatively associated with BMI and MAC but not calf circumference.
- Consumption of fruits but not vegetables is positively associated with BMI and calf circumference alone.
- Consumption of camellia tea is associated with higher BMI and mid-arm and CC.
- Calf circumference reflects body muscle mass better than BMI or MAC during advanced aging. Thus, it is a better indicator of functional decline.
- Because of their simple, accessible, and non-invasive character, and most importantly, the ability to reflect nutritional status, BMI and mid-arm and CC will be the key components in developing a tool for geriatric nutritional and functional assessment.
- Because of the race/ethnic-related anthropometrical variations and differences in healthcare systems, efforts should be made to develop population-specific assessment tools.

Acknowledgment The author of this chapter wishes to express his appreciation to (a) Ms. Tsui-Lan Chang for performing most of the statistical analyses and (b) the Bureau of Health Promotion of the Department of Health, Taiwan for providing the SHLSET data set used in this chapter.

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Chapter 88
Anthropometry and Mortality in Older Women: Potential Survival Benefit of Overweight and Obesity

Chantal Matkin Dolan, Michelle Hansen, and Kathryn Fisher

Abstract This chapter examines the reported relationship between body mass index (BMI kg/m^2) and other measures of anthropometry, such as fat mass and waist circumference, and the risk of all-cause mortality in older women. The World Health Organization (WHO) and the NHLBI have defined overweight as body mass index (BMI) 25.0–29.9 kg/m^2 and obesity as BMI of 30.0 kg/m^2 or greater and stated that all individuals who are overweight or obese are at risk for increased morbidity and mortality. The application of this single set of cutpoints to define mortality risk associated with overweight and obesity is controversial, particularly when applied to older women. Some studies support a linear relation while the majority of studies of older women have reported a J- or U-shaped relation between BMI and mortality in older women. Other studies have reported a "flattening" of this J- or U-shape relation between BMI and mortality among very elderly women. The totality of the evidence suggests that the BMI associated with lowest risk of mortality in older women is much higher than in younger women and that it includes overweight and possibly moderately obese women. The WHO and NHLBI guidelines are not appropriate when interpreting BMI levels and risk of mortality in older women, since many of the women categorized as overweight or obese are at the lowest risk of mortality. There does appear to be some survivor effect or protective effect of increased adiposity for risk of mortality in older women. Recent data suggests, however, that the possible protective effect of obesity on mortality may not provide protection against disability. More data are needed to understand fully the nature of the relation between anthropometry and risk of mortality and the link with morbidity and disability. There continues to be a striking lack of information on the risk of increased adiposity and mortality in non-White women. Although there is very little data on other measures of anthropometry other than BMI, BMI is highly correlated with other measures of anthropometry and is an easy and practical method of studying these relationships.

Abbreviations

BIA	Bioelectric Impedance Analysis
BMI	Body Mass Index
BMD	Bone Mineral Density
cm	Centimeters

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_88,

CI	Confidence Interval
DXA	Dual X-ray Absorptiometry
HR	Hazard Ratio
kg	Kilograms
m	Meters
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute
RR	Relative Risk
SOF	Study of Osteoporotic Fractures
WC	Waist Circumference
WHR	Waist-to-Hip Ratio
WHO	World Health Organization
y	Years

88.1 Introduction

In recent years, the prevalence of overweight and obesity, particularly in USA, has reached dramatically high, even epidemic, levels. According to recent estimates, more than 68.3% of the US adult population is overweight or obese (Flegal et al. 2010). In 2008, among women over 60 years of age, 68.6% were considered overweight and 33.6% were obese (see Table 88.1). Although these levels have dramatically increased over the past several decades, there does appear to be some leveling off of the prevalence rates of overweight and obesity in the most recent data suggesting that, perhaps, a "steady state" of overweight and obesity has been reached in the USA (Flegal et al. 2010). Because such large proportions of the female population are considered overweight or obese and as these proportions are not likely to decrease in the near future, it is important to understand the mortality risk associated with being an older overweight or obese woman.

In 1998, in an expert panel report, the National Heart Lung and Blood Institute (NHLBI) defined overweight as a body mass index (BMI) of 25.0–29.9 kg/m^2 and obesity as a BMI of 30.0 kg/m^2 or greater, and stated that all individuals who are overweight or obese are at risk for increased morbidity and mortality (NHLBI 1998). These guidelines were applied to adults of all ages, of both sexes, and across racial/ethnic groups. The World Health Organization (WHO) has also adopted these same cut-points to identify overweight and obesity (WHO 1998).

Several studies have shown that the risk of mortality associated with high BMI levels is greater for younger women than for older women (Lew and Garfinkle 1979; Lindsted and Singh 1997; Stevens et al. 1998, 1999; Calle et al. 1999; Thinggaard et al. 2010). In addition, the shape of the relationship between BMI and risk of mortality in women has been debated. Several studies have shown a J- or U-shaped relation between BMI and mortality in older women, suggesting elevated risk for mortality at the both low and high levels of BMI (Lew and Garfinkle 1979; Waaler 1984; Folsom et al. 1993; Durazo-Arvizu et al. 1997; Sempos et al. 1998; Bender et al. 1999; Calle et al. 1999; Dey et al. 2001; Katzmaryzk et al. 2001; Flegal et al. 2005; Corrada et al. 2006).

This chapter examines the reported relationship between BMI and other measures of anthropometry and adiposity, such as fat mass and waist circumference (WC), and the risk of all-cause mortality in older women. Particular attention is paid to large cohort studies that have included multiple indicators or measures of anthropometry and adiposity.

Table 88.1 Prevalence of obesity and overweight for adult women in the United States, % (95% confidence interval [CI]) (Flegal et al. 2010)

	All Women		Women 60 years and older	
	BMI ≥ 25 (Overweight and obese)	BMI ≥ 30 (Obese)	BMI ≥ 25 (Overweight and obese)	BMI ≥ 30 (Obese)
All	64.1 (61.3–66.9)	35.5 (33.2–37.7)	68.6 (64.4–72.7)	33.6 (30.2–36.9)
Non-Hispanic White	61.2 (56.7–65.7)	33.0 (29.3–36.6)	67.6 (62.2–73.1)	31.4 (27.3–35.5)
Non-Hispanic Black	78.2 (74.5–81.9)	49.6 (45.5–53.7)	78.2 (70.7–85.8)	50.5 (40.5–60.5)
All Hispanic	76.1 (72.0–80.1)	43.0 (37.9–48.2)	80.7 (77.3–84.1)	46.7 (41.0–52.3)
Mexican–American	76.9 (71.8–81.9)	45.1 (38.9–51.2)	82.6 (77.2–88.0)	48.1 (43.0–53.3)

88.2 Measuring Adiposity in Large Epidemiologic Studies

Most large epidemiologic studies measure adiposity by indirect anthropometric measures of obesity, such as BMI, rather than by more direct but relatively expensive measures of fat mass and lean mass, such as from bioelectrical impedance analysis (BIA) or dual X-ray absorptiometry (DXA). The inability to distinguish lean and fat mass using BMI may be particularly important among older women, who, on average, have a higher percentage of fat mass than younger women with the same BMI (Stevens et al. 1999). The loss of spinal height with age among women may also affect the relationship between BMI and fat mass in older women. However, BMI is easily calculated from weight and height (kg/m^2), and can be estimated based on actual measurements of height and weight in a clinical setting, self-reported height and weight, or recorded height and weight in various medical or population databases.

In addition to being an indirect measure of adiposity, BMI does not detect differences in body fat distribution, which may be important because of the link between abdominal or central adiposity and increased risk of heart disease (Han et al. 1996). Waist circumference and waist-to-hip (WHR) ratio have been used to indicate central adiposity. Although relatively easy to measure, WC or WHR must be collected and measured by trained personnel and cannot typically be self-reported or easily collected from stored records, such as height and weight for BMI calculations. Very few large epidemiologic studies examining obesity and mortality risk in older women have measured central adiposity using either WC or WHR.

Likewise, there are limited data on the relationship between the risk of mortality in older women and direct measures of body fat, such as percent body fat, fat mass, or lean mass, using either BIA or DXA measurements. The BIA technique assumes a two-compartment model of body composition (fat mass and lean mass). Based on the principle that tissues that contain water and dissolved electrolytes conduct electricity, the observed electrical impedance of body tissues can be used to estimate the total body water content, lean mass, and fat mass.

DXA uses a three-component model of body composition and is able to estimate bone mineral content in addition to fat mass and lean mass. By using the attenuation of radiation beams at two different energies, DXA can estimate the composition of body tissue (Mazess et al. 1990). Although considered superior to BIA, DXA is not considered a true gold standard because, like all measures of body composition, it is subject to measurement error and relies on various assumptions.

Thus, because of its low cost and ease of use and interpretability, BMI has been the predominant measure used in studies of adiposity and mortality in older women.

88.3 BMI and Mortality Among Older Women

Several, large, prospective cohort studies have reported a U-shaped relation between body size and mortality among women (Lew and Garfinkle 1979; Waaler 1984; Harris et al. 1988; Folsom et al. 1993; Durazo-Arvizu et al. 1997; Lindsted and Singh 1997; Durazo-Arvizu et al. 1998; Sempos et al. 1998; Allison et al. 1999; Calle et al. 1999; Singh et al. 1999; Dey et al. 2001; Katzmaryzk et al. 2001; Lahmann et al. 2002; Bigaard et al. 2004; Flegal et al. 2005; Corrada et al. 2006; Dolan et al. 2007; Thinggaard et al. 2010). In addition, many of the studies report that the lowest mortality risk in older women is often observed in BMI categories, including overweight and/or even obese women.

Both the American Cancer Society Study (Lew and Garfinkle 1979), which included over 400,000 women aged 30 years and older, and a study from Norway of over 900,000 women aged 15–90 years reported a U-shaped relation between BMI and mortality (Waaler 1984). However, neither the American Cancer Society Study nor the Norwegian study adjusted for smoking. The Nurses Health Study, which includes over 115,000 women aged 30–55 years at baseline, reported that, after adjusting for smoking, the association between BMI and mortality was linear (Manson et al. 1995). They suggested that the U-shaped relation between BMI and mortality reported in the literature could be due to smoking. It is possible that the mortality risk associated with BMI may be more linear in middle-aged women, as shown in the Nurses Health Study, but J- or U-shaped in older women.

However, other studies of women in age groups similar to the Nurses Health Study have controlled for smoking and still reported a U-shaped relation between body size and mortality, including a large cohort of female nonsmokers aged 25–64 years in Finland, the Iowa Women's Health Study, and the Framingham Heart Study (Rissanen et al. 1991; Folsom et al. 1993; Harris et al. 1988)]. A reanalysis of the Framingham Heart Study data concluded that the U-shape was not due to smoking and that the BMI associated with minimum mortality was similar for smokers and nonsmokers (Sempos et al. 1998). The American Cancer Society Cancer Prevention Study II that included more than 588,000 women and 14 years of follow-up data also had a U-shaped relation between BMI and mortality. This relationship was evident for smokers and nonsmokers, although the shape of the curve was flatter for nonsmokers (Calle et al. 1999). Data from a study including a cohort of 6,523 Alameda County Study women up to the age of 75 years concluded that only the underweight and moderately to extreme obese are at increased risk of mortality, more evidence of the U-shape (Strawbridge et al. 2000). The author asserted that the NHLBI guidelines categorize too many people as overweight and do not sufficiently account for sex, race and ethnicity, age, and other differences and fail to consider the health risks of low body weight.

This lower relative risk (RR) of mortality among older women was also observed in data from the American Cancer Society (Calle et al. 1999; Stevens et al. 1999). However, the authors of the Cancer Prevention Study II concluded that there was a consistent increase in mortality observed with increasing weight, supporting the use of a single recommended range of body weight throughout life (Calle et al. 1999). Others maintained that the data did not support age-independent standards and, among older women, only BMI values greater than 28.0 kg/m^2 were associated with increased mortality (Durazo-Arvizu et al. 1997).

A study among Seventh Day Adventists reported that the risk of mortality associated with high levels of BMI was lower for older women (55–74 years old) compared to younger women (30–54 years old) (Lindsted and Singh 1997). In one study from Finland, BMI was not an important predictor of mortality in women 65 years or older (Rissanen et al. 1991). Further, in a recent analysis of the Finnish Twin Cohort, there was no linear association apparent between BMI and mortality in older women (Korkeila et al. 2009). Data from the Leisure World Cohort Study, a population-based cohort from California including 8,571 women, suggested that being underweight or obese was a risk factor

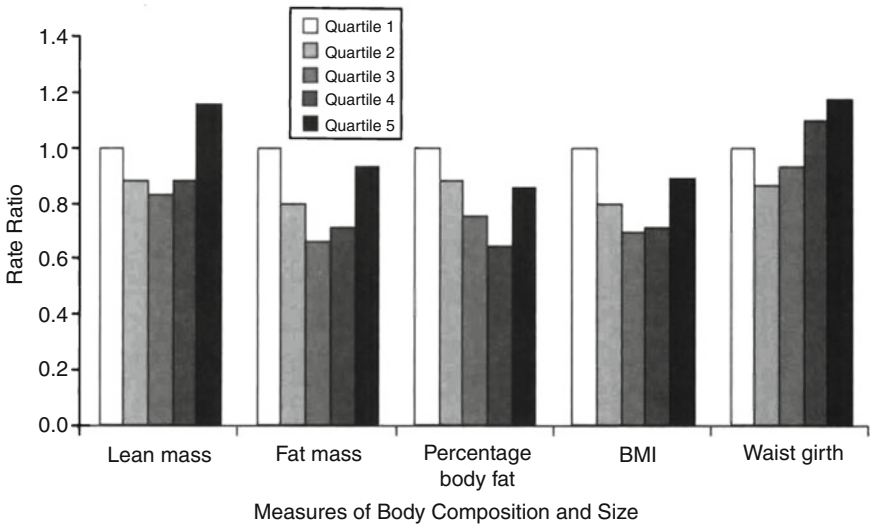

Fig. 88.1 Graphical representation of the linear spline Cox regression for age groups (Thinggaard et al. 2010, ©2010 The Author)

for mortality among those aged 75 years and older (Corrada et al. 2006). Overweight was a risk factor for mortality only in those under 75 years of age, demonstrating the different risks associated with adiposity in the elderly.

Data from the Jerusalem Longitudinal Study also supported a different relation between obesity and risk of mortality in the elderly than in younger populations. They reported that obesity was not associated with increased mortality risk in women when examined at 70, 78, and 85 years of age (Stessman et al. 2009).

In a recent analysis from the Longitudinal Study of Aging Danish Twins, Thinggaard et al. examined the relationship between mortality and BMI and concluded that, in older women, the highest risk of mortality was consistently observed in the underweight and overweight subjects (Thinggaard et al. 2010). They also reported that the U-shaped relationship decreased or flattened with advancing age among women (from age 70 to 95 years) in this Danish cohort (Fig. 88.1). Low BMI was consistently associated with higher mortality than even the highest levels of BMI. This somewhat disputes other data. Although this was a large population-based cohort with high participation rates, it is important to note that the authors did not control for initial health or other risk factors that could potentially confound the relationship.

88.4 Results from Meta-Analysis Studies

In 2007, a large meta-analysis on the association between BMI and risk of mortality in older women and men calculated the summary relative riskRR for all-cause mortality associated with the WHO- and NHLBI-defined BMI categories of overweight and obesity (Janssen and Mark 2007). Overall, the summary RR for all-cause mortality was 1.02 (95% confidence interval (CI) = 0.98–1.05) for overweight women and 1.18 (95% CI = 1.13–1.24) for obese women. BMI in the overweight range (25.5–29.9 kg/m^2) was not associated with an increased risk of mortality in older women, and there was only a modest risk associated with mortality in obese women (BMI ≥ 30 kg/m^2).

Table 88.2 Cohort studies between 1989 and 2009 identifying optimal BMI ranges in older women

Source, year/study	Applicable age or age range (y)	Optimum BMI (kg/m^2)
Korkeila et al., 2009/Finnish Twin Cohort	24–83	27 to <30
Stessman et al., 2009/Jerusalem Longitudinal Study	70	>25
Lang et al., 2008/English Longitudinal Study of Ageing	>65	25–29.9
Reuser et al., 2008/ US Health and Retirement Study	>55	25–29.9
Dolan et al., 2007/SOF	≥65	24.6–29.8 (29.2)
Simpson et al., 2007/Melbourne Collaborative Cohort Study	27–75	25–29.9
Gale et al, 2006/UK Department of Health and Social Security Survey	≥65	25–29.9
Corrada et al., 2006/Leisure World Cohort Study	≥80	25–29.9
Flegal et al., 2005/National Health and Nutrition Examination Survey (NHANES) I–III	≥60	25 to <30
Volpato et al., 2004/Istituto di Riposo per Anzani Study	≥65	>25.4
Miller et al., 2002/Australian Longitudinal Study of Ageing	≥70	>25–30
Taylor et al., 2001/ National Long-Term Care Survey	≥65	30–34.9
Grabowski et al., 2001/Longitudinal Study on Aging	≥70	29–31.9
Dey et al., 2001/Gothenburg Sweden Cohort	70	24.7–26.4
Lahmann et al., 2001/Malmö Cancer and Diet Study	60–73	22–25.7
Landi et al., 1999/Home Health Care Survey of Rovereto, Italy	≥65	>27
Calle et al., 1999/Cancer Prevention Study	64–74	20.5–23.4
	≥75	23.5–24.9
Diehr et al., 1998/Cardiovascular Health Study	≥65	26–28
Stevens et al., 1998/American Cancer Society Cancer Prevention Study	≥75	27.4–28.5
Menotti et al., 1996/Finland, Italy, Netherlands Elderly Study	65–74	29.4
	≥75	30.7
Cornoni-Huntley et al., 1991/NHANES I, Epidemiologic Follow-up Study	65–74	Whites: 24.37–26.95 Blacks: 28.82–34.37
Tayback et al., 1990/NHANES I, Epidemiologic Follow-up Study	65–74	26.5–27
Rissanen et al., 1989/Social Insurance Institute of Finland Survey	≥75	28–31

Another meta-analysis of BMI and mortality confirmed excess mortality among obese women but not among overweight women (McGee 2005). For women in the overweight BMI category, relative to women in the normal-weight category, McGee calculated an RR of 0.968 (95% CI = 0.925 to 0.987). The RR associated with the obese BMI category relative to normal weight was 1.275 (95% CI = 1.183, 1.373). In their models, the author controlled for age, but this analysis did not specifically address the risk in older women. In a review of the evidence regarding the NHLBI and WHO guidelines, Heiat et al. concluded that the data do not support the inclusion of the BMI range between 25 and 27 (part of the overweight category) as a risk factor for all-cause mortality in older women and that most studies show a negative or no association between BMI and mortality (Heiat et al. 2001).

Combining data from studies included in the published meta-analyses and reviews and more recently published data, Table 88.2 shows the BMI ranges that are associated with lowest risk of mortality in several large epidemiologic cohort studies (Janssen and Mark 2007; McGee 2005; Heiat et al. 2001).

In most studies, the BMI in the "optimum range" and thus associated with the lowest mortality risk included or exceeded the BMI categorization for overweight and, in some cases, included the BMI categorization for obese. To this point, in another study combining data from five prospective cohorts in USA, more than 80% of deaths attributable to obesity were among individuals with a BMI greater than 30 kg/m^2, the lower cut-point for obesity (Allison et al. 1999).

88.5 Using Different Measures of Body Composition and Anthropometry to Assess Risk of Mortality

Although BMI has been criticized as a potentially biased measure of anthropometry in older women, most of the large cohort studies only use BMI. In order to more fully understand the nature of the relation between overweight and obesity and risk of mortality in older women, we identified three relatively recent, large cohort studies that included multiple measures of anthropometry and adiposity including BMI (indirect measure of adiposity), BIA (direct measure of adiposity), and WC or WHR (measure of central adiposity): The Study of Osteoporotic Fractures (SOF), The Malmö Diet and Cancer Study, and The Melbourne Study (Dolan et al. 2007; Lahmann et al. 2002; Simpson et al. 2007).

88.6 The Study of Osteoporotic Fractures

One of the few studies to examine the risk of mortality and multiple measures of adiposity in the same cohort is based on data from The SOF, a large, prospective, cohort study of fractures among predominantly white women age 65 years and older, who were being followed up as part of a study on hip fractures. Details of the SOF cohort and its study design have been previously published (Cummings et al. 1990). Direct body composition measures included fat mass (kg), lean mass (kg), and percent body fat and were calculated using BIA. BMI and WC (cm) were also measured.

Women aged 65 years and older were recruited from September 1986 to October, 1988, from community-based listings in the geographic areas of Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley area near Pittsburgh, Pennsylvania. Most of the participants (greater than 98%) were white.

BMI (kg/m^2) was calculated based on measured weight and height. Waist girth (cm) was measured using an inelastic tape measure. Fat mass, lean mass, and percent body fat were calculated from BIA. During the follow-up period, 945 deaths occurred among the 8,029 women who had complete anthropometric measures. All of the measures of body composition and anthropometry were quite highly correlated with one another.

Body measures were categorized into quintiles, and Cox proportional hazards regression models were used to estimate the RR of mortality associated with each body measurement category. There was a U-shaped relation between each of the body-size measures and mortality that persisted when adjustments were made for potential confounding factors, including age, self-reported health, smoking, grip strength, non-thiazide diuretic use, and femoral-neck BMD (Fig. 88.2). Among nonsmokers, the patterns of associations between quintiles of body-size measures and mortality were similar to the results for the entire cohort (Fig. 88.3). The U-shaped relationship between body-size measures and mortality persisted after further controlling for hypertension and diabetes and when exclusions were made for women who died within the first 2 years of follow-up, or for women who had lost greater than 10% of their body weight since age 50 years. Thus, the U-shaped relationship was not likely the result of uncontrolled confounding due to smoking or preexisting medical conditions.

In the SOF cohort, the lowest risk was consistently observed among women falling in the middle of the distributions of all the body composition and anthropometric measures. In this population of older women, BIA, the more costly measure of body composition, did not provide an obvious advantage or difference in predicting mortality over BMI or waist girth.

The BMI values for the two quintiles at lowest risk were between 24.6 and 29.8 kg/m^2, and the optimal value was estimated to be 29.3 kg/m^2. These results cautioned against applying the recent National Institutes of Health classifications for overweight and obesity to older women with BMI greater than 25 kg/m^2, as many of these women are in the lowest risk group for mortality. The results

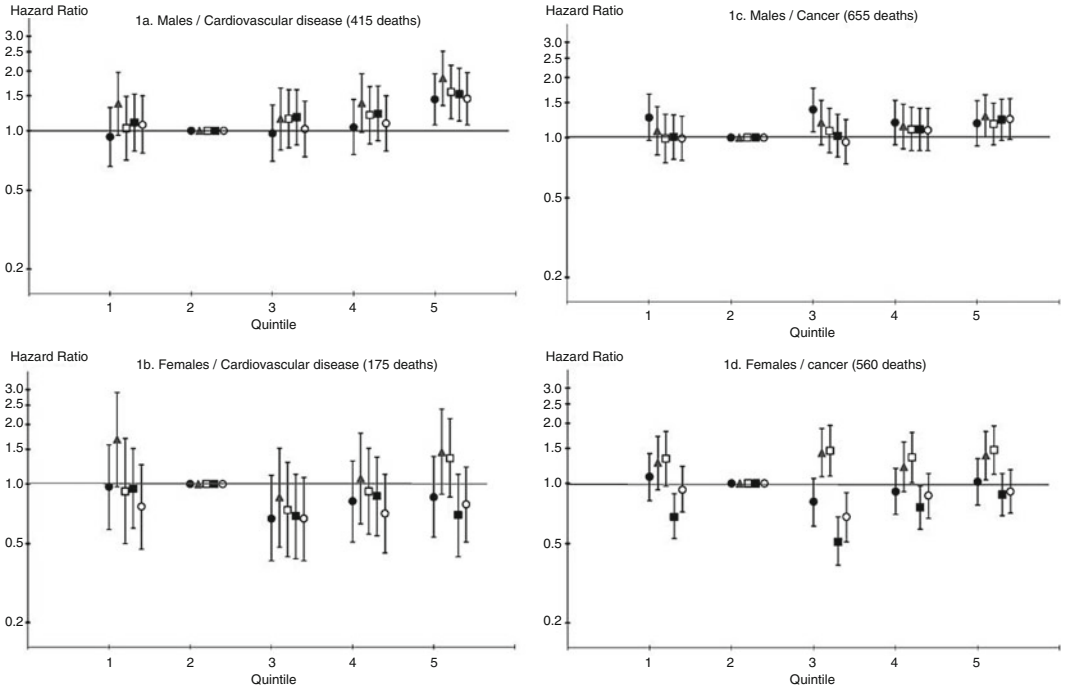

Fig. 88.2 Quintiles of body composition measures and mortality risk in women aged 65 years and older: study of osteoporotic fractures (SOF); Baltimore, MD; Minneapolis, MN; Portland, OR; Monongahela Valley Area, PA; 1986–1997 (Dolan et al. 2007, ©2007 APJH)

showing minimum mortality in the middle of the distribution of BMI and body composition levels are consistent with data from the NHANES-I Epidemiologic Follow-up Study, which demonstrated a broad range of BMI values associated with low risk of mortality (Durazo-Arvizu et al. 1998).

88.7 The Malmö Diet and Cancer Study

The Malmo Diet and Cancer Study is one of only two other large cohort studies besides the SOF cohort that examined the association between adiposity and all-cause mortality, using multiple measures of adiposity in older women. The study was a prospective population-based cohort study among residents of Malmo, Sweden (Lahmann et al. 2002). BMI (kg/m^2) was calculated based on measured weight and height. The waist and hip circumference of each participant were measured by trained personnel and used to construct the WHR. BIA analyses were conducted to estimate lean body mass and percent body fat. Body measures were categorized into quintiles, and Cox proportional hazards regression models were used to estimate the RR of mortality associated with each body measurement category. The lowest quintile was used as the reference category. Models were adjusted for potential confounders including age, height, smoking status, and physical activity.

The final female cohort included 17,035 women born between 1923 and 1950, with complete data for all measurements. Participation rate was approximately 40%. The study found a direct, positive, linear relationship between percent body fat and mortality in the middle-aged women (45–59 years of age). Among older women (60–72 years of age), the study observed a J-shaped association between percent body fat and risk of mortality, with the women in the quintiles 2–5 at lower risk than women in the bottom quintile. The lowest risk for percent body fat was observed in the second quintile RR = 0.47 (95%

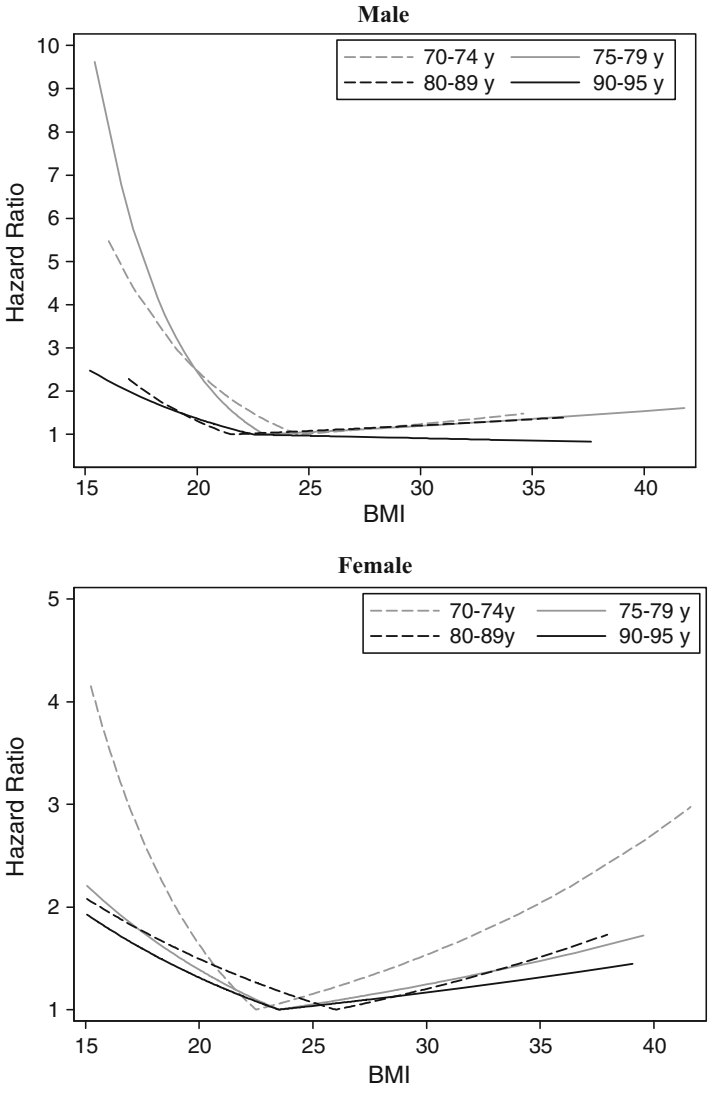

Fig. 88.3 Adjusted rate ratios (RRs, with 95% confidence intervals [CIs]), by quintile of body composition measures in women aged 65 years and older: SOF; Baltimore, MD; Minneapolis, MN; Portland, OR; Monongahela Valley Area, PA; 1986–1997 (Dolan et al. 2007, ©2007 APJH)

CI = 0.30–0.74), corresponding to body fat between 27% and 30%. A U-shaped association was observed between lean mass and mortality, though none of the RRs was statistically significant. A J-shaped association was observed for BMI and mortality risk, though, like lean mass, no significant associations were observed between BMI and risk of mortality. The authors noted that there was no evidence of excess mortality in the WHO- and NHLBI-defined overweight category of 25.0–29.9 kg/m^2 when compared to the normal weight category (BMI 18.5–24.9 kg/m^2). When they analyzed the WHR quintiles, they observed a positive linear association between central adiposity and mortality risk. The highest risk of mortality in older women was observed in the highest quintile of the WHR (RR = 2.13 (95% CI = 1.52 to 3.00). These observations were not due to early death or preexisting illnesses.

These data from the Malmo Diet and Cancer Study support the J- or U-shaped relation between percent body fat, lean mass, and BMI and risk of mortality. However, in this study, only RR estimates for quintiles of percent body fat were statistically significant. The WHR, by contrast, demonstrated

a strong direct linear relation with mortality risk. The authors concluded that central adiposity and WHR constitute a more useful measure of estimating mortality risk in older women than either the more commonly used BMI or the expensive BIA estimates of percent body fat and lean mass.

88.8 The Melbourne Collaborative Cohort Study

The Melbourne Collaborative Cohort Study also examined the relationship between multiple measures of body composition and anthropometry and risk of mortality in a cohort including older women (Simpson et al. 2007). The study participants were recruited from the Melbourne metropolitan area between 1990 and 1994. Weight, height, WC, and hip circumference were measured at baseline using standard protocols. BIA was conducted to estimate fat mass and percent fat mass. The final cohort included 24,344 women with 99% in the age range 40–69 years. There were 1,166 deaths during a median follow-up period of 11 years.

Each body composition and anthropometric measure was divided into quintiles. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) for mortality risk for each anthropometric and body composition measure, using the second quintile as the referent group. The models were stratified for previous history of illness at baseline and adjusted for age, country of birth, physical activity, alcohol intake, education, and smoking status based on descriptive characteristics.

Results from the regression models showed that the association between BMI, WC, fat mass, and percent body fat all had a U-shaped association with mortality risk, whereas WHR demonstrated a linear relationship with mortality (see Fig. 88.4). Women in the highest quintile of WC and WHR had increased risk of mortality compared to women in the referent group (HR = 1.3 (95% CI = 1.1–1.6) and HR = 1.5 (95% CI for HR = 1.2–1.8), respectively). They observed little or no increased risk in the highest quintiles of BMI, fast mass, and percent body fat. They concluded, like the Malmo Diet and Cancer Study, that measures of central adiposity were better predictors of mortality risk than BMI or BIA measures of body composition.

88.9 Measures of Central Adiposity: Are They Better than BMI or Measures of Body Composition at Predicting Mortality Risk?

Interestingly, none of the three large cohort studies that have examined the association between multiple measures of adiposity (including central adiposity) and the risk of mortality were able to detect a clear advantage of using the BIA-estimated percent body fat, fat mass, or lean mass, the more expensive and direct measures of body composition. Both the Malmo Diet and Cancer Study and the Melbourne Collaborative Cohort Study observed a strong, direct, linear (not U-shaped) relation between WC (Melbourne Collaborative Cohort Study) or the WHR (Malmo Diet and Cancer Study) and risk of mortality. By contrast, the SOF study observed a U-shaped relation between all of the measures of anthropometry (including WC) and mortality in older women. Waist circumference was not a stronger predictor of mortality than BMI or body composition measures in the SOF data set.

Unfortunately, studies examining the association of central adiposity and mortality risk in older women are limited. One other large cohort study has examined the association between central adiposity in older women (though they did not include direct measures of adiposity, such as BIA). The Rotterdam Study was a population-based cohort study in Ommoord, the Netherlands (Visscher et al. 2001). Study participants were recruited from 1990 to 1993 and included 3,694 women 55–102 years of age with a mean follow-up period of 5.4 years. There were 477 deaths during this period. BMI was calculated based on measured height and weight (kg/m^2). Waist and hip circumference

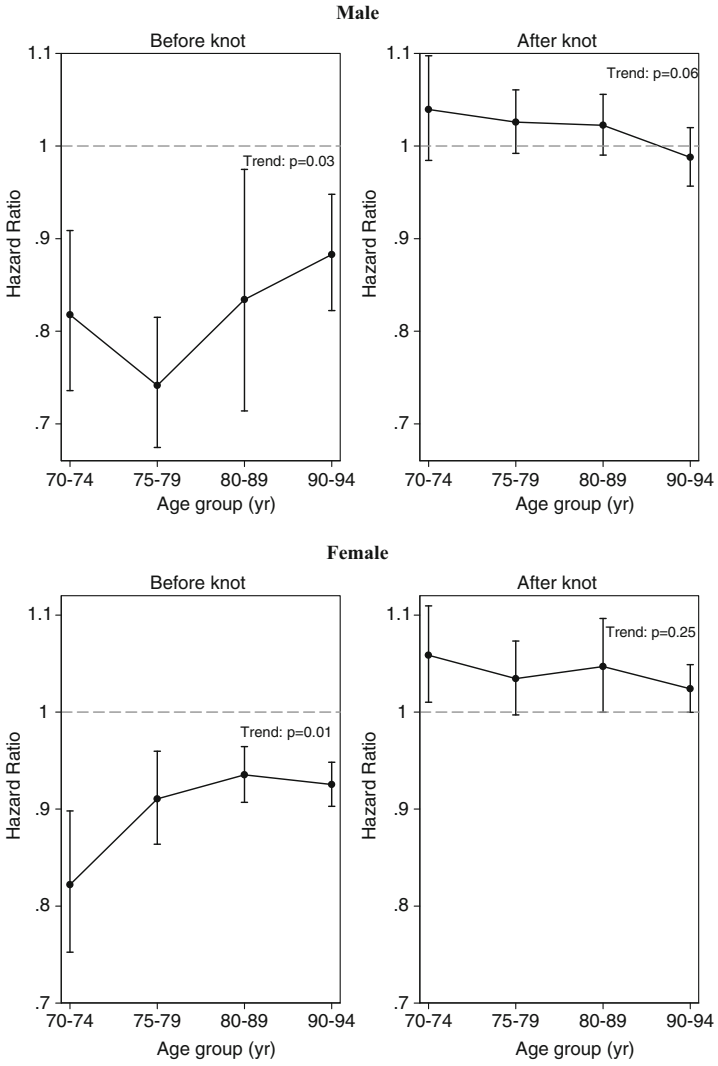

Fig. 88.4 Anthropometric risk factors for all-cause mortality (Simpson et al. 2007, ©2007 NAASO)

were measured by trained study personnel. All the measures of body size were divided into quintiles for analysis. Age-adjusted Cox proportional hazards regression models were used to estimate the RR for each body measure. The second quintile was designated as the reference category. Analyses were stratified by smoking status (never, former, and current).

Among elderly women, high levels of body fatness measured by BMI, WC, or WHR did not predict increased mortality risk. Although the quadratic term for BMI was significant in the regression models for never-smoking elderly women suggesting a U-shaped relation, the individual RR did not appear elevated at either the lowest quintile or highest quintile of BMI.

Thus, in the Rotterdam Study, none of the measures were predictors of mortality risk in these elderly women and the measures of central adiposity did not provide an advantage over BMI. The study may have been limited in size and ability to control for other potential risk factors, such as underlying or preexisting disease.

The data on the association between the measures of central adiposity and mortality risk are quite limited and somewhat contradictory. Although both the Malmo Diet and Cancer Study and the

Melbourne Collaborative Cohort Study suggested that central adiposity measures were strong, linear predictors of mortality in elderly women, neither the SOF cohort nor the Rotterdam Study supports these conclusions. In a study including older Chinese women, Woo et al. concluded that both WC and BMI had an inverse association with mortality and that WHR was not a useful predictor of mortality risk (Woo et al. 2002). Hopefully, more studies will include measures of WC or WHR, so that the relation between central adiposity and risk of mortality is more clearly understood.

Because the link between obesity and risk of mortality is so widely studied and has such significant public-health implications, it would be useful to identify the single body-size measure that best predicts mortality. It is difficult to conclude from the available literature that which of the measures of body composition and anthropometry "best" predicts mortality. Although the data are limited, the three large cohort studies that measured body composition, central adiposity, and BMI in older women concluded that the more direct specific measures of body composition by BIA did not provide a clear advantage over either BMI or the central adiposity measures. The additional cost and difficulty of obtaining BIA or DXA favor the use of BMI and WC, both of which are relatively easy and inexpensive to measure.

88.10 Anthropometric Measures and Mortality in Non-White Ethnic or Racial Groups

The vast majority of the studies examining anthropometric measures and risk of mortality in older women have been in white women in USA, Europe, and Australia. Very few studies have been conducted in older women of other racial or ethnic groups. Data regarding older black women are particularly limited. Using data from the NHANES I Epidemiologic Follow-up Study and the National Health Interview Survey showed that the BMI values associated with minimum mortality risk and the U-shaped association with mortality were very similar among blacks and whites (Durazo-Arvizu et al. 1997). In another analysis of the NHANES data, the optimum BMI range for lowest mortality risk was higher for black women than for white women, although similar risks were associated with high and low BMI for older black and white women (Cornoni-Huntley et al. 1991). Studies in older Asian women are also quite limited. It has been suggested that a lower cut-point to define obesity may be needed in Asian populations (WHO 2000); however, recent data from a cohort of Koreans reported that the obesity-related mortality was similar to that observed in whites (Oh et al. 2004).

88.11 Summary and Conclusions

In summary, it is possible to draw some conclusions about the association between measures of anthropometry and risk of mortality in older women. First, there is strong evidence that the relationship between adiposity is different for older women than younger women. Evidence suggests that the BMI associated with lowest risk of mortality in older women is higher than in younger women and that it includes overweight and, possibly, moderately obese women. There is also substantial support for the U-shaped relation between BMI and mortality in older women, suggesting that women at the lower and higher ends of the BMI spectrum are at greater risk than those in the middle part of the distribution. There is also evidence that this U-shape is attenuated with age and "flattens" with advancing age.

88.12 Practical Application to Future Studies of Anthropometric Measures and Mortality in Older women

Because BMI is easy to measure and calculate, the bulk of the studies examining the association between adiposity and mortality in women has been based on BMI data. In general, in studies with available data, the more direct measures of body composition, such as fat mass, lean mass, or percent body fat estimated by BIA, did not prove to be substantially better at predicting mortality risk in older women than the BMI data in the studies that had BIA-estimated measures of body composition. Although some studies have suggested that measures of central adiposity may be stronger predictors of mortality in older women than BMI, others have not observed that central adiposity is different or better than BMI. In order to more fully understand the complex relation between measures of body size and adiposity and risk of mortality in older women, more studies are needed that measure both BMI and central adiposity.

The vast majority of the large cohort studies on anthropometry and mortality in older women have been confined to populations of white women in USA, Europe, and Australia. More data on other ethnic/racial groups in different areas of the world are needed to better understand the relationship of measures of anthropometry and mortality risk in non-white populations.

88.13 Application to Clinical Guidelines for Overweight and Obesity

Several of the large prospective cohort studies and meta-analyses have concluded that the NHLBI and WHO guidelines for BMI cut-points defining overweight and obesity should be interpreted with caution and are not appropriate when applied to older women. Many studies have found that there is a wide range of optimum BMI levels for minimum mortality risk and that this range includes BMI values in the overweight category and, even in some studies, the obesity category. The totality of the data do not support the classification of older women, who have a BMI of 25–29.9 kg/m^2, as overweight and at risk for increased mortality, as these ranges were associated with the lower risks of mortality in most studies.

88.14 Application to Other Areas of Health and Disease

Among older women, there does appear to be some survival benefit associated with increased adiposity. The reasons for this survival advantage are not well understood. It is possible that those women susceptible to the effects of excess body weight died at younger ages. It is also possible that the excess weight confers some type of real survival advantage in older women, whether through biologic activity of fat cells or through other means. More research is needed to understand the biological mechanism related to this survival advantage.

This review has not addressed the risk of cause-specific mortality or the association between anthropometry and body size and risk, or morbidity, or disability. These results that show a lower risk of mortality among overweight or even obese women in some cases should not be applied to risk of morbidity. Interestingly, a recent examination of the association between obesity on risk of both mortality and disability showed that the protective effect of obesity on mortality did not extend to disability (Lang et al. 2008), thus suggesting a potentially very important paradox and difficult public-health problem in which overweight and obese women may have some type of mortality protection but without an accompanying protection against morbidity or disability.

Table 88.3 Key features of three large cohort studies that included multiple measures of anthropometry and adiposity and risk of mortality in older women

Cohort	Study population	Body-size measures included	Average length of follow-up period	Number of deaths during follow-up period	Variables controlled for in analyses	Study Results
SOF (Dolan et al. 2007)	• Predominantly white (98%) women aged 65 and older • From Baltimore, MD, Minneapolis, MN, Portland, OR, and near Pittsburgh, PA • Recruited from voter registration lists, driver's license and ID card information, and HMO membership lists • Baseline dates: September 1986–October 1988 • $N = 9704$ • Mean Age: 73.2 years • Mean BMI: 26.2 kg/m^2	• BIA (Lean Mass, Fat mass, and % Body Fat • BMI (Height and Weight) • Waist circumference (WC)	8 years	945	• Age • Smoking status • Alcohol use • Femoral-neck bone density • Self-reported health status • Physical activity level • Grip strength • Non-thiazide diuretic use	U-shaped relations were observed between all measures of body size and mortality throughout the age ranges in the study. For BMI, the lowest mortality rates were in the range 24.6 to 29.8 kg/m^2. Results not attributable to smoking or measures of preexisting illness.
Malmö Diet and Cancer Study (Lahmann et al. 2002)	• Men and women aged 45–73 years • Randomly sampled from Sweden's National Population Registry • Baseline dates: 1991–1996 • $N = 16{,}814$* • Mean age: 59.2 years* • Average BMI: 25.5 kg/m^{2*}	• BIA (Lean Mass, % Body Fat) • BMI (Height and Weight) • Waist-to Hip Ratio (Waist and Hip circumference)	5.7 years	392*	• Age • Height • Smoking status • Physical activity level	The association between % body fat and mortality was modified by age. Weaker associations were seen for BMI than for % body fat. WHR stronger predictor of mortality in women Results not explained by bias from early death or preexisting illness.

Melbourne Collaborative Cohort Study (Simpson et al., 2007)	• Men and women aged 27–75 years from the Melbourne metropolitan area (99.3% of subjects were 40–69 years of age) • Recruited through electoral rolls and advertising • Baseline dates: 1990–1994 • *N* = 24,344* • Median BMI: 25.9 kg/m^{2*}	• BIA (Fat Mass, % Body Fat) • BMI (Height and Weight) • Waist-to-Hip Ratio (Waist and Hip Circumference) • WC	11 years	1166*	• Age • Country of birth • Physical activity level • Alcohol use • Education • Previous history of heart attack, angina, diabetes, stroke, and cancer • Smoking status	U-shaped relation between WC and mortality. WHR was positively, linearly related to mortality risk Little or no increased mortality risk for BMI, fat mass, or % body fat

*Women

Summary Points

- The relation between anthropometric measures and mortality is different for older women than younger women; the BMI associated with the lowest risk of mortality is higher among older women than younger women.
- The BMI ranges associated with minimum mortality in older women include WHO and NHLBI categories of overweight and, in some studies, obesity.
- Direct measures of body composition, such as BIA-measured fat mass, lean mass, and percent body fat do not appear to provide an advantage over BMI or measures of central adiposity in predicting mortality risk.
- Limited data on measures of central adiposity and risk of mortality are inconsistent. More research is needed to better understand the association between central adiposity and mortality risk in older women.
- Most of the studies on anthropometry measures and mortality risk in older women have been conducted in white populations in USA, Europe, and Australia. More studies are needed to understand the association of anthropometry and mortality risk in non-white populations.
- The results showing a protective effect of increased adiposity on mortality do not necessarily extend to morbidity or disability.

Acknowledgments We would like to acknowledge Dr. Jennifer Kelsey for her thoughtful review of a draft version of this chapter.

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Chapter 89
Postmenopausal Anthropometric Relationship Between Arm Span and Height in Osteoporosis

Demet Ofluoglu

Abstract Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased of risk fracture. The most frequently observed osteoporotic fracture is a vertebral fracture, resulting in vertebral deformities. In the aging population and especially osteoporotic women, changes in body composition and some anthropometric measurements have been noted. Loss of height increased with age and is frequent in middle-aged women. It is caused by decreasing height of the intervertebral discs and joint cartilage, less pronounced foot arches and postural changes. Another important cause of the age-related height loss is the reduction in vertebral height due to osteoporotic vertebral fractures and structural changes, these being more frequent in women. Arm span is recommended as an acceptable measure for height in clinical situations where it is difficult to measure standing height limited by contractures, fractures, scoliosis, amputation, quadriplegia, paraplegia, coma, or existing osteoporotic fractures. Arm span is a valid measure of height in young and middle-aged adults. Arm span measurements can be used in estimation of youth height and age related loss in stature. Measurement of height loss is a good clinical indicator of vertebral fracture. Greater than 6 cm height loss can be a finding for osteoporotic vertebral fractures, therefore a spinal X-ray should be obtained. The sensitivity and specificity of the arm span – height differences for having osteoporosis is high. Therefore, arm span – height differences can be used for the initial screening of vertebral deformities in postmenopausal women. This chapter discusses the relationship between height and arm span differences in postmenopausal osteoporotic women.

Abbreviations

AS	Arm span
ASHD	Arm span – Height Differences
DEXA	Dual energy X-ray absorptiometry
FEV1	Forced expiratory volume in one second
FVC	Forced Vital Capacity
SD	Standard deviation
VD	Vertebral deformity
WHO	World Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_89,

89.1 Introduction

Osteoporosis is commonly seen in people over 50 years of age, and is a major cause of fractures. In the earlier part of 2000, the estimated worldwide incidence of osteoporotic fractures was nine million (Johnell and Kanis 2006). The incidence of osteoporotic fractures will continue to increase as the population ages. The most frequently observed osteoporotic fracture is in the spine, which causes vertebral deformities. These can lead to morbidity in the form of chronic back pain, loss of height, kyphosis, and functional impairment (Rea et al. 2000).

Anthropometry has been used over the centuries to distinguish the differences between the human races. It plays in important role in industrial design, clothing design, architecture, as well as in medicine. Some diseases and their expression, such as marfanoid stature, can be identified with anthropometric measurements.

Changes in body composition and some anthropometric measurements have been noted in the aging population and in osteoporotic women. In this chapter on postmenopausal osteoporosis, the relationship between arm span and height will be discussed.

89.2 Osteoporosis: Definition, Risks, and Management

Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality (Brown and Fortier 2006; Kanis et al. 2008). Approximately one in four women and one in eight men have osteoporosis, according to fracture data in Canada (Jackson et al. 2000).

Osteoporosis is becoming a major public-health problem, as the population ages all over the world. The prevalence of osteoporosis increases with age, from approximately 6% at 50 years of age to over 50% above 80 years of age (Looker et al. 1997). Generally, osteoporosis is called a silent bone disease till a fracture occurs. However, patients can suffer back pain, loss of height, and postural disorders, such as kyphosis of the spine. The major problem (in osteoporosis) is fractures, the highest incidence being vertebral, followed by wrist and hip fractures (Rea et al. 2000). A 50-year-old Caucasian woman has a residual lifetime fragility fracture risk of 40% for vertebra, hip, or wrist (Brown and Fortier 2006).

There are many risk factors associated with osteoporosis, such as age, sex, low body mass index, glucocorticoid treatment, smoking, alcohol intake, inflammatory disease, and thyroid disorders (see Table 89.1) (Kanis et al. 2008). The main cause of postmenopausal osteoporosis is estrogen withdrawal. Figure 89.1 shows a postmenopausal osteoporotic woman. However, coexistence of other risk factors can facilitate the development of postmenopausal osteoporosis.

The diagnosis of osteoporosis requires a thorough history and physical examination, including family history of osteoporosis, type and location of musculoskeletal pain, general dietary calcium intake, and level of physical activity and height and weight measurements (see Table 89.2) (Sinaki 2000). However, the objective of bone mineral measurements is to provide diagnostic criteria, prognostic information on the probability of future fractures, and a baseline on which to monitor the natural history of the treated or untreated patient (Kanis et al. 2008). Typically, osteoporosis is not visible on conventional radiographs until at least 25–30% of bone mineral has been lost. There are many methods to evaluate bone mineral density; however, the most commonly used technique is dual energy X-ray absorptiometry (DEXA) (Sinaki 2000). The technique has high precision and

Table 89.1 Common risk factors for osteoporosis

Age: over 65 years
Fragility fracture after age 40 years and/or family history of osteoporotic fracture
Early menopause (before age 45 years)
Nutritional factors:
Malnutrition
Anorexia/bulimia
Vitamin deficiency (C or D)
Vitamin overuse (D or A)
Calcium deficiency
High sodium intake
High caffeine intake
High protein intake
High phosphate intake
Alcohol abuse
Sedentary lifestyle, immobility, and smoking
Gastrointestinal diseases (liver disease, malabsorption syndromes, alactasia, and subtotal gastrectomy) or small-bowel resection
Nephropathies
Chronic obstructive pulmonary disease
Malignancy (multiple myeloma and disseminated carcinoma)
Drugs: phenytoin, barbiturates, cholestyramine, and heparin
Endocrine disorders: Acromegaly, hyperthyroidism, Cushing's syndrome, hyperparathyroidism, diabetes mellitus, and hypogonadism

Age, fracture history in both patients and their family, early menopause, malabsorption syndrome, hypogonadism, and primary hyperparathyroidism are very important risk factors for osteoporosis. Bone mineral density should be measured in women under the age of 65 years with these risk factors or for all women age 65 years and older because of the high risk of osteoporosis and fracture after that age

accuracy. According to World Health Organization criteria, bone mineral density is classified as follows: *T*-score > -1 standard deviation (SD), normal; *T*-score -1 to -2.5 SD, osteopenia; *T*-score of -2.5 SD or less, osteoporosis. A *T*-score at or below -2.5 and the presence of one or more fragility fractures is termed severe or established osteoporosis (see Table 89.3) (Wahner 1996; Brown and Josse 2002). The treatment of osteoporosis is planned according to this classification and severity. Apart from the many types of drugs available for the treatment of osteoporosis, exercises and the prevention of bone loss are an important part of the management.

Prevention is as important as the treatment of osteoporosis. The goal for osteoporosis in both prevention and treatment is the same: maintaining bone health to ensure a low risk of fracture and to improve the quality of life. Prevention begins in childhood and continues throughout life. The more the subjects build up bones during their early years, the less likely they are to develop osteoporosis later on. The factors for prevention of osteoporosis include avoiding the risk factors of osteoporosis, good nutrition (adequate intake of calcium and vitamin D), regular physical activity (at least 30 min walking three times a week), healthy habits and behaviors, good posture, and medications. When combined, these factors support and strengthen one another to help prevent or manage osteoporosis.

The treatment goal of osteoporosis includes maximizing the development of the skeleton, preventing fractures, relieving the symptoms of fractures, improving the balance, and the ability to move and be active. Once osteoporosis is diagnosed, in addition to diet and exercise, medications are often prescribed for people at high risk of developing osteoporosis and those who have been diagnosed

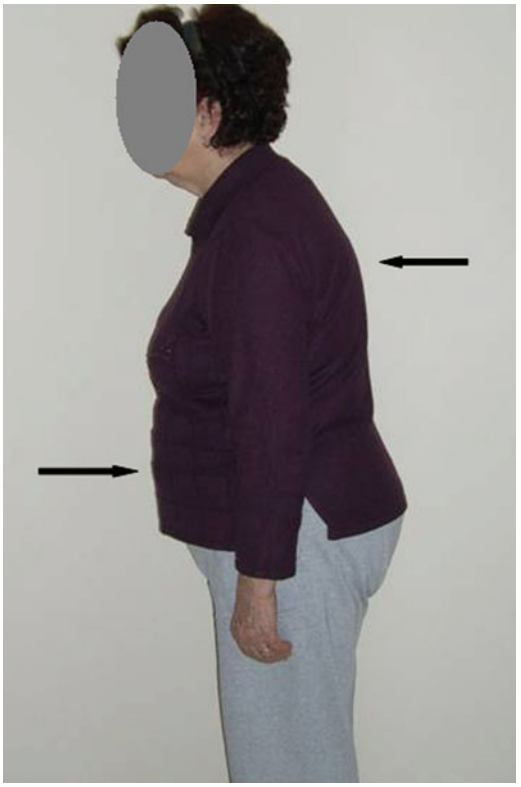

Fig. 89.1 A postmenopausal osteoporotic woman. She was a 73-year-old woman with osteoporosis. The figure indicates increased kyphosis and abdominal protrusion due to thoracic kyphosis. She complained of back pain and loss of height by at least 5 cm. Her height and arm span were 165 and 172 cm, respectively. She had low bone mineral density in her DEXA measurement and two osteoporotic vertebral compression fractures in her T 12 and L 1 vertebrae

Table 89.2 Diagnostic evaluation for osteoporosis

History and physical examination
Radiography of chest and spine
Bone mineral density (hip and spine)
Complete blood cell count
Chemistry group
Erythrocyte sedimentation rate and serum protein electrophoresis
Total thyroxine
Immunoreactive parathyroid hormone
25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D
Urinalysis and 24-h urine
Biochemical markers of bone turnover

Evaluation of osteoporosis in postmenopausal women should include the assessment of clinical risk factors for low bone mineral densitometry and bone mineral densitometry testing. The gold standard method to diagnose for osteoporosis is DEXA. Hip and spine measurements by DEXA should be used for both risk assessment and follow-up, as they provide the most accurate and precise measurements of BMD

with the disease. Most prescription medications for osteoporosis are called antiresorptives. The term refers to action of slowing or stopping the breakdown of bone tissue. Other medications include drugs to build new bone and increase bone mass. All these types of medications should be supplemented with daily calcium and vitamin D. After menopause, a woman needs to take 1,000 mg/day elemental calcium and 800 IU/day vitamin D.

The key features of osteoporosis are summarized in Table 89.4.

Table 89.3 Osteoporosis classification according to bone mineral density

T-score > –1	Normal
T-score between -1 and – 2.5	Osteopenia
T-score < –2.5	Osteoporosis
T-score < –2.5 and at least one fragility fracture	Established osteoporosis

WHO classification of osteoporosis according to DEXA. WHO has proposed four diagnostic categories for postmenopausal Caucasian women according to DEXA. The choice of this 2.5 standard deviation (SD) cutoff by the WHO was based on epidemiological data

WHO World Health Organization

Table 89.4 Key features of osteoporosis

- Osteoporosis is a systemic skeletal disorder characterized by a low BMD and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.
- All postmenopausal women older than 50 years should be assessed for the presence of risks factors for osteoporosis.
- The prevalence of osteoporosis increases with age, from approximately 6% at 50 years of age to more than 50% above 80 years of age.
- There are many risk factors associated with osteoporosis, such as age, sex, low body mass index, glucocorticoid treatment, smoking, alcohol intake, inflammatory disease, and thyroid disorders. The main cause of postmenopausal osteoporosis is estrogen withdrawal.
- The gold standard method for diagnosing osteoporosis is measurement of bone mineral densitometry with DEXA.
- Osteoporotic fractures are a major cause of morbidity in the population. Common sites for osteoporotic fracture are the spine, hip, and wrist. Vertebral fractures may cause acute pain and loss of function but may also occur without serious symptoms.
- The goals of osteoporosis management should be fracture-risk assessment and fracture prevention.

This table lists the key features of postmenopausal osteoporosis

89.3 Practical Methods Measurement of Height and Arm Span

Height is measured as follows: subjects should remove their shoes, stand facing away from and against the wall (buttocks, back, and head against the wall) and hold their head erect. The point at the top of the head should be indicated on the wall and, then, the distance between floor and the point should be measured with the same device each time. However, a standard measurement device can be used (see Fig. 89.2). For arm-span measurement, the subjects should be standing as mentioned earlier and arms spread in a straight line parallel to the floor, as shown in Fig. 89.3. The distance between the right- and left-hand tip of the middle finger is taken as the arm span.

Osteoporosis is commonly seen in people after 50 years of age and is associated with increased risk for fracture and thus has a major impact on the affected patients and on societies. It is the major cause of vertebral, wrist, and hip fractures. The associated morbidity and mortality of osteoporotic fractures are very significant. The most frequently observed osteoporotic fracture is vertebral fracture, which causes vertebral deformities. These deformities are associated with increased morbidity and symptoms, such as loss of height, kyphosis, back pain, functional impairment, depression, and reduced survival rates (Rea et al. 2000).

Changes in body composition and some anthropometric measurements have been noted in the aging population and in osteoporotic women. It is well known that vertebral fracture and loss of height in osteoporotic women are closely linked (Ettinger et al. 1994). Only one-third of these vertebral fractures give rise to symptoms (Versluis et al. 1999). It is therefore necessary to establish a screening method to detect existing vertebral fractures in asymptomatic individuals. There is an excellent correlation between arm span and height in the human body. Arm span is a valid measure

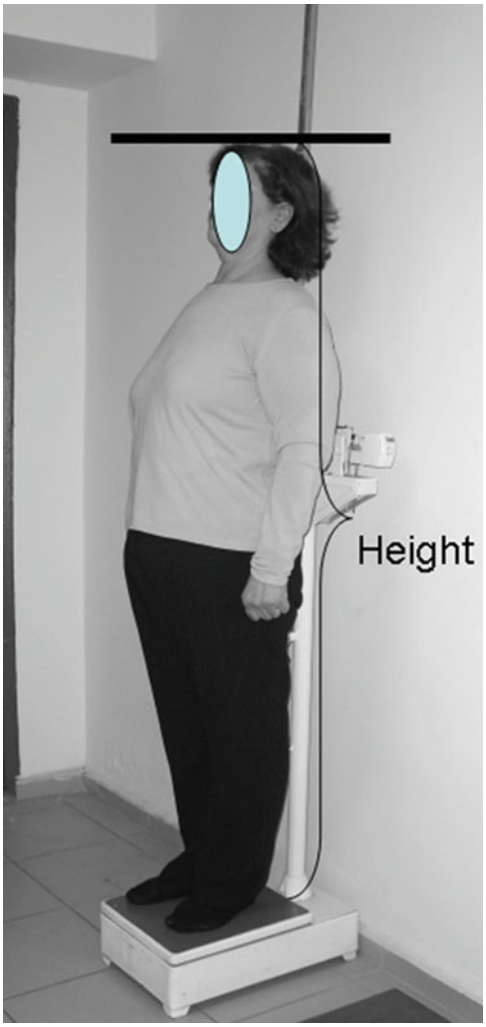

Fig. 89.2 Measurement of height. Height measurement of an example of a woman with osteoporosis. The subjects should remove their shoes, stand facing away from and against the device upright, and hold their head erect. The point at the top of the head should be indicated on the device upright; the distance between floor and the point is the "height"

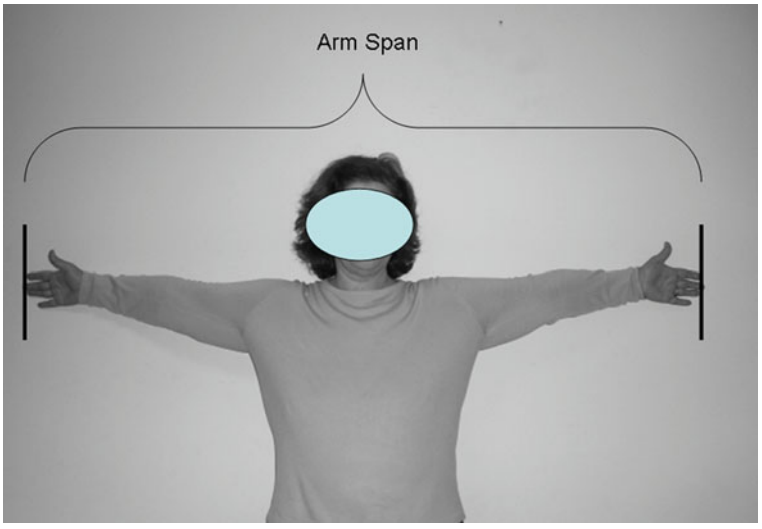

Fig. 89.3 Measurement of arm span. Arm-span measurement of an example of a woman with osteoporosis. The subjects should remove their shoes, stand facing away from and against the wall, and hold their head erect. Arms should be spread in a straight line parallel to the floor. The distance between the right- and left-hand tip of the middle finger is taken as the arm span of the subjects

of height in young and middle-aged adults. Hence, arm-span measurements can be used in the estimation of youth height and age-related loss in stature. This method can be used as a screening tool to determine height loss due to osteoporotic vertebral fracture in patients with osteoporosis.

89.4 The Relationship Between Arm Span and Height

Marcus Vitruvius Pollio was a Roman writer, architect, and engineer who realized that the proportions of the greatest work of anthropometric measurements of the human body, and observed a relation between arm span and height. Leonardo da Vinci depicted his Vitruvian Man as the "Diagram of Man" (Versluis et al. 1999).

Age, gender, and race have been associated with differences in arm span and height. Men have greater differences between arm span and height than women. Normally, the differences between arm span and height are not more than 2 cm in young men and women (Brown et al. 2000). The authors found that there was an excellent correlation between arm span and height.

Steele and Chenier investigated the relation between arm span and height of 591 black and white women in their study (Steele and Chenier 1990). They found that the arm span in black women was 8.7 cm longer than height, whereas the relation was 3.3 cm in white women. However, they showed that there was a good correlation between arm span and height in both black and white women.

Rabe et al., in their study, examined interrelationships of height and arm span in elderly women and men (Rabe et al. 1996). They found that there was good correlation between arm span and height in both female and male groups. Their data graphics for female and male elderly are shown in Figs. 89.4 and 89.5, respectively.

89.5 Arm Span and Height Ratio in Postmenopausal Osteoporotic Women

In postmenopausal osteoporosis, the most common fracture is in the vertebrae, and the prevalence of these fractures increases with age, even though only one-third of these vertebral fractures give rise to symptoms (Versluis et al. 1999). It is therefore necessary to establish a screening method to detect

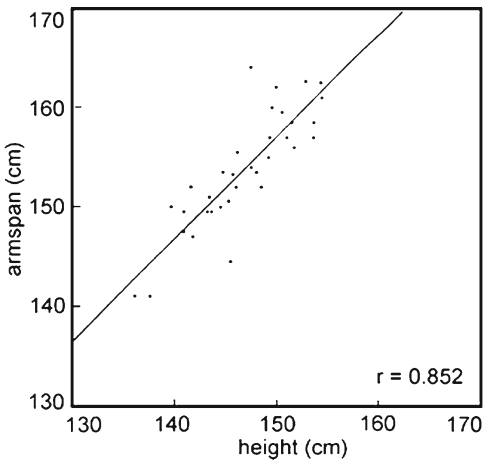

Fig. 89.4 Correlation between height and arm span in elderly females. The figure shows a good correlation between arm span and height in the female group (Reprinted from Rabe et al. 1996. With permission)

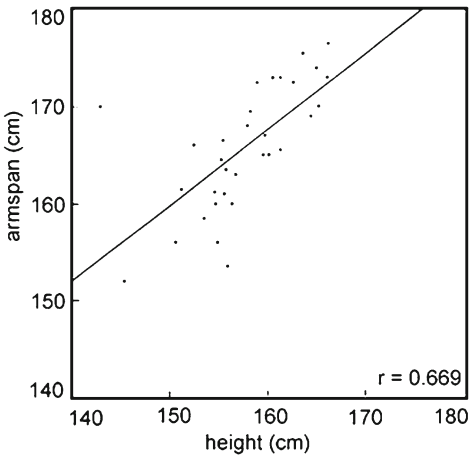

Fig. 89.5 Correlation between height and arm span in elderly males. The figure shows a good correlation between arm span and height in the male group (Reprinted from Rabe et al. 1996. With permission)

existing vertebral fractures in asymptomatic individuals. It is well known that vertebral fracture and loss of height in osteoporotic women are closely linked (Ettinger et al. 1994).

Late in the 1990s, Verhaar et al. studied 36 postmenopausal women with established osteoporosis and 25 women without osteoporosis to identify the usefulness of arm span–height differences (Verhaar et al. 1998). They found that there was a very good correlation between arm span and height in osteoporotic women, and the sensitivity and specificity of the arm span–height differences for having osteoporosis were 81% and 64%, respectively.

Mohanty et al. studied the relationship between anthropometric measurements and standing height of 505 healthy women between the ages of 20 and 29 (Mohanty et al. 2001). They found that arm span was the most reliable body parameter for predicting the height of an individual. They also concluded that arm span was a useful predicting factor for age-related loss in stature. Jalzem and Gledhill investigated the relationship between arm span and height in individuals aged 0.5–56 years (Jalzem and Gledhill 1993). They concluded that height can be predicted reliably from arm measurements.

We published data comparing the relationship between arm span and height in 70 postmenopausal women and 70 young healthy women (Ofluoglu et al. 2008). Mean age of the postmenopausal women (group I) was 64.4 ± 8.6 years and 27.3 ± 3.5 years in young healthy women (group II). Mean height was 152 ± 5.1 cm and 161.5 ± 5.9 cm in groups I and II, respectively. Mean arm span was 159.6 ± 6.3 cm in group I and 163.5 ± 6 cm in group II. The demographic characteristics of these subjects are shown in Table 89.5. The mean arm span–height difference was significantly higher in postmenopausal women when compared to healthy young women (7.7 ± 3.6 and 2 ± 2.9 cm, respectively; $p < 0.001$) (see Table 89.6). We concluded that the arm-span measurements can be used for the estimation of youth height and age-related loss in stature in postmenopausal women.

Recently, Abe et al. evaluated the efficacy of using arm-span height differences, wall–occiput distance, and rib–pelvic distance separately and in combination to screen for undiagnosed vertebral fractures in 116 middle-aged elderly Japanese women (Abe et al. 2008). The mean arm-span–height differences for those participants with and without vertebral deformities were 7 ± 4.1 and 4.2 ± 4.2 cm, respectively. They found that sensitivity and specificity for use of arm span–height differences were 85% and 52%, respectively. They concluded that arm span–height differences effectively predicted vertebral deformities. Some of their important data are shown in Tables 89.7 and 89.8.

By contrast, some other studies did not support the difference between arm span–height for prediction of vertebral deformities. Versluis et al. investigated the differences between arm span and

Table 89.5 Subjects' demographic characteristics (Reprinted from Ofluoglu et al. 2008. With permission)

	Group I	Group II	*P* value
Age (year) (mean ± SD)	64.4 ± 8.6	27.3 ± 3.5	<0.0001
Height (cm) (mean ± SD)	152 ± 5.1	161.5 ± 5.9	<0.0001
Arm Span (cm) (mean ± SD)	159.6 ± 6.3	163.5 ± 6	<0.0001
Height–Arm span Differences (cm) (mean ± SD)	7.7 ± 3.6	2 ± 2.9	<0.0001

There were significant differences between the two groups regarding demographic characteristics. However, most importantly, the study showed a significant difference in height–arm span ratio between osteoporotic women and young women

Table 89.6 Correlation analysis of the parameters (Reprinted from Ofluoglu et al. 2008. With permission)

	R value	*P* value
Age–height	–0.26	0.002
Age–arm span	–0.22	0.05
Vertebral fracture–height	–0.31	0.01
Age–vertebral fracture	0.30	0.02
Vertebral fracture–lumbar *T* score	–0.36	0.02

Height declined with age; vertebral fracture related with loss bone mineral density; and height was decreased with the existence of vertebral fracture

Table 89.7 Arm span–height differences according to age group in the study by Abe et al. (Reprinted from Abe et al. 2008)

(mean ± SD)	Total (n = 116)	49–59 years (n = 22)	60–69 years (n = 26)	70–79 years (n = 52)	80 years + (n = 16)
Height (cm)	148 ± 6.4	152.1 ± 4.8	149.1 ± 6.9	146.6 ± 6.1	145.4 ± 6.3
AS (cm)	152.8 ± 6.7	153.1 ± 6.5	154 ± 7.3	152.5 ± 7.1	151.2 ± 4.1
ASHD (cm)	4.7 ± 4.3	1 ± 3.5	4.9 ± 4.6	5.9 ± 3.5	5.8 ± 4.5

Abe et al. studied the efficacy of using arm span–height differences, wall–occiput distance, and rib–pelvic distance separately and in combination to screen for undiagnosed vertebral fractures in 116 middle-aged elderly Japanese women. The table shows some important data from their study
AS arm span; *ASHD* arm span–height differences

Table 89.8 Arm span–height differences in groups with and without vertebral deformity in the study by Abe et al. (Reprinted from Abe et al. 2008)

	49–59 years (n = 22)		60–69 years (n = 26)		70–79 years (n = 52)		80 years + (n = 16)	
	With VD*	Without VD	With VD	Without VD	With VD	Without VD	With VD	Without VD
Height (cm)	149.2	155.2 ± 4.9	144.9 ± 7.1	149.7 ± 6.8	143.5 ± 7.1	147.5 ± 5.5	144.8 ± 5.8	145.6 ± 6.6
AS (cm)	148.8	153.3 ± 6.4	154.5 ± 6.5	154 ± 7.8	150.6 ± 8.4	153 ± 6.6	151.7 ± 4.9	151.1 ± 4.2
ASHD (cm)	–0.4	1.1 ± 3.5	9.6 ± 4.5	4.3 ± 4.3	7.1 ± 3.8	5.5 ± 3.4	6.9 ± 3.7	5.5 ± 4.9

Arm span–height differences effectively predicted vertebral deformities
AS arm span; *ASHD* arm span–height differences; *VD* vertebral deformity

height in relation to the presence of vertebral deformities in 494 women (Versluis et al. 1999), found no differences, and concluded that this method cannot be used for the detection of vertebral deformities. Recently, Uzunca et al. agreed with the Versluis et al. conclusion. They studied 90 postmenopausal women and their data showed that measurement of arm span–height differences cannot

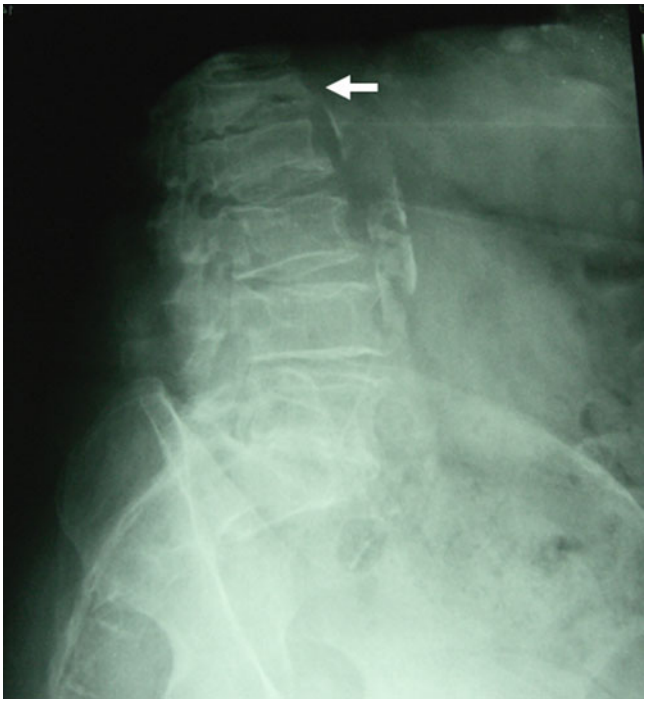

Fig. 89.6 An example of osteoporotic vertebral fracture. *Arrow* indicates osteoporotic L1 vertebral compression fracture

estimate presence of osteoporosis and related fractures (Uzunca et al. 2008). Although Wang et al. found that there was a strong relationship between arm span and standing height in healthy young men and women and in healthy elderly men and women, the difference between arm span and standing height alone predicted only 49–62% fracture cases in women and men (Wang et al. 2004). Therefore, they suggested that the predictive ability of the difference between arm span and height to identify vertebral fractures was limited (Fig. 89.6).

89.6 Application to Other Areas of Health and Disease

Height is a very important parameter for (1) determining basic energy requirements, (2) standardizing measures of physical capacity, and (3) adjusting drug dosage. However, in some situations, such as scoliosis, arthritis, lower-limb amputations, and vertebral fractures, the exact height cannot be measured directly. Estimation of height can be made using arm span. Therefore, arm span can be used for estimating exact height in certain diseases to adjust drug dosage, assess pulmonary function, etc. Tan et al. showed correlation between arm span–height ratio and FEV1 and FVC (Tan et al. 2009). They concluded the importance of arm-span measurements in lung-function assessment.

89.7 Conclusion

Height loss increases with age and is frequent in middle-aged women. It is caused by decreasing height of the intervertebral disks and joint cartilages, less pronounced foot arches, and postural changes. Another important cause of the age-related height loss is the reduction in vertebral height

due to osteoporotic vertebral fractures and structural changes, which are more frequent in elderly women (Tobias et al. 2007). Low bone mineral density and bone loss are strongly associated with height loss. Forsmo et al. showed that there was a significant relationship between the increased rate of height loss and bone loss (Forsmo et al. 2007). Besides low bone mineral density, one vertebral fracture is associated with height loss of about 2.5 cm (Ismail et al. 1999; Siminoski et al. 2006; Tobias et al. 2007).

Arm span has been suggested as a useful predictor of standing height (Jalzem and Gledhill 1993; Mohanty et al. 2001). Measurements of arm span are not affected by height loss and vertebral deformities. Thus, in case of a disease that affects height, such as osteoporotic vertebral fractures, the patient's arm span should be longer than height. The sensitivity of this method is quite high (81%), whereas specificity is about 64% (Verhaar et al. 1998). Therefore, other diseases which affect height should be taken into account. However, apart from vertebral deformities, other factors may contribute to variations in arm span–height differences. For example, degenerative disk disease may lead to height loss in the elderly, leading to differences between arm span and height.

As a result, arm span is a valid measure of height in young and middle-aged adults. Its measurements can be used to estimate youth height and age-related loss in stature, making it a potential tool for screening for vertebral deformities in postmenopausal women, as well as for some other fields in health and disease.

Summary Points

- Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture. Osteoporosis is becoming a major public-health problem as the population ages all over the world.
- There are many risk factors associated with osteoporosis. The main cause of postmenopausal osteoporosis is estrogen withdrawal. The gold standard method for diagnosing osteoporosis is measurement of bone mineral densitometry with DEXA. The goals of osteoporosis management should be fracture risk assessment and prevention of fracture.
- The most important complication of osteoporosis is osteoporotic fractures. They are a major cause of morbidity in the population. The most frequently observed osteoporotic fracture is a vertebral fracture, which causes vertebral deformities.
- Vertebral deformities are associated with increased morbidity and symptoms, such as loss of height, kyphosis, back pain, functional impairment, depression, and reduced survival rates. However, only one-third of these vertebral fractures give rise to symptoms.
- Height loss increases with age and is frequent in middle-aged women. An important cause of the age-related height loss is the reduction in vertebral height due to osteoporotic vertebral fractures and structural changes, which are more frequent in the elderly women.
- There was an excellent correlation between arm span and height. Normally, the difference between arm span and height is not more than 2 cm in young men and women. Therefore, the arm span–height ratio can be used as a screening method to detect existing vertebral fractures in especially asymptomatic individuals with osteoporotic vertebral fractures. This method is inexpensive and reliable.
- If a postmenopausal woman has a historical height loss greater than 6 cm, kyphosis, or acute incapacitating back pain, a spinal radiograph with a specific request to rule out vertebral fractures should be obtained.

Key Points

See Table 89.9.

Table 89.9 Key facts of arm span and height ratio

• Arm span helps to estimate height accurately.
• Arm span is recommended as an acceptable measure for height in clinical situations, where it is difficult to measure standing height.
• An increased arm span to height ratio is an indication of possible loss of height.
• Greater than 6 cm height loss can be a finding for osteoporotic vertebral fractures; therefore, a spinal X-ray should be obtained.
• The sensitivity and specificity of the arm span–height differences for having osteoporosis are high.

This table lists the relationship and the importance of arm span and height ratio for postmenopausal osteoporotic women

Acknowledgments Thanks to Professor Abe and coauthors for sharing some of their data about arm span and height in the study cited earlier and thanks to the Editor of Journal of APJCN for giving permission to show some figures of the study by Rabe et al. in the chapter.

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Chapter 90
Relationship Between Plasma Hormones and Anthropometric Measures of Muscle Mass in Postmenopausal Women

Fábio Lera Orsatti, Erick Prado de Oliveira, and Roberto Carlos Burini

Abstract The muscle undoubtedly pertains to a complex mechano-biological system that primarily enables efficient locomotion but is also involved in other vital physiological functions. Aging is accompanied by progressive reduction in muscle mass (sarcopenia). Sarcopenia is a progressive process that occurs in healthy individuals. Sarcopenia is usually associated with functional impairment and physical disability, especially in women, and is the direct cause of reduction in muscle strength. Muscle mass and strength start declining over the perimenopausal years and this phenomenon seems to be partly estrogen-dependent. The role of estrogen in sarcopenia remains unclear. Epidemiological studies suggest that as estrogen declines with age there is an increase in the levels of pro-inflammatory cytokines suspected to be involved in the sarcopenia process such as tumor necrosis factor alpha and interleukin-6 (IL-6). These cytokines cause an imbalance in muscle tissue synthesis in favor of excess protein breakdown. Epidemiological studies suggest a relationship between low levels of testosterone and loss of muscle mass, strength and function. In post-menopausal women testosterone increases muscle mass. Despite evidence that DHEA supplementation results in an increase of blood testosterone levels in women and increase of IGF-1 in men, few studies have reported an effect in muscle size, strength or function. Insulin-like growth factor-1 (IGF-1) and growth hormone (GH) decline with age. GH replacement therapy lowers fat mass and increases lean body mass. The aging muscle is capable of synthesizing IGF-1 but it may be less sensitive to IGF-1 and could have an attenuated ability to synthesize an isoform of IGF-1 promoting satellite cell proliferation. Exercise may reverse the resistance of aging muscle to IGF-1.

Abbreviations

BIA	Bioelectrical impedance analysis
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CT	Computerized tomography
DHEA	Dehydroepiandrosterone
DXA	Dual X-ray absorptiometry
GH	Growth hormone

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_90,

HRT	Hormone replacement therapy
HT	Hormone therapy
IGFBP	IGF binding protein
IGF-1	Insulin-like growth factor-1
IL	Interleukin
JAK	Janus kinase
LSTM	Derived lean soft tissue mass
MEK	Mitogen-activated protein kinase kinase
MRI	Magnetic resonance imaging
RAS	Renin-angiotensin system
SHBG	Sex hormone binding globulin
SMM	Skeletal muscle mass
SOC-2	Suppression of Cytokine signaling-2
TNF-α	Tumor of necrosis factor-α

90.1 Introduction

The muscle pertains to a complex mechanobiological system that primarily enables efficient locomotion but is also involved in other vital physiological functions (Sievanen 2005).

Principal hormones and muscle and bone tissue have coexisted from the very beginning of the evolution of the present forms of complex life. Over millions of years, these three physiological modules have embodied in such a universal biological protocol that is fit and efficient for all foreseen locomotive and physiological demands that may occur in various forms of life. The muscle is an example of this evolutionary process, as it provides the body not only with a practical locomotive apparatus and protection for internal organs, but also with a reservoir for amino acids needed for physiological functions – several vital functions integrated within a single organ (Sievanen 2005).

Aging is accompanied by progressive reduction in muscle mass (sarcopenia) (Pierine 2010; Data from our laboratory – Fig. 90.1). Sarcopenia is a progressive process that occurs in healthy individuals.

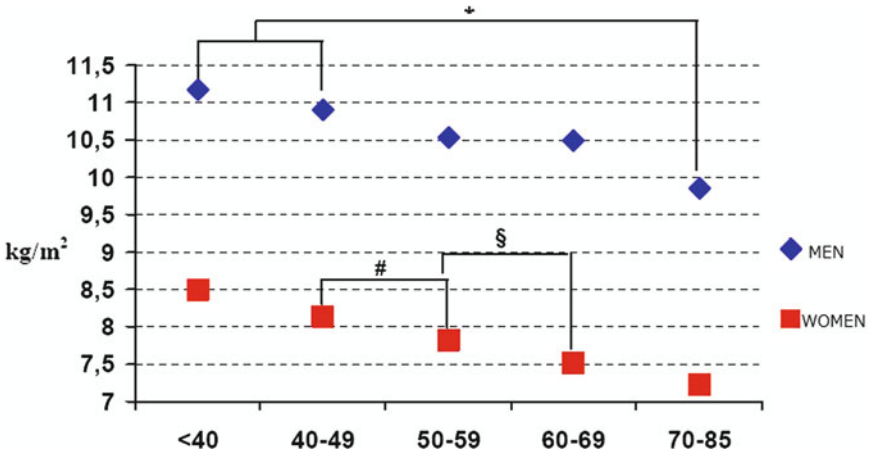

Fig. 90.1 Average of muscle mass index (kg/m^2) according to gender and age. * = $P < 0.001$, # = $P < 0.01$ and § = $P < 0.03$. $n = 734$ (170 men and 564 women)

It is usually associated with functional impairment and physical disability, especially in women, and is the direct cause of reduction in muscle strength. It is widely accepted that the age-related loss of muscle mass has a significant detrimental impact on motor performance in old age. Muscle performance is an important determinant of functional capacity and quality of life among elderly women, and is also involved in the maintenance of balance. Age-related changes in muscle and bone are likely to contribute to an increased risk of falls, an important source of death and injury in elderly people. Therefore, the maintenance of good muscle strength in aging women can prevent fragility fractures and lessen the burden of osteoporosis. The growing population of elderly citizens and the age-related motor handicap have enormous socioeconomic effects on the modern healthcare system (Sirola and Rikkonen 2005).

90.2 Relationship Between Muscle Mass and Hormones in Postmenopausal Women

Several factors such as diet, lifestyle, and metabolic and hormonal parameters influence body composition in postmenopausal women. Menopause may induce a phase of rapid decreases in aerobic fitness, muscle strength, and balance, especially in sedentary women. Muscle mass and strength start declining over the perimenopausal years, and this phenomenon seems to be partly hormone dependent (Figs. 90.2 and 90.4a).

The role of estrogen in sarcopenia remains unclear (Sirola and Rikkonen 2005). Theoretically, estrogen has a direct anabolic action on skeletal muscle that contains estrogenic receptors. However, this effect may also be mediated through the conversion of estrogens into testosterone. Thus, both may inhibit the production of catabolic cytokines (interleukins-1 and -6 and TNF), suggesting that the loss of these hormones at menopause has direct or indirect effects on muscles (Kamel et al. 2002) (Figs. 90.2 and 90.4).

Epidemiological and interventional studies suggest that estrogens prevent the loss of muscle mass. (Greising et al. 2009) accomplished a systematic review and meta-analysis of the research literature (23 relevant studies were found) that compared muscle strength in postmenopausal women, who were or were not on estrogen-based hormone therapy (HT). They concluded that overall, estrogen-based treatments were found to beneficially affect strength.

Conversely, none of five recent clinical trials reported an increase in muscle mass after hormone replacement therapy (HRT) (Jacobsen et al. 2007). Estrogens increase the level of the sex hormone binding protein, which reduces the level of serum free testosterone (Gower and Nyman 2000); thus, HRT should decrease rather than increase muscle mass. The increase in sex hormone binding globulin (SHBG) with age results in lower levels of free or bioavailable testosterone (Morley et al. 1997) (Fig. 90.2).

Estrogen and tibolone increase muscle strength, but only tibolone appears to increase lean body mass and decrease total fat mass (Jacobsen et al. 2007). Tibolone is a synthetic steroid with estrogenic, androgenic, and progesterogenic activity. HRT and tibolone may both react with the intranuclear receptor in the muscle fibers (Wiik et al. 2005), and tibolone may also act by binding androgen receptors in the muscle fibers and increase free testosterone and growth hormone.

Total testosterone decreases by 1% per year and bioavailable testosterone by 2% per year from the age of 30 years onward in males. In women, testosterone levels decrease rapidly from age 20 to 45 years (Morley and Perry 2003). Epidemiological studies suggest a relationship between low levels of testosterone and loss of muscle mass, strength, and function (Rolland et al. 2008).

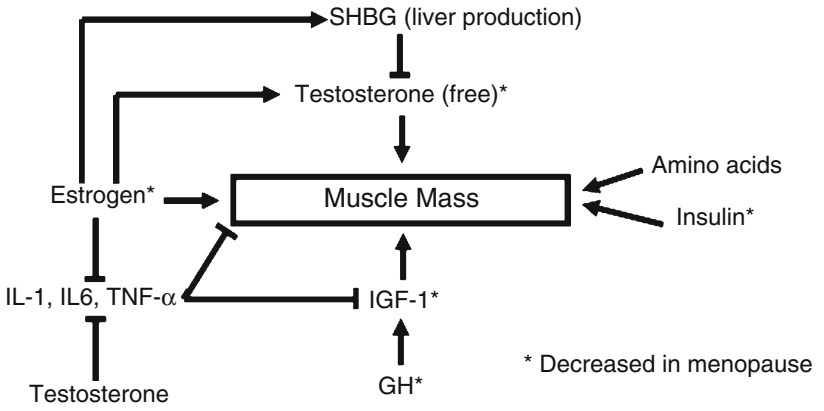

Fig. 90.2 The summary of the hormonal control of the muscular mass. *SHBG* sex hormone binding globulin; *IGF-1* insulin-like growth factor-1; *GH* growth hormone; *IL* interleukin; *TNF-α* tumor necrosis factor-α

Table 90.1 The relationships between muscle strength, muscle mass, and serum hormone concentrations in 37 postmenopausal women

	Muscle strength–leg extension (kg)
Muscle mass (kg)	0.72*
Cortisol (μg/dl)	–0.05
DHEA (μg/dl)	0.36*
Testosterone total (ng/dl)	0.40*

DHEA Dehydroepiandrosterone, * = $P < 0.05$

We observed positive correlation between serum DHEA and testosterone total and leg press strength in 37 postmenopausal women (Table 90.1, data not published). Clinical and experimental studies support the hypothesis that a low testosterone level predicts sarcopenia, resulting in lower protein synthesis and a loss of muscle mass (Galvao et al. 2007).

On the other hand, in the elderly, some interventional studies report a modest increase in lean mass and most report no increase in strength (Borst 2004). Besides, testosterone increases muscle mass and strength by stimulating satellite cell production (Bhasin et al. 2003). In postmenopausal women, testosterone increases muscle mass (Morley and Perry 2003). In supraphysiological doses, testosterone increases muscle mass and strength in young subjects under resistance training (Borst 2004).

Progressive strength training not only in young and middle-aged adults but also in older men and women can lead to substantial increases in muscle mass and strength performance. Heavy resistance exercise is well known to be a potent stimulus for acute increases in circulating anabolic hormones in younger men. In women, the acute response in serum testosterone is lower than in men, whereas no response at all is necessarily observed in older women (Orsatti et al. 2008).

Hakkinen et al. (2001) showed that individual concentrations of serum free testosterone correlated with the individual averaged total CSA of the QF muscle before the training ($r = 0.69$, $P < 0.05$) and after the 21-week training period ($r = 0.65$, $P < 0.05$). The individual concentrations of serum free testosterone correlated with the individual muscle fiber areas of type II before the training ($r = 0.86$, $P < 0.001$) and after the 21-week training period ($r = 0.79$, P, 0.01). The individual mean concentrations (averaged over the 21-week period) of serum testosterone correlated with the changes in the CSA of QF muscle over the 21-week training ($r = 0.64$, $P < 0.05$). The data showed that the individual gains in the CSA of the trained muscles were minor in those older women who demonstrated lower basal

Table 90.2 The relationships between individual changes in serum hormones concentrations (Δ%) and the individual changes in muscle mass (Δ%) during the 4-month resistance training in 21 postmenopausal women

	Muscle mass, kg (Δ%)
Cortisol, μg/dl (Δ%)	–0.09
Testosterone, ng/dl (Δ%)	0.49*
DHEA, μg/dl (Δ%)	0.55*
Estradiol, pg/ml (Δ%)	0.03

Corrected for age and time of menopause; Δ = variation between the final and initial moments, *DHEA* dehydroepiandrosterone, * = $P < 0.05$

Table 90.3 The relationships between serum hormones concentrations in 86 postmenopausal women

	DHEA, μg/dl
Cortisol, μg/dl	0.04
Testosterone, ng/dl	0.08
IGF-1, ng/dl	0.31*
Estradiol, pg/ml	–0.10

DHEA Dehydroepiandrosterone; *IGF-1* Insulin-like growth factor-1; * = $P < 0.05$

testosterone concentrations compared with those with higher testosterone concentrations ($r = 0.64$, $P < 0.05$). The findings strengthen the suggestion that basal concentrations of blood testosterone may be of great importance; even so, a low level of testosterone may be a limiting factor in older women, for both strength development and overall training-induced muscle hypertrophy, when typical total body heavy resistance training programs are taken into account. In this study, only the serum levels of testosterone were measured. It is possible that, even though the blood testosterone levels would remain unaltered, strength training can induce changes, for example, at the receptor level. In our studies, we observed relationships between individual changes in serum total testosterone and DHEA (dehydroepiandrosterone) concentrations (Δ%) and the individual changes in muscle mass (Δ%) during the 4-month resistance training in 21 postmenopausal women (Table 90.2, data not published).

Dehydroepiandrosterone (DHEA) levels decline steeply with aging, and lower levels are associated with low muscle mass and strength in postmenopausal women (Haren et al. 2007). Despite evidence that DHEA supplementation results in an increase of blood testosterone levels in women and increase of IGF-1 in men, few studies have reported an effect in muscle size, strength, or function (Percheron et al. 2003). We also observed positive correlation between serum DHEA and IGF-1 in 86 postmenopausal women (Table 90.3, data not published).

Insulin stimulates skeletal muscle protein synthesis. The weight gain that frequently occurs during middle age results in a decline of the anabolic action of insulin, potentially predisposing to muscle loss, but the presence of amino acids, especially for high intakes, may stimulate the anabolic effect of insulin (Rasmussen and Phillips 2003).

Insulin-like growth factor-1 (IGF-1) and growth hormone (GH) decline with age. GH replacement therapy lowers fat mass and increases lean body mass (Rolland et al. 2008). The aging muscle is capable of synthesizing IGF-1, but it may be less sensitive to IGF-1 and could have an attenuated ability to synthesize an isoform of IGF-1, promoting satellite cell proliferation. Exercise may reverse the resistance of aging muscle to IGF-1 (Clavel et al. 2006).

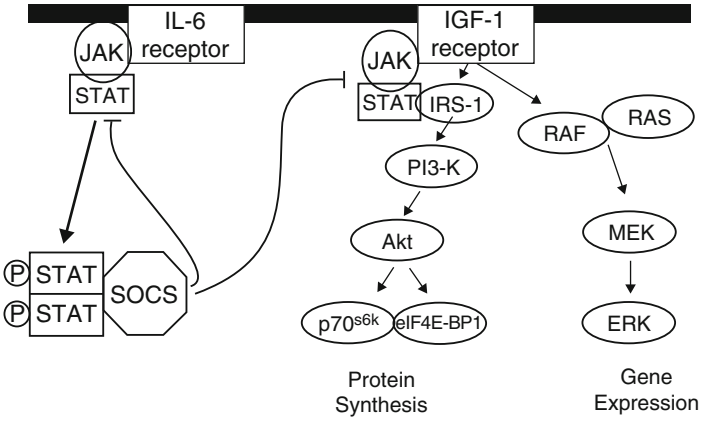

Fig. 90.3 Potential interactions of signaling elements serving the IL-6 and insulin-like growth factor (IGF)-I receptors. *MEK* mitogen-activated protein kinase kinase; *JAK* Janus kinase; *RAS* renin–angiotensin system; *SOCS* suppressors of cytokine signaling

IGF-1 activates satellite cell proliferation and differentiation and increases protein synthesis in existing fibers (Musaro et al. 1999). There is evidence that IGF-1 acts on muscle tissue by interacting with androgens (Chen et al. 2005). Former sedentary postmenopausal women submitted to resistance training for 16 weeks gained on average 1.8 kg of muscle mass, which was positively associated with the increase in plasma IGF-1 ($r = 0{,}45$, $P < 0.05$) (Orsatti et al. 2008). In addition, there is a negative correlation between the individual serum IGF-1 initial and individual change in IGF-1 (delta %) in RT ($r = -0.62$). These data indicated the possibility that women who demonstrated low basal IGF-1 levels were more sensitive at resistance training. Several IGF binding proteins (IGFBP) have been described, but it seems that only IGFBP-5 is reported to be an important modulator of myogenesis (Cobb et al. 2004).

In a study among obese postmenopausal women, the administration of GH alone or in combination with IGF-1 caused a greater increase in fat-free mass and a greater reduction in fat-mass than that achieved by diet and exercise alone (Thompson et al. 1998). In the elderly, most studies report that GH supplementation does not increase muscle mass or strength (Borst 2004). GH increases mortality in ill, malnourished persons, and potential serious and frequent side effects, such as arthralgia, edema, cardiovascular side effects, and insulin resistance occur with GH supplementation (Blackman et al. 2002).

There is some evidence that increased fat mass and reduced circulating levels of sex hormones with aging contribute to the age-related increase in pro-inflammatory cytokines that contribute to catabolic stimulation (Janssen et al. 2004). Epidemiological studies suggest that, as estrogen levels decline with age, there is an increase in the levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6 (IL-6), suspected to be involved in the sarcopenia process (Kramer et al. 2004).

Studies have reported an association between measures of muscle strength and muscle mass and blood levels of TNF-α, IL-6, and C-reactive protein (CRP). High levels of IL-6 and CRP were associated with an increased risk for loss of muscle strength (Schaap et al. 2006) (Fig. 90.2). These cytokines cause an imbalance in muscle tissue synthesis in favor of excess protein breakdown. A chronic elevation in inflammatory cytokines or other pro-inflammatory proteins could result in predisposition to sarcopenia (Roubenoff and Hughes 2000).

High levels of cytokines may also result in loss of muscle mass through increased activation of the ubiquitin–protease pathway and lower production of IGF-1. TNF-α stimulates muscle loss through the activation of the apoptosis pathway. Recent research has demonstrated that intracellular signaling components associated with several pro-inflammatory cytokines have the potential to interact with signaling pathways that regulate anabolic processes in skeletal muscle (Adams 2010) (Figs. 90.3, 90.4B).

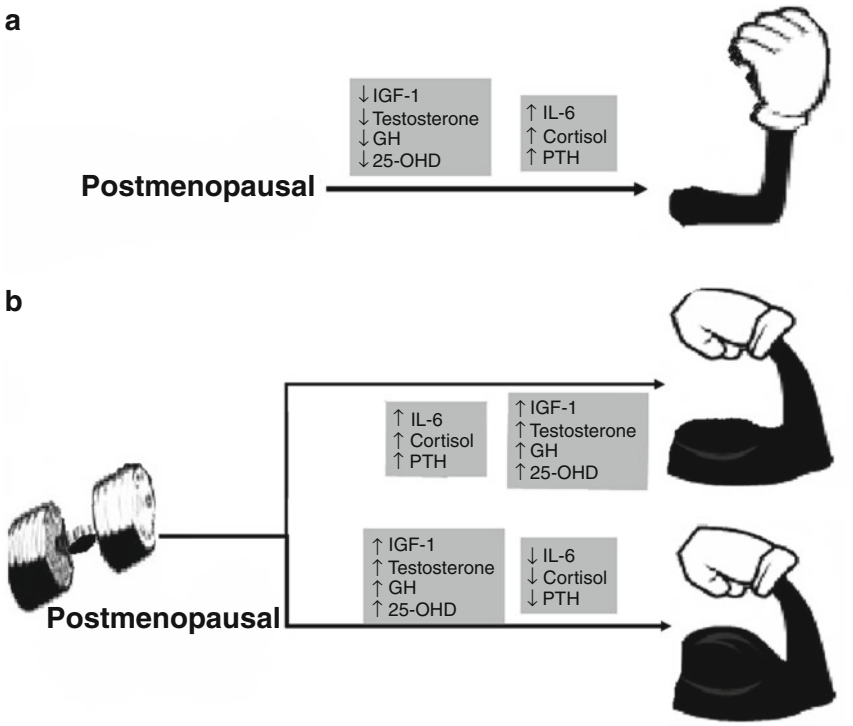

Fig. 90.4 (**a**) Hormone and muscular mass during aging. (**b**) Association between plasma hormones and anthropometric measures of muscle mass during resistance training in postmenopausal women. *GH* Growth hormone; *IGF-1* Insulin-like growth factor-1; *IL* interleukin; *TNF-α* tumor necrosis factor-α

IL-6 signaling may inhibit IGF-I signaling via increased SOCS (suppressors of cytokine signaling). Treatment with IL-6 has been reported to reduce the interaction between IRS-1 and PI3K in skeletal muscle. In addition, IL-6- induced increase in the expression of SOCS1 or SOCS3 can result in ubiquitin-mediated degradation of IRS-1 (Adams 2010) (Fig. 90.3).

GH is able to induce IGF-1 mRNA production and increased suppression of cytokine signaling-2 (SOC-2) in myoblast cell experimentation studies. SOC-2 has been reported to be a major modulator of GH action. It is a cytokine-inducible protein that inhibits cytokine production through a negative feedback mechanism (Leroith and Nissley 2005).

Chronic medical conditions, such as chronic obstructive pulmonary disease (COPD), heart failure, and cancer are associated with an increased serum level of pro-inflammatory cytokines and loss of body weight, including lean mass. This condition can occur in younger adults or elderly persons and is called cachexia. This acute hypercatabolism differs from the long-term age-related process that leads to sarcopenia. However, aging is also associated with a more gradual, chronic, increased production of pro-inflammatory cytokines, particularly IL-6 and IL-1, by peripheral blood mononuclear cells (Roubenoff et al. 1998).

The Longitudinal Aging Study has shown that lower 25-hydroxyvitamin D (25-OHD) and higher PTH levels increase the risk of sarcopenia in older men and women (Visser et al. 2003).

Cross-sectional studies have shown that low 1,25-hydroxyvitamin D and low 25-OHD are related to lower muscle strength, increased body sway, falls, and disability in older men and women. Vitamin D metabolites can influence muscle cell metabolism in three ways: by mediating gene transcription, through using rapid pathways not involving DNA synthesis, and by the allelic variant of the vitamin D receptor (Janssen et al. 2002).

Levels of parathyroid hormone (PTH) increase with age. PTH may also have a direct effect on skeletal muscle because its administration has been shown to impair production, transfer, and utilization of energy in skeletal muscle of rats (Baczynski et al. 1985), and it influences skeletal muscle protein and amino acid metabolism in rats (Garber 1983). PTH is also known to increase free intracellular calcium concentrations in muscle tissue (Begum et al. 1992), which may disrupt muscle structure or function. An indirect effect can also be hypothesized. The hormone is known to induce the production of IL-6 and IL-6sR in rat liver and increase circulating levels of these cytokines in vivo (Mitnick et al. 2001).

90.3 Applications to Other Areas of Health and Disease

Muscle plays a central role in whole body protein metabolism by serving as the principal reservoir for amino acids to maintain protein synthesis in vital tissues and organs, in the absence of amino acid absorption from the gut, and by providing hepatic gluconeogenic precursors. Furthermore, altered muscle metabolism plays a key role in the genesis, and, therefore, the prevention, of many common pathologic conditions and chronic diseases. Hence, it is important for nutritional, exercise, and metabolic areas.

90.4 Perspectives

As sarcopenia affects an increasing amount of the menopausal women, the importance of developing strategies for its prevention grows. The mechanisms behind this condition are complex and involve a variety of factors. To obtain efficient and practical methods of treatment for menopause, a better understanding of the interaction between factors, such as exercise, hormonal secretion, and inflammation, is necessary.

Summary Points

- Sarcopenia (reduce muscle mass) is usually associated with functional impairment and physical disability, especially in women, and is the direct cause of reduction in muscle strength. This decline starts during the perimenopausal years and seems to be partly estrogen dependent.
- On the other hand, estrogens increase the level of the sex hormone binding protein, which reduces the level of serum free testosterone. The increase in sex hormone binding globulin (SHBG) with age results in lower levels of free or bioavailable testosterone, decreasing muscle mass.
- In women, testosterone levels decrease rapidly from age 20 to 45 years. Clinical and experimental studies support the hypothesis that a low testosterone level predicts sarcopenia, resulting in lower protein synthesis and a loss of muscle mass.
- Insulin-like growth factor-1 (IGF-1) declines with age. IGF-1 activates satellite cell proliferation and differentiation and increases protein synthesis in existing fibers. The aging muscle is capable of synthesizing IGF-1, but it may be less sensitive to IGF-1 and could have an attenuated ability to synthesize an isoform of IGF-1.
- Epidemiological studies suggest that, as estrogen declines with age, there is an increase in the level of pro-inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6 (IL-6), suspected to be involved in the sarcopenia process. High levels of cytokines result in a loss of muscle mass and decreased performance.

Key Features

Table 90.4 Key points

1. It is widely accepted that the aging-related loss of muscle mass, strength, and quality has a significant detrimental impact on motor performance in old age, especially in women, and on the ability to recover from falls, resulting in an increased risk of fractures and dependency.
2. A number of factors have been implicated in the pathogenesis of sarcopenia, including hormonal decline (both reproductive hormones and the hypothalamic-GH-insulin like growth factor-I axis) and low-grade systemic inflammation.
3. Thus, the aging-related motor handicap and the growing population of elderly citizens have enormous socioeconomic effects on the healthcare system.

Table 90.5 Key facts

1. The steroidal hormones estrogen and androgen have anabolic effects on muscle mass.
2. The steroidal hormone cortisol has catabolic effects on human muscle mass.
3. Dehydroepiandrosterone (DHEA) is a steroidal precursor of androgens and estrogen.
4. DHEA, androgens, and estrogens decrease upon aging.
5. Cortisol increases with age.

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Chapter 91
Anthropometric Measurements in Adults and Elderly: Cuban Perspectives

Aline Rodrigues Barbosa and Raildo da Silva Coqueiro

Abstract Despite the economic crisis in Cuba over the last few decades, the government has sought to ensure social equality as a development strategy on the basis of universality and free access to social services, health included. Anthropometric measurements are associated with health status and socioeconomic conditions in population groups, as they reflect the exposition to deprivation or excessive food, insufficient physical activity, and occurrence of diseases. This chapter presents and discusses information about anthropometric characteristics of adult and elderly (inclusive centenarian) Cuban individuals. According to the analyzed studies, between 1982 and 2001, there was a reduction in the prevalence of underweight and an increase of overweight/obesity in adults aged 20–59 years. In adult and elderly subjects, the greatest prevalence of underweight is observed in men and overweight/obesity in women. Around the age of 70, there is a reduction in muscle mass and fat mass, which is more prevalent among women and the oldest age groups. The elderly of Cuba have different anthropometric characteristics than those of other cities of Latin America and developed countries. Among centenarians, values for BMI and arm and calf circumferences were greater for men. A significant number of Cuban individuals, independent of age group and sex, present vulnerable nutritional status, in view of the high prevalence of underweight and overweight/obesity. Data from these studies may be used for surveillance and for planning actions that intend to prevent or improve nutritional inadequacy in the Cuban population.

Abbreviations

AAFP	American Academy of Family Physicians
AC	Arm circumference
AMC	Arm muscle circumference
BM	Body mass
BMI	Body mass index
CC	Calf circumference
Infomed	Centro Nacional de Información de Ciencias Médicas
PAHO	Pan-American Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_91,

SABE Survey on Health, Aging and Well being in Latin America and the Caribbean
TSF Triceps skinfold thickness
WHO World Health Organization
WC Waist circumference

91.1 Introduction

The Republic of Cuba, with Havana as its capital city, is an archipelago with a land area of 110,860 kg/m^2 located in the entrance of the Gulf of Mexico, in the Caribbean Sea. The country has the most advanced demographic transition in Latin America and the Caribbean. Its population in 2007 was 11,265,000, out of which 18.7% were aged 60 years and older and 17.5% were younger than 15 years of age (Pan-American Health Organization [PAHO] 2008).

This "premature" aging has direct consequences on changes in the socioeconomic structure, and, more specifically, on matters related to health and disease standards among the population. A reduction in morbidity–mortality due to infectious diseases can be observed, as well as an increase in the prevalence of non-transmittable diseases and injuries (Fraga 2006).

Politics in this country have maintained social equality goals as a development strategy, based on universality and free availability of social services, including health. Basic levels for food and goods of primary necessity are assured, and vulnerable groups receive special treatment (PAHO 2008).

It is widely known that Cuba suffers a strong and long-lasting economic embargo by USA and its allies since 1961, shortly after the Cuban Revolution. However, severe sanctions, in response to the issuing of the Cuban Democracy Act in the early 1990s – when the country could no longer rely on the support of the socialist bloc due to the collapse of the Soviet Union – were to cause one of the worst economic crises ever experienced by the Cuban population. The result was an abrupt reduction of foreign trade, as well as a decline in the availability of fuel, raw material, and other essential goods, such as food and medication (Porrata et al. 2000; Jímenez 2003; Yudkin et al. 2008).

The effects of the economic crisis over public health in Cuba have been documented in the literature; they include a decline in nutritional levels and a rise in infectious disease and total mortality rates (Rodríguez-Ojea et al. 2002). The policy of preferential access to essential goods for children and for women of childbearing age became an example throughout the world, but resulted in the creation of other vulnerable groups. One of the most affected was the elderly individual group (Porrata et al. 2000).

Due to the social and economic context of the past decade in Cuba, the health aspects of the population have drawn the attention of the international scientific community (Barceló et al. 2006; Yudkin et al. 2008). Population data from Cuba provide a unique opportunity to examine the health conditions of a population under the effects of the longest economic embargo in modern history. Furthermore, they can help evaluate the capability of a health system, which, despite political and economic adversities, allows universal access (Garfield and Santana 1997).

Anthropometric measurements and indices are related to health status and socioeconomic conditions in population groups as they reflect the exposure to deprivation or excessive food, insufficient physical activity, and occurrence of diseases (World Health Organization [WHO] 1995).

Anthropometric information on Cuban individuals is still not well known. According to information from the WHO Global InfoBase (2008), between 1982 and 2002, three national studies were carried out (1982, 1995, and 2002) involving Cuban adults. Recently, anthropometric data on elderly individuals from Havana (Coqueiro et al. 2009) and on centenarians living in a province in Central Cuba

Table 91.1 Anthropometric studies in Cuban

References	Data from	Year data collected	Sex	n	Age	Parameters
Berdasco (1994)	National Survey	1982	M F	11,912 19,750	20–29, 30–39, 40–49, 50–59 y	BMI category (kg/m^2) < 18.5 (underweight); 25.0–30.0 (overweight); ≥ 30.0 (obesity)
Acosta Jiménez et al. (2002)	National Survey	2001	M and F	19,519	20–29, 30–39, 40–49, 50–59, and ≥ 60 years	BMI category (kg/m^2) < 18.5 (underweight); 25.0–30.0 (overweight); ≥ 30.0 (obesity). Waist circumference.
Coqueiro (2008)	Havana (SABE Survey)	2000/2001	M F	708 1195	≥ 60 years	BMI category (kg/m^2) < 22 (underweight); > 27 (overweight)
Coqueiro et al. (2009)	Havana (SABE Survey)	2000/2001	M F	708 1195	60–64, 65–69, 70–74, 75–79 and ≥ 80 years	Body mass; height; BMI; arm, calf and waist circumference; arm muscle circumference; and triceps skinfold thickness. (mean, standard deviation, percentiles)
Prado Martinez et al. (2009)	Villa Clara	1996/1997	M F	76 49	≥ 100 years	BMI category (kg/m^2) <18.5 (underweight); 25.0–30.0 (overweight); ≥30.0 (obesity)

This table lists the studies analyzed in this chapter, including location, year of collection, sex and number of participants (*n*), and age group and anthropometric variables
M male; *F* female; *BMI* body mass index; *SABE* Survey on Health and Well-Being of the Elderly

(Prado Martinez et al. 2009) were published. This chapter presents and discusses information about the anthropometric characteristics of adult and elderly Cuban individuals. The analysis is limited to population studies that were published in the last 2 decades and are available online (Table 91.1).

91.2 Overview of Anthropometry

Anthropometry is a noninvasive method used to evaluate size, proportions, and body composition (bone, muscle and adipose tissue). The relevance of anthropometric measurements and indices, in all life cycles, has lately been reinforced, as they relate with the health status and socioeconomic conditions of individuals and/or population. As body dimensions in all ages reflect the general health and welfare conditions of individuals and populations, anthropometry can also be used to predict performances, health, and survival (WHO 1995).

The use of anthropometry helps characterize the nutritional status that expresses the degree by which physiological needs for nutrients are being met, maintaining adequate body composition and functions. This means that the type and amount of food ingested, the energetic needs of the body, and the efficiency of the biological use of nutrients should all be balanced (Kuczmarski et al. 2005). Whenever a factor interferes in any step of this process, risks of nutritional inadequacy are imminent.

Changes in nutritional status, either by malnutrition or by excessive food, contribute to an increase of morbidity–mortality in individuals of all ages, especially in the elderly (WHO 1995).

Adult individuals (20–59 years of age) represent that proportion of the population that is related, almost totally, with the capability of production and services upon which individuals in the phase of growth (under 20 years of age) depend. This makes nutritional/anthropometric evaluations in this group relevant for any population, in both developed and developing countries (Berdasco 2002).

Elderly persons are rather susceptible to nutritional problems, mainly due to factors concerning physiological alterations, social conditions, occurrence of chronic diseases, use of several medications, problems with food intake (chewing and swallowing), depression, and alterations in mobility with functional dependence (Kuczmarski et al. 2005).

Moreover, with advancing age, alterations can be observed in body composition, which can be assessed by anthropometric measurements. After 20–30 years of age, relative body fat seems to increase until around the age of 70 years, when it starts to reduce (WHO 1995). Even when the percentage of body fat remains constant, intra-abdominal fat tends to increase, whereas subcutaneous fat tends to decrease. Concomitantly to the increase in body fat, after 20–30 years of age, fat-free mass progressively decreases. The fat-free mass peak is reached around the age of 20 years, and it reduces by up to 40%, primarily in the skeletal muscle, from 20 to 70 years of age, growing in intensity from that age onward (Hughes et al. 2004; Santos et al. 2004; Barbosa et al. 2005).

91.3 Adults

91.3.1 Body Mass Index Category

In adult individuals of all ages, the body mass index (BMI), obtained through the division of body mass (BM) by height [BMI = BM (kg)/height $(m)^2$], is the most commonly used indicator for identifying subjects at risk of being underweight and overweight. This anthropometric indicator can be applied to large population groups and in clinical practice because of its ease of attainment and interpretation, low cost, and little inter- and intra-evaluator variation.

In Cuba, two national surveys carried out in 1982 (Berdasco 1994) and 2001 (Acosta Jiménez et al. 2005) presented BMI data from adult individuals. The 1982 survey measured height and weight in 31,662 adults (20–59 years of age), out of whom 11,912 were men and 19,750 were women. The Second National Survey on Risk Factors and Chronic Diseases, conducted in 2001 (Acosta Jiménez et al. 2005), presented data from 22,851 subjects aged 15 years and older, 19,519 of them being adults (over 20 years of age). The prevalence of underweight (BMI < 18.5 kg/m^2) and overweight/obesity (BMI ≥ 25 kg/m^2) was available from each survey.

Comparing data from both national surveys performed in Cuba, in 1982 and 2001, it can be observed that the Cuban population faced a challenge (Figs. 91.1 and 91.2, for women and men, respectively). In 1982 (Berdasco 1994), underweight was higher than 11% in all age groups, in both genders, and was greater in the youngest age group (20–29 years). In 2001 (Acosta Jiménez et al. 2005), the prevalence of underweight was nearly half of that of 1982.

In women, the subsequent shift to lower BMI categories resulted in increases by 16.2, 8.5, 7.6, and 2.4 percentage points in the normal weight category (BMI > 18.5 and < 25 kg/m^2) for age groups 20–29 years, 30–39 years, 40–49 years, and 50–59 years, respectively. In men, the alterations resulted in an increase of overweight/obesity by 8.7, 8, 2.9, and 10.2 percentage points for the same age groups. In both surveys, overweight/obesity was most prevalent in women, in all age groups. However, although that prevalence remained similar in women, data from 2001 showed that men were more susceptible to overweight/obesity than women were.

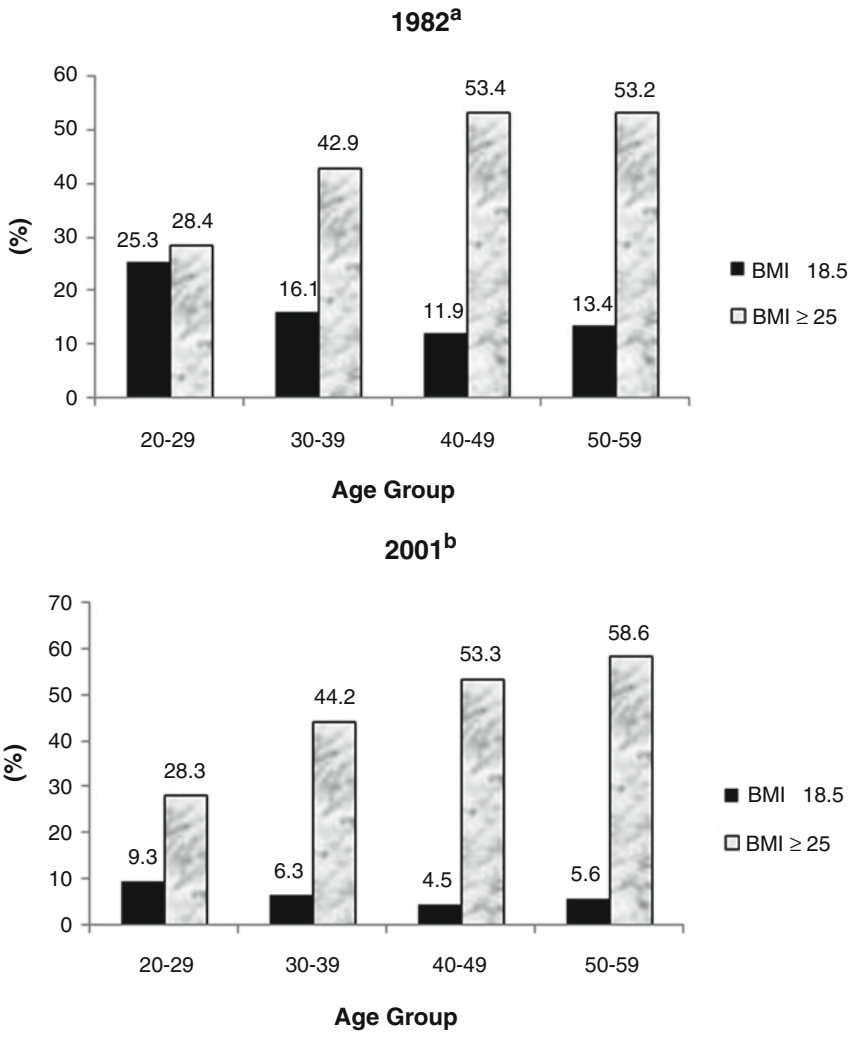

Fig. 91.1 Distributions of body mass index categories in women of Cuba, according to age group, in 1982 and 2001. In 2001, the prevalence of underweight was nearly half of that of 1982, in all age groups ([a]Adapted from Berdasco 1994. With permission; [b]Adapted from Acosta Jimènez et al. 2005. With permission)

Data from the study by Berdasco (1994) probably reflect the modifications since the 1960s, after the Cuban Revolution, which resulted in social changes. Furthermore, the implementation of a health policy led to progressive improvements in the health situation. The socialist nature of the revolution created a rationed distribution system that intended to allow equitable access to food (72% of the supply of energy and proteins), with regulated prices subsidized by the State. This phase lasted until 1989. During this period, there was greater meat and fat consumption and a decrease in the consumption of carbohydrates and fibers, as well as a decline in labor-intensive activities, which resulted in an increase of the number of people with overweight/obesity (Porrata et al. 2000).

In 1989/1990, following the disintegration of the Soviet Union and the Eastern Europe socialist countries, Cuba was mired in a severe economic crisis. There was a 25% decrease in food availability *per capita* and a rise in non-labor physical activity (Jiménez 2003). These shifts in diet and physical activity had a great impact on the nutritional status of the population. Although there are no data

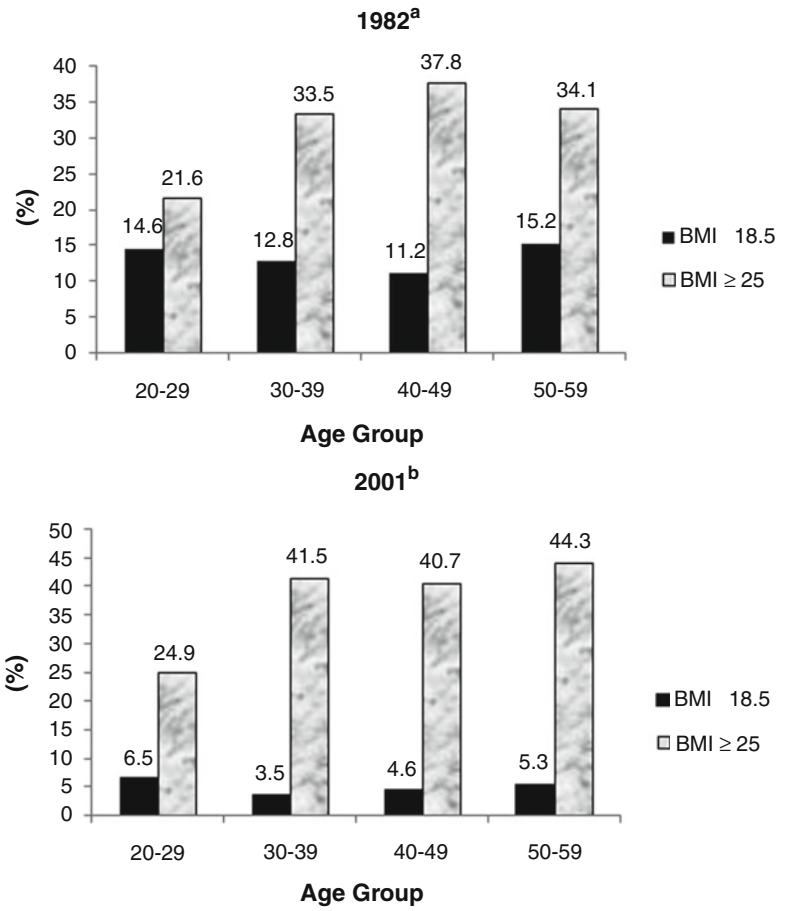

Fig. 91.2 Distributions of body mass index categories in men of Cuba, according to age group, in 1982 and 2001. The prevalence of underweight declined between 1982 and 2001, whereas the overweight/obesity BMI prevalence rates (BMI ≥ 25) grew ([a]Adapted from Berdasco 1994. With permission; [b]Adapted from Acosta Jimènez et al. 2005. With permission)

available online, according to Rodríguez-Ojea et al. (2002), between 1982 and 1994, there was an increase in the prevalence of underweight and normal BMI and a reduction in the number of individuals with overweight/obesity.

From 1996 to 1998, as the Cuban economy gradually recovered, there was an increase in food availability *per capita*, albeit still at lower levels than those observed in the 1980s (Jiménez 2003). Therefore, the data from the 2001 National Survey (Acosta Jiménez et al. 2005) reflect the recovery period, which is made evident by the reduction in the prevalence of underweight (approximately 50%) in men and women aged 20–59 years. Although women in all age groups present a greater frequency of BMI ≥ 25 kg/m^2, a comparison of data from 1982 and 2002 shows that men were more susceptible to overweight/obesity.

Data from the 2001 National Survey (Acosta Jiménez et al. 2005) showed that the prevalence of obesity (BMI ≥ 30 kg/m^2) grows with increasing age, up to 50–59 years, and affects 7.9% of men and 15.4% of women aged 20 years and older (Fig. 91.3).

When the data for Cuban residents were compared with data from another developing country, it was found that the prevalence of obesity was respectively smaller in Brazilian women (13%) and

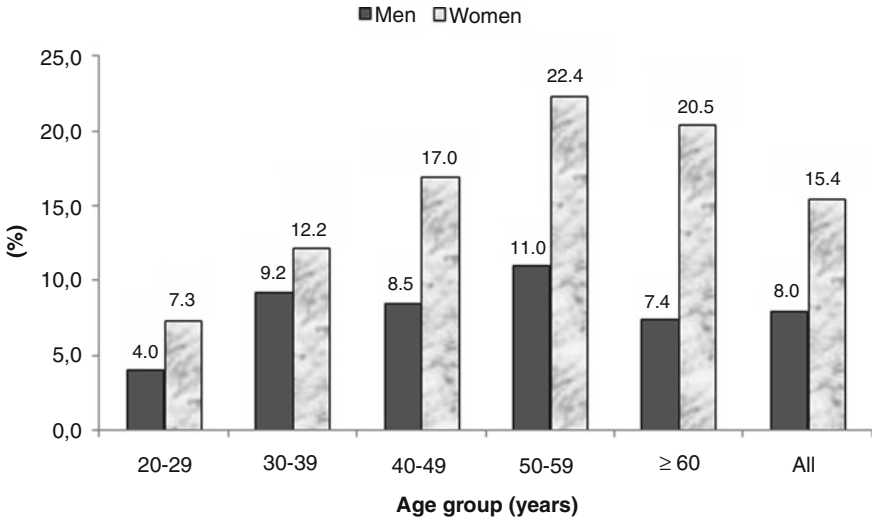

Fig. 91.3 Obesity prevalence rates (BMI ≥ 30), by age group, among men and women Cubans (2001). In men and women, obesity prevalence rates (BMI ≥ 30) grow with increasing age, up to 50–59 years (Reprinted from Acosta Jimènez et al. 2005. With permission)

greater in men (8.8%) (Monteiro et al. 2007). Similarly, between 1975 and 2003, Brazil found its increase in the rate of obesity to be greater in men (92% for males and 63% for females) in the first 14-year period examined (1975–1989). A further increase in obesity among men (70%) and among those in lower-income groups in the second period (1989–2003) was also observed.

Changes in the Cuban population's nutritional status, as a consequence of the collapse of the Eastern European countries and the Soviet Union, show that the reduction in food consumption and the increase in physical activity patterns had a positive impact on mortality trends. Conversely, the increase in the prevalence of overweight/obesity observed in 2002, which is due to undesirable changes in diet composition and reduction in physical activity levels, has important policy implications as it is associated with the increase of chronic disease risk. Thus, the promotion of a healthy diet and an active lifestyle is part of the program "Propositos, Objetivos y Metas para mejorar la salud de la población Cubana para el año 2010" (Rodríguez-Ojea et al. 2002).

91.4 Older Adults

91.4.1 Weight and Height

Height and body mass are routine measurements at health screenings, physical examinations, and nutritional assessments, and are affected by the aging process. An individual's weight can vary normally due to daily fluid retention or loss. In older persons, a weight loss ≥ 5% of the body weight in the last month or ≥ 10% in the last 6 months indicates an associated risk to a subsequent mortality (American Academy of Family Physicians [AAFP] 2002; Kuczmarski et al. 2005). Adult height is an indicator for the nutrition and health environment experienced in early life. Height changes with aging due to alterations in the skeletal integrity. BMI is an indicator frequently used to assess nutritional status in the elderly (WHO 1995).

Table 91.2 Body mass (BM), height, and body mass index (BMI) in women (≥60 years) (SABE Survey), Havana, Cuba, 2000 (Reprinted from Coqueiro et al. 2009. With permission)

Variable				Percentile						
Age group (years)	*n*	Mean	SD	5	10	25	50	75	90	95
Body mass (kg)‡										
60–64	234	64.95	13.84	45.00	49.00	55.78	63.50	73.00	83.00	89.00
65–69	217	62.97	14.81	41.90	45.00	52.08	62.17	71.00	81.00	85.30
70–74	213	59.19	12.30	38.00	43.22	51.00	58.10	68.00	75.00	78.72
75–79	181	56.72	12.51	37.00	40.00	47.00	57.50	65.00	71.00	78.15
≥80	197	53.19	11.56	35.12	37.90	44.58	52.50	60.95	68.36	73.00
Height (m)‡										
60–64	235	1.55	0.07	1.43	1.46	1.50	1.55	1.60	1.63	1.65
65–69	218	1.54	0.07	1.43	1.45	1.49	1.54	1.59	1.63	1.65
70–74	214	1.53	0.07	1.43	1.45	1.49	1.54	1.58	1.62	1.65
75–79	180	1.52	0.06	1.41	1.45	1.48	1.52	1.56	1.59	1.64
≥80	197	1.50	0.07	1.37	1.41	1.45	1.50	1.55	1.59	1.63
Body mass index (kg/m^2)‡										
60–64	234	27.23	5.59	17.84	20.17	23.28	26.51	30.77	34.21	36.82
65–69	217	26.57	6.12	17.45	18.83	22.68	26.24	29.79	33.07	37.65
70–74	213	25.15	4.89	17.29	18.86	21.45	25.36	28.29	31.12	32.98
75–79	180	24.53	5.11	16.04	17.45	20.61	24.44	27.80	31.22	33.13
≥80	196	23.58	4.84	16.07	18.08	20.36	23.31	26.35	29.36	32.44

All measurements were greater in younger groups, compared to older ones (‡$p = 0.000$; ANOVA)
SD standard deviation

The study carried out by Coqueiro et al. (2009) used data from the *Survey on Health, Aging and Well being in Latin America and the Caribbean* (SABE) (Pélaez et al. 2004) and analyzed anthropometric characteristics in 1,905 elderly individuals (≥60 years) from Havana, comprising 1,197 women and 708 men. Results have shown greater height values for men and younger age groups, according to what was expected. Women (Table 91.2) and men (Table 91.3) presented a difference of 5 cm in mean height between the 60–64-year age group and the oldest individuals (≥80 years) (Fig. 91.4).

The proportion of height reduction with increasing age is not yet well defined: values seem to vary from 0.5 cm to 3 cm per decade, after the age of 60 (WHO 1995; Perissinotto et al. 2002; Santos et al. 2004; Barbosa et al. 2005), more markedly in the oldest individuals and in women. Such alterations are consequences of vertebral compression, changes in intervertebral disk thickness and shape, loss of muscle tone, and posture changes and osteoporosis (WHO 1995).

As observed for height, data from Havana (Coqueiro et al. 2009) show that BM and BMI were greater in the youngest as compared with the oldest elderly (Tables 91.2 and 91.3, for women and men, respectively). The reduction in BM values, with increasing age, was stronger in women, as observed in other studies with elderly individuals in Latin America (Santos et al. 2004; Barbosa et al. 2005) and developed countries (WHO 1995; Perissinotto et al. 2002).

Usually, BM tends to reach a plateau around the age of 65 in men and 75 in women, when it begins to decrease. It is believed that reductions with increasing age are consequences of the loss of total body water and general cellular mass (WHO 1995; Hughes et al. 2004), not to mention the likely cohort effect and selection bias, due to institutionalization or premature death of persons with overweight or obesity.

Table 91.3 Body mass (BM), height, and body mass index (BMI) in men (≥60 years) (SABE Survey), Havana, Cuba, 2000 (Reprinted from Coqueiro et al. 2009. With permission)

Variable				Percentile						
Age group (years)	*n*	Mean	SD	5	10	25	50	75	90	95
Body mass (kg)‡										
60–64	195	68.78	12.05	49.80	52.64	59.90	68.10	77.20	86.00	90.18
65–69	148	65.02	12.56	46.45	49.00	55.03	64.00	74.25	82.65	89.10
70–74	109	63.04	11.84	43.50	49.00	55.00	64.00	70.65	77.50	83.00
75–79	85	60.74	14.69	40.00	44.00	49.00	58.00	72.50	80.20	87.80
≥80	95	59.26	10.48	43.40	45.60	52.50	59.00	65.50	72.56	79.60
Height (m)‡										
60–64	195	1.68	0.07	1.57	1.60	1.64	1.68	1.72	1.77	1.80
65–69	147	1.67	0.07	1.55	1.58	1.62	1.67	1.71	1.76	1.79
70–74	109	1.67	0.06	1.56	1.59	1.63	1.67	1.71	1.74	1.76
75–79	85	1.65	0.07	1.53	1.55	1.60	1.66	1.70	1.77	1.78
≥80	95	1.63	0.08	1.48	1.55	1.59	1.64	1.69	1.73	1.75
Body mass index (kg/m^2)‡										
60–64	195	24.35	4.04	17.70	18.77	21.27	24.57	26.97	29.35	31.46
65–69	147	23.32	4.16	16.61	18.11	20.26	23.08	25.80	28.65	30.45
70–74	109	22.70	3.98	16.52	17.80	20.49	22.41	25.42	27.59	29.39
75–79	85	22.20	5.09	15.26	16.31	17.97	21.33	25.75	29.15	32.08
≥80	94	22.20	3.76	16.45	17.29	19.92	21.82	24.18	27.96	29.17

All anthropometric variables showed decrease in mean values with increasing age (‡$p = 0.001$; ANOVA)
SD standard deviation

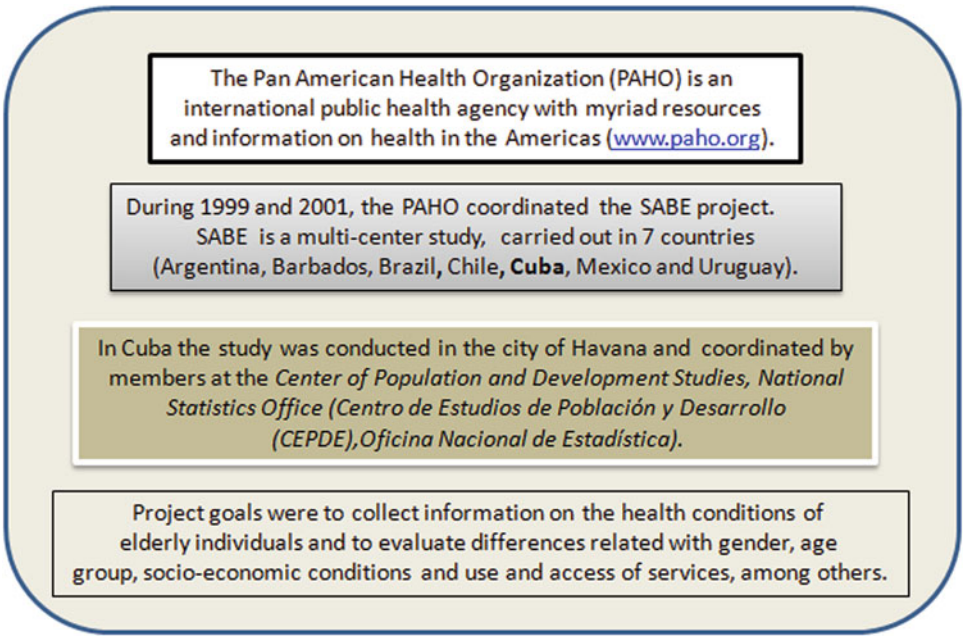

Fig. 91.4 Key features of Survey on Health, Aging and Well being in Latin America and the Caribbean (SABE). This table lists the key facts of the SABE survey including the participant countries, research coordination, and main goals

91.5 Body Mass Index

Among the elderly of Havana (Coqueiro et al. 2009), reductions in BMI values occurred after the ages of 65 and 70, for men (Table 91.3) and women (Table 91.2), respectively. Differently from Havana, recent studies have shown that significant declines in BMI seem to occur from the age of 75 in men and women (Kuczmarski et al. 2000; Perissinotto et al. 2002; Barbosa et al. 2005) (Table 91.4).

BMI values were lower for the elderly in Havana for both sexes and the same age groups as compared with results from other studies in Latin America (Santos et al. 2004; Barbosa et al. 2005). Differences were more expressive when data were compared with those of USA (Kuczmarski et al. 2000) and Italy (Perissinotto et al. 2002). In the study carried out by Acosta Jimènez et al. (2005), of elderly subjects (60 years and older) sampled nationally, the percentile distributions presented for BMI (Table 91.7) were slightly higher, from 1.0 to 0.2 points, compared to men and women from Havana (Coqueiro 2008).

Although a lower BMI provides evidence of less obesity among Cubans, it may be a sign of greater nutritional vulnerability. This concern becomes apparent in the classification of nutritional status (Figs. 91.5 and 91.6, for women and men, respectively). Results from Coqueiro (2008) have

Table 91.4 Key features of American Academy of Family Physicians (AAFP)

- The AAFP is one of the biggest health organizations in the USA, with over 94,600 members in 50 states (http://www.aafp.org).
- The AAFP, in a partnership with the American Dietetic Association and the National Council on Aging, developed the Nutrition Screening Initiative, a project that aims to promote good nutrition, working along with physicians, politicians, and population.
- The Nutrition Screening Initiative provides tools and recommendations for nutritional status evaluation and a guide to nutrition in chronic disease management for older adults.

This table lists key facts of the AAFP including partner organizations in the development of strategies for good nutrition in elderly adults

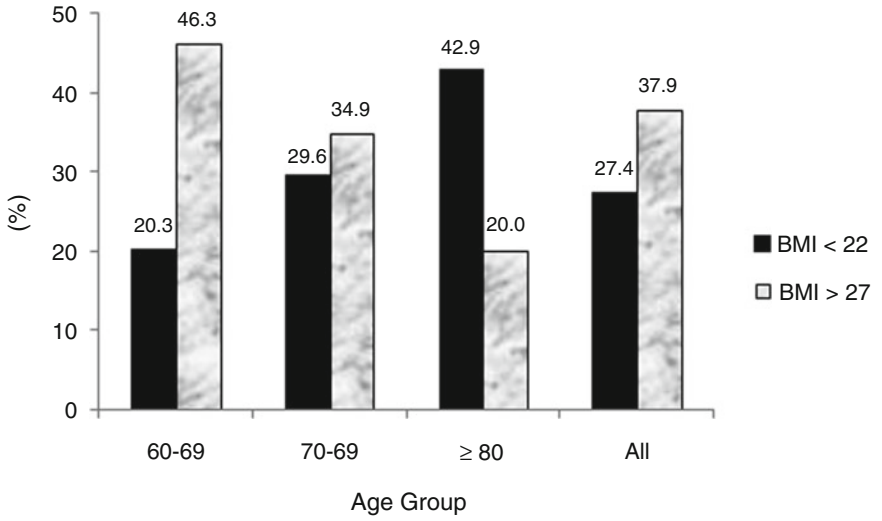

Fig. 91.5 Distributions of body mass index categories in elderly women of Havana, according to the age group (SABE Survey), Havana, Cuba, 2000. Overweight (BMI > 27 kg/m^2) is more frequent among the youngest age group (60–69 years) (Adapted from Coqueiro 2008. With permission)

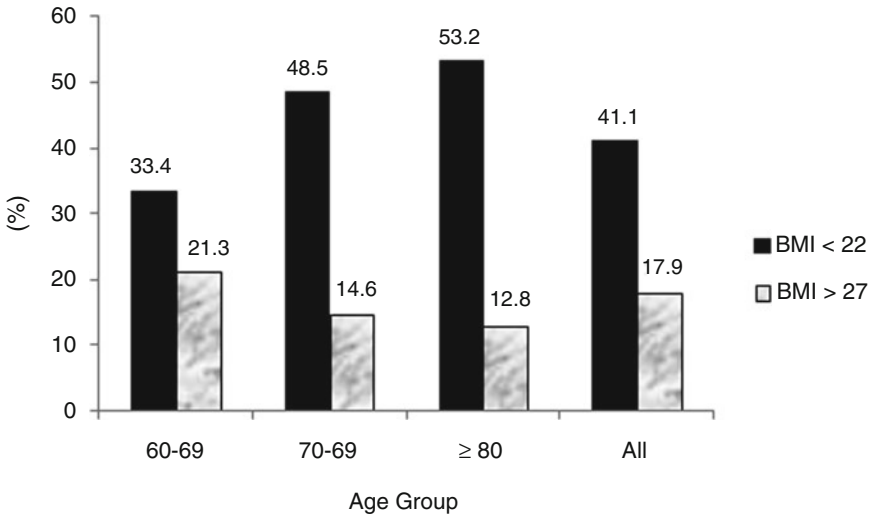

Fig. 91.6 Distributions of body mass index categories in elderly men of Havana, according to the age group (SABE Survey), Havana, Cuba, 2000. Underweight (BMI < 22 kg/m^2) is more prevalent among the oldest age group (≥80 years) (Adapted from Coqueiro 2008. With permission)

shown that underweight (BMI < 22 kg/m^2) and overweight (BMI > 27 kg/m^2) presented high proportions in the elderly of Havana. With increasing age, there is an increase in the number of underweight persons, with a greater prevalence for males, in all age groups, when compared to women. Overweight was most frequent in women, in all age groups.

When the results of Coqueiro (2008) are compared with those from researches that used the same cutoff points, it can be noted that Cuba was the country with the greatest prevalence of underweight. Prevalences of approximately 12% (according to the distribution of the reference curves) in Italy (Sergi et al. 2005) and 13.4% in the USA (Diehr et al. 1998) were observed.

Data from the elderly of the countries that took part in the SABE survey show that BMI < 22 kg/m^2 corresponds approximately to the 10th and 25th percentile, respectively, for women and men of São Paulo, Brazil (Barbosa et al. 2005). In Santiago, Chile, this value is closest to percentile 10, for both sexes (Santos et al. 2004). BMI > 27 kg/m^2 corresponds approximately to percentiles 50 and 75 for women and men of São Paulo, respectively (Barbosa et al. 2005), whereas in Santiago, this value is closest to percentile 50 for both sexes (Santos et al. 2004). This means that the prevalence is greater for underweight and lower for overweight among the Cuban elderly, when compared to the elderly individuals of other Latin American cities.

There is no consensus in literature about optimal values to classify underweight and overweight in older persons. WHO (2006) presents BMI values under 18.5 kg/m^2 as a sign of underweight and values over 24.9 kg/m^2 and from 30 kg/m^2 onward indicate overweight and obesity, respectively, for adults of all ages. However, it recommends that the values 23, 27.5, 32.5, and 37.5 kg/m^2 are to be used in public policies, making international comparisons easier.

The *Nutrition Screening Initiative* suggests BMI values < 22 kg/m^2 and > 27 kg/m^2 as indicative of underweight and overweight, respectively (AAFP et al. 2002). Sergi et al. (2005) have suggested that BMI ≤ 22 kg/m^2 should be adopted as a classification of individuals at risk. The PAHO (2001) has used the BMI value ≤ 23 kg/m^2 to classify underweight and values 28 ≤ BMI < 30 kg/m^2 and BMI ≥ 30 kg/m^2, respectively, for overweight and obesity.

It is known that any BMI value corresponds to more fat in the elderly body composition, when compared to the BMI in younger adults; this is probably due to the reduction of thin body mass, mainly muscle mass, with increasing age. This means that the application of the same classification used for adults may underestimate the prevalence of overweight in the older adults. Moreover, several studies show that, in elderly, the curves of mortality related to BMI differ from those observed in young and middle-aged adults, and point out different values for the classification of underweight and overweight. Independently of the cutoff point used, underweight and overweight are factors associated with morbidity–mortality in the elderly (Allison et al. 2002; Sergi et al. 2005).

Independently of the cutoff point used, the percentile BMI distribution values for the Cuban elderly indicate a nutritional risk for a large proportion of these individuals and an direct relationship between underweight and age.

Several factors can justify the greater underweight risk in the oldest age groups, such as smell and taste reduction, teeth and mouth problems, reductions in physical activity levels and a consequent reduction in nutrition and energy needs, social isolation, and functional dependence, which can discourage or complicate the preparation of food. Moreover, polypharmacy, which is frequent in the elderly, may result in nutritional disorders and harm nutrient absorption and use (Kuczmarski et al. 2005).

Underweight is associated with an increased risk of hospitalization and delay in illness recovery and higher costs for the public health service, with physical, functional, and psychological impairment. Although underweight seems to be a better predictor of negative outcomes than obesity, overweight/obese elderly subjects are certainly at risk of disability, morbidity, and mortality (Sergi et al., 2005).

91.6 Indicators of General and Central Adiposity and Muscle Mass

Circumferences and skinfold-thickness measurements allow a fairly accurate assessment of distribution and reserves for body fat and muscle mass. With increasing age, there is a reduction in muscle mass, which can be observed by measuring arm and calf circumferences (AC and CC, respectively) and arm muscle circumference (AMC). Moreover, the adipose tissue is redistributed: there is an increased tendency in the intra-abdominal level and a reduction in subcutaneous fat in the limbs, which can be assessed by measuring waist circumference (WC) and triceps skinfold thickness (TSF), among others (Kuczmarski et al. 2000; Santos et al. 2004; Barbosa et al. 2005).

The data on the elderly of Havana (Coqueiro et al. 2009) show that women (Table 91.5) have presented more subcutaneous fat (greater TSF values), whereas muscle mass indicators (AMC and CC) were slightly greater for men (Table 91.6). Differences between the extreme age groups (60–64 years and ≥ 80 years) in AC, TSF, AMC, and CC mean values, as observed in weight, were greater for females (in percentage). These results suggest that elderly women undergo slightly more intense reductions in subcutaneous fat and muscle mass when compared to men, although at the age of 80 women continue to have more subcutaneous fat, as observed in other studies with elderly subjects (Kuczmarski et al. 2000; Barbosa et al. 2005). Probably, since women are predominant among the oldest individuals, and report more chronic non-transmittable diseases (Barceló et al. 2006), they are more adversely affected in nutritional conditions.

In the study carried out by Coqueiro et al.(2009), more than 5% of women aged 75 and older and men aged 65 and older present inadequate AC (≤ 22 cm) and over 10% of the elderly present a CC lower than 31 cm, considered malnourished or at risk of malnutrition (Guigoz 2006). Even though these measurements consider bone and adipose tissues, they indicate muscle reserve and are regarded as a valid nutritional screening instrument for malnutrition in the elderly. The values of these

Table 91.5 Anthropometric values for women (≥60 years) (SABE Survey), Havana, Cuba, 2000 (Reprinted from Coqueiro et al. 2009. With permission)

Variable				Percentile						
Age group (years)	*n*	Mean	SD	5	10	25	50	75	90	95
Arm circumference (cm)‡										
60–64	235	30.28	4.83	22.49	24.04	27.00	30.00	33.40	36.68	38.00
65–69	218	29.23	5.19	22.00	22.97	25.87	29.00	32.39	35.94	37.68
70–74	214	28.43	4.49	21.75	22.50	24.93	28.35	31.40	34.13	36.00
75–79	180	27.74	4.61	21.00	21.50	24.00	27.58	31.00	34.00	35.95
≥80	198	26.32	4.51	19.10	21.00	23.00	26.00	29.02	33.00	34.11
Arm muscle circumference (cm)‡										
60–64	235	24.48	4.36	18.20	19.54	21.23	23.98	27.03	30.40	32.38
65–69	218	23.79	4.36	18.14	19.09	20.50	23.29	26.40	28.88	30.98
70–74	213	23.37	3.89	17.27	18.72	20.50	23.19	25.62	29.23	30.08
75–79	180	22.80	4.07	16.48	17.81	19.54	22.41	25.64	28.43	30.24
≥80	197	21.87	3.79	16.41	17.35	19.08	21.23	24.02	27.47	29.05
Triceps skinfold thickness (mm)‡										
60–64	235	18.45	8.22	7.00	8.00	11.67	18.00	24.00	30.00	33.00
65–69	218	17.31	7.17	8.00	9.00	11.00	16.00	22.00	26.00	30.00
70–74	213	15.91	7.71	6.00	7.47	10.00	15.00	20.33	25.00	30.00
75–79	181	15.76	7.28	6.00	7.00	10.00	15.00	20.00	25.00	29.90
≥80	197	14.21	6.82	5.00	6.00	9.33	12.00	19.00	24.07	28.07
Waist circumference (cm)‡										
60–64	235	90.32	13.20	68.78	72.12	81.30	90.00	99.00	107.07	111.47
65–69	218	89.06	13.71	65.04	70.33	79.28	89.92	99.00	105.02	109.53
70–74	212	86.62	12.33	65.61	70.00	77.63	87.00	95.33	101.81	105.35
75–79	180	86.01	12.03	67.18	71.00	77.01	86.00	94.03	99.91	105.95
≥80	197	83.96	11.96	65.45	68.96	75.10	85.00	92.67	99.00	104.10
Calf circumference (cm)‡										
60–64	234	35.63	3.98	29.92	30.82	33.00	35.45	38.00	41.00	42.13
65–69	218	34.59	4.18	28.10	29.41	32.00	34.98	37.00	39.00	41.04
70–74	213	33.82	3.67	28.00	29.11	31.00	34.00	36.47	38.95	40.00
75–79	181	33.32	4.23	26.05	28.00	30.68	33.27	36.00	38.63	40.00
≥80	198	31.89	4.14	25.06	26.48	29.00	31.77	34.33	37.01	40.00

All anthropometric variables showed a trend for decreased values in older age groups (‡$p = 0.000$; ANOVA)
SD standard deviation

measurements in the elderly of Havana were lower than the ones observed in the SABE survey carried out in São Paulo, Brazil (Barbosa et al. 2005) and may indicate a greater risk of malnutrition among Cubans.

As for central adiposity (WC), data from Havana (Coqueiro et al. 2009) showed a reduction in the values from ages older than 70 in women and 75 in men. In other Latin American countries (Santos et al. 2004; Barbosa et al. 2005) that took part in the SABE Survey, this reduction occurred at a greater age (by 10 years for both genders), similar to what was observed for BMI.

A comparison between WC values from the elderly individuals analyzed in the 2001 National Survey (Acosta Jiménez et al. 2005) and those from Havana (Coqueiro 2008) shows that men from Havana, throughout the percentile distribution, had higher percentile values by 2–4 points (Table 91.7). In women, WC median values were similar in both studies. Percentile distribution values for WC in Cubans were, in both surveys, lower than those observed in the elderly of Santiago, Chile (Santos et al. 2004). Despite the fact that risk values for metabolic disorders and cardiovascular

Table 91.6 Anthropometric values for men (≥60 years) (SABE Survey), Havana, Cuba, 2000 (Reprinted from Coqueiro et al. 2009. With permission)

Variable				Percentile						
Age group (years)	*n*	Mean	SD	5	10	25	50	75	90	95
Arm circumference (cm)‡										
60–64	195	29.42	3.73	23.05	24.56	27.00	29.50	32.00	34.00	36.00
65–69	146	28.34	3.82	22.00	23.76	25.68	28.00	31.00	34.02	35.28
70–74	109	27.53	3.45	20.97	23.00	25.08	27.50	30.00	32.00	33.25
75–79	85	26.83	4.39	20.25	21.07	23.75	26.10	29.65	32.40	36.30
≥80	96	26.35	3.39	21.94	22.00	23.50	26.00	28.98	31.00	32.25
Arm muscle circumference (cm^2)‡										
60–64	195	24.87	3.30	19.76	20.76	22.74	24.82	26.92	29.18	30.91
65–69	146	24.34	3.56	19.20	19.83	22.18	23.89	26.74	28.84	31.22
70–74	109	23.68	2.97	18.17	19.86	21.80	23.65	25.43	27.33	28.95
75–79	85	23.14	3.61	17.55	18.64	20.65	22.96	25.41	27.49	29.99
≥80	96	22.72	3.18	18.39	19.04	20.72	22.13	24.51	26.93	29.25
Triceps skinfold thickness (mm)‡										
60–64	195	14.49	7.17	6.00	7.00	9.00	13.00	18.00	24.27	29.47
65–69	147	12.71	5.91	5.00	6.00	8.00	12.00	15.00	22.00	25.00
70–74	109	12.24	5.74	5.33	6.00	8.33	10.67	15.00	20.00	23.33
75–79	85	11.76	5.95	4.30	5.20	7.00	10.00	16.00	20.40	23.70
≥80	96	11.56	5.49	5.00	5.00	8.00	10.33	14.00	20.30	23.30
Waist circumference (cm)‡										
60–64	195	92.20	11.06	73.92	77.00	84.00	92.47	100.00	107.00	109.60
65–69	146	89.88	10.80	74.00	76.94	81.88	88.07	96.00	105.00	108.72
70–74	109	89.09	10.85	69.00	74.40	82.17	90.00	97.00	102.00	105.50
75–79	84	87.36	13.59	71.00	71.67	77.00	83.75	97.21	106.70	112.63
≥80	96	87.10	10.43	71.00	73.41	79.25	86.32	94.08	100.30	105.00
Calf circumference (cm)‡										
60–64	195	34.51	3.60	28.87	29.97	32.00	35.00	37.00	39.00	40.51
65–69	147	34.02	3.48	29.00	30.00	32.00	33.50	36.00	38.47	40.28
70–74	109	33.03	3.56	27.03	29.00	30.90	33.13	35.00	37.33	39.67
75–79	85	32.31	3.84	25.65	28.00	29.33	32.00	35.00	37.70	38.47
≥80	96	32.38	3.86	26.00	27.74	30.00	32.38	35.00	38.00	39.00

All measurements were greater in younger groups, compared to older ones ($^*p = 0.000$; ANOVA)
SD standard deviation

diseases in the elderly are not established, when the cutoff points proposed by Lean et al. (1995) (WC ≥ 88 for women and 102 for men) are considered, it can be observed that approximately 50% of women and 10% of men, from both studies, are at risk.

The characteristics of the studies (Coqueiro 2008; Coqueiro et al. 2009; Acosta Jiménez et al. 2005) do not make it possible to infer whether the nutritional status attributes of the elderly of Cuba relate with the economic and political status of the country. However, it is known that the major economic crisis of the 1990s resulted in a reduction of over 35% in the Cuban population's *per capita* energy ingestion (Jímenez 2003). As the Cuban policy of access to essential goods prioritized children and women in childbearing age, the eldest age groups became quite vulnerable, mainly due to the lack of food and medication (Garfield and Santana 1997). It seems reasonable to consider that the data from 2000 to 2001, with its high underweight rate, may be a consequence of the years of food deprivation.

Table 91.7 Percentile values (BMI and WC) for elderly (≥60 years) in Cuba (2001) and Havana (2000) ([a]Reprinted from Acosta Jiménez et al. 2005. With permission; [b]Reprinted from Coqueiro 2008. With permission)

	Percentile						
Variable	3	10	25	50	75	90	97
Body mass index							
Female							
National Survey[a]	17.5	19.8	22.3	25.4	29.0	32.6	37.3
Havana[b]	16.3	18.6	21.6	25.3	28.8	32.4	36.9
Male							
National Survey[a]	17.2	19.1	21.2	23.7	26.5	29.2	32.4
Havana[b]	16.2	17.6	20.3	23.0	25.9	28.6	31.9
Waist circumference							
Female							
National Survey[a]	67.0	72.0	78.3	87.0	95.0	102.0	110.0
Havana[b]	64.5	70.3	77.7	87.0	96.0	104.0	111.3
Male							
National Survey[a]	67.0	72.0	78.3	87.0	95.0	102.0	110.0
Havana[b]	71.0	75.0	81.0	89.0	97.2	105.0	112.0

Men from Havana presented lower BMI and higher WC values than those evaluated in the National Survey. Women, in both studies, had BMI values that were quite similar

91.7 Centenarians

In a study carried out between 2004 and 2008, data from all Cubans aged more than 100 years (1,448 individuals) were analyzed. Results showed that centenarians had long-living parents, feel satisfied with life, live with their families, are mostly women, and have physical and mental limitations (Infomed 2009).

The study published by Prado Martinez et al. (2009) interviewed 134 individuals (82 women, 52 men) of 100 or more years of age living in the province of Villa Clara, Cuba. The maximum age recorded for both genders was 106 and, above 102 years, the sample size lessened by 50%. Information from approximately 125 individuals was collected, concerning weight, height, knee height, BMI, AC, and CC (Table 91.8).

Data on the nutritional status of centenarians are basically scarce and a comparison pattern is not yet available. BMI for the Cuban centenarians was 1.1 points lower than that observed in Italians of the same age (21.1 × 22.2 kg/m^2) (Paolisso et al. 1999).

When comparing data on the centenarians (Table 91.8) with the elderly aged 80 years and older (Tables 91.2 and 91.3, for women and men, respectively), a reduction can be observed in all measurements. Differences in stature were 7 and 10 cm, for men and women respectively, whereas the weight was approximately 9 kg lower. Average BMI for the centenarians was 13% (women) and 1.5% (men) lower to that observed in the individuals from Havana (≥ 80 years). Values related to muscle mass (AC and CC) were 11% and 17% lower in women and men, respectively. Although there are no values of normality for centenarians, according to the values suggested by Guigoz (2006), centenarian men and women presented inadequate AC and CC figures. It is worth noting that, although the average BMI for men was close to the value that is considered normal, according to AAFP et al. (2002), standard deviation was quite high, which indicates a large variability in the measurements.

Table 91.8 Anthropometric characteristics of the Cuban centenarian population of Villa Clara province (Reprinted from Prado Martinez et al. 2009. With permission)

	Male			Female			Total		
Variables	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Weight (kg)	42	50.32	12.06	53	42.58	8.35	95	46.00	10.77
Height (cm)	49	153.82	13.11	76	143.36	7.86	125	147.51	11.44
Knee Ht(cm)	49	49.73	6.90	76	46.45	4.96	125	47.75	6.04
BMI	42	21.87	7.41	53	20.54	4.10	95	21.13	5.82
AC	49	23.36	4.41	76	21.91	5.25	125	22.48	4.97
CC	49	28.32	4.09	76	26.93	3.96	125	27.46	4.05

The mean values of all anthropometric measures and indexes were greater in men
Knee Ht knee height; *BMI* body mass index; *AC* arm circumference; *CC* calf circumference; *SD* standard deviation

Key Features

Table 91.9 Key features of calf circumference

- Calf circumference (CC) is a sensitive indicator of lean mass loss among the elderly.
- Among the elderly, CC (<31 cm) provides information on muscle-related disability and physical function (Rolland et al. 2003).
- This measurement is more affected in cases of malnutrition.
- Malnutrition in older adults is common and is associated with poor clinical outcomes.
- The cutoff of 30.5 cm provides a good diagnostic capacity of the nutritional status of a hospitalized elderly person (Bonnefoy et al. 2002).

This table lists key facts of the CC including main uses

91.8 Final Considerations

Cuba is a country with unique social–political and health characteristics and presents a rather advanced demographic transition. The several transformations that occurred in the past decades seem to have reverberated as changes in the individual nutritional/anthropometric characteristics.

Between 1982 and 2001, there was a reduction in the number of underweight adults and an increase in the prevalence of overweight/obesity. The reduction in the frequency of underweight was found to be greater in the young age groups, whereas the rise in overweight/obesity was more pronounced in the 50–59-year age group, with disparity between men and women. The proportion of individuals with an inadequate nutritional status (underweight and overweight/obesity) is rather high.

The elderly of Cuba, specifically those from Havana, present different anthropometric characteristics than the ones featured in other cities of Latin America and developed countries. Such differences can be related to political, social, economic, and lifestyle issues, among other factors. However, the nature of the analyzed data (cross-sectional) does not allow the establishment of a cause-and-effect relation. Alterations in body dimensions that occur with increasing age differ between men and women. There is a loss of muscle mass, as well as a redistribution and reduction of fat mass, which are observed to be more severe in women. Many of the anthropometric differences are remarkable from age 70 onward.

According to the analyzed results, it is possible to conclude that a great number of the Cuban individuals, independently of age group and sex, present a vulnerable nutritional status, in view of the high prevalence of underweight and overweight/obesity.

91.9 Applications to Other Areas of Health and Disease

This material provides relevant empirical arguments that can be used for the development of health and social policies for nutritional surveillance, concerning overweight/obesity prevention as much as underweight, which are prevalent among individuals of all ages.

Anthropometry is a noninvasive, low-cost method used in research and clinical practice. Certain anthropometric measurements can be correlated with other body dimensions and are comparable to dimensions measured in other studies/populations.

BMI is the most important anthropometric index for the assessment of nutritional status, in individuals of all ages. Weight, BMI, AC, AMC, TSF, and CC are variables of currently used nutrition instruments developed for the elderly (Kuczmarski et al. 2005; Guigoz 2006). Underweight is an independent predictive factor of short-term mortality in older adults, and obesity causes serious medical complications and can exacerbate the age-related decline in physical function and lead to frailty (Sergi et al. 2005; Villareal et al. 2005). Particularly for very old persons, indicators of muscle mass may be helpful in determining their need for interventions, such as nutrition programs and assistance in activities of daily living (Kuczmarski et al. 2000).

Data from this chapter may be used for comparison and evaluation of the nutritional status of adults and elderly individuals from Cuba, including centenarians, whether in clinical practice or in epidemiological studies. Moreover, the data can be used for comparisons between different populations from developed and developing countries.

Summary Points

- The use of anthropometry helps characterize the nutritional status that expresses the degree by which physiological needs for nutrients are being achieved to maintain adequate body composition and functions.
- Sex and age are determining factors for anthropometric characteristics.
- In young adults (20–39 years), the prevalence of underweight is greater for women.
- On the basis of two population-based surveys conducted in Cuba (1982 and 2001), we identified clear changes in the prevalence of underweight and overweight/obesity in the 20–59-year-old population.
- In 1982, underweight was frequent in over 11% of men and women (25% of 20–29-year-old women). In 2001, there was a reduction of approximately 50% in underweight prevalence, in both genders. Men were more susceptible to overweight/obesity than women were.
- In Havana, in 2000, there were nearly two obese elderly women for each obese elderly man. For each obese man, there were two underweight; for women, the proportion was closer to 1/1.
- With increasing age, there is a reduction in height, body mass, muscle mass, and fat mass, which differed for each sex; this reduction is greater among women.
- Many of the anthropometric differences are remarkable from age 70 onward.
- Underweight and overweight presented high proportions in the elderly population of Cuba.
- When comparing data on the centenarians (mean) with the elderly aged 80 years and older, a reduction can be observed in all anthropometric measurements.

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Chapter 92
Anthropometric Indices and Nutritional Assessments in the Elderly: Brazilian Perspectives

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Abstract Anthropometry is a low-cost, easy-to-perform method that allows diagnosis, stratification, and monitoring of the nutritional status of the elderly, indicating that it is useful to assess the health conditions of the elderly population. Brazil is going through a rapid aging process and some studies, carried out in the last 20 years, presented the anthropometric characteristics and the nutritional status of the Brazilian elderly individuals (≥60 years). The data from the population-based and household studies have been discussed in this study. According to earlier studies, sex and age are factors that determine the anthropometric changes. The patterns of alterations with increasing age in anthropometric characteristics are similar; however, the intensity of the alterations varies between populations and studies. With increasing age, there is a reduction in the stature and body mass, which is more intense for women. In addition, there is a reduction in muscle mass and subcutaneous fat, which is greater for men and women, respectively. Along with the loss of muscle mass, there is a greater accumulation of central adiposity in women. However, after the age of 75 years, central adiposity reduction occurs more rapidly in men. Overweight or obesity is more prevalent among women and underweight is more common in men, irrespective of their age. With increasing age, there is a reduction in the prevalence of obesity and an increase in the prevalence of being underweight, which is more evident after the age of 75 years. Data from earlier studies can be used for surveillance and for planning actions that intend to prevent or improve nutritional inadequacy in the Brazilian elderly population.

Abbreviations

AAFP	American Academy of Family Physicians
AC	Arm circumference
AMC	Arm muscle circumference
BM	Body mass
BMI	Body mass index
CC	Calf circumference
IBGE	Instituto Brasileiro de Geografia e Estatística

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_92,

PNSN National Survey on Health and Nutrition (Pesquisa Nacional sobre Saúde e Nutrição)
PAHO Pan-American Health Organization
SABE Survey on Health, Aging and Well being in Latin America and the Caribbean
TSF Triceps skinfold thickness
WC Waist circumference
WHO World Health Organization

92.1 Introduction

Population aging is a phenomenon observed in many parts of the world. In Brazil, this process began only from the 1960s on, when a decrease in the fertility rates was noticed in some regions. This reduction became stronger in the following decades, and its association with the decrease in mortality led to a change in the Brazilian age composition, as the country experienced an aging process, with an increase in life expectancy (Carvalho and Garcia 2003).

In 1940, the average life expectancy was 39 years and 43 years for men and women, respectively. In 2008, the average woman had a life expectancy of 76.6 years, whereas men lived up to 69.0 years. The percentage of elderly individuals in the population was 2.5% in 1940, which reached 9.5% in 2008, corresponding to an absolute number of approximately 18 million individuals (Instituto Brasileiro de Geografia e Estatística [IBGE] 2008).

Demographic changes have been occurring at a rapid and more intense pace: according to the predictions, by 2025, Brazil will have the world's sixth greatest population of individuals aged 60 years and older, in absolute numbers (Carvalho and Garcia 2003). It is believed that the Brazilian population's average life span will increase by a few more years, reaching 81.29 years by 2050 (IBGE 2008).

This phenomenon of population aging has an impact on the prevalence of chronic diseases, which are most frequent in adult and elderly individuals. It is also an important issue for investigating, monitoring, and planning public policies, owing to the inevitable growth in the demand on the health system (Tavares and Anjos 1999).

One change that is rather evidenced with increasing age is body composition, which can influence the nutritional status of elderly individuals. With aging, there is a progressive increase in fat mass, with a greater deposit in the upper body. The amount of fat in the limbs decreases. Reductions are observed in height, body mass (BM), and lean body mass, especially in relation with muscle mass decrease (Kuczmarski et al. 2000; Santos et al. 2004; Barbosa et al. 2005; Coqueiro et al. 2009).

In this context, anthropometry is useful to assess the health conditions of the elderly individuals, as many disorders are associated with dietary and nutritional problems (Barbosa et al. 2007; Munaretti 2009). Traditionally, anthropometric measurements (e.g., BM, height, circumferences, and skinfold thickness) are used for the physical examinations of the elderly in clinical studies, especially in population studies. These measurements, which are low cost and easy to perform, allow for the diagnosis, stratification, and monitoring of the nutritional status in the elderly. They can also estimate, fairly accurately, the subcutaneous fat or muscle reserve in certain parts of the body (Tavares and Anjos 1999). However, the utility of these indicators depends on the availability of reference data related to age, sex, and age group, specific to each population (World Health Organization [WHO] 1995).

In Brazil, not many population studies, carried out in different regions of the country, attempted to identify the anthropometric characteristics in the elderly. These studies have their differences concerning height, body mass, adiposity, and muscle mass, according to sex, age group, and region.

The purpose of this study is to examine the anthropometric characteristics and the nutritional status in Brazilian elderly individuals, by analyzing the data from the population-based- and household studies that were carried out in the last 20 years (Tables 92.1 and 92.2).

Table 92.1 Anthropometric studies in older adults

References	Data from	Year data collected	Sex	*n*	Age	Parameters
Tavares and Anjos (1999)	National Survey	1989	M and F	4277	60–64, 65–69, 70–74, 75–79 and ≥ 80 years	BMI category (kg/m^2) <18.5 (underweight); 25.0–30.0 (overweight); ≥30.0 (obesity)
Barreto et al. (2003)	Bambui, Minas Gerais State	1997	M F	613 417	60–69, 70–79 and 80–89 years	BMI category (kg/m^2) ≤20 (underweight); ≥30 (obesity)
Barbosa et al. (2005)	São Paulo, São Paulo State	2000/2001	M F	770 1124	60–64, 65–69, 70–74, 75–79 and ≥ 80 years	Body mass; height; BMI; arm, calf and waist circumference; arm muscle circumference; and triceps skinfold thickness (mean, standard deviation, and percentiles)
Santos and Sichieri (2005)	Rio de Janeiro, Rio de Janeiro State	1995/1996	M F	248 385	60–69, 70–79 and ≥ 80 years	Body mass; height; BMI; arm and waist circumference; arm muscle circumference; and triceps skinfold thickness. (mean and standard error) BMI category (kg/m^2)
Campos et al. (2006)	Northeastern and Southeastern region	1996/1997	M and F	1519	≥ 60 years	BMI category (kg/m^2) < 18.5 (underweight); 25.0–30.0 (overweight); ≥ 30.0 (obesity)
Barbosa et al. (2007)	São Paulo, São Paulo State	2000/2001	M F	770 1124	60–69, 70–79 and ≥ 80 years	BMI category (kg/m^2) < 23 (underweight); ≥ 28 (obesity)
Menezes et al. (2007)	Fortaleza, Ceará State	2002	M F	156 327	60–69, 70–79 and ≥ 80 years	Triceps skinfold thickness, arm circumference, and arm muscle circumference. (mean, standard deviation, and percentiles)
Menezes et al. (2008)	Fortaleza, Ceará State	2002	M F	156 327	60–69, 70–79 and ≥ 80 years	BMI category (kg/m^2) Percentile distribution (Kuczmarski et al. 2000), according sex and age group. > percentile 25 and < percentile 75 (normal range).
Silveira et al. (2009)	Pelotas, Rio Grande do Sul State	1999/2000	M F	242 354	60–65, 66–70, 71–75 and 76–88 years	BMI category (kg/m^2) > 27 (obesity); ≥ 30 (obesity)

This table lists the studies analyzed in this chapter, including location, year of collection, sex and number of participants (*n*), age group, and anthropometric variables
M male, *F* female, *BMI* body mass index
SABE Survey Survey on Health and Well-Being of the Elderly

Table 92.2 Key features of Survey on Health, Aging and Well being in Latin America and the Caribbean (SABE)

- During 1999 and 2001, the PAHO coordinated the SABE project. This is a multicenter study, carried out in seven countries (Argentina, Barbados, *Brazil*, Chile, Cuba, Mexico, and Uruguay).
- In each participant country, the SABE project was coordinated by a team of researchers, consisting of a main investigator and their associates.
- Project goals were to collect information on the health conditions of elderly individuals (chronic and acute diseases, disability, nutritional status, physical and/or mental impairment, etc.) and to evaluate differences related with gender, age group, socioeconomic conditions, and use and accessibility of services, among others.
- SABE is the first survey of its kind in the region and was simultaneously and rigorously comparable for the purpose of compiling information of persons aged 60 and older.
- Anthropometric data were obtained by health professionals who received special training, including a video for standardization and better visual presentation of the anthropometric techniques to be used in all countries.

This table lists the key facts of the SABE Survey including the participant countries, research coordination, and main goals. PAHO, Pan American Health Organization

92.2 Body Mass and Height

Decline in the BM and height with age has been observed in studies throughout the world (WHO 1995; Kuczmarski et al. 2000, Perissinotto et al. 2002; Santos et al. 2004; Coqueiro et al. 2009), although the pattern of change is different and varies with sex. Usually, men tend to reach a plateau in their BM by the age of 65 years, decreasing from then on. In women, the raise usually continues until around 75 years of age, and then starts to reduce (WHO 1995; Kuczmarski et al. 2000). Such a reduction is more strongly related to the decrease in the muscle mass in men, and in body fat in women. For subjects aged 80 years and older, body water is the most important cause for BM reduction (Stenn 1988). With respect to height, there has been no agreement on the value of its reduction with increasing age; it appears to reduce by 0.5–3 cm per decade after the age of 60 years, and becomes steeper in older ages for both the sexes (WHO 1995; Perissinotto et al. 2002).

In the elderly, BM assessment is considered when the person presents an illness. In the absence of confounding factors, BM < 80% of the recommended value (using age-adjusted norms) can be considered as low BM (Andres et al. 1985), necessitating an assessment over time. This indicates that unintentional weight loss in 1 month (2%), 3 months (5%), or 6 months (10%) may also be owing to associated nutritional compromise (Jensen et al. 2001; Huffman 2002; American Academy of Family Physicians [AAFP] 2002).

Although BM and height are the commonly recorded anthropometric measurements, only two Brazilian studies presented these values for older adults (Tables 92.3 and 92.4, showing data for the elderly in São Paulo and Rio de Janeiro, respectively).

Data from São Paulo (Barbosa et al. 2005) showed that BM was lower in the oldest than in the youngest individuals, and was higher in men than in women in all age groups, similar to that observed in the Rio de Janeiro study (Santos and Sichieri 2005) and in other studies on elderly populations (Perissinotto et al. 2002; Santos et al. 2004; Velasquez-Alva et al. 2004; Coqueiro et al. 2009).

Furthermore, some factors appear to contribute to such a reduction in body weight with increasing age, such as selection bias, institutionalization or earlier death of overweight or obese individuals (a relation impossible to assess in a household survey), cohort effect, and reduction in total body water and muscle mass (WHO 1995; Perissinotto et al. 2002, Barbosa et al. 2005).

A comparison between the two extreme age groups (60–64 years and ≥80 years group) showed that the reductions in the mean BM were 13.6% (9 kg) for women and 11.2% (7.9 kg) for men in São Paulo (Barbosa et al. 2005). For the elderly in Rio de Janeiro (Santos and Sichieri 2005), the differences in the mean BM values were 8% (5 kg) and 10% (6.4 kg) for men and women, respectively,

Table 92.3 Body mass, height, and body mass index for men and women (≥60 years). Survey on Health and Well-Being of the Elderly (SABE), São Paulo, Brazil, 2001 (Reprinted from Barbosa et al. 2005. With permission)

Age Group	*n*	Means	SD	Percentiles 5	10	25	50	75	90	95
Men										
Body mass (kg)‡										
60–64	155	70.80	13.26	50.80	55.80	62.40	70.00	78.50	85.96	92.50
65–69	104	71.22	12.81	52.00	57.00	63.63	69.90	77.75	86.80	89.25
70–74	108	68.43	12.00	48.73	52.00	61.00	68.75	75.88	85.50	90.46
75–79	181	67.71	12.50	48.07	51.00	58.25	66.60	76.00	84.84	90.90
≥ 80	186	62.88	11.50	44.18	47.94	54.00	63.00	71.62	78.50	82.30
Height (m)‡										
60–64	155	1.65	0.07	1.54	1.57	1.61	1.65	1.70	1.75	1.78
65–69	104	1.66	0.05	1.57	1.58	1.61	1.65	1.70	1.74	1.77
70–74	109	1.64	0.07	1.51	1.55	1.60	1.64	1.70	1.74	1.76
75–79	180	1.64	0.06	1.54	1.56	1.60	1.64	1.69	1.74	1.76
≥ 80	185	1.63	0.08	1.52	1.54	1.59	1.62	1.68	1.72	1.75
Body mass index (kg/m²)‡										
60–64	155*	25.81	4.28	19.32	20.95	23.53	25.64	27.83	29.88	34.09
65–69	104*	25.92	3.92	19.06	20.42	23.94	25.67	28.21	30.61	31.09
70–74	108*	25.39	4.11	18.58	20.30	22.65	25.11	28.57	30.41	31.64
75–79	180†	25.01	3.95	18.53	19.90	22.27	25.09	27.56	30.47	31.97
≥ 80	185*	23.58	3.70	17.56	18.83	21.14	23.41	26.24	28.44	29.75
Women										
Body mass (kg)‡										
60–64	223	66.37	13.17	46.60	50.40	57.00	65.00	75.50	82.72	90.72
65–69	204	63.90	12.75	45.15	48.00	55.00	62.00	71.48	80.00	88.75
70–74	180	63.30	13.60	44.00	46.50	54.13	60.50	72.38	83.80	88.48
75–79	235	61.95	11.83	44.00	48.00	54.00	61.60	70.00	77.00	83.40
≥ 80	229	57.36	12.14	37.40	42.00	49.00	56.00	64.25	74.00	79.25
Height (cm)‡										
60–64	221	1.53	0.06	1.43	1.45	1.49	1.52	1.57	1.61	1.63
65–69	204	1.53	0.06	1.41	1.44	1.49	1.53	1.57	1.61	1.65
70–74	180	1.51	0.06	1.40	1.43	1.47	1.52	1.58	1.60	1.62
75–79	232	1.51	0.07	1.40	1.43	1.46	1.51	1.56	1.60	1.62
≥ 80	229	1.48	0.06	1.37	1.39	1.44	1.49	1.53	1.57	1.59
Body mass index (kg/m²)‡										
60–64	221*	28.34	5.34	20.36	22.25	24.34	27.59	32.04	35.42	38.40
65–69	204*	27.32	4.90	19.96	21.77	24.01	26.48	30.14	34.61	37.61
70–74	180*	27.63	5.79	18.64	20.25	23.67	27.19	30.81	34.72	37.70
75–79	232†	27.12	4.71	19.87	21.16	23.65	27.12	30.04	33.49	35.35
≥ 80	227*	26.01	5.06	17.72	19.70	22.37	25.80	29.09	32.44	35.19

Body mass, height, and body mass index (BMI) were significantly lower in the oldest than in the youngest individuals (‡$p \leq 0.001$; ANOVA). In general, mean body mass and height in women were less than those reported for men at each age group. Mean BMI was higher in women than in men (*$p \leq 0.001$; †$p = 0.007$; Student's *t*-test)
SD standard deviation

between the 60–69 years and the >80 years age groups. Furthermore, divergences concerning the values of reduction may be related to the extension of the age groups and sample characteristics. It is worth mentioning that, for the oldest individuals, the BM values were similar among the women in both the studies and were greater for men in Rio de Janeiro.

Table 92.4 Anthropometric values for men and women (≥ 60 years). Rio de Janeiro, Brazil (1995/1996) (Reprinted from Santos and Sichieri 2005. With permission)

Variables	60–69 years		70–79 years		≥80 years	
	Mean	SE	Mean	SE	Mean	SE
Men						
Height (m)	1.67	0.61	1.65	0.73	1.65	1.61
Body mass (kg)	70.5	1.00	67.6	1.25	65.5	1.92
Body mass index (kg/m^2)	25.2	0.32	24.5	0.42	24.0	0.64
Waist circumference (cm)	89.9	1.08	90.1	1.28	90.5	1.94
Arm circumference (cm)	29.9	0.30	29.1	0.40	27.9	0.73
Triceps skinfold thickness (mm)	17.0	0.70	18.1	0.94	14.9	1.43
Arm muscle circumference (cm^2)	49.0	1.17	44.7	1.40	43.8	2.20
Women						
Height (m)	1.55	0.48	1.53	0.72	1.51	1.09
Body mass (kg)	63.7	0.84	60.2	1.02	57.3	1.54
Body mass index (kg/m^2)	26.3	0.33	25.5	0.41	24.9	0.68
Waist circumference (cm)	86.7	0.88	85.2	1.09	85.2	1.73
Arm circumference (cm)	30.0	0.30	29.2	0.35	28.4	0.68
Triceps skinfold thickness (mm)	25.0	0.59	23.1	0.75	22.5	1.16
Arm muscle circumference (cm^2)	39.8	0.78	39.2	0.93	37.1	1.85

There was a significant difference between men and women ($p < 0.001$) in all the analyzed anthropometric variables. For men, body mass, arm circumference (AC), and arm muscle circumference (AMC) values were greater in younger groups compared with older ones. For women, AC and AMC did not show a variation with age
SE standard error

This difference in BM reduction between the sexes was observed in the elderly in Mexico City (Velasquez-Alva et al. 2004), Havana (Coqueiro et al. 2009), and Santiago (Santos et al. 2004). This may be because women are predominant among the elderly and report more chronic diseases (Friedmann et al. 2001), and, hence, are more adversely affected by nutritional conditions.

In the above-mentioned studies (Barbosa et al. 2005; Santos and Sichieri 2005), height reduction differed between the sexes. Women from São Paulo and Rio de Janeiro showed statistically significant differences between the age groups, whereas for men, the differences were not significant. In a study carried out by Barbosa et al. (2005), throughout the percentile distribution, the reductions varied from 1 to 3 cm/decade for women, whereas for men, the variations in percentiles were from 1 to 2 cm/decade. Among the elderly in Rio de Janeiro, the reduction was 2 cm/decade, and no changes were observed between men aged 70–79 years and 80 years and older.

The differences between men and women with regard to height reduction with aging were also observed in other populations (Perissinotto et al. 2002; Santos et al. 2004; Coqueiro et al. 2009), and some previously discussed factors (Barbosa et al. 2005) appeared to justify these divergences. The loss of muscle tone and greater muscle contraction, as well as alterations in intervertebral disks, vertebral bodies, and postural modifications, may be more intense among women, as osteoporosis is more frequent among them. Similarly, the effects of the differences between the cohorts and the secular height trend are also considered to be important, which may reflect the influences from the intrauterine period until the end of development, when improvements in the living conditions and population health may have affected men and women differently. In the developed countries, the positive secular height trend was more evident in men than in women (WHO 1995), but the same cannot be stated for the elderly in São Paulo and Rio de Janeiro.

The mean height values for the elderly in São Paulo (Barbosa et al. 2005) were lower than those observed in men and women from Rio de Janeiro (Santos and Sichieri 2005), in spite of the difference

between the analyzed age groups. It is presumed that environmental and sample selection aspects may have contributed to such differences.

A comparison of the data from the National Survey on Health and Nutrition (PNSN), carried out between July and September 1989 (WHO 1995), with those from São Paulo (Barbosa et al. 2005) and Rio de Janeiro (Santos and Sichieri 2005) showed a slight height difference (0.5–3 cm) between the sexes in the same age groups (60–69 years and 70–79 years), with higher values in the elderly of the last study. This height increase may reflect the cultural differences and an improved quality of health and nutritional status in the population, and may also be owing to the sampling differences, as the PNSN covered individuals from various regions of Brazil, with different socioeconomic and cultural characteristics.

When compared with international studies, the height values for women in São Paulo (Barbosa et al. 2005) were greater than those observed in the elderly females in Santiago (Santos et al. 2004) and Mexico City (Velasquez-Alva et al. 2004), and were lower than observed for the women of Havana (Coqueiro et al. 2009). Men from São Paulo and Rio de Janeiro showed height values similar to those of the elderly from Santiago, and greater than those from Mexico City and lower than those from Havana.

92.3 Body Mass Index and Nutritional Status

The relation between height and BM has proven itself a good way to assess nutritional status in adults. The body mass index (BMI = BM(kg)/height $(m)^2$) is mentioned as most advantageous due to its ease of calculation, bad correlation with height and good correlation with the body fat, as well as the fact that it relates with morbidity–mortality (WHO 1995). BMI is used as a measure of underweight, overweight, and obesity, being one the most important anthropometric measures for both initial and follow-up assessments of nutritional status (Kuczmarski et al. 2000).

Data from older adults of São Paulo show that BMI values (Table 92.3) were greater among women, in all age groups, and lower in the oldest age groups, as shown in other studies on elderly populations (Barreto et al. 2003; Velasquez-Alva et al. 2004; Santos et al. 2004; Santos and Sichieri 2005; Coqueiro et al. 2009). The reduction was more pronounced after the age of 75 years, converging with the trend observed in developed countries (WHO 1995; Kuczmarski et al. 2000).

Mean BMI was greater for the men and women of São Paulo (Barbosa et al. 2005), when compared to the Brazilian elderly sample (Tavares and Anjos 1999) analyzed in the PNSN/89, or to men and women of Bambuí-MG (Barreto et al. 2003), and also the women from Rio de Janeiro (Table 92.4), in the study by Santos and Sichieri (2005).

Divergences in BMI values between studies carried out in Brazil can be explained by differences in socioeconomic development, lifestyle, health conditions, sampling process, as well as possible differences in migration patterns among the analyzed populations.

In Brazil, as well as in developed countries, the rating of the elderly according to BMI is still rather debated, and there are disagreements among several studies as to the values used (Barreto et al. 2003; Santos and Sichieri 2005; Barbosa et al. 2007; Menezes et al. 2008; Silveira et al. 2009). It is known that any BMI value corresponds to more fat in the body composition of the elderly, when compared to adults, probably due to the reduction of muscle mass with age (WHO 1995). This means that using the same cutoff point utilized for adults may underestimate the prevalence of obesity in the elderly. Moreover, the reduction in height (the denominator for the BMI equation) with age may cause an "artificial" raise in the index, without a real increase in adiposity (Sorkin et al. 1999).

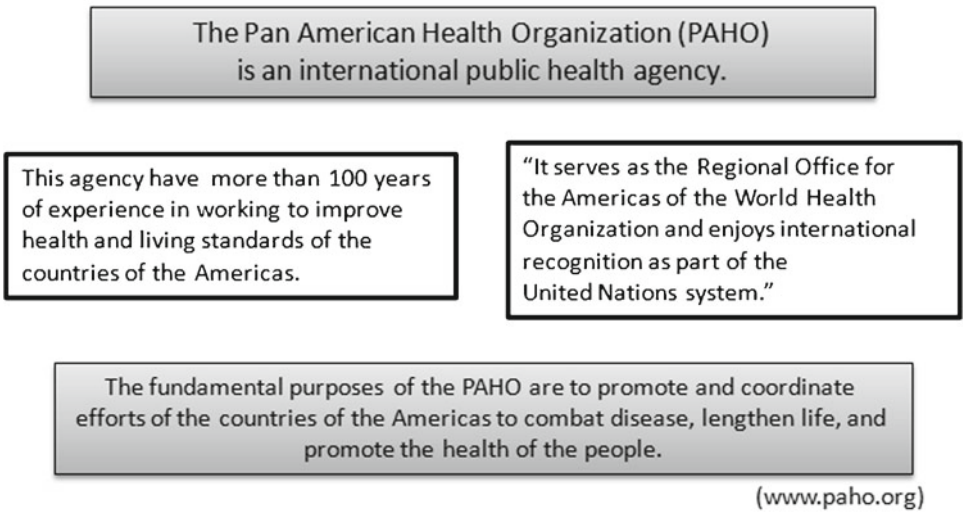

Fig. 92.1 Key features of Pan American Health Organization. This figure presents the key facts of the PAHO, including the main goals

Body mass index values ≤23 kg/m^2 rated as underweight, ≥28 for overweight, and ≥30 kg/m^2 for obesity were used by the PAHO (2001) in the data on elderly individuals from the Survey on Health, Aging and Well being in Latin America and the Caribbean (SABE). In Brazil, the Ministry of Health (2008) recommends BMI values <22 kg/m^2 and >27 kg/m^2 (AAFP et al. 2002), as indicating underweight and overweight, respectively (Fig. 92.1).

Data from several studies indicate that the relation between BMI and all causes of mortality is similar to an U-shaped curve; this means that there are health hazards for both underweight and overweight, and recommendations for a healthy life must take these hazards into account (Troiano et al. 1996; Sergi et al. 2005).

Likewise, the lack of studies involving elderly persons from developing countries suggests the need for larger investigations in order to delimit underweight and overweight/obesity for this group of individuals.

The WHO (1995) recommends, for adults and elderly individuals, the following rating: underweight (BMI < 18.5 kg/m^2), overweight (BMI > 25 kg/m^2), and obesity (≥30 kg/m^2), even though it acknowledges the limitation of its use for subjects over 69 years, due to the lack of data for older individuals. The values 23, 27.5, 32.5, and 37.5 kg/m^2 are to be used in public policies, making international comparisons easier (WHO 2006).

In Barreto et al. (2003), underweight (BMI > 20 kg/m^2) and obesity (BMI ≤ 30 kg/m^2) were determined by the mean BMI ± a standard deviation from what was verified for the sample. The authors observed that 14.4% of the individuals were underweight and 12.8% were obese. The prevalence of obesity was greater among women and those with higher income and educational levels. As in other studies, there was a reduction in the obesity prevalence with increasing age. However, this reduction was only significant in women. Due to the lack of cutoff points for the elderly population, the authors also calculated underweight and obesity by the cutoff point BMI < 23 or >28 kg/m^2 (Troiano et al. 1996) and observed that the prevalence of underweight in this community would be 35% and of obesity 24.8%.

Data from Rio de Janeiro (Santos and Sichieri 2005) showed a greater proportion (54.6%) of overweight women (BMI ≥ 25 kg/m^2), compared to men (47.9%). In the three analyzed age groups

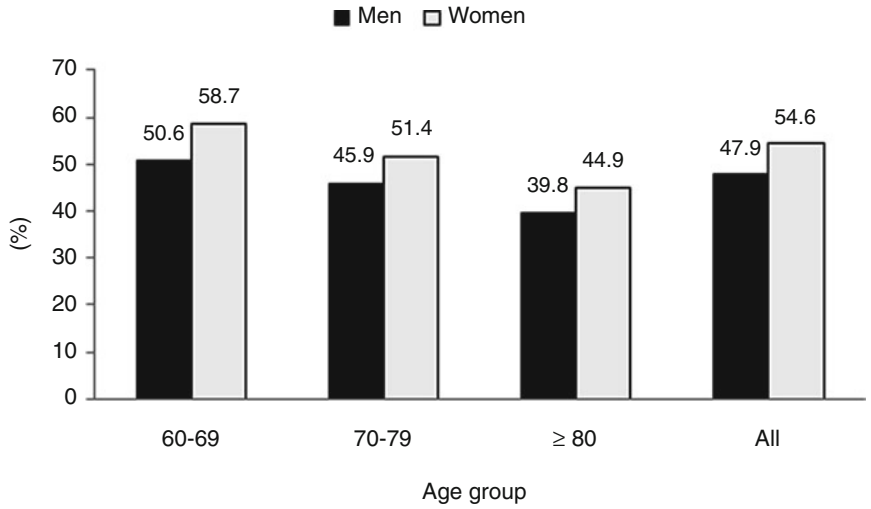

Fig. 92.2 Prevalence of overweight (BMI ≥ 25) in the elderly of Rio de Janeiro, according to sex and age group. The prevalence of overweight was greater in women than in men, in all age groups (Adapted from Santos and Sichieri 2005, With permission)

(60–69 years, 70–79 years, and ≥80 years), a greater proportion of overweight was observed among women (Fig. 92.2). For men, the overweight prevalence decreased with age, and this reduction was lower for women. The prevalence of underweight (BMI ≤ 18.5 kg/m^2), especially in women, was lower than that observed for Brazil in 1989 (Tavares and Anjos 1999).

The evaluation of the nutritional status in the elderly of São Paulo (Barbosa et al. 2007) shows that men and women, with increasing age, present a raise in the number of underweight individuals (BMI < 23 kg/m^2), with a greater prevalence for males, in all age groups, when compared to women (Fig. 92.3). The difference between sexes in the underweight prevalence was more pronounced for the group aged 80 and over. Obesity was most frequent in women, in all age groups, and there was no difference in the percentage of obese men and women between age groups 60–69 and 70–74. The reduction in the proportion of obese elderly was only verified concerning the oldest age group (≥80 years).

When data from São Paulo (Barbosa et al. 2007) were compared with data from Bambui (Barreto et al. 2003), using the cutoff points suggested by Troiano et al. (1996), it was found that the prevalence of underweight is greater for the elderly of Bambui, whereas the obesity frequency is greater for older adults of São Paulo.

According to Campos et al. (2006), the prevalence of the categories of nutritional status among men was 6% for underweight (BMI ≤ 18.5 kg/m^2), 31.9% for overweight (25.0 ≤ BMI < 30), and 5.6% for obesity (BMI ≥ 30 kg/m^2). For women, prevalences were, respectively, 5.4%, 32.7%, and 16.3%. With increasing age, the chance of obesity and overweight decreased, and the chance of underweight increased. A comparison with data from the PNSN/89 (WHO et al. 1995; Tavares and Anjos 1999), carried out seven years earlier, shows that the prevalence of underweight decreased, whereas those of adequate weight and obesity remained stable.

Data from the elderly of Fortaleza (Menezes et al. 2008) show similar proportions of normal weight between sexes (47.4% for men and 47.2% for women). Men presented a lower prevalence (13.5%) of overweight (based on the percentile distribution of Kuczmarski et al. 2000) when compared to women (21.9%). The study did not show data according to age group, specifically for each sex (Fig. 92.4). Analysis of all the elderly individuals showed that the 60–69 age group was the one with the greatest proportion of underweight (36%). The overweight proportion was similar among

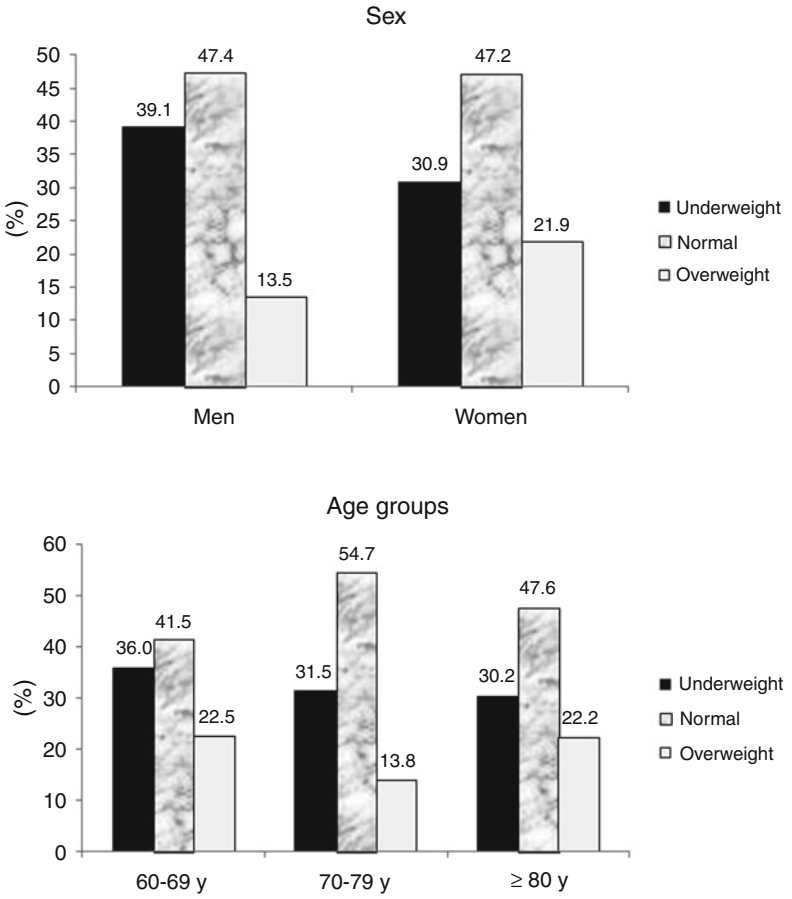

Fig. 92.3 Prevalence of underweight and obesity according to age group for men and women. Survey on Health and Well-Being of the Elderly (SABE), São Paulo, Brazil, 2001. Underweight (BMI < 23 kg/m^2); obesity (BMI ≥ 28 kg/m^2). For both genders, the prevalence of obesity was similar between groups aged 60–69 and 70–79 and the underweight frequency was greater in the oldest individuals. Differences were statistically significant for men and women ($p \leq 0.001$) (Reprinted with permission from Barbosa et al. 2007)

groups aged 60–69 (22.5%) and over 80 (22.2%). Probably, the fact that there was no stratification by sex may have contributed to the high prevalence of underweight within the youngest age group.

According to Silveira et al. (2009), the prevalence of obesity (BMI ≥ 30 kg/m^2) was 25.3%, classed into 30.8% in women and 17.4% in men. Using the BMI > 27 kg/m^2 cutoff point, the prevalence was 48.0%, 53.4%, and 40.1%, respectively. The oldest subjects show lower obesity prevalence. Underweight, independently of the cutoff point (BMI < 18.5 kg/m^2 or BMI < 22 kg/m^2), was more prevalent in men. The results, in spite of being based on self-referred information on body mass and height, are consistent with other studies carried out in Brazil.

A comparison between the several studies made in Brazil is hard to make, mainly due to the different cutoff points used to rate nutritional status, as well as differences in age-group extension. Results have shown that the nutritional profile for the Brazilian elderly, in the past decade, is characterized by a high prevalence of individuals with adequate weight and by a low prevalence of underweight. The prevalence of overweight/obesity has been increasing, similar to what was observed in developed countries, and is much more associated with females and with the urban population.

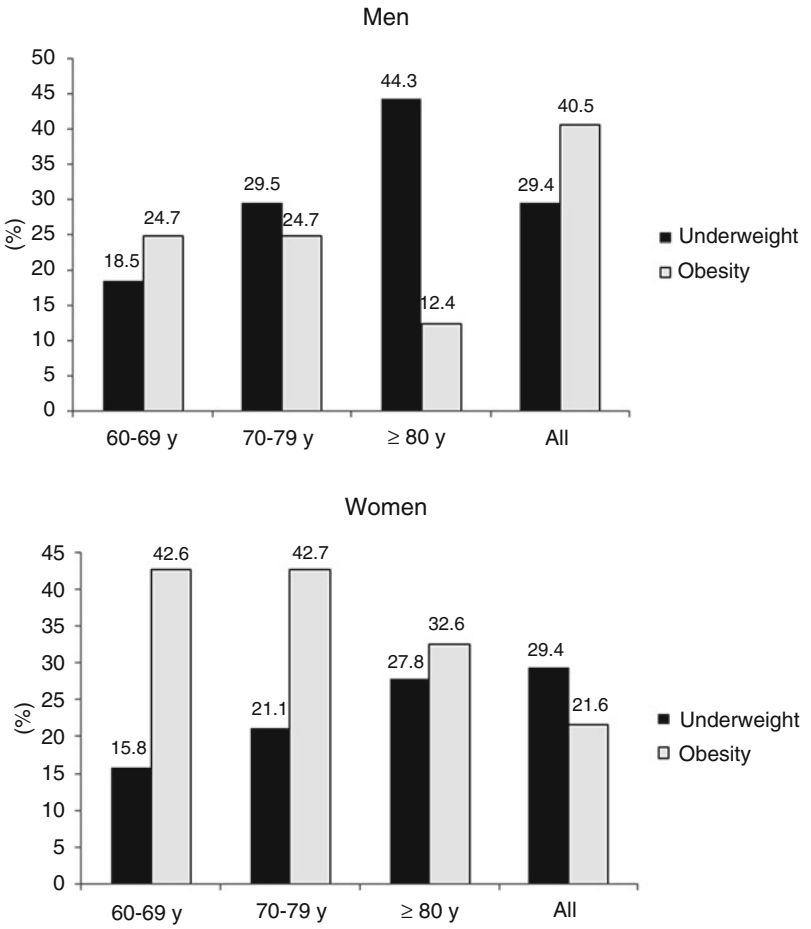

Fig. 92.4 Distributions of body mass index categories in elderly of Fortaleza/CE, according sex and age group. Fortaleza, Ceará, Brazil (2003). Underweight was more common among men and the youngest age group (60–69 years). There was a statistically significant difference between sexes ($p \leq 0.001$) (Adapted from Menezes et al. 2008. With permission)

92.4 Central Adiposity

Several studies have been pointing out a progressive increase of individual body fat with increasing age (until 75 years), as well as a redistribution of body fat. There is a greater deposit in the abdominal area and an internalization of subcutaneous fat, and it is possible to observe increase in waist circumference measurements (Perissinott et al. 2002; Santos et al. 2004).

The waist circumference (WC) is an indicator used to assess fat deposition in the central region, which characterizes the visceral abdominal obesity. Abdominal obesity is considered a major metabolic cardiovascular risk factor (e.g., high blood pressure, plasma lipids, and insulin resistance) (Lean et al. 1995), including in the elderly (Okosun et al. 2000; Munaretti 2009). However, there is still no agreement on the best cutoff point to identify the risk in elderly individuals and different populations (Okosun et al. 2000).

The study carried out by Barbosa et al. (2005) showed that WC decreased, with aging, more rapidly in men than in women (Tables 92.5 and 92.6, respectively), and lower values were observed in the more advanced age groups, as was showed by Santos and Sichieri (2005) in Rio de Janeiro

Table 92.5 Anthropometric values for men (≥60 years) Survey on Health and Well-Being of the Elderly (SABE), São Paulo, Brazil, 2001 (Reprinted from Barbosa et al. 2005. With permission)

Age Group	*n*	Means	SD	Percentiles 5	10	25	50	75	90	95
Arm circumference (cm)‡										
60–64	157	30.50	3.42	24.90	27.00	29.00	30.00	32.00	35.00	37.00
65–69	110	30.55	3.72	24.55	27.00	29.00	30.00	32.00	34.90	36.00
70–74	114	29.58	3.28	24.00	26.00	27.00	30.00	32.00	34.00	35.25
75–79	189	28.90	3.45	23.00	24.00	26.00	29.00	31.00	33.00	35.00
≥ *80*	199	27.42	3.30	22.00	23.00	25.00	28.00	30.00	32.00	33.00
Arm muscle circumference (cm)‡										
60–64	154	25.57	2.65	20.74	21.97	23.86	25.60	27.29	28.82	29.86
65–69	103	25.53	2.37	21.18	22.36	24.12	25.72	27.17	28.49	29.20
70–74	103	24.99	2.51	20.99	21.77	23.49	25.03	26.52	28.19	28.91
75–79	177	24.60	2.59	20.34	21.11	22.79	24.60	26.32	28.12	28.73
≥*80*	190	23.52	2.51	19.15	20.12	21.65	23.66	25.49	26.60	27.41
Triceps skinfold thickness (mm)‡										
60–64	154	15.35	6.55	5.75	7.00	10.00	15.00	20.00	26.00	27.00
65–69	103	14.52	6.04	6.00	7.00	10.00	14.00	19.00	23.00	26.00
70–74	103	13.42	5.27	6.00	7.00	9.00	13.00	17.00	20.60	22.60
75–79	177	13.41	5.29	6.00	6.80	9.00	13.00	17.00	21.00	24.10
≥*80*	189	12.38	5.21	5.00	6.00	8.00	11.00	16.00	21.00	23.00
Calf circumference (cm)‡										
60–64	157	36.22	3.84	30.90	32.00	34.00	36.00	38.50	40.20	43.00
65–69	109	36.14	3.85	31.50	32.00	34.00	36.00	38.00	40.00	42.50
70–74	113	35.33	3.22	30.70	31.00	32.50	35.00	38.00	39.00	40.00
75–79	188	35.22	3.89	29.00	30.90	33.00	35.00	38.00	40.00	41.50
≥*80*	199	33.58	3.63	27.00	29.00	31.00	34.00	36.00	38.00	39.00
Waist circumference (cm)*										
60–64	155	96.48	11.80	77.80	83.00	90.00	96.00	104.00	109.40	112.60
65–69	105	97.48	10.86	80.00	81.60	91.00	97.00	105.00	110.00	112.70
70–74	110	95.20	10.46	74.55	82.00	88.75	95.50	102.00	106.90	114.00
75–79	179	95.59	11.74	77.00	81.00	87.00	96.00	103.00	111.00	116.00
≥*80*	183	92.46	11.83	70.40	77.00	84.00	93.00	101.00	107.00	109.80

All anthropometric measurements decreased significantly with increasing age (‡$p \leq 0.001$; *$p \leq 0.002$; ANOVA) (‡$p \leq 0.001$; *$p \leq 0.002$; ANOVA)
SD standard deviation

(Table 92.4). In men, differences between age groups were significant. For women, there were no significant differences between age groups (Barbosa et al. 2005), as was observed by Perissinotto et al. (2002) in Italian elderly subjects.

Men and women from São Paulo (Barbosa et al. 2005) presented WC values (mean and percentiles) lower than those observed in elderly individuals in Chile (Santos et al. 2004) and Italy (Perissinotto et al. 2002) and greater than in Cuba (Coqueiro et al. 2009). When compared to the elderly of Rio de Janeiro (Santos and Sichieri 2005), men and women from São Paulo presented higher values, in spite of age-group extension.

Based on risk indicators for cardiovascular disease and metabolic disorders (WC ≥ 88 and 102 for women and men, respectively) (Lean et al. 1995), WC data from São Paulo indicate that approximately 25.0% and 50.0% of elderly men and women, respectively, from all age groups, may be at risk. Compared to the Cuban elderly (Coqueiro et al. 2009), the percentage of individuals at risk was greater for males and females in São Paulo.

Table 92.6 Anthropometric values for women (≥60 years). Survey on Health and Well-Being of the Elderly (SABE), São Paulo, Brazil, 2001 (Reprinted from Barbosa et al. 2005. With permission)

Age				Percentiles						
Group	*n*	Means	SD	5	10	25	50	75	90	95
Arm circumference (cm)‡										
60–64	227	32.42	3.88	26.00	28.00	30.00	33.00	35.00	37.00	39.00
65–69	210	31.12	4.03	25.00	27.00	28.00	31.00	34.00	36.00	38.45
70–74	185	31.35	4.78	24.00	25.00	28.00	31.00	34.00	37.00	40.00
75–79	242	30.87	4.30	24.00	26.00	28.00	31.00	33.00	36.00	38.00
≥80	256	28.56	4.27	22.00	23.00	26.00	29.00	31.00	34.00	35.15
Arm muscle circumference (cm)‡										
60–64	224	23.24	2.62	18.77	19.89	21.46	23.21	24.94	26.32	28.14
65–69	210	22.99	2.64	19.00	20.09	21.14	22.55	24.66	26.19	27.85
70–74	180	22.71	2.74	18.49	19.22	21.02	22.52	24.43	26.32	28.11
75–79	238	22.83	2.57	18.52	19.70	21.03	22.82	24.46	25.89	27.06
≥80	249	21.97	2.41	18.17	18.86	20.31	22.01	23.62	24.78	25.96
Triceps skinfold thickness (mm)‡										
60–64	224	28.85	7.71	17.00	20.00	23.00	29.00	35.00	39.00	42.00
65–69	210	25.88	7.31	15.00	17.00	20.75	26.00	30.00	35.00	38.00
70–74	180	26.61	8.67	11.05	14.00	21.25	27.00	32.00	39.00	42.00
75–79	238	25.25	8.14	11.95	15.00	20.00	25.00	30.00	37.00	39.00
≥80	249	20.35	7.48	8.00	10.00	15.00	20.00	25.50	30.00	33.50
Calf circumference (cm)‡										
60–64	225	36.85	4.21	31.00	32.00	34.00	36.00	40.00	42.00	44.00
65–69	209	35.86	4.04	29.50	31.00	33.0	36.00	38.00	41.00	42.00
70–74	184	35.76	4.07	29.00	30.00	33.00	36.00	39.00	41.00	42.00
75–79	241	34.95	3.90	29.00	30.00	32.00	35.00	37.50	40.00	41.00
≥80	255	33.57	4.05	27.00	28.00	31.00	34.00	36.00	38.00	41.00
Waist circumference (cm)										
60–64	224	94.58	14.01	73.00	76.00	85.00	94.00	104.00	110.00	120.50
65–69	205	91.86	13.12	71.00	75.60	83.00	91.00	100.00	110.00	114.00
70–74	180	95.21	14.71	70.50	76.10	84.00	96.00	105.75	113.80	118.00
75–79	232	94.92	12.75	75.65	78.00	86.00	94.50	104.00	111.00	114.35
≥80	228	93.32	13.66	70.00	74.00	84.00	94.00	102.00	110.00	116.00

Arm and calf circumference, muscle circumference, and triceps skinfold thickness were significantly higher in the youngest elderly (‡$p \leq 0.001$; ANOVA). For waist circumference, there were no significant differences between age groups

SD standard deviation

Using data from the SABE Survey, São Paulo, and considering the cutoff points from which men and women should avoid gaining weight (WC ≥ 94 cm for men and ≥ 80 cm for women) (Lean et al. 1995), the study carried out by Munaretti (2009) showed an independent association between WC and hypertension. The prevalence of individuals with inadequate WC values was 56.1% in men and 83.9% in women from São Paulo, which is greater than that observed in Rio de Janeiro (Santos and Sichieri 2005), being 39.2% and 65.9%, respectively (Fig. 92.5).

92.5 Body Fat and Muscle Mass Indicators

With aging, there is a redistribution of body fat and fat-free mass. The amount of fat in the upper and lower limbs decreases, and it is possible to observe reductions in the arm circumference (AC) and triceps skinfold (TSF) measurements. A decrease in the fat-free mass can be observed, especially concerning

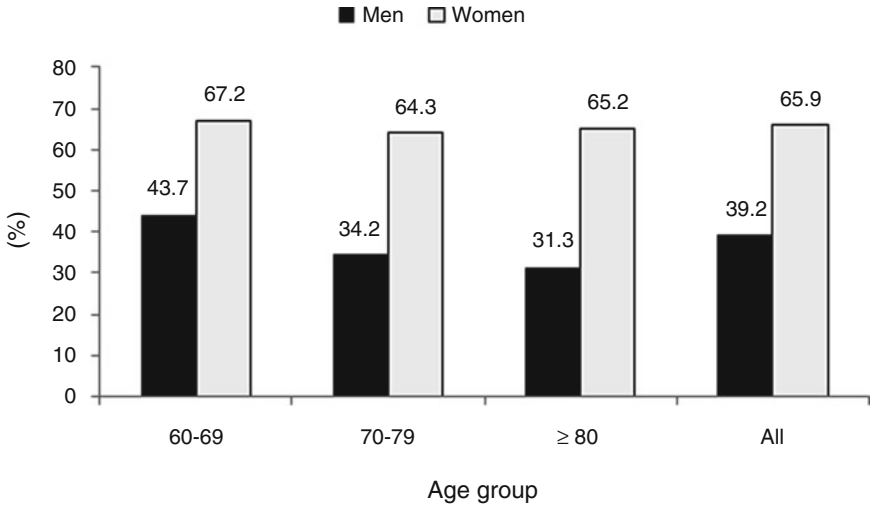

Fig. 92.5 Distributions of overweight (WC ≥ 94 e ≥ 80 cm)* in the elderly of Rio de Janeiro, according to sex and age group. *waist circumference for men and women, respectively. In all age groups, the prevalence of overweight was greater for women (Adapted from Santos and Sichieri 2005. With permission)

the reduction of muscle mass, the body's largest protein reserve (WHO 1995). Reductions in muscle mass can be identified in a decrease in calf circumference (CC) and in the arm's muscle circumference (Perissinotto et al. 2002; Barbosa et al. 2005; Menezes and Marucci 2007; Coqueiro et al. 2009); these regions provide estimates of the protein reserves, and can also indicate muscle use, or lack thereof.

Arm muscle circumference (AMC), AC, and CC estimate muscle reserves (the first two estimate arm muscle tissue and the last represents leg muscle tissue) and are considered good indicators for malnutrition in the elderly; also, CC has lately been recommended as a sensitive measurement for muscle mass loss in these individuals (WHO 1995). However, although AC and CC are anthropometric variables recommended for verifying muscle mass reserves, they represent the sum of bone, muscle, fat, and epithelial tissues for arms and legs, respectively, and should not be used independently (Menezes and Marucci 2007).

For the elderly of São Paulo (Barbosa et al. 2005), in all age groups, AC and TSF values were greater for women than men, whereas the latter presented greater AMC values. Calf circumference values were similar between men and women (Tables 92.5 and 92.6, respectively). Probably, such similar values occur due to gender-related differences in the proportion between fat and muscle mass. With increasing age, both sexes showed significant reductions in all measurement values.

The data from the elderly of Fortaleza (Menezes and Marucci 2007) show (Table 92.7) that TSF and AMC values were greater for men and women, respectively, as observed in the elderly of São Paulo (Barbosa et al. 2005) and Rio de Janeiro (Santos and Sichieri 2005). Arm circumference values were similar in both sexes. As the age groups increased, there was a significant reduction in AC and AMC values for men, and in TSF and AC for women.

A comparison between the data on the elderly of São Paulo, Fortaleza, and Rio de Janeiro is difficult, due to the difference in age-group intervals (shorter in São Paulo) and the lack of a percentile distribution by Santos and Sichieri (2005). However, it can be noticed that the differences are more evident for AC and TSF values, which are greater among men and women from Rio de Janeiro. It can also be observed that differences appear to be greater among women and younger age groups. As for the oldest age group, mean and percentile AMC values were rather close, in male and female elderly from Fortaleza and São Paulo.

Table 92.7 Anthropometric values for men and women (≥ 60 years). Fortaleza, Ceará, Brazil (2003) (Reprinted from Menenzes and Marucci 2007. With permission)

Age Group	*N*	Means	SD	Percentiles 5	10	25	50	75	90	95
Men										
Triceps skinfold thickness (mm)										
60–69	79	13.2	5.7	4.8	6.0	9.0	12.8	15.7	22.2	24.2
70–79	61	12.9	4.8	6.7	7.1	8.5	12.2	15.9	20.0	21.8
≥*80*	16	12.6	4.3	6.0	6.2	9.4	12.6	15.3	19.6	20.5
Arm circumference (cm) *										
60–69	79	29.7	3.5	24.1	25.4	27.6	29.8	31.6	34.1	36.0
70–79	61	29.2	2.7	24.6	26.0	27.5	29.0	31.6	32.8	33.0
≥*80*	16	27.1	3.1	20.5	22.2	25.4	26.7	29.2	31.8	31.9
Arm muscle circumference (cm) ‡*										
60–69	79	25.6	2.6	21.2	22.4	24.0	25.8	27.0	28.8	29.7
70–79	61	25.2	2.5	20.4	22.1	23.8	25.2	26.5	28.4	28.7
≥*80*	16	23.1	2.4	18.7	19.5	20.6	22.9	25.4	28.3	29.1
Women										
Triceps skinfold thickness (mm) ‡*										
60–69	159	23.0	7.3	11.5	12.7	17.2	22.7	28.0	32.3	35.0
70–79	121	20.2	6.1	9.9	12.0	16.4	20.0	23.4	29.4	31.5
≥*80*	47	18.2	7.0	6.3	8.5	12.7	19.2	23.3	27.5	30.1
Arm circumference (cm)										
60–69	159	30.2	4.9	23.8	24.5	26.8	29.6	33.1	36.2	39.3
70–79	121	28.6	3.9	22.1	23.7	26.0	28.4	30.8	33.6	35.9
≥*80*	47	27.7	4.9	18.3	21.3	24.0	28.4	31.3	34.0	35.5
Arm muscle circumference (cm) ‡*										
60–69	159	23.0	3.4	18.8	19.4	20.7	22.6	24.4	26.8	29.1
70–79	121	22.3	3.0	17.8	18.8	20.1	22.1	24.3	25.9	28.1
≥*80*	47	22.0	3.1	16.2	18.2	19.8	21.6	24.5	26.1	27.0

With increasing age, there was a significant reduction in arm circumference and triceps skinfold thickness (TSF) values, for men and women, respectively (*p <0.001; ANOVA). The mean value for arm muscle circumference and TSF was greater among men and women, respectively (‡$p \leq 0.001$; Student's t-test)
SD standard deviation

In the elderly of the three studies (Barbosa et al. 2005; Santos and Sichieri 2005; Menezes and Marucci 2007), AC values appear to indicate a greater quantity of subcutaneous fat for women, as females present greater TSF and lower AMC values. With increasing age, subcutaneous fat reduction is stronger for women and muscle mass loss is greater for men. In spite of these reductions, even the oldest men (≥80 years) continue to present greater muscle mass values (AMC) and women still present more subcutaneous fat (TSF), as was assessed in elderly individuals from other countries (Kuczmarski et al. 2000; Santos et al. 2004; Coqueiro et al. 2009).

92.6 Final Considerations

The data from the analyzed studies show that reductions in BM, height, and BMI with increasing age are reflected in the other anthropometric measurements, and show a stronger reduction in the oldest age group – although it should be stated that it is also the most heterogeneous group.

The patterns of alterations in anthropometric characteristics with increasing age are similar; however, the intensity of the differences varies between the populations, even in the same country. Anthropometric comparison of different populations should be carried out with caution because normal effects of aging result from both genetic differences and exogenous factors (socioeconomic and lifestyle differences, among the other factors) (Barbosa et al. 2005).

Bambuí, São Paulo, and Rio de Janeiro, in the southeast; Fortaleza, in the northeast; and Pelotas, in the south, are cities with diverse socioeconomic and environmental characteristics. São Paulo and Rio de Janeiro are the two most populous cities of Brazil, and the former is the capital of the state with the biggest industrial park and economic production in the country. Fortaleza is the capital of the state of Ceará, and its service sector comprises the largest part of the wealth produced in the state. Bambuí is a small town with 77.6% urban and 22.4% rural population (21,850 inhabitants), whereas Pelotas is a city with nearly 300,000 inhabitants and a 93.2% urbanization rate (IBGE 2009).

Besides the differences between the populations, other factors, such as method characteristics, number of participants, criteria for inclusion or exclusion of the sample, and the way in which the results are presented (Menezes and Marucci 2007), limit the comparisons.

92.7 Applications to Other Areas of Health and Disease

Anthropometry is a noninvasive, low-cost, and easy-to-apply method. Arm muscle circumference and CC, which estimate the muscle reserve, are considered as good indicators of undernourishment in the elderly, and CC has been considered as a sensitive measurement tool to measure the muscle mass loss in elderly individuals (WHO 1995). Weight change, BMI, TSF, AC, and CC are the essential components of several nutrition screening instruments developed for the elderly (Jensen et al. 2001; Huffman 2002; Guigoz 2006). Waist circumference has been used to identify central adiposity (visceral), and is also a measurement used to verify the risk of developing cardiovascular diseases and metabolic disorders.

The information from early studies may be used to compare and assess anthropometric characteristics (e.g., nutritional status, central adiposity, subcutaneous fat reserve, and muscle mass) in the elderly, in either clinical practice or epidemiological studies. If there is a lack of reference values for the Brazilian elderly, then these data can be used as a reference for the elderly individuals in other regions of the country, rather than comparing with the international data. The data can also be used for planning actions that intend to prevent or improve the nutritional inadequacy in the elderly, as well as for verifying the improvements achieved by the implemented actions.

92.8 Key Points of Anthropometry of Brazilian Elderly

The elderly have heterogeneous anthropometric characteristics that are specific to the location (city/region). Anthropometric alterations such as reductions in height, BM, BMI, increase in the proportion of body fat, changes in skin texture, and loss of muscle tissue, may be universal, but how they occur and their incidence may vary considerably within and between the groups of elderly individuals (whether genetically similar or not) owing to the action of environmental factors on normal aging effects.

Summary Points

- Sex and age are the determining factors in anthropometric changes.
- With increasing age, there is a reduction in height and BM, which are different for each gender. This reduction is greater among women.
- Muscle mass in the limbs decreases progressively and fat centralization increases with increasing age, especially in women.
- After 75 years, waist circumference (central adiposity) decreases more rapidly with aging in men than in women.
- Women accumulate more subcutaneous fat and have less muscle mass than men. With increasing age, subcutaneous fat reduction is greater in women, and the loss of muscle mass is greater in men.
- Independent of the cutoff point used to evaluate the nutritional status (BMI), overweight/obesity is more prevalent in women, and underweight is more common in men.
- With increasing age, there is a reduction in the prevalence of obesity and an increase in the prevalence of underweight, which is more evident after the age of 75 years.

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Chapter 93
Assessment of Sarcopenia

Daniel Bunout, Gladys Barrera RN, Pia de la Maza, Laura Leiva RT, and Sandra Hirsch

Abstract Sarcopenia is defined as the loss of muscle mass that occurs during normal aging and is associated with functional impairment. This is a dynamic concept that should consider the reduction of muscle mass over time but, for practical purposes, we must rely on cross-sectional measures to determine the presence of a significant loss of muscle mass. Double energy X ray absorptiometry is a reasonably accurate and inexpensive method to determine body composition. Knowing the body composition of a representative sample of older subjects in a specific community, regression equations to predict muscle mass can be derived to determine which individuals are sarcopenic using the residuals method. Functional measures should also be incorporated in the assessment of sarcopenia. The most popular assessments include walking capacity, the ability to rise from a chair and the measurement of muscle strength using dynamometers. A lower muscle mass and function in older subjects are risk factors for mortality and disability. Physical training is the only intervention capable of reverting the adverse consequences of sarcopenia.

93.1 Definition and Pathogenesis of Sarcopenia

Sarcopenia is defined as the loss of muscle mass that occurs during normal aging (Bales et al. 2002). It is associated with a deterioration of muscle strength and walking capacity leading to dependence. The causes are not completely known, but it is probably related to oxidative damage of muscle, nutritional or endocrinological changes that occur during the aging process.

Accumulation of reactive oxygen species in tissues is closely related to the aging process and caloric restriction the only experimental procedure that may retard the aging process, considerably reduces the accrual of these species (Zainal et al. 2000). The most probable target of oxidative damage is mitochondrial DNA, which leads to derangements of oxidative phosphorylation.

Several nutritional factors have been implicated in sarcopenia. Older people have higher protein requirements than young adults and they tend to fall in a negative nitrogen balance. Amino acid supplementation increases lean body mass (Dillon et al. 2009). Also, vitamin D deficiency, highly prevalent in the elderly, may also play a role in muscle loss (Bunout et al. 2006). Somatopause or

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_93,

the decline in growth hormone secretion with aging has also been related to sarcopenia and the supplementation with ghrelin, an enhancer of pulsatile growth hormone secretion (Nass et al. 2008), reverts it. Finally successive bouts of weight loss during late life contribute to muscle loss. Even if lost weight is regained, there is always a net loss of muscle, which is replaced by fat (Lee et al. 2009).

Whatever the cause of sarcopenia, the therapeutic options to revert it or decrease its functional consequences are limited to exercise training, the only intervention that has shown universal benefits for older subjects with sarcopenia, in a variety of scenarios (Bunout et al. 2005). This is a simple, safe and thrifty intervention that should be widely recommended to older people. Its drawback is the lack of compliance with exercise sessions. Probably, better educational campaigns encouraging older subjects to engage in physical activities and sports will partially overcome these limitations.

93.2 Measurement of Muscle Mass and Function

93.2.1 Muscle Mass

Anthropometry is practically useless as an assessment method of sarcopenia since it must relay on the estimation of body fat, using calipers to measure skin fold thickness. This measurement has a low inter observer concordance and a very low correlation with body fat measured with more accurate methods, such as those described below To determine the total or appendicular amount of muscle in an individual, radiological methods or densitometry, should be used.

Double energy X-ray absorptiometry (DEXA) is a relatively inexpensive method to assess body composition and it is accurate if used in a homogeneous group of subjects in terms of age and health status (Williams et al. 2006). The case of subjects in whom shifts in body hydration produce significant errors in the estimation of body compartments is different (Georgiou et al. 1997). This method gives a good estimate of fat free mass, which also can be divided easily in different body segments to calculate appendicular (limb) and truncal composition. A recent study compared DEXA with magnetic resonance imaging to determine the amount of skeletal muscle mass in older women, obtaining a correlation of over 0.9 between both methods (Chen et al. 2007).

Bioelectrical impedance is another inexpensive method that relies on the fact that body impedance is inversely proportional to body water content. When multi-frequency bioelectrical impedance is used, the concordance with DEXA measurements is acceptable, if local regression equations are generated for the population that is being studied (Shafer et al. 2009).

Computed tomography and magnetic resonance are highly accurate to measure body composition, but also very expensive. These methods measure not only the amount of muscle but also its quality. In older subjects, there is a progressive fat infiltration of muscle (Cree et al. 2004), which not only replaces functional muscle fibers but also damages the remaining ones. This infiltration may be recognized as a reduction in radiological density of muscle in computed tomography (Goodpaster et al. 2000) or using magnetic resonance spectrometry, that is a far more exact method (Torriani et al. 2005). Probably, in the future the radiological density of muscle will have to be added to volume measures to obtain a better prediction of muscle strength. The disadvantage of these methods is that their cost precludes their widespread application in clinical or epidemiological settings and must be reserved for research purposes.

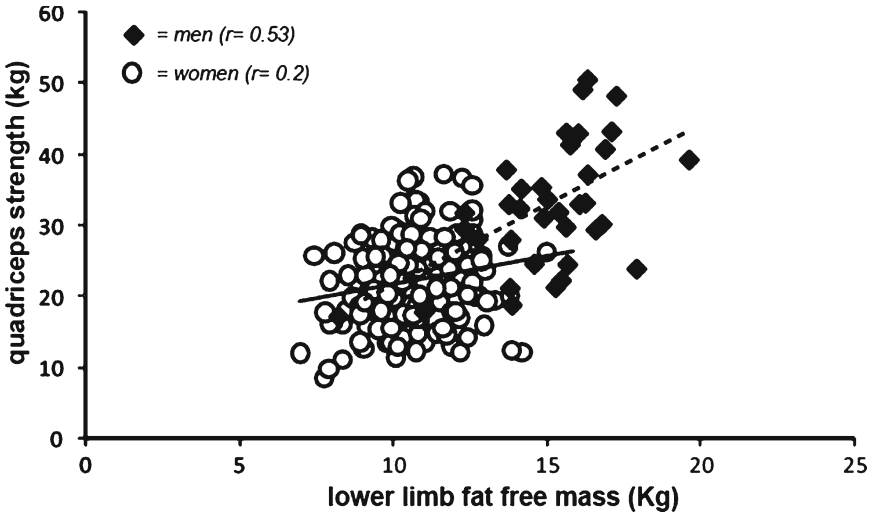

Fig. 93.1 Correlation between lower limb fat free mass measured by Double energy X Ray Absorptiometry (DEXA) and quadriceps strength in a group of healthy men and women. There is a positive correlation between quadriceps strength and lower limb fat free mass in both men and women. However, the correlation coefficients are low

93.2.2 Muscle Function

Functional measures have also been used as surrogate measures of muscle mass and quality in the elderly. The main parameters used are:

Muscle strength measurement using dynamometers: The most widely used is hand grip strength. We have used it to predict the muscle mass of older subjects (Arroyo et al. 2007), but it must be borne in mind that the correlation of strength with mass, although significant, is weak. The strength of other muscles such as quadriceps and biceps can be measured using hand held dynamometers or quadriceps tables but still, the correlation with muscle mass is low (Fig. 93.1).

1. *Walking capacity assessment using the 6 or 12 min test*, which consists in recording the maximal distance that a subject can walk at a constant pace in a flat surface during 6–12 min (McGavin et al. 1967). It was originally devised to evaluate patients with respiratory diseases, but has proven very useful to assess the functional capacity of older subjects. Moreover, during a 3 year follow up, we observed a close association between the evolution of fat free mass and walking capacity in this age group (Fig. 93.2). Although the association of walking capacity with muscle mass is low, other authors reported that it has a good prognostic value for future disability in the elderly (Tainaka et al. 2009).
2. *Composite functional tests*: The most popular are the timed up and go (Rockwood et al. 2000) and the short physical performance battery (Guralnik et al. 1995). Both are based on the assessment of the capacity of standing up from a chair, walking a short distance and being able to maintain a standing position. These tests are very useful to predict frailty and are relatively simple to use, but their association with muscle mass is weak, at best. An interactive program with Spanish versions of these tests can be found in: http://www.inta.cl/Estudiantes/programas/ProgramasInteractivos.htm.

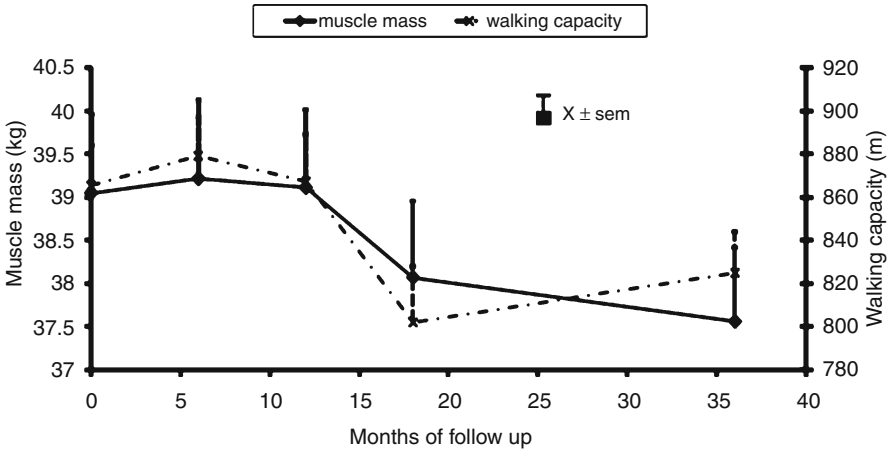

Fig. 93.2 Association between the evolution of walking capacity measured using the 12 min test and total fat free mass measured by Double energy X Ray Absorptiometry (DEXA) in a group of 86 older subjects followed up for 3 years. This figure shows repeated assessments during a 36 months follow up. A close concordance between the evolution of total fat free mass and walking capacity, was observed

93.3 Defining Cutoff Points to Diagnose Sarcopenia

Sarcopenia is a functional concept, since it encompasses muscle mass loss throughout time. Therefore, from a purist's point of view, the real way of diagnosing sarcopenia is to follow up older subjects after a lapse of more than 1 year and to define the muscle mass attrition that they have experienced. We have followed subjects for 3–5 years to calculate it. The mean loss of fat free mass, measured by DEXA is 221 ± 399 and 521 ± 454 g/year in females and males, respectively (Bunout et al. 2007) (Fig. 93.3). However the dispersion of values is high, and there is a group of subjects that do not lose fat free mass.

However, this type of follow up is normally done only in research facilities. What clinicians and epidemiologists require is to predict which subjects are sarcopenic, based on cross sectional assessments. This cross sectional definition of sarcopenia can be done in several ways:

93.3.1 Statistical Definition

This means to define as sarcopenic those individuals with a low amount of muscle mass, compared to subjects of the same age and gender or compared to young counterparts, which becomes the "gold standard" for muscle mass. Most authors have divided the amount of appendicular muscle mass by the squared height in meters, in a manner analogous to body mass index (appendicular fat free mass index). Afterwards, they defined as sarcopenic those individuals who have an appendicular skeletal muscle mass/height^2 two standard deviations below reference values of young individuals. This is similar to the t- score calculated to define osteoporosis (World Health Organization 1994). To test the value of this assessment, they have calculated the association of this parameter with functional measures such as muscle strength and gait speed. Using this definition of sarcopenia, its observed prevalence in subjects aged 60 years or more ranges from 15% to more than 50% in the oldest individuals.

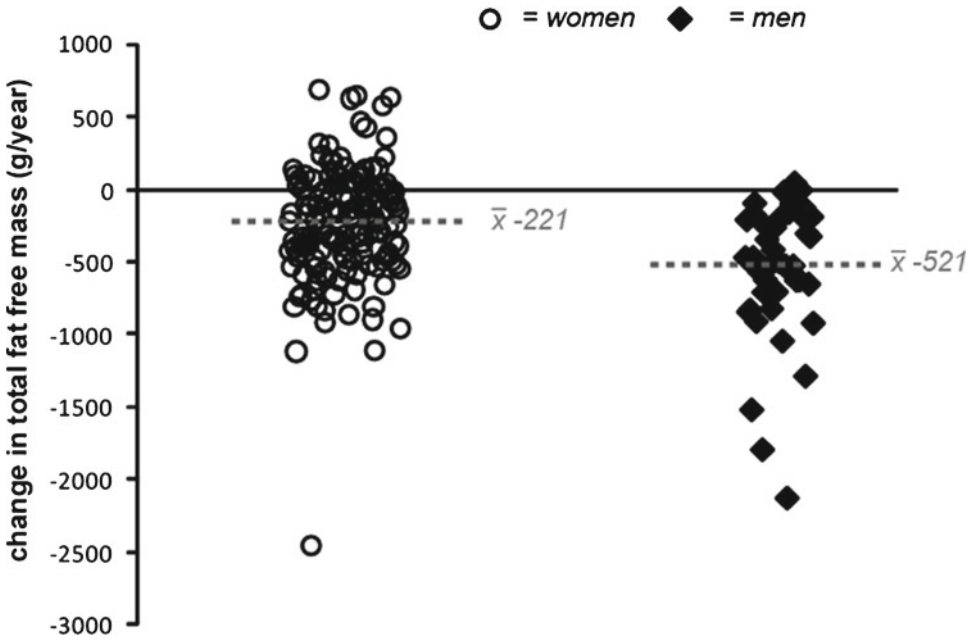

Fig. 93.3 Loss of fat free mass measured by Double energy X Ray Absorptiometry (DEXA) in 148 women and 45 men aged 70 years or more, followed for a mean of 5 years. The figure show the individual changes in total fat free mass in a group of healthy older men and women followed with repeated measurements during 5 years. There is a great dispersion of values and a small group of subjects that did not lose fat free mass during the follow up

The problem with this method is that a reference database with body composition data of young individuals of the same ethnicity and socioeconomic condition is required to calculate the t-score. This information is not always available or reliable.

To overcome this drawback, the other alternative is to calculate the amount of muscle and relate it to peers of the same age, overcoming the requirement of data from young people. When performing the calculations in this manner, gender-specific tables must be generated since there is a huge difference in the amount of muscle between men and women. Secondly, the amount of total or appendicular lean body mass must be corrected by height (dividing by the height or the squared height). Again, the ideal is to have a large set of data to obtain confident results.

A simpler method of determining which individuals are sarcopenic is to define sex-specific quartiles or quintiles and to consider as sarcopenic those individuals located in the lower quintile of lean body mass. Another way to perform the same calculation is to determine a regression equation in which the dependent variable is lean body mass and the independent variables are all those that are predictors of the former in an univariate analysis. Once the regression equation is obtained, the residuals or the difference between the actual and predicted lean body mass may be calculated (Fig. 93.4). The cutoff point where a residual becomes significant must be decided. In a recent paper, we compared the quartiles and residuals of lean body mass in a group of healthy elderly subjects followed for 4.8 years. Both methods resulted as significant predictors of fat free mass loss, assessed during the follow up. Therefore, even without having available data of young subjects, sarcopenic individuals can be identified as those that have the lowest amounts of lean mass, when compared to their peers. As an example, Table 93.1 depicts the cutoff values for fat free mass, to consider a subjects as sarcopenic, based on equations derived from subjects studied by the authors (Bunout et al. 2007).

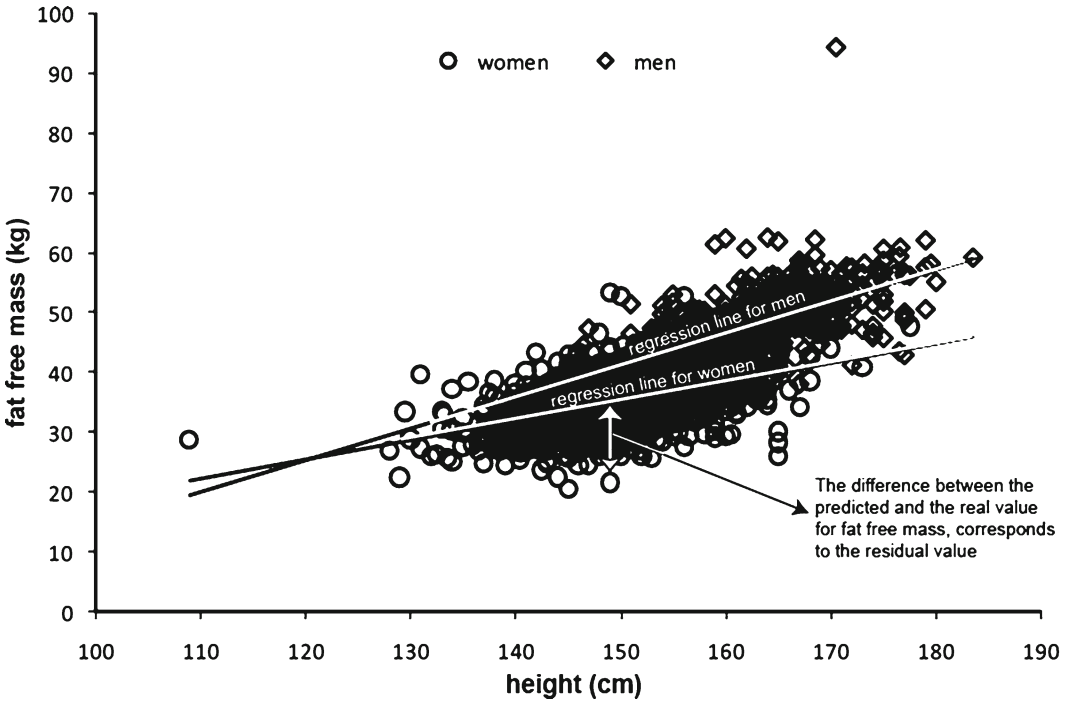

Fig. 93.4 An example of how to calculate residual values of fat free mass using a regression equation with height and age as independent factors. A regression equation for fat free mass is calculated for each gender, using height and age as independent factors. The difference between the measured and the predicted value (*arrow*) corresponds to the residuals and is used to diagnose sarcopenia, using cutoff points that are specific for each population of individuals

93.3.2 Prognostic Definition

Even though we can identify those subjects that have lost the greatest amount of muscle mass, the real reason to identify those individuals are prognostic or therapeutic issues. As mentioned before, the only available treatment for sarcopenia that is universally accepted is exercise and it should be prescribed to all individuals. Therefore, the identification of sarcopenia from a therapeutic point of view is worthless. However, the use of sarcopenia as a prognostic indicator of mortality or disability is attractive. Moreover, a working definition of sarcopenia should ideally be based on prognostic indicators rather than on statistical parameters. The most commonly used end points to determine prognosis are mortality and disability.

Mortality: Longitudinal studies have shown that muscle strength measured using a hand grip dynamometer or functional capacity measured using walking speed are better predictors of 6 years mortality than muscle mass measured by DEXA or 24 h urine creatinine excretion (Metter et al. 2002). Other studies have demonstrated that frailty, defined as a low muscle strength, a low walking speed or a low amount of appendicular muscle mass, increased the risk of mortality among men older than 65 years by a factor or two (Cawthon et al. 2007).

We recently analyzed the data of 1,500 elderly subjects that had a measurement of muscle mass and were followed for a median of 5 years. Among subjects older than 74 years, the amount of appendicular fat free mass was a significant predictor of mortality (Fig. 93.5).

(a) *Disability*: As stated before, the correlation between muscle mass and strength is generally low (Bunout et al. 2004). However if a functional parameter is used as endpoint, such as walking capacity, muscle strength becomes an excellent predictor of disability (Arroyo et al. 2007).

Table 93.1 Prediction of sarcopenia based on fat free mass measured by Double energy X Ray Absorptiometry (DEXA) and equations published in Aging (2007) 19:295

		Females		Males	
Age (years)	Height (cm)	Predicted fat free mass (kg)	Sarcopenic if fat free mass is below (kg)	Predicted fat free mass (kg)	Sarcopenic if fat free mass is below (kg)
65	150	35.3	32.7	44.6	41.9
	160	37.6	35.0	48.6	45.9
	170	40.0	37.4	52.6	49.9
	180	42.3	39.7	56.6	53.9
	190	44.7	42.1	60.6	57.9
70	150	35.0	32.4	43.6	41.0
	160	37.4	34.8	47.6	45.0
	170	39.7	37.1	51.6	49.0
	180	42.1	39.5	55.6	53.0
	190	44.4	41.8	59.6	57.0
75	150	34.5	31.9	42.3	39.7
	160	36.9	34.3	46.3	43.7
	170	39.2	36.6	50.3	47.7
	180	41.6	39.0	54.3	51.7
	190	44.0	41.3	58.3	55.7
80	150	34.2	31.5	41.3	38.7
	160	36.5	33.9	45.3	42.7
	170	38.9	36.2	49.3	46.7
	180	41.2	38.6	53.3	50.7
	190	43.6	40.9	57.3	54.7
85	150	33.6	31.0	40.0	37.4
	160	35.9	33.3	44.0	41.4
	170	38.3	35.7	48.0	45.4
	180	40.6	38.0	52.0	49.4
	190	43.0	40.4	56.0	53.4
90	150	32.6	30.0	36.7	34.1
	160	35.0	32.3	40.7	38.1
	170	37.3	34.7	44.7	42.1
	180	39.7	37.0	48.7	46.1
	190	42.0	39.4	52.7	50.1

An 8 year follow up study showed that the risk of developing disability, determined using a mailed questionnaire, was 27% higher in elderly men and women with a low muscle mass (Janssen 2006). Another study observed a relationship between health-related quality of life in older people and hand grip strength (Sayer et al. 2006). There is also an association between weakness and poor function and the risk of hospitalization in older subjects (Cawthon et al. 2009).

(b) *Composite indexes*: There is always a temptation to combine several parameters in a single score to obtain better prognostic yields in the evaluation of patients. Sarcopenia is not the exception and a group of authors developed an index that combines measures of muscle mass, strength and function, demonstrating its validity for epidemiological research (Miller et al. 2009). The problem with this type of composite indexes is that they must be validated in each new population where they will be used; they are seldom used by clinicians, who prefer simple and single measurements to assess risk.

(c) *Sarcopenic obesity*: Recently, the concept of sarcopenic obesity has been incorporated and several studies and have observed that obesity, defined as a percentage of body fat over 35%, is a better predictor of physical disability than sarcopenia and that the latter, in the absence of obesity, is not associated with physical difficulties (Rolland et al. 2009).

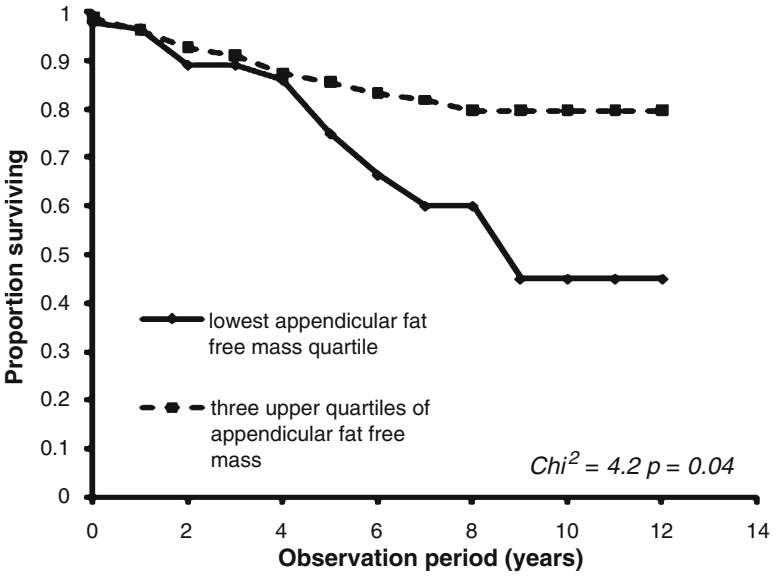

Fig. 93.5 Mortality of elderly subjects according to their appendicular fat free mass measured by Double energy X Ray Absorptiometry (DEXA). Mortality of healthy older subjects was recorded during a 12 year follow up. Subjects aged over 74 years in the lowest quartile of appendicular fat free mass had a significantly higher mortality than their counterparts without sarcopenia

We have some doubts about the real influence of obesity on the risk of elderly subjects. These apprehensions are based on the observation that mortality among this age group is higher among those with a low body mass index and the factor that is related to mortality is the presence of excessive visceral fat (Price et al. 2006). Probably, extreme degrees of obesity influence the functional performance of older subjects, but a body mass index between 27 and 30 kg/m^2 appears more as a protective rather than a risk factor.

93.4 Conclusions

Sarcopenia is a dynamic process whose importance lies in its functional consequences and its association with mortality among older people. Therefore we need to determine the cutoff points to define sarcopenia based on prognostic rather than statistical factors. According to the literature and our own experience, the assessment of muscle mass in the elderly can be performed reliably and economically using double energy X-ray absorptiometry (DEXA) equipment. On the other hand, the measurement of hand grip strength and walking capacity are simple to use functional measures. A set of data of an important number of elderly subjects should be obtained in every country to define sex and age stratified quartiles or quintiles. Subjects in the lowest quartile or quintile of any of the functional or mass measures may be considered, without fear of sinning, as sarcopenic. This assumption is based on data from all the prospective studies on sarcopenia. Obviously, the ideal is to follow the subjects to determine local risk factors for disability or mortality, but this is not always feasible.

Finally, it is important to remember again that the best measure to prevent muscle loss and its consequences is to recommend physical activity to all older subjects.

Summary Points

- Sarcopenia is defined as the loss of muscle mass that occurs during normal aging and is associated with functional impairment
- The only intervention considered useful thus far to prevent the consequences of sarcopenia is physical training
- Anthropometry is not useful to assess sarcopenia
- Double energy X ray absorptiometry should be used to assess body composition in the elderly
- The short physical performance battery (SPPB), the timed up and go (TUG), the 6 min walk and hand grip dynamometry are good functional indicators of disability associated with sarcopenia
- Sarcopenia is a risk factor for disability and mortality

Key Points

- Sarcopenia is a dynamic concept indicating a loss of muscle mass with aging
- Sarcopenia is associated with a higher risk of disability and mortality
- Measurement of muscle mass is best achieved by double beam X-ray absorptiometry (DEXA)
- The determination of cutoff points to diagnose sarcopenia can be accomplished using regression equations based on local data.

Key Features of Dynamometers

- These are simple devices used to measure muscle strength
- They are hand held and will measure the strength of specific muscle groups
- The most commonly used are those that measure the hand grip strength
- There are also dynamometers that measure the strength of proximal muscles of upper and lower limbs

Key Features of 6 or 12 min Walk

- This test is a simple measure of endurance
- It only requires a flat surface such as a football or baseball field
- The perimeter of the field must be measured
- The number of laps that a subject is capable of walking in 6 or 12 min at a constant pace is recorded
- A walking speed of less than 1 m/s is considered abnormal
- This measure is a good predictor of future disability

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Chapter 94
Body Mass Index and Cardiac Events in Elderly Patients

John A. Batsis and Silvio Buscemi

Abstract Body Mass Index has been challenged as an anthropometric measurement in elderly patients. Recent data, even in elderly patients, has demonstrated that elevated body mass index affords a worse long-term prognosis, although the magnitude of this relationship weakens as one ages. Underweight patients, possibly due to elements of sarcopenia and/or frailty, are also at a higher risk of overall mortality. A number of inflammatory mediators may be responsible for such factors which likely contribute to the increased risk of cardiovascular events observed. Although body mass index has been implicated in the development of heart failure, coronary artery disease and mediates its effects through other cardiovascular risk factors, it appears that it may indeed be protective in elderly patients who are overweight or mildly obese. Conversely, low body mass index may be harmful, a concept known as the obesity paradox which has been observed in a number of settings including congestive heart failure following cardiac surgery and in particular following hip fracture repair. This chapter examines the impact of body mass index on overall mortality and cardiovascular events in elderly patients. Although there are similarities between older patients and those of young and middle age, there are striking differences which will be delineated in this review.

Abbreviations

BIA	Bioelectrical impedance
BMI	Body Mass Index
CABG	Coronary artery bypass graft
CV	Cardiovascular
CRP	C-reactive protein
DEXA	Dual energy x-ray absorptiometry
IL-6	Interleukin 6
TNFα	Tumor necrosis factor α

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_94,

94.1 Introduction

Obesity has been deemed a modifiable cardiovascular risk factor according to the American Heart Association. Obesity not only mediates traditional cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia, but also reduces insulin sensitivity, enhances free fatty acid turnover and promotes systemic inflammation, all of which induce atherosclerosis and lead to the development of coronary artery disease (Domfeld and Maxwell 1985; Gregg et al. 2005; Grundy et al. 2005). Other adverse effects of obesity are listed in Table 94.1 (Lavie et al. 2009). The impact of obesity on non-cardiac outcomes has been covered in other chapters of this Handbook.

94.2 Challenges and Limitations of BMI in Elderly Patients

Both the World Health Organization and the National Institutes of Health use body mass index (BMI) to define and classify patients with obesity (Quetelet 1871). However, the diagnostic performance of BMI has repeatedly been challenged for some very important reasons, particularly in elderly patients (Jackson et al. 2002). There are conflicting results when examining the correlation between BMI and key clinical outcomes, such as mortality, disability and cardiovascular events. In addition, the ability of BMI to accurately discriminate adiposity has also been called into question. BMI is calculated by using total body mass in kilograms, divided by the square of height (kg/m^2). This calculation incorporates both adipose tissue and lean mass, both of which have biochemical and mechanistic differences in terms of bodily function and outcome measures (Smalley et al. 1990). BMI can overestimate adiposity in younger patients with increased musculature, but can underestimate adiposity in elderly patients who have age-related reduction in lean mass and increasing amounts of fat deposition.

Previous studies using bioelectrical impedance (BIA) have demonstrated the poor relationship between BMI and adiposity (Blew et al. 2002). Although BIA has been used to accurately assess adiposity in nationally representative databases because it is reproducible and easy to perform, unfortunately it is impractical in a primary care office setting. One significant limitation in using BMI in elderly populations is that it simply cannot account for differences in fat mass and lean mass (Bales and Ritchie 2002; Dey et al. 1999). In elderly patients, lean mass and percent body fat correlate with BMI to a lesser degree than a corresponding younger cohort (Prentice and Jebb 2001). The calculation of absolute values of BMI in the elderly is influenced by changes that commonly occur as people age in both the numerator (weight) and the denominator (height). Weight often changes either intentionally or not, and loss of height occurs, both physiologically and pathologically, such as with vertebral compression fractures. Due to reduction in height with age, the possibility exists that BMI in the elderly is falsely elevated and may thus be a poor predictor of CV events. Furthermore, because of changes in body composition in the elderly occurring even in the female sex, the comparison of what BMI represents in these populations may not be equal across sex and age. Hence it may seem inappropriate to extrapolate data obtained in young and middle age patients to an elderly cohort (Prentice and Jebb 2001). In this respect, it has also been proposed that the optimal range of BMI in elderly people should be increased with respect to that considered for younger subjects (Beck and Ovesen 1998; Villareal et al. 2005).

By using BMI, inherent misclassification of patients that are obese may occur, particularly in the primary care setting where this anthropometric measurement is commonly utilized. Other anthropometric measures, including waist circumference, waist-hip ratio or hip circumference, have been proposed to be used in lieu of BMI as a means of identifying and defining obesity, particularly in elderly patients (Price et al. 2006). Studies have demonstrated that death may be better predicted by

Table 94.1 Disorders associated with obesity

1. Increases in insulin resistance
   (a) Glucose intolerance
   (b) Metabolic syndrome
   (c) Type 2 diabetes mellitus
2. Hypertension
3. Dyslipidemia
   (a) Elevated total cholesterol
   (b) Elevated triglycerides
   (c) Elevated LDL cholesterol
   (d) Elevated non-HDL cholesterol
   (e) Elevated apolipoprotein-B
   (f) Elevated small, dense LDL particles
   (g) Decreased HDL cholesterol
   (h) Decreased apolipoprotein-A1
4. Increased systemic inflammation and prothrombotic state
5. Endothelial dysfunction
6. Abnormal left ventricular geometry
   (a) Concentric remodeling
   (b) Left ventricular hypertrophy
7. Systolic and diastolic dysfunction
8. Heart Failure
9. Coronary artery disease
10. Atrial fibrillation
11. Obstructive sleep apnea/sleep-disordered breathing
12. Albuminuria
13. Osteoarthritis
14. Cancers

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waist circumference than BMI, both in men and women (Folsom et al. 2000; Heitmann et al. 2000). Ideally, methods including CT scanning, dual-energy x-ray absorptiometry (DEXA) and BIA, or hydrostatic measures, can all assess adiposity with greater accuracy and precision (Fogelholm and van Marken Lichtenbelt 1997). Despite this advantage, these modalities have significant disadvantages including increased cost, subjecting patients to possible radiation and harm and being clinically impractical in a busy office setting.

94.3 Body Mass Index and Mortality

94.3.1 Studies Using the National Health and Nutrition Examination Surveys (NHANES)

The relationship between BMI and mortality appears to be "U" or "J" shaped. This was well characterized in a study using data obtained from NHANES which examined BMI categories and subsequent risk of all-cause mortality in a cross-sectional manner (Flegel et al. 2005). In elderly patients, stratified between ages 60 and 69 and >70, underweight patients appear to have a higher relative risk of mortality

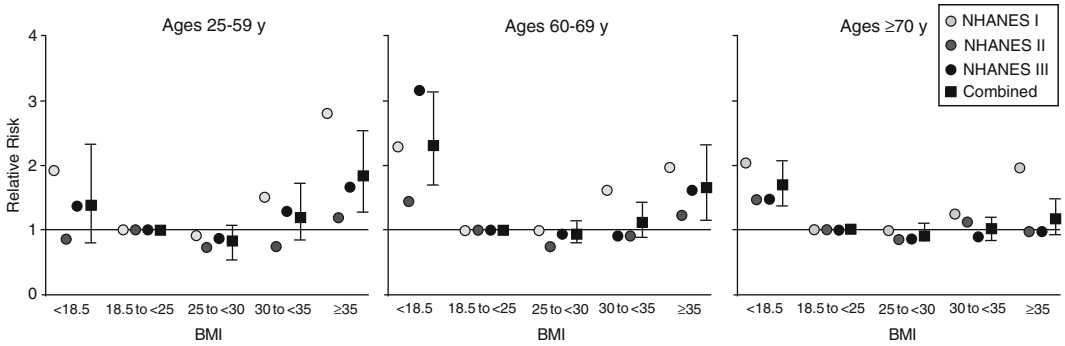

Fig. 94.1 Relative risks of mortality by BMI category, survey, and age BMI indicates body mass index, measured as weight in kilograms divided by the square of height in meters. The reference category with relative risk 1.0 is BMI 18 to <25. Error bars indicate 95% confidence intervals (Obtained with permission from Flegal et al. 2005. Copyright © 2005 American Medical Association. All rights reserved)

Table 94.2 Key features of the National Health and Nutrition Examination Survey (NHANES)

1. Assesses health and nutritional status of adults and children in the United States
2. Began collecting data in the 1960's in the United States population and is now a continuous program
3. Examines a nationally representative sample of ~5,000 persons yearly
4. Data includes questionnaires, an examination and laboratory component
5. Findings from the survey data are used in determining prevalence of major diseases and risk factors in disease-related epidemiology
6. Important in guiding health policy to help improve health status and prevent future health problems

than normal BMI patients, even higher than obese patients (Fig. 94.1). Examining cause-specific mortality using NHANES data (Table 94.2), the same group ascertained that for cardiovascular disease, obesity (BMI>30 kg/m^2) was positively associated with excess mortality and significantly increased mortality from both coronary heart disease and other forms of cardiovascular disease including cancers considered obesity related, than other BMI categories (Flegal et al. 2007) (Fig. 94.2). In this analysis, underweight or overweight patients were not at any different risk. Other studies confirm that obesity may have a higher hazard ratio than under or overweight.

94.3.2 Accuracy of BMI in Elderly

In general, BMI has often been challenged as an accurate anthropometric measure in predicting the risk of mortality in elderly patients. Results of studies have often been conflicting with regard to type of risk. Much of the controversy stems from biases and confounding variables. When data are corrected for smoking, a linear relationship has resulted between BMI and the risk of mortality (Ajani et al. 2004). However, some studies showed that an increased BMI value in elderly patients has a protective effect in terms of mortality risk. These confusing results are probably the consequence of many potential specific biases; for example, a history of weight change may influence mortality risk. Some studies provide evidence that the median survival is reduced in those subjects who have reached an increased BMI in elderly (Whitlock et al. 2009). Other studies showed an increased risk in those elderly subjects who lost weight (Strandberg et al. 2009). A significant problem is the difficulty in

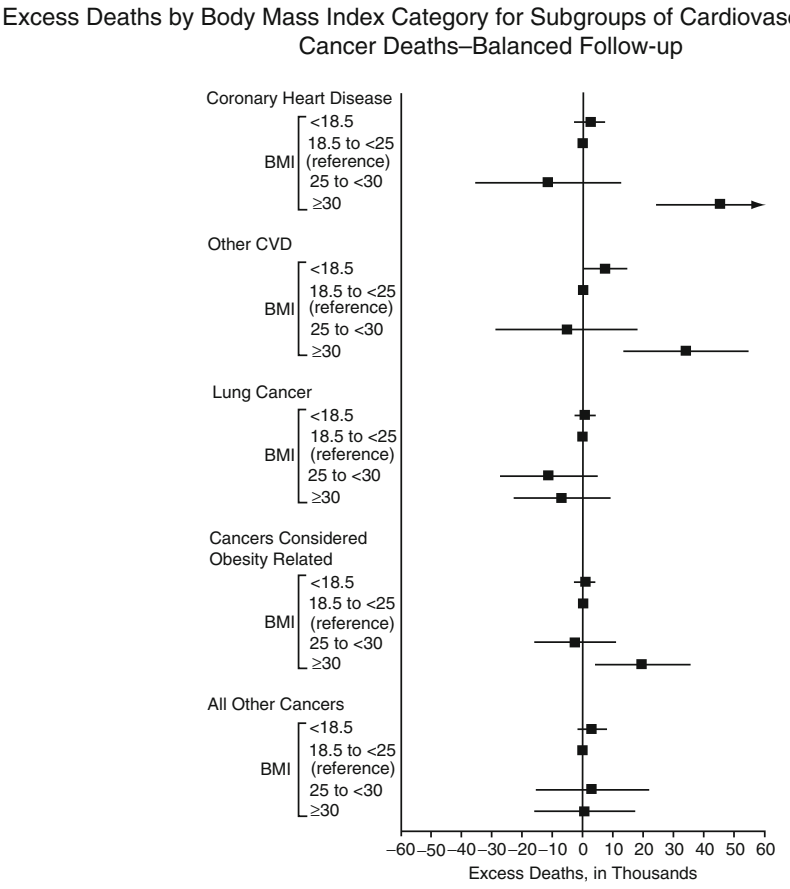

Fig. 94.2 Excess deaths by body mass index category for subgroups of cardiovascular disease and cancers BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; *CVD* cardiovascular disease. Error bars indicate 95% confidence intervals (Obtained with permission from Flegal et al. 2007. Copyright © 2005 American Medical Association. All rights reserved)

establishing whether the body weight change is intentional or unintentional in this class of subjects. Furthermore, death events related to an increased BMI may occur earlier in life and it may be the case that those subjects who reach the elderly age group are less prone to cardiovascular complications.

94.3.3 Overall and Cardiac Mortality in Elderly – Meta-Analyses

Most studies examining overall or cardiac mortality have used BMI as a surrogate for obesity, and this is no exception in elderly patients. Many studies were retrospective cohorts, or prospective cohorts that were otherwise underpowered to prove any causal association between these entities. Stevens et al suggested that approximately 400 events in each age category are needed to detect a relative risk of 1.5 (Stevens et al. 1998). A recent meta-analysis determined the association between obesity and overall mortality and cardiovascular events in all patients (Romero-Corral et al. 2006). In this analysis, over 40 studies with a mean follow-up of 3.8 years were identified, consisting of 250 and 152 patients. Their results suggested that patients with a low BMI, defined as a BMI ≤ 20, had a

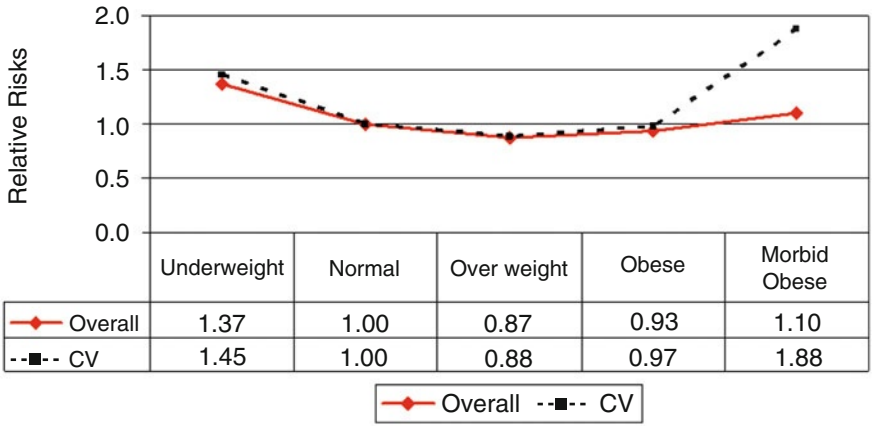

Fig. 94.3 Mortality in coronary artery disease patients. Adjusted relative risks in each category of BMI (<18.5, 18.5–24.9, 25–29.9, 30–34.9, 35+) for mortality in patients with coronary disease. Overall mortality and cardiovascular specific mortality risks are demonstrated. The referent category is patients with a normal BMI (18.5–24.9 kg/m^2). (Reprinted and adapted from Romero-Corral et al. (2006) © 2006. With permission from Elsevier)

higher risk of overall and cardiovascular mortality than patients with a BMI between 25–29.9 kg/m^2 (Fig. 94.3). There was no increased risk for patients with a BMI between 30–35 kg/m^2 other than in those with a history of having a coronary artery bypass graft (CABG). Class II+III obese patients (BMI ≥ 35 kg/m^2) had higher cardiovascular mortality but not overall mortality. Although this study did not differentiate between age groups, it provides important information about the utility of BMI as a discriminatory anthropometric variable. As is mentioned subsequently, elders with low BMI may have an element of sarcopenia, or decreased muscle mass (Lauretani et al. 2003). This entity is known to be an independent mortality predictor in elders. However, this population is also known to have reduced exercise tolerance and reduced functional status both of which are associated with increased overall mortality (Roubenoff 2000b). Nonetheless, morbidly obese patients, with increased amounts of excess body fat, had significantly higher risks for cardiovascular events, confirming the importance of excess adiposity on the impact of cardiovascular events (Eckel et al. 2002).

One of the many challenges in examining the impact of BMI on mortality or cardiovascular events, particularly in looking at the elderly, is adjusting for potential confounding variables. In a recent meta-analysis, a definitive collaborative study analyzed the relationship between BMI and cause-specific mortality in over 900,000 adults in 57 prospective studies predominantly from Western nations (Whitlock et al. 2009). There were 6.5 million years of person-follow-up. This was a study of epic proportions demonstrating that BMI between the ages of 35 and 89 years in both sexes, as a surrogate for obesity, is associated with increased overall mortality. Their data suggested that all-cause mortality, between a BMI 15–50 kg/m^2 demonstrated a J-shaped association in both males and females at all age levels, including 60–69 years, 70–79 years and 80–89 years. These associations persisted in 70–79 year olds between smokers and non-smokers (mortality risk ratio <2.5). They also demonstrated that in patients with a BMI between 25–50 kg /m^2, the effects of BMI and smoking were additive for vascular mortality and all-cause mortality. They additionally ascertained relative risk of different diseases according to BMIs as demonstrated in the Figs. 94.4–94.6. The author's overall conclusions from this study hold true, even in elderly patients, that BMI may indeed be a strong predictor of overall mortality at opposite ends of the optimal 22.5–25 kg/m^2 range. They suggested a causal association between BMI and vascular disease above this range. In addition,

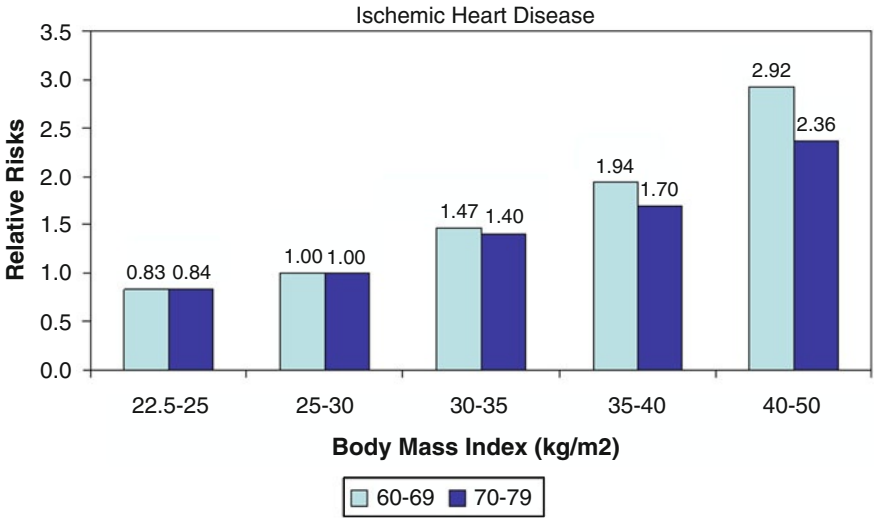

Fig. 94.4 Assumed causal relative risks for mortality estimates – ischemic heart disease. Figure represents relative risks for mortality estimates for ischemic heart disease. Data represents relative risks in each BMI category (referent is 25–30 kg/m^2) in the 60–70 and 70–79 year age groups. (Reprinted and adapted from The Whitlock et al. (2009). Web tablet 10. Prospective Studies Collaboration, Body Mass Index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies, © 2009, with permission from Elsevier)

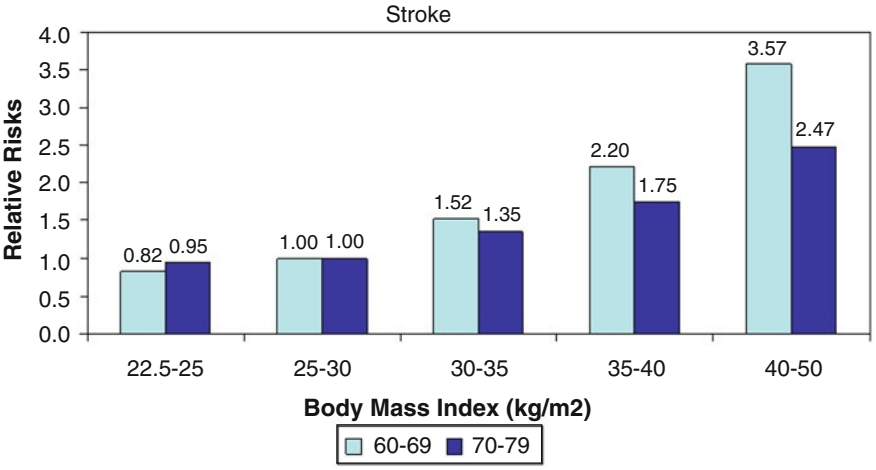

Fig. 94.5 Causal Relative Risks for Mortality Estimates – Stroke. Figure represents relative risks for mortality estimates for stroke. Data represents relative risks in each BMI category (referent is 25–30 kg/m^2) in the 60–70 and 70–79 year age groups (Reprinted and adapted from The Whitlock et al. (2009). Web tablet 10, Prospective Studies Collaboration. Body Mass Index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies, © 2009. With permission from Elsevier)

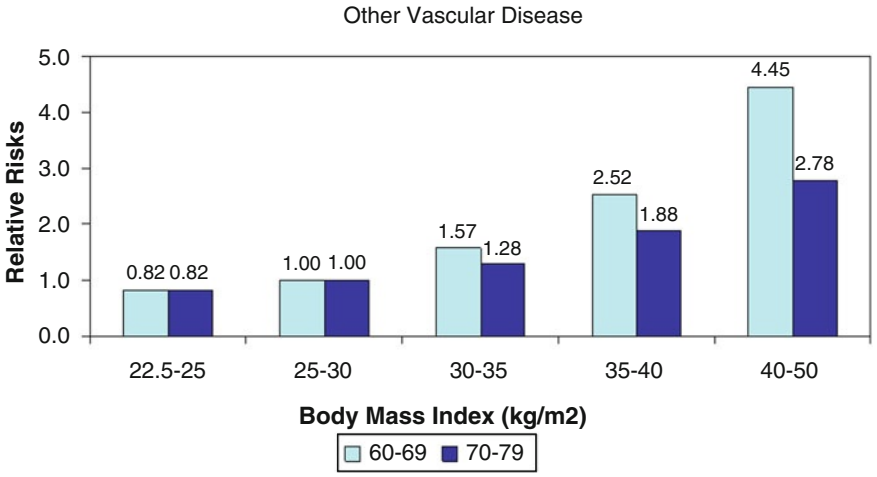

Fig. 94.6 Causal Relative Risks for Mortality Estimates – Other Vascular Disease. Figure represents relative risks for mortality estimates for other vascular disease. Data represents relative risks in each BMI category (referent is 25–30 kg/m^2) in the 60–70 and 70–79 year age groups. (Reprinted and adapted from The Whitlock et al. (2009). Web tablet 10, Prospective Studies Collaboration. Body Mass Index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies, © 2009, with permission from Elsevier)

the authors confirmed that cause-specific mortality is due primarily to ischemic heart disease, stroke, diabetes and liver disease in patients with high BMIs. The low-normal BMI (18.5–22.5) group also has an increased risk of death as well.

An accompanying editorial provided possible explanations for these findings (Lopez-Jimenez 2009). First, there may be a protective effect of fat storage on acute disease or chronic wasting. This reserve of adiposity may be absent in the low-normal BMI group. Secondly, the amount of lean mass which is required not only for overall homeostasis but also oxygen consumption is limited in these patients, both of which are important contributors to survival. However, the authors do demonstrate that this inverse relationship between lower BMI and mortality is predominantly related to smoking-related pulmonary diseases. Although the associations presented in this study were slightly weaker in the 70–79 year age group, particularly from mortality of ischemic heart disease, this may transpire from the reduced associations of blood pressure and dyslipidemia with mortality or possibly due to age-related muscle loss and the impact on metabolic variables (Lewington et al. 2002, Lewington et al. 2007).

The third important meta-analysis published to date specifically identifies elderly patients, aged 65 years and older (Janssen and Mark 2007). They ascertained that elderly overweight patients with a BMI of 25–29.9 kg/m^2 were not associated with a significantly increased risk of mortality while those who were moderately obese, BMI 30–34 kg/m^2 had only a modest increase in mortality (RR 1.10 [1.06–1.13]). They also concluded in the oldest old (age > 75 years), an elevated BMI had no impact on the risk of death. These results preceded the definitive meta-analysis discussed above, but the authors state valid conclusions as to why they observed these results. First, patients with an elevated BMI may have already died at an early age; thus, those still alive may be resistant, for whatever reason, to the effect of an elevated BMI, the phenomenon of selective survival. Second, one cannot ascertain the differences between lean mass and excess body fat in these patients, both of which impact mortality and cardiovascular events(Kyle et al. 2001a, b; Roubenoff et al. 1995). The limitations of this work were that it used population-based and retrospective analyses and had a number of missing studies in their criteria.

94.4 The Risk of CV Events Associated with Underweight and Obesity in Midlife and in the Elderly

Despite obesity being a well-established risk factor for cardiovascular (CV) events, few studies have specifically addressed this point in elderly patients. In general, it is difficult to distinguish the independent effect of obesity on CV morbidity from those of obesity-related conditions such as metabolic syndrome, diabetes, hypertension or dyslipidemia and, even more, when they are pharmacologically or surgically treated (Batsis et al. 2007). In this context, abdominal obesity measured by means of waist circumference, has been confirmed to be an independent risk factor for heart failure even in older people (Nicklas et al. 2006). On the contrary, a low BMI was independently associated with an increased risk of silent cerebral infarction in the elderly, a condition that can predict clinical overt stroke or vascular dementia (Kotani et al. 2004). Recently, data from the Chicago Heart Association study (Yan et al. 2006) were analyzed to control for the role of obesity-related CV risk factors and to address the issue of whether midlife BMI had an independent impact on CV outcomes, including mortality from diabetes and hospitalization in survivors to the age of 65 years and older. The results indicated that being obese (BMI>30 kg/m^2) but not overweight, in middle age has a higher risk of mortality in older age. In this study, however, about 2,500 subjects (6% of the participating cohort) died before the age of 65 years and no information was available about the relationships between BMI and CV risk factors in these subjects. Interestingly, the midlife prevalence (referred to the years 1967–1973) of low risk subjects with normal BMI was low (<4%), a prevalence which may have been lower currently given the increasing prevalence of obesity and its associated risk factors. Another study (Adams et al. 2006) indicated that in older adults recalled BMI at middle age was a stronger mortality predictor than current BMI. A recent study from the Framingham cohort found that the risk of all-cause mortality was not increased in obese subjects older than 70 years who were not obese at 50 years; on the contrary, elderly subjects with midlife obesity were at an increased risk, independently if they were actually obese or nonobese (Janssen and Bacon 2008). A possible study bias was that confounding information of both health risk and BMI, such as smoking, alcohol intake or socioeconomic status was not taken into consideration. However, globally considered, these observations are in agreement with the concept that current and midlife BMI provide independent information on health risk in elderly subjects with different clinical implications.

94.5 Other Anthropometric Variables and Mortality

Although outside the scope of this chapter, waist circumference and waist-to-hip ratio are other well known surrogate measures of abdominal obesity or body fat distribution. Many of the limitations that plague BMI in ascertaining obesity can be seen with these measures as well. Waist circumference changes with age because of changes in vertebral column and in truncal posture and are therefore independent in part from visceral fat size modifications. No extensive data are available that consider these potential biases.

Waist circumference and waist-hip ratio, which probably reflect the nature of both adiposity and body fat distribution measures, generally provide improved prediction of mortality risk among the elderly (Pischon et al. 2008; Price et al. 2006; Visscher et al. 2001). Some studies demonstrated an inverse association between BMI and mortality while the latter was positively associated with waist-hip-ratio. No extensive data are available between mortality risk and body composition in elderly subjects. However, similar to BMI, skinfold thickness was inversely associated with mortality (Kalmijn et al. 1999). When BMI and waist circumference were considered together, it showed that higher BMI values were associated

with lower mortality risk once the risk attributable to waist circumference (WC) was accounted for(Janssen et al. 2005).Therefore, taken as a whole, these data seem to indicate that in elderly subjects abdominal fat mass rather than the excess of body weight in itself, is closely associated with mortality.

94.6 Special Considerations in an Elderly Population

94.6.1 Sarcopenia and Cardiovascular Disease

Sarcopenia is defined as age-related loss of muscle mass that usually results in a decline in strength and power leading to frailty and disability. This becomes increasingly prevalent as one ages and the financial burden in one study was in excess of $18 billion annually in the United States alone (Singh et al. 2008). There is atrophy of muscle fibers, in tandem with an increase in fat mass. Although the most effective method of measuring whether a patient is sarcopenic is DEXA scanning, it is the costliest of all methods. Anthropometry, although operator-dependent, may crudely estimate the degree of sarcopenia. There has been little information published on the impact of sarcopenia specifically on cardiovascular outcomes. It appears that on a biological front, there are common underlying inflammatory pathways among sarcopenia, obesity, and insulin resistance, the latter two of which have been demonstrated to be related to adverse cardiovascular outcomes(Singh et al. 2008).The cytokine surge produced by adipocytes may directly impact patient physical function in the aging process, particularly interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP) (Fig. 94.7). These components are well correlated with BMI, total mass and sarcopenia, the latter as measured by appendicular lean mass. However, whether these relationships have any impact on cardiovascular disease remains unknown.

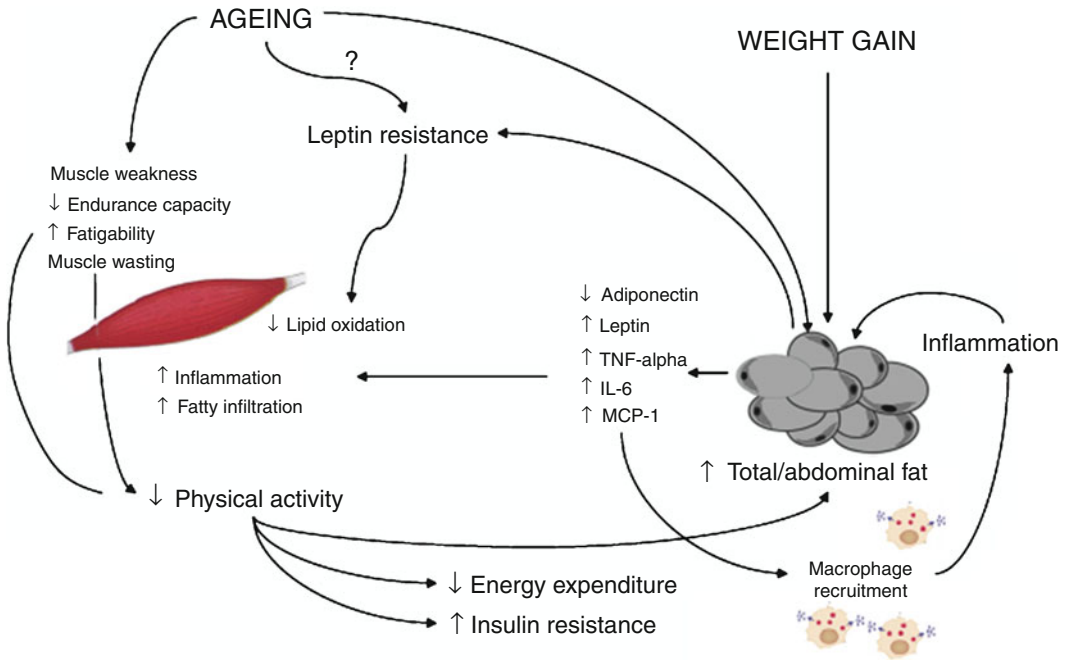

Fig. 94.7 Ageing and muscle. Inter-relationships between adipose tissue and muscle (Reprinted from Zamboni et al. (2008). With permission from Elsevier)

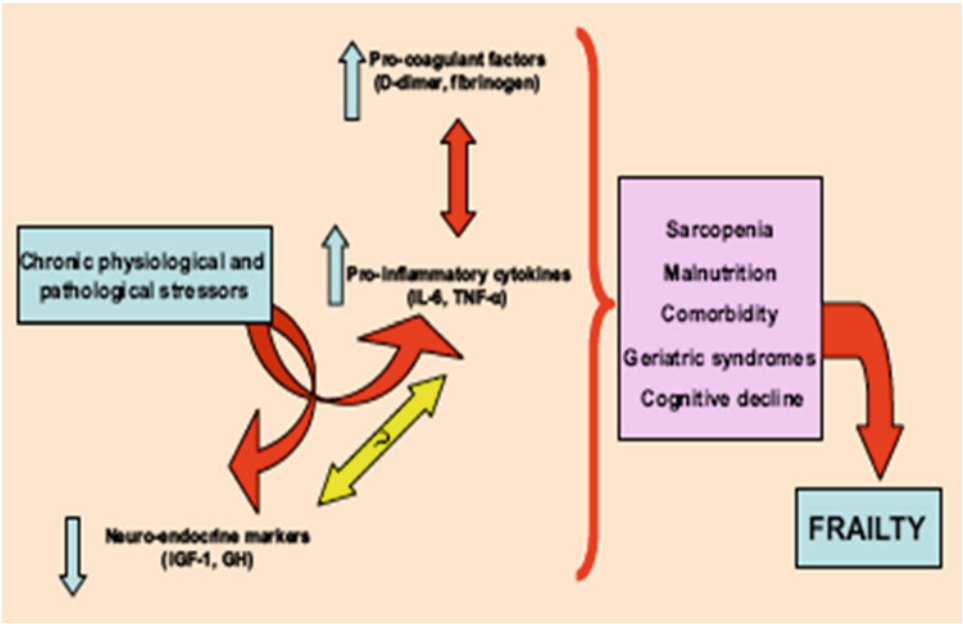

Fig. 94.8 Pathway to frailty. Pro-inflammatory signals, including IL-6 and TNF-a increase with age, as do markers of activated coagulation, including D-Dimer, fibrinogen, PAI, and Favor VIII. To the extent that these are primary processes, they may contribute to a cycle of physiologic changes that, in composite, are described as "frailty" (Reprinted from Kanapuru and Ershler (2009). With permission from Elsevier)

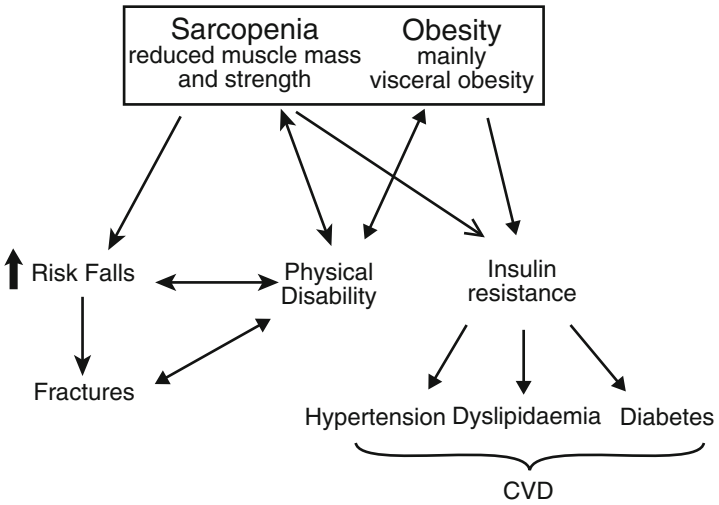

Fig. 94.9 Sarcopenia and Obesity. Possible relationships between sarcopenia, obesity, disability and cardiovascular disease. (Reprinted from Zamboni et al. (2008). With permission from Elsevier)

Patients with frailty and perhaps sarcopenia may indeed be at higher risk of developing atherosclerotic disease. This mechanism is likely mediated through a reduction in muscle blood flow as suggested by Morley (2008). Frailty and CV disease inherently share many of the same risk factors (Figs. 94.8 and 94.9). Obesity may also be associated with pre-frailty, but further studies are needed to ascertain the interplay between BMI, frailty and cardiovascular disease.

94.6.2 Frailty and Risk of Cardiovascular Events

Frailty is a construct that is difficult to define, but one that is debated in the geriatric literature. Such patients often have multiple co-morbid conditions, homeostasis is impaired in the context of acute stressors and physiologic reserves are slim, leading to an overall decline in functional status and health. The purpose of this section is not to define or debate the definitions of frailty, as these have been reviewed elsewhere, but to illustrate that such patients may be at higher risk for cardiac disease.

In epidemiologic studies, the prevalence of death from cardiovascular disease, from 1980 through 2000, fell from 542.9 to 266.8 deaths per 100,000 population among men, and from 263.3 to 134.4 deaths in women, in US adults between the ages of 25–84 years of age (Ford et al. 2007). Much of this was attributable to reductions in CV risk factors and evidence-based therapies. However, concomitant with this reduction, there continues to be a shift in population trends into the geriatric age group. In one study, it was estimated that 7% of elders are frail and this number increases to 30% in octogenarians (Fried et al. 2001). Depending on the criteria of frailty used, the prevalence can range between 6.9% in the Cardiovascular Health Study to 19% in the Longitudinal Aging Study Amsterdam (Puts et al. 2005). With the burgeoning elder population, these numbers have significant public health implications and these estimates are likely to be conservative because institutionalized patients are often excluded from these analyses. Patients with cardiovascular disease have a higher prevalence of frailty, particularly in those undergoing percutaneous coronary interventions or those with serious CAD (Purser et al. 2006). However, very little information has been published in this population group. Often, clinicians consider patients with frailty as those who are underweight, malnourished, or have poor physical performance status. One can consider a theoretical construct of patients who are frail to be equated to those who are underweight according to NHLBI criteria for obesity (Eckel et al. 2002). This has important clinical implications in that frailty predicts death, disability and institutionalization (Baumgartner et al. 2004). Two studies have determined that frailty predicts 1 year mortality and stroke after acute myocardial infarction (Krumholz et al. 2001; Lichtman et al. 2002). Although the reductions in lean mass may promote hormonal dysregulation, cytokine upsurge and increased systemic inflammation, all of which are associated with cardiovascular morbidity, further studies, specifically identifying this population, would be needed to better delineate the relationships involved.

There is an underlying inflammatory syndrome in patients who are frail, similar to that observed in sarcopenia, where many components share common links to those in cardiovascular disease. IL-6, a cytokine associated with sarcopenia and which may place patients at an increased susceptibility to infection and higher risk of disability, is often increased (Fried et al. 2001). It has also been associated with insulin resistance. Furthermore, CRP and D-dimer, both markers of inflammation, are elevated in the frailty syndrome (Fried et al. 2001, Walston and Fried 1999). CRP is an independent, non-traditional marker of CV disease and recent evidence suggests that the anti-inflammatory effects of statins in lowering CRP may indeed confer a CV disease benefit (Ridker et al. 2008). Although the study does not give particular hazard ratios, those over the age of 65 years did not have a HR or confidence intervals crossing 1.0 for their primary endpoint of nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina or confirmed death from cardiovascular causes following rosuvastatin administration. The subgroup results suggest that even elder patients may benefit from the CRP lowering effects of statins (Ridker et al. 2008). In a study of over 4,700 community dwelling elders, both CRP and D-Dimer were elevated in frail patients, characterized by a promotion of inflammation and enhanced markers of a potential coagulopathy (Walston et al. 2002). Indeed, much research in the cardiovascular community has focused on inflammation as a potentiating feature in the development of cardiovascular disease, much associated with pro-inflammatory cytokines and cell signaling.

94.7 Obesity Paradox

Observational studies suggested the expression of "*obesity paradox*" to indicate that among patients with chronic diseases and specifically in elderly patients, excess weight is paradoxically associated with decreased (Diehr et al. 2008) mortality. In fact, despite epidemiologic studies indicating obesity as a well established risk factor for mortality and CV disease, overweight and obesity have often resulted in protective effects not only in older subjects (Diehr et al. 2008) but also in patients with pre-existing CV disease (Curtis et al. 2005; Lavie et al. 2009), in subjects with advanced chronic kidney disease who require maintenance dialysis (Kalantar-Zadeh et al. 2005) or in those with malignancy (Chao et al. 1975) or AIDS(Roubenoff 2000a). Even more recently, it was reported that late-life obesity reduced the risk of dementia, including Alzheimer's disease, despite midlife (50 years) obesity, diagnosed on the basis of self-reported body weight, increased this risk (Fitzpatrick et al. 2009). Even those studies that reported an increased risk of death associated with increased BMI among elder subjects evidence that the relative risk of death declines with increasing age (Calle et al. 1999, Stevens et al. 1998).

The obesity paradox is an example of *reverse epidemiology*, a recently proposed construct (Kalantar-Zadeh et al. 2003) (also referred as *risk factor reversal* or *paradoxical risk factors*) indicating an alteration in the normal relation between risk factors and clinical outcomes that can result in the exact opposite of the usual association between a risk factor and the outcome found in the general population. Several potential explanations for obesity as a paradoxical risk factor in the elderly have been proposed (Strandberg et al. 2009) but, until now, a complete and satisfactory explanation has not been suggested. As previously mentioned, smoking may contribute in inducing such reverse epidemiology. In fact, the prevalence of smoking is known to be lower in the elderly. As such, patients often quit smoking later in life which leads to an increased BMI. However, the health benefits of quitting smoking far outweigh any harms of weight gain (Wannamethee and Shaper 1989).

Another possible bias may be the phenomenon of "*reverse causality*" which consists of obesity-related diseases that can lead to both weight loss and mortality, a possibility that has not been completely analyzed thus far (Flanders and Augestad 2008). Since some reports indicate that midlife overweight or obesity are associated with an adverse prognosis in old age (Adams et al. 2006), it might be the case that the progression of obesity-related diseases leads to unintentional weight loss especially in the elderly. Therefore, a significant proportion of the normal BMI group in elderly cohorts may include individuals who were once overweight or obese and experienced a sustained unintentional weight loss. Another possible interpretation may be that patients who lost weight after midlife may inherently develop "frailty", a predisposing condition to CV disease (Ahmed et al. 2007), as discussed earlier. Again, it seems that body weight history has a crucial role suggesting that those subjects who lose weight after midlife, especially unintentionally, require special attention. These data also confirm that caution should be addressed to intentional weight loss in elderly people**.** Data from the last NHANES (Olshansky et al. 2005) indicate that the excess of mortality associated with overweight and obesity is considerably lower than that reported by previous US cohort studies (Allison et al. 1999; Mokdad et al. 2004). It has therefore been proposed (Flegel et al. 2005) that as a consequence of the improved treatments for the major metabolic complications of obesity such as diabetes, dyslipidemia and hypertension, the impact of obesity may be decreasing over time, which may further explain the obesity paradox. Other possible biases have been indicated. Study sizes have sometimes been considered insufficient to perform age-specific estimates (Stevens et al. 1998) and the frequent use of self-reported weight and height to calculate BMI has been criticized (Niedhammer et al. 2000; Stevens et al. 1990). Furthermore, as reported earlier, BMI does not have the same adiposity significance at all ages in terms of body fat mass and distribution, especially in the elderly

and in females. It has been shown, in fact, that the elderly tend to have a shift of fat from peripheral to central sites without a concomitant increase in body mass index (Borkan et al. 1983), a phenomenon that is particularly true in the female sex. Peripheral body fat is considered to be associated with higher adiponectin production and with favourable cardiovascular and metabolic profile (Tanko et al. 2003; Tanko et al. 2004). Given this consideration, it seems inappropriate to compare the BMI of the elderly with those of the young and midlife ages.

Undoubtedly, the mechanisms behind the obesity paradox need to be clarified together with its clinical relevance. In fact, with the increasing prevalence of obesity and the improved life expectancy, many people may be subjected to reverse epidemiology. Whether current treatment guidelines and advice for risk factor reduction should be extrapolated to elderly patients should be further investigated.

94.8 Body Mass Index and Heart Failure

BMI has also been implicated as a predictor of heart failure in elderly patients. In a community-based, population-based study of 1,749 subjects aged 65 years and older, a BMI of ≥ 28 kg/m^2 compared to a BMI ≤ 24 kg/m^2 demonstrated a RR 1.6 of developing heart failure (Chen et al. 1999). As adiposity comprises a substantial proportion of total body weight and large volumes of fluid accompany this, the increased intravascular volume may lead to increases in cardiac contractility, cardiac output and subsequently increases hemodynamic load, leading to cardiac hypertrophy, cardiac dilation and inevitably increases the patient's risk for developing cardiac failure. The increase in left ventricular end-diastolic pressures over time leads to ventricular dilatation as well leading to increased myocardial stress, increases in myocardial mass and left ventricular hypertrophy. Alternatively, obesity may lead to excessive myocardial adipose deposition leading to a condition known as Adipositas Cordis (cardiomyopathy of obesity). An infiltrative-like cardiomyopathy may occur, ensuing not only to ventricular failure, but also to sinus node dysfunction.

Interestingly, the prognostic significance of obesity in the setting of patients with established heart failure is unclear. Patients with a low BMI may represent a cachectic group that leads to poor outcomes in this population. As described above, such a group reflects the obesity paradox or phenomenon of reverse epidemiology, whereby patients with an elevated BMI, in fact fare better clinically, than those who are not. Recently, a meta-analysis by Oreopoulos et al (2008a) identified 9 studies that met their inclusion/exclusion criteria. They determined that patients who were overweight or obese with heart failure, actually had lower all-cause mortality, than patients with normal BMI levels [RR 0.84 (0.79–0.90) vs. RR 0.67 (0.62–0.73)]. Furthermore, there were lower rates of cardiovascular mortality in the overweight (RR 0.81 [0.72–0.92]) or obese (RR 0.60 [0.53–0.69] groups than patients with a normal BMI. In fact, patients with a BMI <23 kg/m^2 (underweight/low normal), had an associated higher CV mortality (RR 1.20 [1.04–1.38]) than the other corresponding groups. This study demonstrated an inverse relationship between BMI and survival. Whether such results can be extrapolated to the extremely obese groups requires further investigation. The mean age range of the study populations examined was in the 60s, suggesting that such results may indeed be generalized to an elder population group. These authors suggest that the elevated risk of death in the low BMI groups may perhaps be due to hypoproteinemia, low energy intake, malnutrition, and possibly cachexia. Further, as chronic heart failure can be considered a catabolic state with muscle wasting, overweight or obese patients may have higher metabolic reserves than their counterparts at lower BMIs and hence can better tolerate changes in body composition, catabolic processes and metabolic stressors.

94.9 BMI and Cardiac Surgery

In a cardiac surgery population, BMI has been associated in a "U" or "J-shaped" fashion, with underweight and obese patients having higher mortality rates(Rahmanian et al. 2007; Reeves et al. 2003; Whitlock et al. 2002). This has been well documented both following cardiac surgery but also following percutaneous coronary intervention. The relationship is non-linear in nature. It appears, from other studies (Yap et al. 2007), that there are no differences in cardiac outcomes, including atrial fibrillation, myocardial infarction or heart failure, while sternal wound infections are definitively higher. Many studies are limited by sample size and a lack of information pertaining to relative confounders. In a study by the Northern New England Cardiovascular Disease Study Group that prospectively examined 11,101 patients undergoing coronary artery bypass graft (CABG), there were no differences between groups with regard to post-operative cardiac outcomes, including cerebrovascular accidents (Birkmeyer et al. 1998). In reviewing the existing literature, there is little information on the oldest old (age > 80 years). A study by Maurer et al (2002) retrospectively reviewed 1,448 patients aged >75 years undergoing cardiac surgery in the 1990's. This study divided their cohort into tertiles based on BMI and demonstrated that the patients with a low BMI had a higher incidence [OR = 1.59], of cardiovascular complications (defined as stroke, MI or arrhythmia) than subjects in higher tertiles. Although the multivariable model included many patient co-morbidity co-variates, over-adjustment of variables was a possibility. In addition, these authors hypothesize, as have others, that patients with a lower BMI have less nutritional reserve, hindering their ability to manage stressors.

In addition to cardiac surgery, examination of BMI as a predictor of outcomes following percutaneous coronary interventions (PCI) is a concern. As the prevalence of cardiovascular disease both symptomatic and asymptomatic increases with age, this procedure becomes increasingly prevalent particularly in patients with obesity. As in other populations, obesity is presumed to be a risk factor for post-operative morbidity and mortality; however, data has been conflicting at best. One study examining a registry in British Columbia, Canada, demonstrates a "U" shaped relation between BMI and mortality, which was particularly evident in underweight patients (Byrne et al. 2009). However, Oreopoulos further examined the impact of obesity on both short and long-term mortality following PCI in a meta-analysis of 22 studies (Oreopoulos et al. 2008b). Following PCI, overweight and obese patients had lower short-term or in-hospital mortality (OR 0.71 [0.62–0.81], OR 0.63 [0.54–0.73]), respectively, and lower long-term (>5 years) mortality than normal BMI patients (OR 0.66 [0.55–0.79], 0.65 [0.51–0.83]). These results were observed in post-CABG patients as well. Of note, the mean age was 66.1 years, 62.9 and 60.4, in the normal, overweight and obese categories. As in patients with heart failure, these results suggest an inconsistent protective effect of elevated BMI levels on mortality. The authors in fact excluded, in a sensitivity analysis, patients who were underweight to exclude possible confounding of their results and their outcome measures changed minimally.

94.10 BMI and Orthopedic Surgery

As the public health implications of an increasingly obese and elderly population are increasing, the need for joint replacement subsequently increases as well. Studies examining the impact of BMI on perioperative outcomes in an elderly orthopedic population have been limited to either non-cardiac complications, or have not ascertained any complications. In patients undergoing elective spine surgery, there does not appear to be any solid association between BMI and cardiac events. However, in one study of 229 patients undergoing revision total hip arthroplasty, no differences in the

Table 94.3 Multivariable analysis for overall adverse cardiac events in 1,180 hip fracture repairs in Olmsted county

Underweight < 18.5 kg/m^2 [c]$n = 184$	Normal 18.5–24.9 kg/m^2 [c]$n = 640$	Overweight 25–29.9 kg/m^2 [c]$n = 251$	Obese ≥ 30 kg/m^2 [c]$n = 105$	Age[b]	Male sex[b]	Revised Cardiac risk Index[b]	Beta-blocker[b]	Surgical year[b]
1.48 (1.17–1.87)*	Referent	1.15 (0.91–1.46)	1.36 (0.98–1.88)	1.04 (1.03–1.05)*	–	–	–	–
1.51 (1.20–1.91)*	Referent	1.04 (0.82–1.31)	1.14 (0.83–1.58)	–	1.24 (0.99–1.55)	–	–	–
1.52 (1.20–1.93)*	Referent	1.01 (0.80–1.26)	0.97 (0.70–1.35)	–	–	1.43 (1.32–1.55)*	–	–
1.49 (1.17–1.88)*	Referent	1.05 (0.83–1.33)	1.14 (0.82–1.58)	–	–	–	1.15 (0.91–1.46)	–
1.50 (1.18–1.89)*	Referent	1.06 (0.84–1.35)	1.14 (0.83–1.58)	–	–	–	–	1.02 (1.00–1.04)
[a]1.56 (1.22–1.98)*	Referent	1.07 (0.85–1.35)	1.12 (0.81–1.56)	1.04 (1.03–1.05)*	1.23 (0.99–1.54)	1.39 (1.28–1.51)*	0.97 (0.75–1.24)	1.01 (0.99–1.03)

Adapted from Batsis et al. (2009), Wiley-Blackwell Publishers

Each row represents a separate multivariable analysis. All values listed as Hazard Ratios (95% Confidence Intervals)

*$P < 0.05$

[a]Final Multivariable model after adjusting for age, sex, Lee's Revised Cardiac Risk Index, use of beta-blockers, and year of surgery

[b]Hazard Ratio for variable, after adjusting for body mass index category

[c]The number of observed events of this type

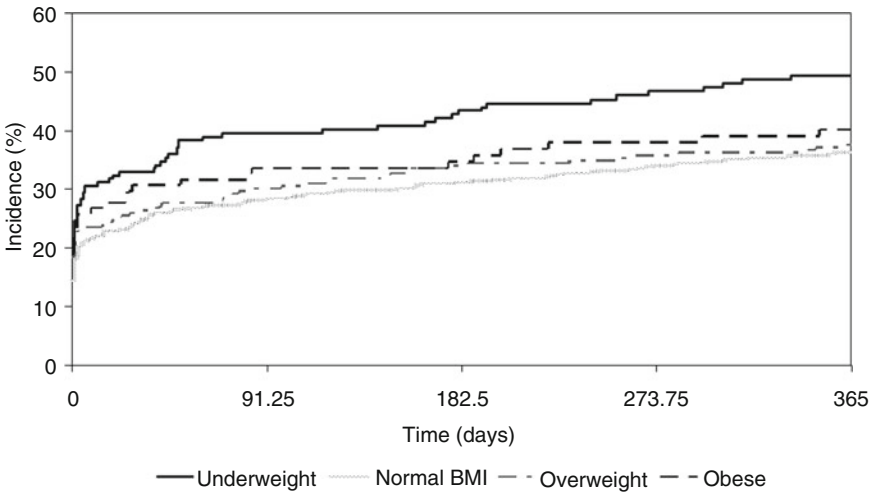

Fig. 94.10 Incidence of Any Cardiac Event Following Hip Fracture Repair by Body Mass Index Cumulative incidence of any cardiac event up to 1 year post-operatively in 1,180 Olmsted County residents undergoing urgent hip fracture repair, 1988–2002. (Adapted from Batsis et al. 2009. Wiley-Blackwell Publishers)

frequency of cardiac complications, defined as myocardial infarction or heart failure, between any of the obese groups (BMI > 25 kg/m^2 and BMI < 25 kg/m^2) were observed (Perka et al. 2000). This was mirrored in another study of patients undergoing total knee arthroplasty (Miric et al. 2002). Although elective arthroplasty is considered a safer procedure than that of urgent hip fracture repair, only one study has ascertained the incidence of cardiac events in a hip fracture population (Batsis et al. 2009). As BMI is known to be inversely correlated with osteoporosis and patients with a low BMI are at a higher risk of developing a fragility fracture, the magnitude of the incidence of cardiac events has not been well investigated. Obese patients were at no greater adjusted risk of having a cardiac event than patients with a normal BMI (Table 94.3). Interestingly, this study demonstrated an increased risk among underweight elders (Fig. 94.10), regardless of the multivariable model used. The authors hypothesized that their results, in a population-based study of Olmsted County, Minnesota hip fracture surgeries from 1998–2002 was a further example of the obesity paradox. In addition, such frail elders who are at a higher risk of fracturing their hips are known to have reduced functional capacity, as compared to their obese counterparts. Alternatively, there may be alterations in systemic inflammatory components that have been associated with low bone mineral density, vitamin D metabolism, and serum lipids, all of which have been demonstrated to lead to greater cardiovascular disease and mortality in geriatric patients (Bagger et al. 2007; Walston et al. 2002). The above studies likely demonstrate that elevated BMI may have a protective effect on cardiac outcomes and mortality; yet further investigation would be needed.

94.11 Application to Other Areas of Health and Disease

Further research is needed to better characterize the impact of body mass index on cardiac events in elderly patients. Easier characterization of body composition in a cost-effective and practical manner that can easily be ascertained in clinical practice should be the focus of initial work. Epidemiological

studies need to better characterize the underlying inflammatory state that is present in both underweight and obese patients and the interplay of these factors with the development of cardiovascular disease. Identification of elderly subjects at high risk will allow both primary and secondary prevention strategies with the overall goal of reducing disease burden, improving quality of life and minimizing disability.

Summary Points

- Body mass index may be an inaccurate surrogate for obesity in elderly patients but is easy to use and widely accepted
- A J-shaped or U-shaped mortality curve is observed, including in elderly patients
- Midlife obesity may afford worse outcomes than midlife overweight or normal weight patients
- Sarcopenia and/or Frailty may contribute to increased cardiovascular disease and mortality likely to be mediated by similar inflammatory mediators observed in obese patients
- Low body mass index predicts a higher cardiovascular morbidity and mortality possibly reflecting the obesity paradox in congestive heart failure, cardiac surgery and hip fracture disease states.

Key Points of Obesity in Elderly Patients

- Improved methods of measuring adiposity is necessary in elderly patients
- The prevalence of sarcopenia and/or frailty increases with age which leads to a pro-inflammatory state
- Body mass index is a strong mortality predictor even in elderly patients, although the magnitude of the effect is diminished as one ages
- Confounders complicate the ability to better utilize BMI as an anthropometric measure in assessing cardiovascular events and mortality
- The obesity paradox plays a paramount role in the pathophysiology of many disease states in elderly patients

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Part XV
Anthropometry in Genetic Disease and Polymorphisms

Chapter 95
Anthropometry of Twins

Sergio Demarini

Abstract Twins are smaller than singletons at birth, due to both shorter gestational age and intrauterine growth restriction. Additionally, an intrapair discordance in birth weight is quite frequent. In twins, as in singletons, body weight and body composition vary with gestational age. However, in each pair of twins, a difference in birth weight, although correlated with, is not proportional to differences in body composition components. When compared to singletons, normally grown twins show similar body composition components. In contrast, growth-restricted twins have lower lean mass and possibly lower fat mass and bone mineral content when compared to singletons matched for gestational age. During the first 2 years of life, twins show a catch-up growth but do not reach the body size of singletons. Between 2 and 9 years of age, height in twins is only marginally lower than singletons, whereas weight gain is considerably less. Monozygotic twins are both lighter and shorter than dizygotic twins. Birth weight, parental height, zygosity, and gender are the determinants of somatic growth of twins in the first 9 years of life.

In adulthood, twins seem to have a slightly lower weight than singletons. With regard to body composition, there is a persisting correlation between birth weight and body composition components.

Abbreviations

AGA	Appropriate for gestational age
BMC	Bone mineral content
BMI	Body mass index
DXA	Dual energy X-ray absorptiometry
DZ	Dizygotic twins
FM	Fat body mass
LM	Lean body mass
MZ	Monozygotic twins
SGA	Small for gestational age

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_95,

95.1 Introduction

Twin deliveries have been rising considerably in recent years, due to assisted reproduction technology. Most twins are dizygotic twins, that is, they result from a double ovum. A minority of twins are monozygotic, as they originate from a single ovum that subdivides subsequently. Spontaneous monozygotic twins appear to have a fairly stable rate at 1:250, independent of race and genetic factors. Conversely, the rate of dizygotic twins is quite variable, depending in part on factors such as maternal age, race, parity, genetics, and hormonal treatment.

Twins have an increased risk of being born preterm and perinatal mortality rate is considerably higher than in singletons. Additionally, abnormal fetal growth is quite frequent, as the incidence of low birth weight (i.e. birth weight < 2,500 g) is about 5–7 times higher than in singletons. Dizygotic twins have the same rate of congenital anomalies as singletons, whereas birth defects are about 2–3 times more common in monozygotic twins.

Monozygotic twins are genetically identical and share an almost identical intrauterine environment, whereas dizygotic twins are not genetically identical but share a very similar intrauterine environment. Consequently, twins appear to be ideal candidates to study the relative roles of genetics and environment on health outcomes.

95.2 Fetal Growth

The main determinant of fetal growth is gestational age. In normal singleton pregnancies, somatic growth is linear up to the 37th week. Twins are smaller than singletons at birth not only due to earlier delivery, but also due to decreased fetal growth. Twin fetuses grow similarly to singletons approximately up to the 32nd week of gestation: thereafter, their growth slows down. Even taking into account a shorter gestation, twins are significantly smaller than singletons at birth (Loos et al. 2005; Naeye et al. 1966). Mean birth weight for gestational age in twins and singletons is shown in Fig. 95.1. Whether intrauterine growth restriction in twins depends on limited placental supply or limited uterine size is a matter of debate. Whatever the cause, at birth, twins on average are more than 500 g lighter than singletons.

Even within twins, there are often considerable discrepancies in growth, as frequently one twin grows more than the other. Moreover, fetal growth does vary according to zygosity and chorionicity. The mean birth weight of a male twin is 2,538 g if he is dizygotic, 2,453 g if monozygotic–dichorionic, and 2,423 g if monozygotic–monochorionic. The corresponding figures for female twins are 2,443, 2,377, and 2,329 g (Loos et al. 2005). Umbilical cord insertion may influence fetal growth too: In all three categories of twins (dizygotic, monozygotic–dichorionic, and monozygotic–monochorionic), birth weight is higher if the umbilical cord insertion into the placenta is central (as is normal) than if the insertion is peripheral. Fusion of placentas also is associated to lower birth weight. In conclusion, while gestational age is the main determinant of birth weight, factors possibly associated with reduced placental function may have minor effects on intrauterine growth of twins.

95.2.1 Twins at Birth

Assessment of fetal growth is traditionally based on birth weight. Twins, however, may grow differently in utero in spite of sharing a common environment and similar genetics. Discrepant fetal growth has been defined as a birth weight difference greater of 15–30% between twins. Such discrepancy may be of clinical relevance, as it has been associated with an increased risk of both short- and long-term

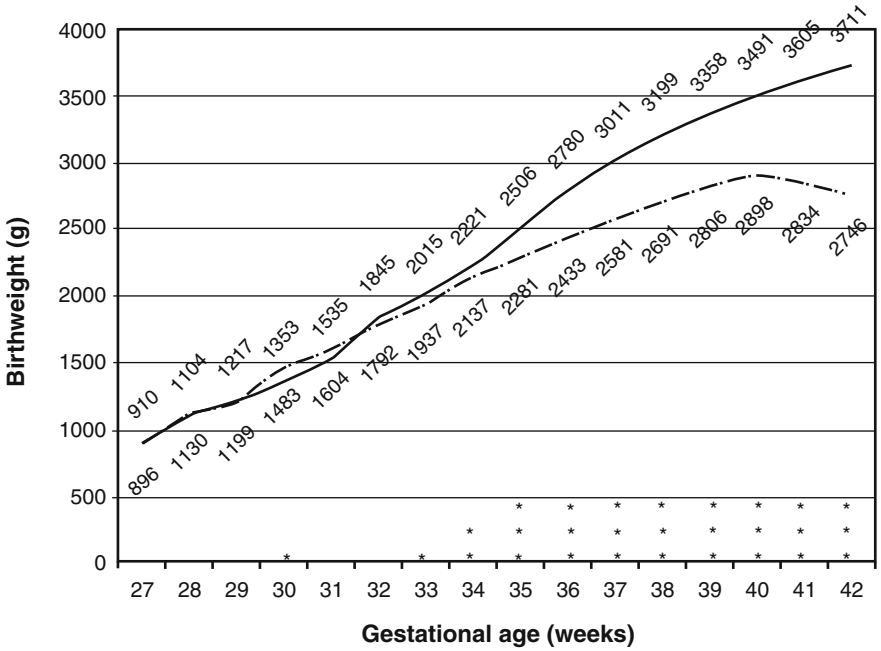

Fig. 95.1 Mean birth weight vs. gestational age for twins (*dotted line*) and singletons (*black line*) (From Loos et al. 2005)

adverse outcomes (Hollier et al. 1999; Blickstein and Lancet 1988). The use of birth weight alone does not provide information on body composition. Body composition of twins at birth was assessed in two studies, by the same group of investigators.

Koo et al. studied 48 pair of twins with birth weights from 976 to 3,135 g and a gestational age ranging from 30 to 40 weeks (Koo et al. 2002). In 29 pairs, both infants had birth weight appropriate for gestational age (between 10th and 90th percentiles). In one pair, both infants were born small for gestational age (birth weight < tenth percentile). In the remaining 18 pairs, one infant was appropriate for gestational age and the other small for gestational age. In 23 pairs, the difference in birth weight between twins was >15%. The aim of the study was to test the hypothesis that, in twins, differences in body weights are reflected by differences in the components of body composition. Body composition was studied by dual energy X-ray absorptiometry (DXA). Scans were performed at 3.8 ± 3.2 days of life, with a whole body scanner (Hologic QDR 1000/W), using a specific software, to measure bone mineral content (BMC), lean mass (LM), and fat mass (FM). In individual infants, both DXA and anthropometric measurements were higher with higher gestational age. When considering body composition components as percentage of body weight, there was an increase in BMC and FM, but a decrease in LM with increasing gestational age. With regard to intrapair differences, the percent difference in weight was correlated with percent difference in each of the body composition components. However, the percent difference in fat mass was higher than that in lean mass and bone mineral content (Table 95.1). The conclusions were that in twins, as in singletons, body weight and body composition vary with gestational age. In each pair of twins, a difference in weight, although correlated with, was not proportional to differences in body composition components.

In another study, body composition measurements of twins were compared to those of singletons (Demarini et al. 2006). There were 96 twin infants, 76 were appropriate for gestational age and 20 were small for gestational age. Each appropriate for gestational age twin was matched as closely as possible for birth weight to an appropriate for gestational age singleton. Each small-for-gestational-age twin

Table 95.1 Discrepant growth of twins at birth. Percent difference in anthropometric and dual energy X-ray absorptiometry (DXA) measurements in 48 pairs of twins (From Koo et al. 2002)

	Mean ± SD	Range
Anthropometric measurements		
Head circumference	4.0 ± 3.5	0–16
Length	4.3 ± 3.5	0–15.9
Weight	14.3 ± 10.0	0.1–42.2
DXA measurements		
Lean body mass	13.4 ± 9.0	0.1–31.1
Fat body mass	26.0 ± 15.0	0.2–67.7
Bone mineral content	15.9 ± 11.6	0.4–45.0

Table 95.2 Body composition of twins and singletons at birth. Body composition components, measured by dual energy X-ray absorptiometry, in twins vs. singletons matched for birth weight or for gestational age (From Demarini et al. 2006)

	BMC (g)	Fat mass (g)	Lean mass (g)
AGA twin vs. AGA singleton (n = 76 per group)			
Twin	38.2 ± 10.0	243 ± 97	1,926 ± 357
Singleton	39.5 ± 10.9	235 ± 83	1,939 ± 387
SGA twin vs. AGA singleton (n = 20 per group)			
Twin	34.7 ± 11.4	211 ± 108	1,700 ± 375[a]
Singleton matched for birth weight	32.1 ± 12.2[a]	197 ± 104	1,614 ± 455[b]
Singleton matched for gestation	43.0 ± 11.7[a]	266 ± 82	2,081 ± 380[a,b]

BMC bone mineral content; *AGA* appropriate for gestational age; *SGA* small for gestational age
Values expressed as means ± SD
For each component of body composition, groups with the same superscript differed by: [a] <0.05, [b] <0.01

Table 95.3 Body composition of twins and singletons at birth. Body composition components measured by dual energy X-ray absorptiometry, and expressed as percentage of total body weight in twins vs. singletons matched for birth weight or for gestational age (From Demarini et al. 2006)

	BMC (%)	Fat mass (%)	Lean mass (%)
AGA twin vs. AGA singleton (n = 76 per group)			
Twin	1.71 ± 0.18	10.4 ± 2.7	87.5 ± 2.9
Singleton	1.76 ± 0.18	10.4 ± 2.1	87.9 ± 2.2
SGA twin vs. AGA singleton (n = 20 per group)			
Twin	1.76 ± 0.23	10.6 ± 3.2	87.6 ± 3.4
Singleton matched for birth weight	1.71 ± 0.14	10.1 ± 2.5	88.2 ± 2.6
Singleton matched for gestation	1.78 ± 0.19	10.9 ± 1.8	87.3 ± 1.9

Values expressed as means ± SD. No significant difference in any comparisons between groups or within each body composition component
BMC bone mineral content; *AGA* appropriate for gestational age; *SGA* small for gestational age

was matched with two cohorts of appropriate-for-gestational-age infants: one with similar birth weight and another with similar gestational age. The aim of the study was to compare the body composition (bone mineral content, lean mass, and fat mass) of normally grown and growth-restricted twins to those of singletons. DXA scans were performed with a whole body scanner (Hologic QDR 1000/W), in the first few days of life. Between appropriate for gestational age twins and birth weight-matched singletons, there were no significant differences in bone mineral content, fat mass, and lean mass, either as absolute values or as percentage of weight.

With regard to small for gestational age infants, there was also no difference in body composition components when compared to singletons matched for birth weight. In contrast, small for gestational age twins, when compared to appropriate for gestational age singletons, matched for gestational age, showed significantly lower absolute amounts of lean mass and a tendency to lower fat mass and bone mineral content (Table 95.2). When body composition data was analyzed as a percentage of weight, small for gestational age twins had similar proportions of each body composition component to appropriate singletons, matched for gestational age (Table 95.3). The conclusion was that in

normally grown infants, body composition components are similar regardless of whether they are twins or singletons. In contrast, growth-restricted twins have lower lean mass, and possibly lower fat mass and bone mineral content, when compared to singletons matched for gestational age.

95.2.2 Growth in the First Decade of Life

Being born smaller than singletons, twins may be expected to grow more slowly than their singleton counterparts. Most singleton infants born small for gestational age show a catch-up growth during the first 2 years of life. A minority remain smaller and lighter than infants born appropriate for gestational age.

95.2.2.1 Growth from Birth to 2.5 years

Data from the Netherlands Twin registry were used to assess growth of twins vs. singletons in the first 2.5 years of life (Van Dommelen et al. 2008). Over 4,000 twin infants were enrolled into the registry. As expected, twins were growth-retarded when compared to singletons, at birth. Subsequently, twins showed a catch-up growth but could not reach the body size of singletons, at least over the study period. The authors estimated that about 50% of the growth retardation in the first 18 months of life could be attributed to the difference in gestational age. This difference decreased to about one third at 2.5 years of age. There was a statistically significant, but clinically irrelevant, difference in growth between monozygotic and dizygotic twins. As differences in growth between twins and singletons persist in the first 2.5 years of life, in spite of correction for gestational age, the authors recommended using specific growth charts for twins.

95.2.2.2 Growth Between 2 and 9 years

In a study of over 1,500 twins, Buckler and Green studied the effect of birth weight and parental height on somatic growth of twins up to the 9th year of age (Buckler and Green 2008). Height in twins resulted only slightly lower than singletons, whereas weight gain was considerably less (Fig. 95.2). Gender seemed to have some effect, as weight difference was higher in males than in females. Head circumference was also smaller in twins, with a different gender effect, as females had smaller heads than males. As expected, parental height did account for the height difference of twins, but only in part. With regard to zygosity, monozygotic twins remained both lighter and shorter than dizygotic twins. Additionally, monozygotic boys had decreased height and weight when compared to monozygotic girls. In conclusion, twins are smaller and thinner than singletons during the first decade of life. Birth weight, parental height, zygosity, and gender are the determinants of somatic growth of twins in the first 9 years of life.

95.2.3 Twins in Adulthood

In adulthood, twins seem to have a slightly lower weight than singletons (Andrew et al. 2001). With regard to body composition, there appears to be a significant correlation between birth weight and

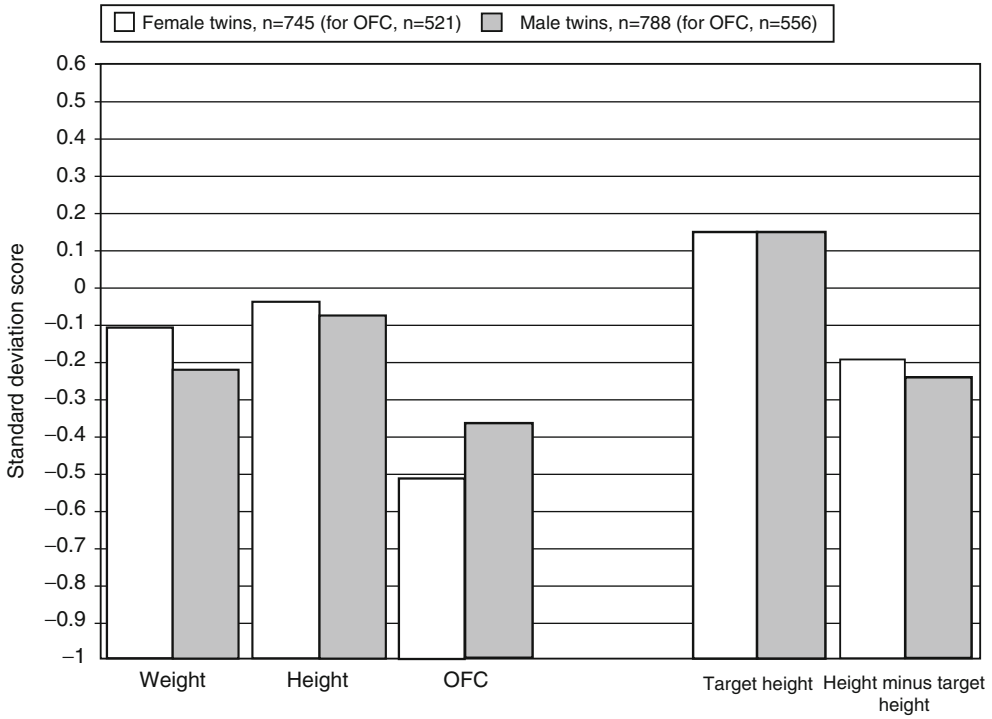

Fig. 95.2 Growth of twins between 2 and 9 years of age. Mean standard deviation scores are shown as histograms for twin boys and twin girls (From Buckler and Green 2008)

body composition components in twins aged between 18 and 80 years (Skidmore et al. 2009). Every 1.0 kg increase in birth weight was associated with: (1) a 1.7 kg increase in lean body mass, (2) a 0.25 kg increase in fat body mass, and (3) a 0.05 unit increase in lean:fat body mass ratio. Lean body mass was positively associated with birth weight both within and between twin pairs. Consequently, both individual intrauterine factors and shared environmental factors had an influence. In the correlation between body fat mass and birth weight, there were within-pair differences, possibly indicating individual intrauterine factors. With regard to lean: fat body mass ratio, the positive relation with birth weight was seen only between pairs, and thus believed to be mediated through the shared environment of the twin pairs. The authors concluded that, in twins, a greater birth weight is associated with a higher lean: fat body mass ratio in adults. Such effect appeared mediated through environmental factors common to twin pairs.

95.3 Applications to Other Areas of Health and Disease

The association between low birth weight and risk for cardiovascular disease and dysmetabolic syndrome is well described. The relative contribution of genetic and environmental factors (intra- and extrauterine) is less clear. Studies on twins may be helpful to clarify the relative influence of genetic and environmental factors on a given outcome.

Twins frequently show a difference in birth weight, in spite of sharing many factors during gestation. Consequently, discordance in birth weight cannot be explained by shared factors and must

Table 95.4 Studies of twins: hypothetical results of within-cohort vs. within-pair analyses on the association between birth weight and blood pressure (From Morley and Dwyer 2005)

	β within cohort	β within pairs	Inference
(a) In all twins	–2.0	–2.0	Shared factors *are not* involved in the association
	–2.0	–0.5	Shared factors *are* importantly involved in the association
(b) In MZ and DZ twins separately			
DZ	–2.0	–1.0	
MZ	–2.0	–1.0	Genes *are not* importantly involved in the association
DZ	–2.0	–1.5	
MZ	–2.0	–0.5	Genes *may be* importantly involved in the association (alternatively, the "healthy" MZ twin might be programmed for adult disease by the "compromised" twin by circulating factors, due to intraplacental vascular anastomoses)

Regression coefficient (β) for difference in systolic blood pressure (mmHg) per 1.0 kg increase in birth weight
MZ Monozygotic twins; *DZ* Dizygotic twins

depend on factors influencing the individual twin. If the correlation between a given factor and birth weight (or other variables) remains significant in analysis within pair, factors specific to individuals must play a role. If the correlation disappears, factors common to the twin pair must be involved. If the correlation diminishes but not disappear, both shared and individual factors may be involved. The role of genetic factors can be assessed studying monozygotic (MZ) and dizygotic (DZ) twins, both within cohort and within pairs. If a similar correlation is found between birth weight and a given outcome, in both MZ and DZ twins, genetic factors are unlikely to play a prominent role. If the correlation disappears within pairs in MZ twins, but not in DZ twins, then genetic factors are likely to play a role (Table 95.4).

A review of twin studies regarding the issue of origins of adult diseases is clearly beyond the scope of this chapter. However, a few significant examples of such studies are reported hereafter. (a) In twins, as in singletons, there appears to be a negative correlation between birth weight and systolic blood pressure, independent of factors such as length of gestation and catch-up growth (Morley and Dwyer 2005). (b) Although there are significant genetic influences on body mass index (BMI), physical activity appears to be a likely environmental contributor to BMI. As a matter of fact, the effect of vigorous exercise on BMI significantly affects BMI in both DZ and MZ twins (McCaffery et al. 2009). (c) Birth weight appears to be positively associated with adult height and fat mass. In turn, birth weight and fat mass are correlated to insulin sensitivity later in life. Such association appears to be mediated non-genetically and to possibly depend on the intrauterine environment (Monrad et al. 2009).

95.4 Practical Methods and Techniques

In infants, body composition has been assessed mainly by four methods: DXA, air displacement pletismography, skin fold thickness, and bioelectrical impedance.

95.4.1 Dual Energy X-Ray Absorptiometry (DXA)

DXA is an established method to study body composition in newborn infants. It is an X-ray-based method, using X-ray beams at two energies to scan the whole infant body. DXA represents the current standard for the detection of low bone mineral content in adults and children. Although designed to assess primarily bone mineral content, it provides values for both lean and fat body mass. Precision is generally considered excellent for bone assessment, good for lean mass, but only fair for fat mass. DXA was not designed for newborns and body scanners should be operated with software specific for newborn infants. Additionally, DXA is sensitive to motion artifacts and infants are usually scanned while asleep or tightly wrapped in a cotton blanket. Scan acquisition must be interrupted if significant movement artifacts are noted, as this significantly decreases the quality of the results. Reference ranges of body composition components (bone mineral content, lean mass, and fat mass) in infants are available (Koo et al. 2000).

95.4.2 Air Displacement Pletismography

Air displacement pletismography utilizes the principle of whole body densitometry to estimate the amount of body fat and lean mass. The method is based on the determination of body density by the measurement of body mass and body volume. Mass (weight) is measured by an electronic scale and volume is measured by air displacement pletismography in a test chamber, using the relationship between pressure and volume. Once body density is known, both the percentage and the absolute amounts of fat and lean mass are calculated using whole body densitometry principles. The instrument was initially created for adults, but has subsequently been adapted to study body composition in infants. The instrument has been validated against deuterium dilution method and a four-compartment body composition model, in healthy infants (Urlando et al. 2003; Ellis et al. 2007). Measurement precision appears to be good. The instrument is housed in a movable cart, and thus can be used in the ward, and is easy to operate. Measurements are obtained in approximately 2 min and the infant needs not be restrained during the procedure. Limitations of this instrument include: (a) lack of validation in preterm infants; (b) lack of data on ill newborns; (c) unsuitability for infants older than 6 months.

95.4.3 Skin Fold Thickness

Apart from measuring weight and length, skin fold thickness measurements are the simplest method to assess body composition and nutritional status. In general, two types of skin fold measurement techniques are utilized. The static skin fold thickness represents the reading obtained 60 s after the application of a caliper and is generally thought to be representative of subcutaneous fat. The dynamic skin fold thickness measures the difference between the caliper readings at 15 and 60 s and is thought to correlate with extracellular water content (Thornton et al. 1982). Dynamic skin fold thickness is calculated according to the formula: [(SFT at 15 s – SFT at 60 s)/SFT at 15 s] × 100 = % dynamic skin fold thickness. Standard measurement sites include midtriceps, subscapular area, and anterior abdominal wall. In infants, dynamic skin fold thickness measurements may be averaged to minimize the effect of gravity (body position) on body fluid distribution (Demarini and Pickens 1993).

95.4.4 Bioelectrical Impedance

Total body water is a major contributor to body weight and is also the main component of lean mass. Bioelectrical impedance is based on the electrical properties of hydrated tissues that is fat-free mass. It is based on the assumption that the resistance of human body to alternating electrical current is inversely proportional to the hydrated tissue mass. This technique has several advantages: (a) it is inexpensive, (b) it is compact and portable; (c) it is easy to measure, and the measurement can be repeated frequently. The instrument uses two electrodes, attached to hand and foot, to measure resistance to the current. Then, it converts resistance into an estimate of fat-free mass and calculates fat mass. Limitations are: (a) algorithms to calculate fat-free mass appear to be instrument specific and (b) measurements do not seem to offer important advantages over simple anthropometric measurements (Ellis 2007). Due to its simplicity, this technique has been used to assess body composition in newborns receiving intensive care (Tang et al. 1997).

Summary Points

- Twins are smaller than singletons at birth.
- Normally grown twins have a body composition similar to singletons.
- Growth-restricted twins have different body composition when compared to singletons.
- Twins, as a group, grow more slowly than singletons in the first decade of life.
- As adults, twins seem to remain slightly thinner than singletons
- A correlation between birth weight and body composition components persists well into adulthood.

Key Facts of Twin Anthropometry

- Twin deliveries have been rising considerably in recent years, due to assisted reproduction technology.
- Twins are smaller than singletons at birth and show intrapair discordance in birth weight.
- In twins, as in singletons, body weight and body composition vary with gestational age. In a given twin pair, a difference in weight is not proportional to differences in body composition components.
- In normally grown infants, body composition components are similar regardless of whether they are twins or singletons. In contrast, growth-restricted twins have lower lean mass, when compared to singletons matched for gestational age.
- In adults, both lean body mass and lean:fat body mass ratio appear to be related to birth weight.

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Chapter 96
Anthropometry in Children with Cystic Fibrosis

Alexia J. Murphy and Peter S.W. Davies

Abstract Cystic fibrosis is the most common life shortening autosomal recessive disorder in Caucasians. The main symptoms are evident in the respiratory system, the gastrointestinal tract and the sweat glands. Anthropometric assessment of children and adolescents with cystic fibrosis is an obvious and worthwhile endeavour as there are many aspects of the disease that could directly or indirectly impact upon growth. The past stereotype of children with cystic fibrosis was that they had growth delay with relatively short stature and delayed puberty. There have been many improvements in the anthropometric status of children with cystic fibrosis over the recent decade in response to improved understanding of the disease, treatment and recognised need for nutritional support. Thus to ensure that all individuals with cystic fibrosis reach their anthropometric potential, the measurement of anthropometry is made all the more important. To measure and interpret anthropometry correctly and clinically worthwhile in this population, there are specific features of the disease that need to be considered such as reduced height, bone age and tissue hydration. The aim of this chapter is to introduce cystic fibrosis, discuss the anthropometric status of children with CF and detail some practical methods for measuring body composition in this population.

Abbreviations

ADP	Air displacement plethysmography
BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis trans-membrane regulator
DXA	Dual energy X-ray absorptiometry
ECF	Extracellular fluid
FM	Fat mass
FFM	Fat free mass

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_96,

SDS Standard deviation score
TBK Total body potassium
%IBW Percent ideal body weight

96.1 About Cystic Fibrosis

Cystic fibrosis (CF) is a common serious genetic condition in children today, affecting about 70,000 people worldwide. CF is a recessive genetic disease that mainly affects Caucasians, being the most common life shortening autosomal recessive disorder in this population. The inheritance pattern is shown in Fig. 96.1.

Cystic fibrosis is caused by mutations in a single gene on the long arm of chromosome 7, named the cystic fibrosis trans-membrane regulator (CFTR), which was detected in 1989 (Riordan et al. 1989). The defect in the CF gene causes flawed ion transport as it acts on chloride channels in epithelial membranes, and results in the development of thickened mucus in all organs with mucus secreting glands. The principal effects are seen in the respiratory system, the gastrointestinal tract and the sweat glands. The clinical manifestations of CF include progressive lung disease and pancreatic insufficiency. The key features of CF are listed in Table 96.1.

96.1.1 Symptoms

For the typical CF patient the common symptoms are recurrent respiratory infections, coughing and wheezing, failure to thrive, fatigue, diarrhoea and male infertility. Other complications may include sinusitis, pancreatitis, nasal polyps, clubbing, liver disease, diabetes, gallstones and low bone density. As there are more than 1,000 mutations of the CF gene, symptoms of CF differ from person to person. The common component of CF is an abnormality in the function of the exocrine glands. The CFTR acts as a channel regulator and when the CFTR contains mutations and does not function, the movement of chloride across the membrane is affected and the epithelial secretions are more viscous. This increase in mucous thickness causes obstruction and lack of gland function. Cystic fibrosis leads to pathological changes in organs that express CFTR including the lungs, pancreas, liver and reproductive tract.

The lungs are structurally normal at birth, when in the first weeks of life sub-mucosal gland hypertrophy, duct obstruction and mucus cell hyperplasia occurs. Patients soon develop bacterial infections that are hard to destroy, specifically Staphylococcus aureus and Pseudomonas aeruginosa. The inflammatory response by the CF lungs to the bacterial pathogens causes progressive irreversible lung damage. The cellular response to bacteria combined with the excessive mucus production in the lungs causes difficulty with breathing and frequent infections. More than 90% of the mortality rate in CF can be attributed to chronic pulmonary disease (Rosenstein and Zeitlin 1998).

Pancreatic insufficiency is present in around 90% of patients with CF. Without sufficient fluid and low concentrations of bicarbonate, digestive pro-enzymes are retained in pancreatic ducts and are prematurely activated. This leads to the progressive loss of functioning tissue, replaced by fibrosis and fatty tissues. The fibrosis causes malabsorption of fat, protein and fat-soluble vitamins and contributes to the malnutrition seen in CF patients. CF can also cause problems in the liver and gallbladder with a third of CF patients having abnormal liver results and around 30% have a poorly functioning gallbladder.

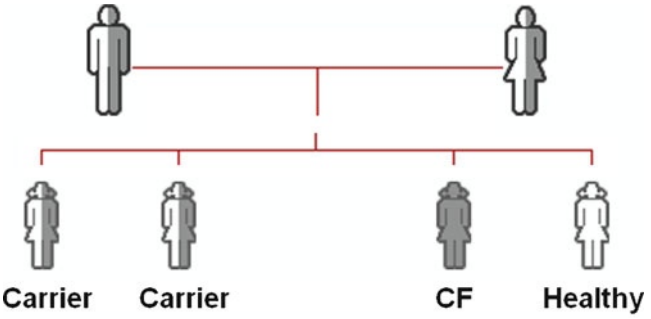

Fig. 96.1 Cystic fibrosis inheritance pattern. This figure shows the inheritance pattern for children born with cystic fibrosis. If both the mother and father are carriers of the gene then they have a one in four chances of having a child with cystic fibrosis

Table 96.1 Key features of cystic fibrosis

1. It is the most common life shortening autosomal recessive disorder.
2. It is caused by mutations in a single gene on the long arm of chromosome 7, the CFTR.
3. The principal effects from the defect in the CFTR are seen in the respiratory system, the gastrointestinal tract and the sweat glands.
4. Common symptoms are recurrent respiratory infections, coughing and wheezing, failure to thrive, fatigue and diarrhea.
5. Life expectancy for patients with CF has greatly improved due to neonatal screening, improved treatment regimes, lung transplantation and overall better understanding of the disease.

This table lists some key facts of cystic fibrosis
CFTR cystic fibrosis trans-membrane regulator

96.1.2 Management

The goal of CF management is to prevent infections, reduce the amount and thickness of lung secretion and maintain adequate nutritional status. Management of CF primarily involves pulmonary and dietetic treatment, but medication may also be needed to manage osteoporosis and liver problems. The purpose of pulmonary treatment is to keep the airway clear which reduces the severity of lung infections and improves lung function. Postural drainage and percussion combined with inhaled medication and antibiotics are the common components of a treatment program. Recent research has found several drugs which are improving the prognosis for patients with CF. Ibuprofen has been found to slow down the progression of lung disease in CF and Azithromycin, a common antibiotic, has shown to reduce the rate of decline in lung function.

The role of dietetic treatment for CF has increased in previous years due the recognised strong link between optimal nutritional status and improved pulmonary function, reduced hospitalizations and increased longevity. Most patients with CF will require enzyme supplements to treat pancreatic insufficiency and assist in nutrient absorption. Microspheres coated enzyme beads have been a treatment breakthrough for people with CF and significantly contribute to maintaining health and improving prognosis for patients with CF. Patients with CF will also require a high energy diet and may need fat-soluble vitamin supplements. Treatment may encompass behavioural interventions to increase calories, oral supplements, enteral feedings or parenteral nutrition.

Lung transplantation is an important option for patients with CF when they develop serious lung disease. A study which looked at the outcomes of transplant in a UK cohort noted survival figures of 82% at 1 year, 70% at 3 years, 62% at 5 years and 51% at 10 years (Meachery et al. 2008).

96.1.3 Prognosis

The prognosis for patients with CF has greatly improved over recent decades due to neonatal screening, improved treatment regimes, lung transplantation and overall better understanding of the disease. The earlier diagnosis of CF ensures that aggressive treatment can begin before the lung damage begins. When CF was first described in the 1930s, approximately 70% of the children died within their first year. The CF Foundation Patient Registry showed that the median age of survival was 31.6 years in 2002 (Cystic Fibrosis Foundation 2002) and in 2006 the CF Foundation reported the median survival age to have increased to 36.8 years (Cystic Fibrosis Foundation 2008).

Female patients with CF have shown to have a poorer prognosis than male patients, perhaps due to a more rapid decline in nutritional status in females and earlier acquirement of Pseudomonas aeruginosa in female patients. However, recent findings suggests that modern aggressive treatment regimens have removed any adverse female gender bias from lung function and that there is no intrinsic reason why females with CF should not have lung function and nutrition similar to their male counterparts.

96.2 Anthropometric Status in Children with CF

Anthropometric assessment of children and adolescents with CF is an obvious and potentially worthwhile endeavour as there are many aspects of the disease that could impact upon growth directly via alterations in endocrine status or indirectly via alterations in energy balance. Growth is impaired in children with CF due to nutritional deficiency caused by aspects of the disease. In CF, there are increased energy losses due to malabsorption of fat and nitrogen, impaired mucosal uptake, altered gut motility, increased energy cost of breathing due to altered pulmonary mechanics, hepatobiliary disease, reflux and CF-related diabetes. The increase in energy needs is further affected by the fact that children with CF have also been shown to have reduced energy intake which may be caused by feeding disorders, oesophagitis, iatrogenic fat restriction and cytokine release. Concentrations of insulin-like growth factor I and thyroid hormones are also lower in patients with CF and these hormones play an important role in increasing height. Loss of fat-free mass (FFM) and maintenance of fat mass (FM) in CF subjects may also be caused by the enhanced utilisation of protein for energy production in response to a negative energy balance and the pro-proteolytic effects of the catabolic intermediary metabolism. With aggressive nutritional support and adequate replacement therapy to combat these symptoms of the disease, normal growth in children with CF is possible.

The nutritional status and growth and development have often been studied in CF since the disease was described in the late 1930s and poor growth and development in children with CF was documented on many occasions since that time (Sproul and Huang 1964; Vaisman et al. 1987; Preece et al. 1986) through to the 1980s. Indeed, one of us was able to conclude in a publication not 25 years ago, that "…the pattern is growth delay with relatively short stature and delayed puberty. Weight is more severely affected than height so that these children are often extremely thin and further weight loss occurs during acute pulmonary complications" (Preece et al. 1986).

At that time in children with CF, height and weight were typically between one and two standard deviations below the mean and the longitudinal pattern of growth was consistent with retardation and delayed pubertal events. A basic endocrine disorder that would account for the reduction in stature and body weight had not been found in children suffering from CF. Levels of growth hormone were found to be normal in many studies, but a reduced somatomedin level was reported by some workers, although this was not a consistent finding. Despite these and other contradictory reports, a primary

Table 96.2 Cross sectional measurements of body composition of CF population

	CF subjects (mean ± SD)		Control subjects (mean ± SD)	
	Females	Males	Females	Males
Age (year)	11.6 ± 3.3	12.9 ± 3.1	11.6 ± 3.3	12.9 ± 3.1
HT SDS	–0.49 ± 1.06[1]	–0.69 ± 0.82[3]	0.09 ± 0.78	0.56 ± 0.84
WT SDS	–0.30 ± 1.14	–0.63 ± 0.93[3]	0.07 ± 0.72	0.51 ± 0.89
BMI SDS	–0.01 ± 0.95	–0.34 ± 0.92[2]	0.07 ± 0.71	0.33 ± 0.84
BCMI SDS	0.22 ± 1.17	0.16 ± 1.19	0.22 ± 0.96	–0.18 ± 1.15

This table shows the body composition of a group of 82 children with CF against the body composition of age and sex matched healthy peers. Groups were compared by independent *t* test: [1]$p < 0.05$; [2]$p < 0.005$; [3]$p < 0.0001$
SDS standard deviation scores

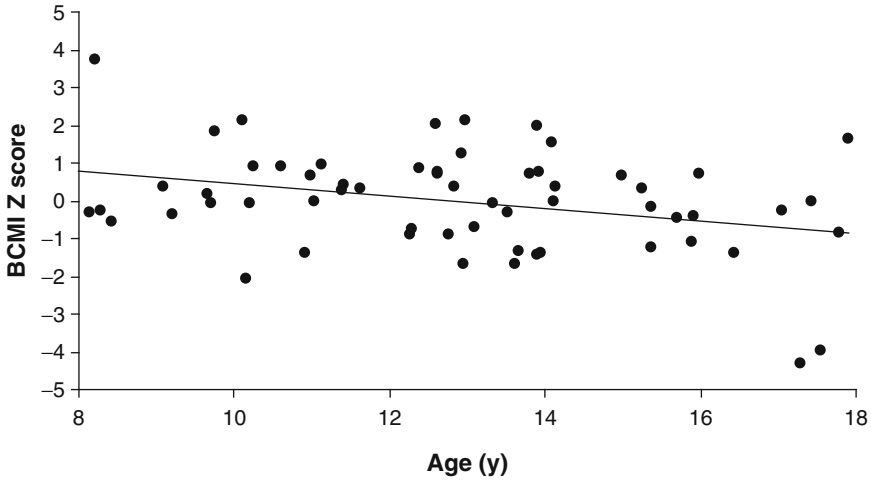

Fig. 96.2 The relationship between BCMI *Z* scores and age in children with CF. This figure shows the decline in age of the body cell mass index *Z* score with age in a group of children with cystic fibrosis. The regression line is BCM/Ht^p = -0.1642age + 2.0967

endocrine disorder resulting in poor growth and development in children with cystic fibrosis was not supported.

Clearly, there have been important changes in both nutritional and pharmaceutical interventions over recent years with a significant improvement in both morbidity and mortality in children, adolescents and young adults with CF. It would also seem that in parallel with these improvements, growth status and nutritional status have also changed for the better in many populations studied. Our own work, (Murphy et al. 2004a) reported mean SDS for weight and height of -0.36 (SEM ± 0.12) and -0.46 (SEM ± 0.14) in a population of 52 children with CF with a mean age of 10.8 years (SD 2.7). Moreover, the assessment of nutritional status in a slightly larger cohort of children from the same clinic (Murphy et al. 2006) revealed that only a small percentage were malnourished using Body Cell Mass adjusted for height (a technique discussed later) as the index of nutritional status (Table 96.2). The female CF patients were significantly shorter than the controls ($p = 0.01$); however, there was no significant difference in weight or BMI. The male CF subjects were found to be significantly shorter ($p = 0.02$) and lighter ($p = 0.003$) than their matched healthy controls, with resulting BMI also significantly lower ($p = 0.004$). A note of caution against complacent should be injected as this point, however, as these same data showed clearly that although children with CF appear better nourished, there was a small but statistically significant relationship between nutritional status and age in this group, suggesting that nutritional status may decline with age (Fig. 96.2). However, recent longitudinal

Table 96.3 Longitudinal measurements of body composition in children with cystic fibrosis

	CF (mean ± SD)		Control (mean ± SD)	
	T1	T2	T1	T2
Age (years)	8.0 ± 1.4	14.9 ± 1.8	8.6 ± 1.5	14.1 ± 1.5
Height SDS	–0.05 ± 1.21	–0.12 ± 1.12	–0.26 ± 1.01	–0.13 ± 0.99
Weight SDS	0.08 ± 1.01	0.06 ± 0.82	–0.29 ± 0.99	–0.13 ± 0.85
BMI SDS	0.28 ± 0.85	0.14 ± 0.66	–0.18 ± 1.00	–0.17 ± 0.82
BCMI SDS	0.81 ± 1.00	0.12 ± 1.14	0.14 ± 1.33	0.14 ± 1.51
Fat (%)	18.8 ± 10.4	24.4 ± 11.0	18.8 ± 5.2	24.0 ± 10.3

This table shows the body composition measurements of a group of 13 children with cystic fibrosis and age- and sex-matched healthy peers at 2 time points: T1 as the initial measurement and T2 as the follow-up measurement 6 years later. *SDS*, standard deviation scores

unpublished data in 13 CF children and controls shows that the small population of children with CF had similar BCM and percent fat to matched healthy controls over a 6 year period, concluding that the CF subjects were well nourished and that there is no evidence that nutritional status was affected by age (Table 96.3).

Much can be gained from appropriate anthropometric assessment in children and adolescents with cystic fibrosis. A minimal anthropometric set of analyses should include weight, height and some measure of body composition as described later. Equally important is that these data be evaluated and interpreted correctly so that interventions nutritional or otherwise might be appropriate.

96.3 Practical Methods and Considerations in Children with CF

96.3.1 Cystic Fibrosis and Body Composition Measurements

Research has shown that when the causes of malnutrition, that is, increased requirements, inadequate intake and inadequate absorptions are managed appropriately, then clinical outcomes are improved. Therefore, early detection of nutritional problems is essential to allow for intervention. Anthropometric measurements vary in their complexity, suitability and validity in children and the CF population; common methods will be addressed below.

96.3.1.1 Anthropometry

Anthropometry includes measurements of weight, height, circumferences and skinfolds. These methods are often used for assessing children with CF as they are simple, inexpensive, safe and portable; however, they are not recommended for individual clinical subject evaluations or for examining short-term changes in body fat. Anthropometric techniques usually demonstrate the largest standard error and lowest correlation coefficients when compared against other techniques for estimating total-body fat such as dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), or in vivo neutron activation analysis. The standard anthropometric approaches of measuring weight and height can yield useful information and in conjunction with more appropriate estimates of body compositions as described later can offer insight into the clinical manifestations of the disease.

Interpretation of measurements of height, weight and BMI are clearly enhanced by the conversion of such measures to standard deviation score (SDS) using an appropriate reference data set. If there

is a suggestion that an inherent part of the natural history or progression of the disease is a delayed bone age then expressed weight, height or body mass index (BMI) as a SDS relative to estimated bone age may enhance further the analyses of growth data in this circumstance.

Indices of weight and height have been developed to provide a simple method of body composition. For years, percentage ideal body weight (%IBW) was recommended by the CF Foundation Consensus Report as the preferred measure of nutritional status. However, recent studies have found that this method underestimates the severity of malnutrition. A recent study compared %IBW to body mass index (BMI) percentiles in 4,577 children with CF (Wiedemann et al. 2007). They found that when using %IBW their population was reasonably nourished, but that BMI percentiles placed the population below the reference median. These findings were also supported by another study who reported that %IBW underestimated the prevalence of malnutrition in children with short stature and overestimated in children with tall stature (Zhang and Lai 2004).

These studies have led the CF Foundation to amend their recommendations and now advises that the BMI percentile method is used in weight for stature assessment for children and adolescents aged 2–20 years (Stallings et al. 2008). The use of BMI percentile only plays a role in determining whether weight is appropriate for stature. They should only be used in combination with other methods to detect malnutrition as BMI is not able to quantify fat mass or distinguish between fat and lean tissues, and subjects of the same BMI may differ widely in fatness. The normal relationship between height and weight is altered in CF and with the limited sensitivity of BMI percentiles to predict increased body fat in both a clinical and a healthy population; BMI is considered a poor measure of body fat in clinical situations. A study found that the number of CF patients diagnosed as malnourished depends on the assessment technique, with weight for height indices not performing well compared to total body potassium (TBK) measurements (McNaughton et al. 2000). Another study examined BMI values against skinfolds and BIA (Groeneweg et al. 2002). Their results indicated that BMI plots were within normal range despite a significant decrease in FFM in these children; thus proving that BMIs are not accurate reflections of body composition in children with CF.

Skinfold measurement is commonly used in children with CF because of their low cost, portability and simplicity. The measurement of skinfold thickness is taken by grasping the skin between thumb and forefinger and measuring this thickness with callipers. A number of measurements at different sites can be used in age- and gender-specific equations to determine body composition. Skinfold measurement is based upon two assumptions; that the thickness of subcutaneous fat represents a constant proportion of the total body fat, and that the measurement sites represent the thickness of the total body fat. Neither of these assumptions has been proven. The high variability of skinfold measurement may be due to the callipers used, the technique applied, the increased error with high fat content and the inappropriate application of equations.

A study examined the use of skinfolds in adults with CF (King et al. 2005). Compared to DXA, the authors found that FFM from the sum of skinfolds overestimated FFM on average by 2.2 kg compared to DXA. In children with CF, skinfolds have been compared to deuterium dilution measurements (de Meer et al. 1999). These results agreed with the adult findings, showing that skinfolds overestimate FFM in CF populations. The reason for skinfolds overestimating FFM may be because the prediction equations are validated in a healthy population and that skinfolds will be influenced by regional fat distribution.

Arm anthropometry is another simple method often used in CF patients. Arm anthropometry may include measures of triceps skinfolds, mid upper arm circumference and equations to estimate arm muscle area. When the use of arm anthropometry in children with CF has been compared to DXA and the four compartment model, it has been shown that this method was useful for predicting FM in a CF population (Chomtho et al. 2006).

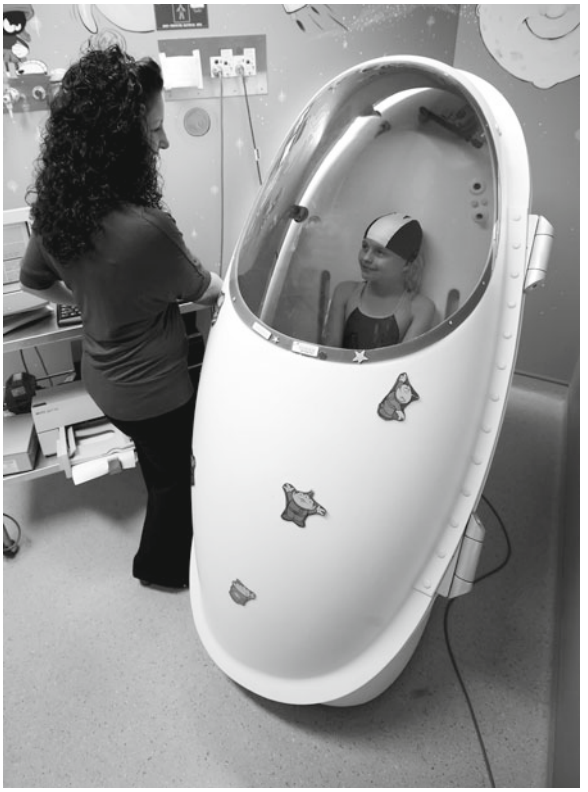

Fig. 96.3 The Bod Pod®. This figure shows the Bod Pod® which uses air displacement plethysmography to measure body volume

96.3.1.2 Air Displacement Plethysmography

Air displacement plethysmography (ADP) is a relatively new method available to measure body composition and presents a preferred alternative to underwater weighing. The only available system for ADP is the Bod Pod® (Life Measurements Instruments, Inc., Concord, CA) (Fig. 96.3). The Bod Pod® measures body volume and body density is then calculated. Body density can be used to estimate body fat with a two-component body composition model or can be used in combination with other methods for a four-component model.

A publication compared FFM from the Bod Pod® to DXA in 52 children with CF and found it is an appropriate technique for use in children and adolescents with CF (Murphy et al. 2004a). Figure 96.4 shows the Bland-Altman Plot when the Bod Pod® is compared against DXA in a group of children with CF. The advantages of the Bod Pod® for children with CF are that it is quick, simple and non-invasive. The limitations of the Bod Pod® lie with the limitations of densitometry when used as a two-compartment technique; the Bod Pod® assumes the density of the FFM is similar in all ages and disease. However, assuming this constant in CF may lead to overestimation of fatness because altered fluid distribution and under mineralisation decreases the density of the FFM in children with CF depending on the extent that CF has affected the FFM density in the individual.

96.3.1.3 Bioelectrical Impedance Analysis

Bioelectrical impedance analysis measures the impedance of the body tissues to the flow of a low level alternating current. The principle of BIA is that when a current is passed through the body it will only pass through the water and electrolyte containing tissues which have low impedance, not the body fat

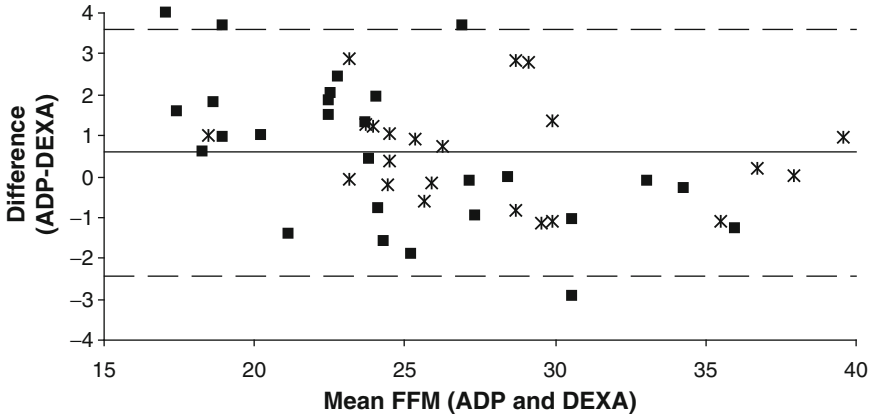

Fig. 96.4 A bland-Altman plot of the Bod Pod® versus dual energy X-ray absorptiometry (DXA). This figure shows the difference in FFM between ADP and DEXA against the mean FFM from the two methods. The squares represent females and crosses represent males. The correlation between the difference in FFM and the mean FFM from the two methods is $r = -0.26$, $p = 0.07$

or bone which have poor conduction properties. Impedance is therefore related to total body water, and by using this relationship in prediction equations, the clinically important value of FFM can be estimated from BIA. There are two assumptions involved in this measurement to determine body volume; the body is a collection of cylinders with their length proportional to their height, and the reactance contributing to impedance is small, with the resistance considered equivalent to impedance.

Recent studies suggest that BIA is not an accurate method in CF patients and that BIA equations will incorrectly estimate FFM in patients with CF. A study has shown that selected equations created to measure FFM from BIA in children are not optimal for use in the clinical population of CF (Murphy et al. 2004b). The problem with the prediction of FFM from BIA in CF patients is that the theory of BIA and the FFM prediction equations employ several assumptions that may not be applicable in children and adolescents with CF. It has been found that CF causes a disturbance in skin electrolyte composition, abnormal fluid distribution, sodium depletion and hydration levels, all of which could affect either the prediction of total body water or its use to calculate FFM.

96.3.1.4 Dual Energy X-Ray Absorptiometry

A DXA scan requires an X-ray source to produce a broad photon beam that is filtered, yielding two different energy peaks. The photons pass through the body's tissues and the resulting attenuation between the two energy peaks is characteristic for each tissue. The concept of DXA technology is that photon attenuation is a function of tissue composition, with bone, lean tissue and fat being distinguishable by their X-ray attenuation properties.

Although DXA studies are increasing in popularity in nutritional studies, such studies should be interpreted with caution as the technique does not represent a complete reference technique, especially in the CF population. Studies have shown that the bias of DXA is unreliable for monitoring body composition longitudinally or in case-controlled studies as results vary with gender, size, fatness and disease state, including CF (Williams et al. 2006). The findings indicate that caution is necessary when DXA is used to compare CF patients with healthy peers or used to longitudinally assess body composition if weight has changed significantly between measurements.

Issues such as hydration and tissue thickness have also been investigated for their effect on DXA measurements. Dual energy X-ray absorptiometry assumes that the lean tissue is normally hydrated.

Fig. 96.5 The total body potassium counter. This figure shows the total body potassium counter which uses sodium iodide detectors to measure the amount of potassium-40 in the body

In patients with CF, the addition of fluid is likely and may result in an underestimation of FM changes. It is suggested that a 5% change in the hydration of FFM will affect the estimate of body fat using DXA by 1–2.5% (Lohman et al. 2000). Dual energy X-ray absorptiometry also assumes a constant distribution of fat over bone tissue and bone-free tissue, which means that estimates of soft tissue may not be as accurate over regions with high bone content as the regions with low bone content (Genton et al. 2002). This also may lead to error in children with CF, who may have regional differences in bone content. There are also several technical factors that may affect DXA measurements of body composition. Results have been shown to differ with manufacturer, software version and beam mode (Kistorp et al. 2000).

Despite the limitations of DXA, the technology provides a body composition technique that with some further research will be useful in the CF setting, particularly as body composition and bone density measurements can be taken with the one test. The measurements are simple, quick and painless to perform, give immediate results, require minimal radiation dose and are available in many clinical settings.

96.3.2 Total Body Potassium Counting

An assessment method that is considered suitable for use in children with CF is TBK counting which provides a measure of body cell mass (BCM) (Fig. 96.5). BCM is the metabolically active component of FFM and is hence, the component of the FFM that is reduced most significantly in malnutrition.

Unlike measurements of FFM, measurements of BCM are a better reflection of nutritional status in children with CF because they are independent of extracellular fluid shifts that may occur as a result of disease state.

Typically, TBK measurements are reported as a raw value in grams or converted to BCM, or reported as a predicted TBK based on control values to represent nutritional status. The use of gender-specific BCMI *Z* scores to report TBK values has only been developed recently (Murphy and Davies 2008). The use of BCMI SDS allows adjustment for height and gender, and ensures that appropriate comparisons can be made within and between groups. This is especially important in children with CF who may be shorter than healthy peers.

96.4 Application to Other Areas of Disease

There are many chronic childhood illnesses that have as a component or consequence poor growth and development. The role of under nutrition or malnutrition in the aetiology of growth retardation in such illnesses has been actively investigated by a number of groups. For growth failure to be a consequence of under nutrition, an individual must be in negative energy balance for substantial periods of time. After the first few years of life, growth is not a major energy consuming process. The energy cost of synthesis and deposition of new tissue during the growth process accounts for between 1.5% and 2.0% of daily energy intakes in normal healthy children. Prolonged periods of negative energy balance could be produced in CF by a reduction in energy intake or an increase in energy expenditure or a combination of both of these factors. Indeed, it is not difficult to investigate both such scenarios in an affected child, and evidence has been produced that in CF this combination did occur frequently when the comments above relating to growth retardation, growth failure and pubertal delay were postulated.

An appropriate and efficient approach to the anthropometric monitoring of growth and development in children with CF can be applied to many chronic diseases of childhood and adolescence. A minimum requirement should be some assessment of linear growth, that is supine length, stature or in some cases limb lengths, some assessment of "body size", that is body weight and/or BMI and finally an estimate of body composition. Acceptable, reliable and accurate measures of body composition have been described in some detail in this chapter, and the method used will depend to some degree on practical issues such as availability and appropriateness.

As with all anthropometric assessments, interpretation is the key, and so the clinician, researcher or student should establish which are the best anthropometric references to use in any given situation. Variation in age and sex, for example, can be "adjusted for" by the use of SDS as previously mentioned and this approach makes statistical analysis and evaluation much easier. Often growth velocity ($cm/year^{-1}$) is an important factor in evaluating the effect of the disease or indeed the effect of an intervention. Growth velocity varies markedly throughout growth with significant changes occurring around puberty. Thus, again, physical maturity should be taken into account via bone age whenever possible. Unfortunately, there are scant data that allow the calculation of a height velocity SDS and it is perhaps better to consider the change (delta) SDS relative to bone age in this circumstance.

The choice of body composition technique is also an important consideration in children with CF and the logic that underpins that choice is equally valid in other circumstances. One notable important issue is the fact in many chronic diseases there is often an expansion of the extracellular fluid (ECF) compartment. Methods of body composition assessment that use a two-compartment model will likely overestimate the FFM in this situation as the model is unable to distinguish the expanded ECF as not being associated with FFM. This error might be especially important when attempting to evaluate changes in body composition either throughout disease progression or recovery.

Summary Points

- Cystic fibrosis (CF) is a common serious genetic condition in children. The principal effects are seen in the respiratory system, the gastrointestinal tract and the sweat glands. The goal of CF management is to prevent infections, reduce the amount and thickness of lung secretion and maintain adequate nutritional status.
- There have been improvements in anthropometric status of children with CF, paralleling improvements in treatment.
- Measurement and interpretation of anthropometric measurements in children with CF is vital. Basic measurements of growth need to be supported with body composition measurements. Delayed bone age should be considered by expressing weight, height or BMI as a SDS relative to estimated bone age.
- The choice of body composition technique is an important consideration in children with CF as in other diseases, considering the limitations of the technique for the population.
- Considerations of body composition interpretation in children with CF need to include height, bone age and hydration.

Key Features

- Cystic fibrosis is a common serious genetic disorder that affects children.
- Anthropometric assessment of children with cystic fibrosis is essential as the symptoms of the disease directly and indirectly impact upon growth and body composition.
- Height, weight and BMI need to be converted to standard deviation scores to understand their value in children with cystic fibrosis.
- Basic measurements of growth need to be supported with body composition measurements in children with cystic fibrosis.
- Bioelectrical Impedance Analysis, Total Body Potassium counting, Dual Energy X-ray Absorptiometry and the Bod Pod® are all suitable methods for use in children with CF.
- Height, bone age and hydration need to be considered when interpreting body composition in children with cystic fibrosis.

This table lists the key facts covered in this chapter

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Chapter 97
Facial Anthropometry in Hypohidrotic Ectodermal Dysplasia (HED)

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Abstract Ectodermal dysplasias are a large and heterogeneous group of heritable disorders, with an estimate prevalence of 1/100,000 births. Hypohidrotic ectodermal dysplasia (HED) is the most frequent ED variant, and it is identified by the triad of hypotrichosis, hypohidrosis, and hypodontia. Patients with HED also have an abnormal craniofacial morphology.

Common phenotypic characteristic of patients suffering from HED is a generalized, but non-uniform, reduction of facial and head dimensions as compared to normal subjects. In particular, there is frontal bossing, reduced vertical facial height and cranial base width, maxillary and mandibular hypoplasia with small hard tissue palate, high-set orbits with increased biorbital and intercanthal widths, and prominent chin. Facial convexity in the horizontal plane (in all three facial thirds) is increased. The nose and ears are narrow and short, the mouth is narrow with protuberant and everted lips. The nasio-labial angle is acute, the supramental sulcus increased, and the vermilion area of the lips augmented.

The midface hypoplasia produces a skeletal Class III tendency (maxillary retrusion associated with mandibular protrusion) with flat or concave facial profile, and the reduction of the vertical dimension turns out an "aged" appearance. Overall, the largest deviations from the norm are found in facial height and anterior-posterior dimensions of facial lower two-thirds, while facial widths are more similar to reference values.

Patients with HED have extensive lack of both deciduous and permanent teeth and with hypoplasia of the alveolar processes. The severe facial and dental deficiencies induce alterations not only in masticatory function and in spoken communication, but also in esthetics, with subsequent psychological problems of self-confidence.

Overall, the facial soft-tissue of subjects with HED can be successfully measured and monitored with non-invasive computerized anthropometry. Diagnosis, treatment planning, and evaluation of results can be based on global, three-dimensional, quantitative assessment of the craniofacial characteristics of patients with HED. Both the hard- and the soft-tissue structures should be analyzed to provide a complete evaluation of any patient, and should be compared to those of healthy subjects of the same age, sex, race, and ethnic group.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_97,

Abbreviations

3D	Three-dimensional
CVI	Craniofacial variability index
ED	Ectodermal dysplasia
HED	Hypohidrotic ectodermal dysplasia
SD	Standard deviation

97.1 Introduction

The overall form (size, shape, and reciprocal arrangement of the parts) of the human craniofacial skeleton and of its soft-tissue covering is dependent upon the coordinated pattern of development of separate cartilaginous, skeletal, dental, and soft-tissue elements. The complex harmony of the various developmental programs can be altered by genetic modifications.

Among the various genetic modifications affecting the craniofacial complex, the ectodermal dysplasias (ED) are characterized by anomalies in the embryonic development of ectodermal tissues and derivates (Ward and Bixler 1987; Saksena and Bixler 1990; Pinheiro and Freire-Maia 1994; Bondarets and McDonald 2000; Priolo and Laganà 2001; Ruhin et al. 2001; Bondarets et al. 2002; Johnson et al. 2002; Skrinjaric et al. 2003; Ferrario et al. 2004; Sforza et al. 2004). The ED are a large and heterogeneous group of heritable disorders, with an estimate prevalence of 1/100,000 births (Lamartine 2003). Patients with ED have altered epithelium-mesenchyme interactions, which produce modifications in the embryonic development of the ectodermal appendages (teeth, nails, hair, and sweat glands) (Priolo and Laganà 2001; Lamartine 2003).

According to the degree of sweat glands dysfunction, ED can be divided into the hidrotic and hypohidrotic variants. Hypohidrotic ectodermal dysplasia (HED), also called Christ-Siemens-Touraine syndrome, is the most frequent ED variant, and it is identified by the triad of hypotrichosis, hypohidrosis, and hypodontia (Ward and Bixler 1987; Pinheiro and Freire-Maia 1994; Pigno et al. 1996).

Genetic alterations in ED may involve the protein ectodysplasin-A (X-linked ED, ED1, MIM305100) (OMIM 2009), or the cellular receptor for its most important isoform (autosomal recessive ED, MIM224900; autosomal dominant ED, MIM606603) (OMIM 2009). Ectodysplasin-A is a collagenous trimeric transmembrane protein, a member of the tumor necrosis factor family. The proteins of this family regulate apoptosis and cell death, as well as cell adhesion (Priolo and Laganà 2001; Lamartine 2003). Activation of the ectodysplasin-A receptor starts a nuclear factor involved in the regulation of cellular fate, thus regulating cell survival, growth, and differentiation (Lamartine 2003).

Patients with HED have not only alterations of the teeth, nails, hair, and sweat glands, but also of the meso-ectodermal layer constituted by the neural crest, which results in an abnormal craniofacial morphology (Ward and Bixler 1987; Saksena and Bixler 1990; Pinheiro and Freire-Maia 1994; Montonen et al. 1998; Bondarets and McDonald 2000; Ruhin et al. 2001; Bondarets et al. 2002; Johnson et al. 2002).

Indeed, while the alterations in ectodermal derivates in patients with HED have been widely described in the literature, and are currently used for diagnosis, the effect of this group of genetic diseases on the craniofacial structures derived from the neural crest has received attention only more recently (Figs. 97.1 and 97.2). Considering that there are ED coupled with multiple congenital anomalies, always involving the skeleton, a relationship between epidermal alterations and modifications in the craniofacial skeleton might be hypothesized even in "pure" ED (those with abnormality in epidermal derivatives only). Accordingly, the gene defective in HED is also expressed in the neuroectoderm and developing bone (Montonen et al. 1998).

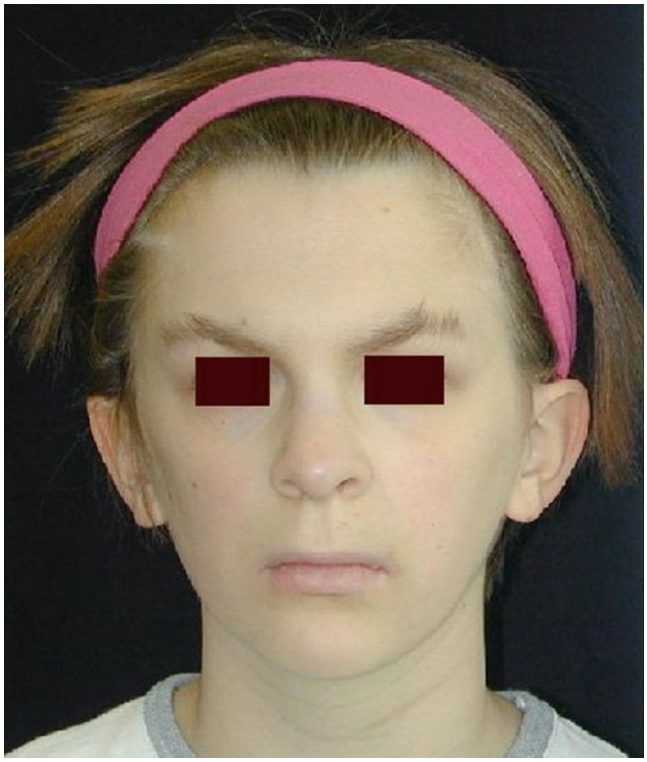

Fig. 97.1 A 10-year old girl with hypohidrotic ectodermal dysplasia. This girl has sparse hairs, with a facial phenotype typical of a mild expression of hypohidrotic ectodermal dysplasia

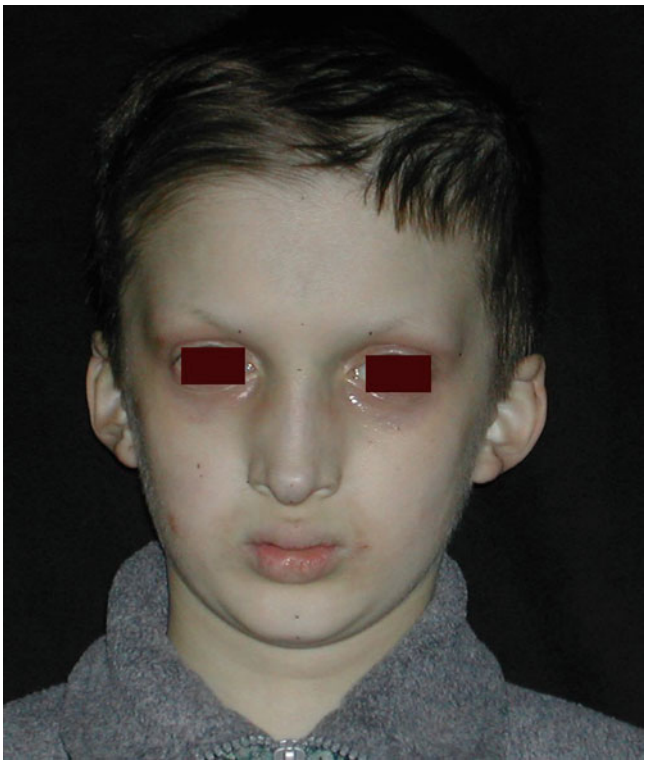

Fig. 97.2 A 7-year old boy with hypohidrotic ectodermal dysplasia. This boy has sparse hairs, narrow mouth, protuberant and everted lips, with a facial phenotype typical of a full expression of hypohidrotic ectodermal dysplasia

Craniofacial morphology in patients with HED has been investigated by lateral head radiographs, conventional anthropometry, and computerized anthropometry, and a set of alterations have been described both in children and in adults (Ward and Bixler 1987; Saksena and Bixler 1990; Bondarets and McDonald 2000; Bondarets et al. 2002; Johnson et al. 2002; Skrinjaric et al. 2003; Ferrario et al. 2004; Sforza et al. 2004, 2006; Dellavia et al. 2008).

In the current chapter, the methods used for the assessment of craniofacial phenotype in patients with HED will be briefly described, and the main results will be presented and discussed.

97.2 Phenotypic Assessment of the Craniofacial Complex in Patients with HED – Methods for Data Collection

Facial features in HED affected subjects have been analyzed using both qualitative and quantitative descriptors obtained by cephalometry and anthropometry.

Several quantitative investigations performed on patients with HED analyzed the hard tissue situation of the craniofacial skeleton, as depicted by lateral plane head radiographs (Bondarets and McDonald 2000; Bondarets et al. 2002; Johnson et al. 2002; Lexner et al. 2007). Head radiographs are currently part of the diagnostic procedures in almost all maxillo-facial, plastic, orthodontic, and dental clinical assessments, providing information about the morphology and reciprocal positions of the skeletal and dental structures. Unfortunately, they have several limitations. They use ionizing radiations, thus being potentially harmful to the subject; they provide a two-dimensional assessment of the skeletal configuration, neglecting most of the soft-tissues and projecting all structures on a single (usually mid-sagittal) plane.

On ethical grounds, radiographic analyses cannot be performed on healthy subjects without a medical indication, and even the longitudinal repetition of X-rays in patients should be limited. These limitations impede the use of radiographs for the construction of reference standards, and restrict their application for growth studies, and to assess the longitudinal effects of treatments.

The three-dimensional information of the entire craniofacial skeleton, together with the soft tissue structures, can currently be provided by computed tomography (a X-ray based technique) and magnetic resonance (a method that assess the behavior of living tissues introduced into magnetic fields). Novel computed tomograms (cone-beam, multislice) allow a detailed reconstruction of the hard- and soft-tissue components of the cranium and face with a significantly reduced exposure to ionizing radiations (Maal et al. 2008). Unfortunately, both methods are too expensive and have limited availability outside well-selected clinical settings. Also, it seems very difficult to obtain a database of normative values from healthy, non-patient subjects for both radioprotection concerns (computed tomography) and monetary considerations (magnetic resonance).

In contrast, anthropometry is non-invasive, three-dimensional, and it considers all the facial structures that contribute to the face of the single patient (Ward and Bixler 1987; Ward et al. 2000; Sforza and Ferrario 2006). Neither the collection of normative data, nor longitudinal examinations, infringe any current ethical consideration.

Conventional, direct anthropometry is currently considered the gold standard for patient assessments: the method is simple, low-cost, and it does not require complex instrumentation (Allanson and Newbury-Ecob 2003; Skrinjaric et al. 2003). A further advantage is the existence of normal databases for almost all craniofacial measurements, at least for white Caucasians, while norms for other ethnicities are scantier (Sforza and Ferrario 2006).

Several investigations assessed the facial characteristics of patients with HED using conventional direct anthropometry (Ward and Bixler 1987; Saksena and Bixler 1990; Skrinjaric et al. 2003; Lexner et al. 2007). Unfortunately, conventional anthropometry is time-consuming, very demanding on both the clinician and the patient, and needs very well trained and experienced examiners. Each measurement is taken individually, and the procedure does not leave permanent records of the facial morphology: missing values, miscalculations or reading errors cannot be corrected off-line. Additionally, no digital coordinate data are available, and new sets of features cannot be measured, nor more complex calculations be performed (surface and volume estimations, analyses of symmetry, form and shape quantification) (Douglas et al. 2003; Ferrario et al. 2004; Hammond et al. 2004).

In contrast, digital, computerized anthropometry currently allows a non-invasive, fast, and simple data collection (Douglas et al. 2003; Ferrario et al. 2004; Hammond et al. 2004; Sforza et al. 2004, 2006; Dellavia et al. 2008). Digital data allow the creation of computerized data bases, implementation of pattern recognition algorithms, and use of the computerized techniques of visualization and simulation of treatment (Sforza and Ferrario 2006).

Current instruments available for computerized, soft-tissue three-dimensional facial anthropometry can be divided into two main categories: optical, non-contact instruments (laser scanners, 3D range-cameras, optoelectronic instruments, stereophotogrammetry, Moiré topography), and contact instruments (electromagnetic and electromechanical digitizers, ultrasound probes). Both kind of instruments are non-invasive, not potentially harmful, and do not provoke pain in the subject (Douglas et al. 2003; Hammond et al. 2004; Sforza and Ferrario 2006; Maal et al. 2008).

The optical instruments allow a fast analysis of the facial surface, providing data on facial surface area and estimates of facial volume, and for indirect anthropometric assessments. The most used instruments are laser scanners and stereophotogrammetric systems. Laser scanners illuminate the face with a laser light source while digital cameras capture the images; triangulation geometry provides the depth information. In stereophotogrammetry a light source illuminates the face, and two or more coordinated cameras record the images from different points of view. A computerized stereoscopic reconstruction is then obtained (Sforza and Ferrario 2006).

Contact instruments digitize single selected facial landmarks (Fig. 97.3), thus reducing the information obtained from each face, but they provide the coordinates of facial features that directly correspond to anatomical and anthropometric structures (Ferrario et al. 2004; Sforza and Ferrario 2006; Sforza et al. 2004, 2006; Dellavia et al. 2008). Ultrasound probes, electromagnetic and electromechanic digitizers are currently in use, and collected data have been used for the characterization of normal individuals, and selected groups of patients. Data collection with these instruments is longer than with the optical devices, but they are less expensive, and can be moved with more ease to meet the patients even outside clinical settings. In particular, electromagnetic digitizers have been used for soft-tissue facial analysis of patients with HED (Ferrario et al. 2004; Sforza et al. 2004, 2006; Dellavia et al. 2008).

97.3 Phenotypic Assessment of the Craniofacial Complex in Patients with HED – Methods for Data Analysis

Craniofacial data collected from patients with HED have been analyzed using two principal approaches. Cephalometric and anthropometric measurements (distances, angles, ratios, but also areas and volumes) can be listed, and the distance of each from a reference assessed, thus providing a detailed, localized description of the altered morphology (Ward and Bixler 1987;

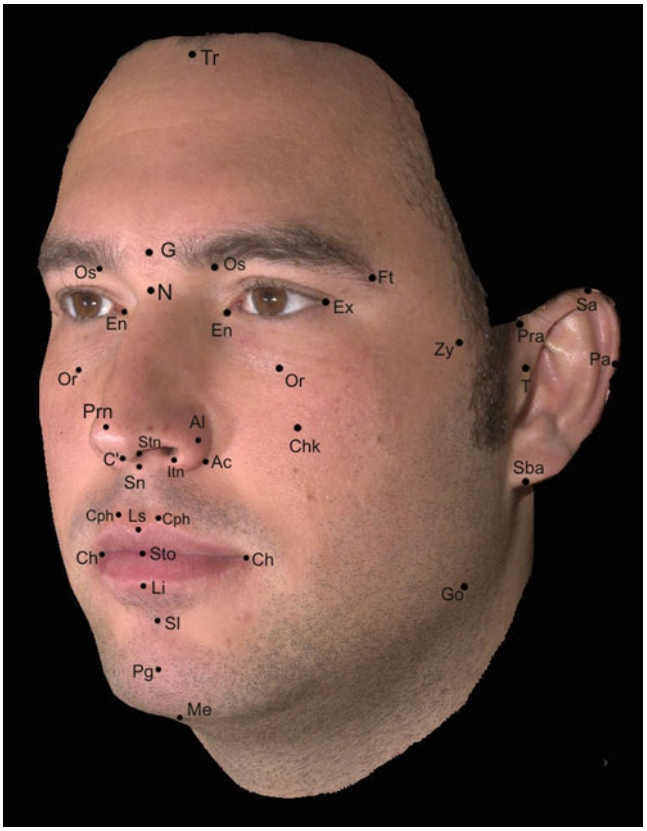

Fig. 97.3 Soft tissue facial landmarks digitized on all analyzed subjects. A detailed description of the method can be found in the chapter "Three-dimensional facial morphometry: from anthropometry to digital morphology" in this book. A set of 50 soft-tissue facial landmarks is marked on the face before data acquisition

Bondarets and McDonald 2000; Johnson et al. 2002). Data are transformed to *z*-scores by subtracting each from its sex and age reference mean value, and dividing by the relevant reference standard deviation (Garn et al. 1984; Skrinjaric et al. 2003; Ward and Bixler 1987; Ward et al. 2000). The *z*-scores are standardized measurements that quantify the distance of an individual from the reference population in terms of standard deviation; in other words, a *z*-score outside the ±2 interval means that the measurement is smaller (or larger) than the reference value of two standard deviations.

Furthermore, anatomic features can be combined, and global indices obtained (Saksena and Bixler 1990; Ward et al. 2000). Among the others, two summary anthropometric measurements have been used for quantifying craniofacial variations: the mean *z*-score (an index of overall facial size, compared to a reference population), and its standard deviation, called the craniofacial variability index (CVI) (Ward et al. 2000). CVI represents the amount of variability across the analyzed *z*-scores: it is low in subjects whose *z*-scores are all of analogous dimensions and in the same direction (increment or decrement) relative to the reference means. In contrast, CVI is high in subjects with disharmonious relationships between individual facial measurements.

For a global comparison of the craniofacial characteristics of two subjects or of two groups (for instance males and females, or subjects of different ages) a correlation analysis between the paired *z*-scores of the individuals of the two groups can be run: high correlation coefficients indicate very similar patterns (Garn et al. 1984).

97.4 Phenotypic Assessment of the Craniofacial Complex in Patients with HED – Main Results

Common phenotypic characteristics of patients suffering from HED is a generalized, but non-uniform, reduction of facial and head dimensions as compared to normal subjects (Ward and Bixler 1987; Saksena and Bixler 1990; Bondarets and McDonald 2000; Johnson et al. 2002; Sforza et al. 2004). In particular, there is frontal bossing, reduced vertical facial height and cranial base width, maxillary and mandibular hypoplasia with small hard tissue palate, high-set orbits and prominent chin. Facial convexity in the horizontal plane (in all three facial thirds) is increased. The nose and ears are narrow and short, the mouth is narrow with protuberant and everted lips. The nasio-labial angle is acute, the supramental sulcus increased, and the vermilion area of the lips augmented (Ward and Bixler 1987; Saksena and Bixler 1990; Bondarets and McDonald 2000; Ruhin et al. 2001; Johnson et al. 2002; Skrinjaric et al. 2003; Ferrario et al. 2004; Sforza et al. 2004, 2006; Suri et al. 2004; Dellavia et al. 2008).

The midface hypoplasia produces a skeletal Class III tendency (maxillary retrusion associated with mandibular protrusion) with flat or concave facial profile, and the reduction of the vertical dimension turns out an "aged" appearance (Sforza et al. 2006; Dellavia et al. 2008). Overall, the largest deviations from the norm are found in facial height and anterior-posterior dimensions of facial lower two-thirds, while facial widths are more similar to reference values (Ward and Bixler 1987; Skrinjaric et al. 2003).

The principal facial features of patients with HED are summarized in Table 97.1.

This kind of modification was further investigated using the mean *z*-score and the CVI, finding an averaged reduction in the mean *z*-score, and an increased CVI in comparison with the reference population (Sforza et al. 2004). In particular, 60% of the analyzed patients had a CVI larger than the normal interval, thus indicating a global disharmonious appearance, and 70% of patients fall outside of the quantitative definitions for normal facial size (*z*-score) and/ or harmony (CVI) (Sforza et al. 2004). A moderate relationship between the total number of maxillary and mandibular teeth present

Table 97.1 Key features of patients suffering from HED as compared to normal subjects

General	Generalized, but non-uniform, reduction of facial and head dimensions
	Increased facial convexity in the horizontal plane
	Reduced vertical facial height and cranial base width
	Narrow and short ears
	Flat or concave facial profile
Upper facial third	Frontal bossing
	High-set orbits
	Reduced orbital dimensions
	Increased biorbital and intercanthal widths
Middle facial third	Maxillary hypoplasia with small hard tissue palate
	Narrow and short nose
Lower facial third	Mandibular hypoplasia
	Narrow mouth
	Protuberant and everted lips
	Increased vermilion area of the lips
	More acute nasio-labial angle
	Increased supramental sulcus
	Prominent chin

This table lists the key facial features of patients with HED (hypohidrotic ectodermal dysplasia), divided into the three facial thirds

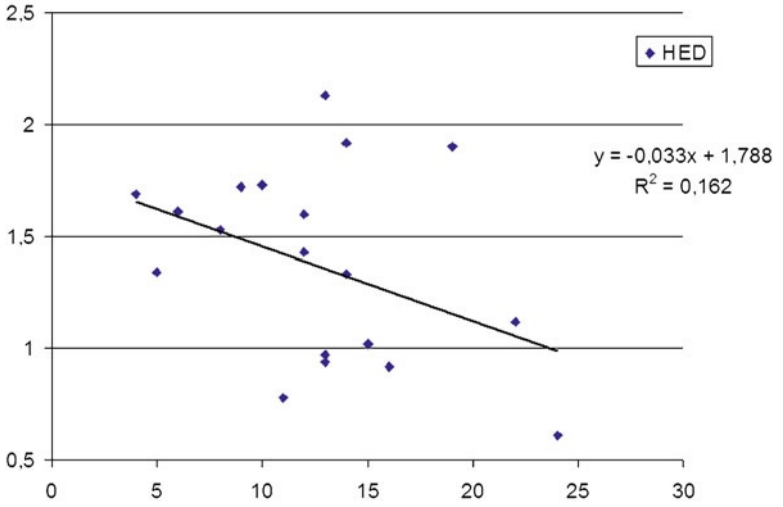

Fig. 97.4 Craniofacial variability index (CVI) as a function of the total number of teeth present in the mouth in 20 patients with hypohidrotic ectodermal dysplasia. Data were partly published by Sforza et al. (2006). The relevant regression line and its equation are also reported. The figure shows that the larger the number of teeth, the smaller is the deviation from the norm

in the mouth and the CVI was found: subjects with more teeth had a smaller CVI (that, a somewhat more harmonious phenotype) than subjects with fewer teeth (Fig. 97.4). Similarly, Sforza et al. (2006) reported that the facial soft tissues differed less from the norm in patients who had a larger number of mandibular teeth.

Indeed, patients with HED present with extensive lack of both deciduous and permanent teeth and with hypoplasia of the alveolar processes. Oligodontia (agenesis of more than six permanent teeth) is associated with growth disturbances of the maxillofacial skeleton leading to an atrophy and a reduced development of the stomatognatic system (Ward and Bixler 1987; Bondarets and McDonald 2000; Ferrario et al. 2004; Tarjan et al. 2005). The severe facial and dental deficiencies induce alterations not only in masticatory function and in spoken communication, but also in esthetics, with subsequent psychological problems of self-confidence.

For instance, the number of teeth was significantly related to the soft-tissue gonial angles: subjects with more teeth differed less from the norm (Sforza et al. 2006). This effect was tentatively explained hypothesizing a relationship between masticatory support (the teeth), chewing function (the masticatory muscles), and skeletal growth (all four masticatory muscles are inserted on the ramus and condylar process of the mandible) (Escobar and Epker 1998; Ruhin et al. 2001; Sforza et al. 2006). Additionally, significant relationships between the number of missing teeth, and mandibular plane inclination, gonial angle and mandibular prognatism have been reported for children and young adults with congenitally missing permanent teeth (but without ED) (Ben-Bassat and Brin 2003): the larger the number of missing teeth, the larger the deviation from the norm.

Nevertheless, the facial phenotype of patients with HED cannot be completely explained by hypodontia (Bondarets and McDonald 2000; Bondarets et al. 2002). While vertical growth seems to depend on the teeth in both HED patients (Bondarets and McDonald 2000; Ruhin et al. 2001) and in non-syndromic children with hypodontia (Ben-Bassat and Brin 2003), midfacial hypoplasia and a modification of the patterns of craniofacial growth appear to be peculiar to HED.

97.5 Phenotyptic Assessment of the Craniofacial Complex in Patients with HED – Ears and Orbital Region

Among the various parts of the face investigated in patients with HED, the eyes and the ears have not been analyzed in detail. For instance, Ward and Bixler (1987) reported a reduction in the dimensions of palpebral fissures, a finding substantiated by our previous study where we measured the soft tissue area of the orbital region (Ferrario et al. 2004). In contrast, the reduction in ear dimensions reported by Ward and Bixler (1987) and Skrinjaric et al. (2003) was not documented in the same subjects (Ferrario et al. 2004).

In our laboratory, ongoing investigations examining the soft-tissue facial characteristics of child and adult patients with HED, on both cross-sectional and longitudinal bases are being conducted. All patients with HED came from the Associazione Nazionale Displasie Ectodermiche (ANDE, Italy). Diagnosis was provided from clinical assessments of hypohidrosis, hypotrichosis, and hypodontia. None of the patients has clefting, syndactyly, or other alterations. Soft-tissue facial data were collected outside clinical settings, usually during meetings of the ANDE. Part of the data collected on these subjects have been previously reported (Ferrario et al. 2004; Sforza et al. 2004, 2006; Dellavia et al. 2008).

Data collected in patients with HED were compared to data collected in healthy persons of the same age, sex, and ethnic group.

In the present report, detailed quantitative data of ear and orbital morphology were reported in a group of 34 subjects with HED. A wide age range was covered, with children (seven boys aged 6–8 years, six girls aged 6–9.5 years), adolescents (six males, age range 11–14 years; four females, age range 10.9–12.6 years), and adults (four men, 21–31 years of age; seven women, 26–41 years of age). Mean age in females was 18.7 years, SD 12.1; in males, 13.6 years, SD 8.3; mean ages were not significantly different between sexes (unpaired Student's t test, $p > 0.05$).

A set of 50 soft-tissue facial landmarks was marked on the face of each subject (Fig. 97.3), and the digital, three-dimensional coordinates of the landmarks were obtained using an electromagnetic digitizer (Sforza and Ferrario 2006). Using custom software, linear distances, angles, and areas were automatically computed from the landmark coordinates (Ferrario et al. 2004; Sforza et al. 2004, 2006; Dellavia et al. 2008). A detailed description of the methods used in our laboratory can be found in the chapter "Three-dimensional facial morphometry: from anthropometry to digital morphology" in this book.

All data were converted into z-scores using our data bank of normal subjects of the same sex, age, and ethnic group. Some of the subjects were relatives (mother and two children of both sexes; two couples of mother and son; father and son; two sisters).

In the analyzed male subjects with HED, significant (Student's t tests for paired samples, 16 degrees of freedom) reductions in the right and left heights of the orbit (os-or), and external orbital surface areas were found (Table 97.2). Also the right and left lengths of the eye fissure (en-ex) were reduced, but the mean z-score was not significantly different from zero. In contrast, both the biorbital (ex_r-ex_l) and the intercanthal (en_r-en_l) widths were increased in the analyzed HED subjects when compared to the reference subjects, the second width also being significant at Student's t test.

The present findings contrast with the report by Skrinjaric et al. (2003), and only partly agree with that by Ward and Bixler (1987); in the present subjects with HED, transverse head dimensions in the orbital region were increased relative to a reference population, but their soft tissue orbital dimensions were smaller. Additionally, significant reductions of the right and left inclinations of the orbit (angle of the os-or line versus the true horizontal, head in natural head position) were found, with more vertical soft tissue orbits in male HED subjects than in the reference population.

Table 97.2 Three-dimensional soft-tissue orbital morphometry in subjects with hypohidrotic ectodermal dysplasia (HED) as compared to their reference groups matched for sex, age, and ethnicity. All values are *z*-scores [(HED subject value – reference mean)/reference standard deviation]

			Right side							Left side						
	ex_r-ex_l	en_r-en_l	os_r-or_r	en_r-ex_r	H/L	area	os_r-or_r vs. TH	en_r-ex_r vs. TH	os_r-or_r vs. FH	os_l-or_l	en_l-ex_l	H/L	area	os_l-or_l vs. TH	en_l-ex_l vs. TH	os_l-or_l vs. FH
Males																
Mean	0.31	1.18	–0.77	–0.50	–0.29	–0.84	–0.59	–0.73	0.03	–0.77	–0.56	–0.62	–0.93	–0.92	–0.78	–0.45
SD	1.08	1.61	1.55	1.30	1.47	1.38	0.94	1.50	1.46	1.02	1.63	0.79	1.30	0.85	1.61	1.14
t-Paired	NS	0.010	0.064	NS	NS	0.027	0.023	NS	NS	0.008	NS	0.006	0.011	0.001	NS	NS
Females																
Mean	–0.19	0.31	0.06	–0.19	0.17	–0.18	–0.48	0.33	–0.28	–0.39	–0.26	–0.18	–0.53	–0.80	0.36	–0.21
SD	1.31	1.16	0.99	1.86	1.18	1.62	2.95	1.09	2.79	1.00	1.80	1.11	1.33	2.55	0.94	1.86
t-Paired	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
M vs. F	NS	NS	NS	NS	NS	NS	NS	0.024	NS	NS	NS	NS	NS	NS	0.017	NS

Ex-ex: biorbital width; en-en: intercanthal width; os-or: right and left height of the orbit; en-ex: right and left length of the eye fissure; H/L: right and left height of the orbit to length of the eye fissure ratio (os-or/en-ex × 100); area: right and left external orbital surface area (area of the quadrangle between ex, os, en and or); os-or vs. TH (true horizontal): right and left inclination of the eye fissure (angle of the en-ex line versus the true horizontal, head in natural head position); en-ex vs. TH: right and left inclination of the orbit (angle of the os-or line versus the true horizontal, head in natural head position); os-or vs. FH (Frankfurt plane): right and left inclination of the orbit relative to Frankfurt plane (angle between the os-or and t-or lines)

t-Paired: *p* value of Student's *t* tests for paired samples, 16 degrees of freedom for each sex; *NS*: not significant ($p > 0.05$)

Comparison males vs. females, Student's *t* test for independent samples, 52 degrees of freedom

On average, patients with HED have smaller eyes and orbital regions than reference subjects

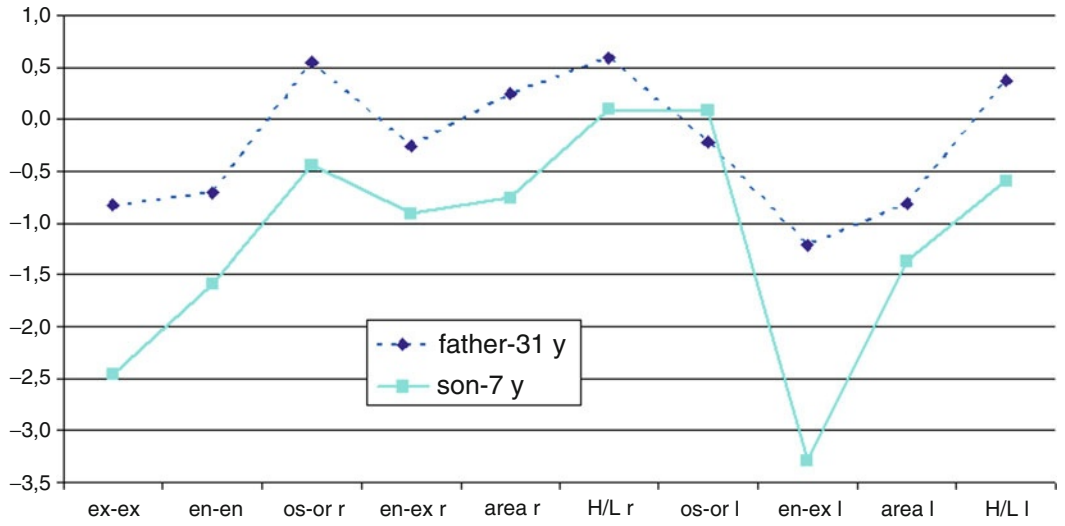

Fig. 97.5 Anthropometric pattern profile of the soft-tissue orbital measurements (linear distances, areas, ratios) made in a father and his son, both affected by hypohidrotic ectodermal dysplasia. Ex-ex: biorbital width; en-en: intercanthal width; os-or: right and left height of the orbit; en-ex: right and left length of the eye fissure; area: right and left external orbital surface area (area of the quadrangle between ex, os, en and or); H/L: right and left height of the orbit to length of the eye fissure ratio (os-or/en-ex × 100). Overall, father and son possess the same kind of deviation from the norm

No significant *z*-score values were found in the analyzed 17 females with HED (Table 97.2). Some sex-related differences were found in the mean *z*-scores, with significant *p* values (Student's *t* test for independent samples, 52 degrees of freedom) for the right and left inclinations of the eye fissure (angle of the en-ex line versus the true horizontal, head in natural head position): in males, the eye fissure was more vertical (angle to the true horizontal) relative to the norm than in females.

Previous reports on craniofacial morphology found no differences between male and female patients with either X-linked ED or autosomal HED (Saksena and Bixler 1990; Bondarets et al. 2002; Johnson et al. 2002; Ferrario et al. 2004; Sforza et al. 2004), in good agreement with current clinical reports (Priolo and Laganà 2001; OMIM 2009). The altered pathways in both the X-linked ED and the autosomally inherited EDs appear to converge in their final step on the same nuclear factor (Johnson et al. 2002; Lamartine 2003), thus producing a common phenotype from different genetic origins, a finding also reported for the murine model of ED (Priolo and Laganà 2001).

To assess the effect of family connections on soft-tissue orbital morphology, the subset of HED subjects who were relatives was analyzed in detail. Correlation analyses were run between the paired *z*-scores of 10 measurements of linear distances, areas, and ratios of the related subjects (Garn et al. 1984). The largest values $r = 0.841$ (correlation coefficient, $p < 0.01$) values were found between a father and his son (Fig. 97.5), and a 41-year-old mother and her 6-year-old son ($r = 0.744$, $p < 0.05$). More limited, non significant ($p > 0.05$), and even negative, correlations were found between a 32-year-old mother and her 7-year-old son ($r = 0.558$), two sisters (Fig. 97.6, $r = –0.108$), and a mother and her two children (Fig. 97.7, mother vs. son, $r = –0.49$; brother vs. sister, $r = –0.644$; mother vs. daughter, $r = 0.382$).

High correlation coefficients indicate very similar patterns of deviation of paired measurements from the norm (Garn et al. 1984). For instance, the father and his son had very similar patterns (Fig. 97.5), notwithstanding that the variations from the norm were more limited in the man than in the boy. In contrast, distinct patterns were observed in the two sisters, with the older sister being less

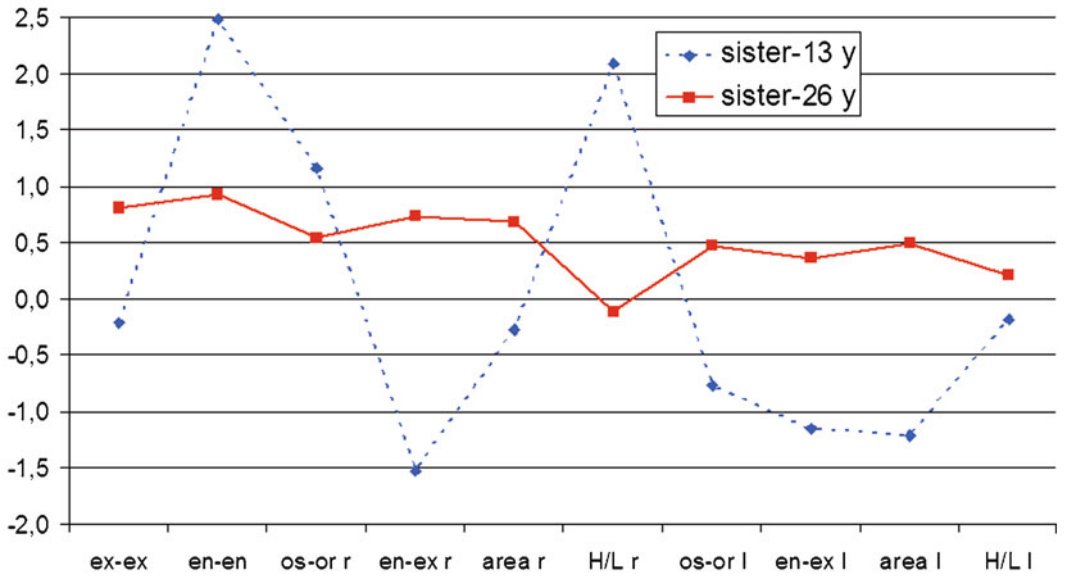

Fig. 97.6 Anthropometric pattern profile of the soft-tissue orbital measurements (linear distances, areas, ratios) made in two sisters, both affected by hypohidrotic ectodermal dysplasia. Ex-ex: biorbital width; en-en: intercanthal width; os-or: right and left height of the orbit; en-ex: right and left length of the eye fissure; area: right and left external orbital surface area (area of the quadrangle between ex, os, en and or); H/L: right and left height of the orbit to length of the eye fissure ratio (os-or/en-ex × 100). The younger sister deviates more from the norm than the older sister

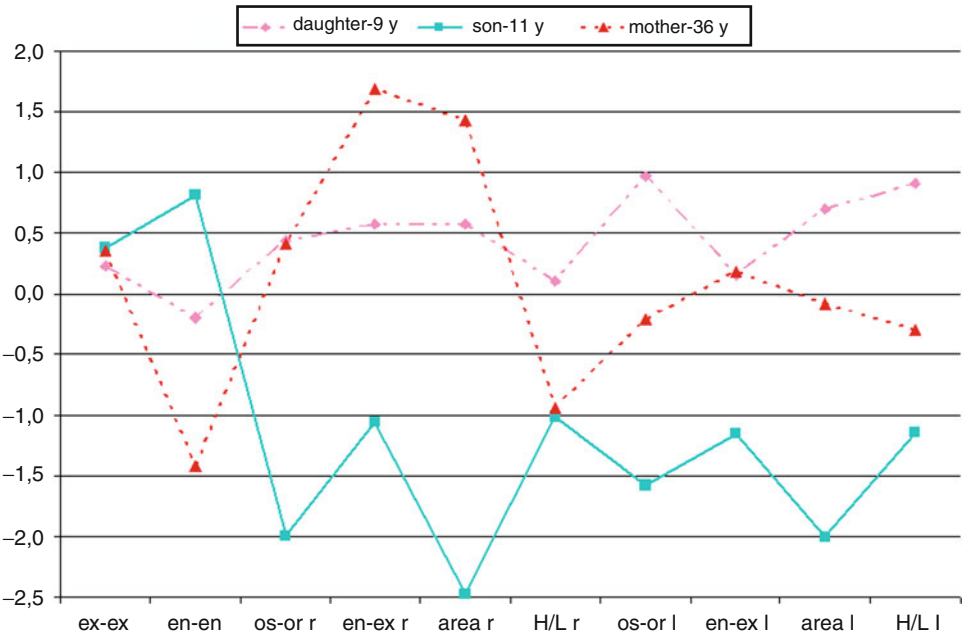

Fig. 97.7 Anthropometric pattern profile of the soft-tissue orbital measurements (linear distances, areas, ratios) made in a mother and her children, all affected by hypohidrotic ectodermal dysplasia. Ex-ex: biorbital width; en-en: intercanthal width; os-or: right and left height of the orbit; en-ex: right and left length of the eye fissure; area: right and left external orbital surface area (area of the quadrangle between ex, os, en and or); H/L: right and left height of the orbit to length of the eye fissure ratio (os-or/en-ex × 100). The brother and sister have contrasting patterns of deviation from the norm, while more similar patterns are observed between the mother and her daughter

Table 97.3 Three-dimensional ear morphometry in subjects with hypohidrotic ectodermal dysplasia (HED) as compared to their reference groups matched for sex, age, and ethnicity. All values are *z*-scores [(HED subject value – reference mean)/reference standard deviation]

	Right-side ear					Left-side ear					3D symmetry index
	Length	Width	W/L	Area	Angle	Length	Width	W/L	Area	Angle	
Males											
Mean	–0.51	–0.38	0.18	–0.43	0.14	-0.78	–0.53	0.09	–0.53	0.47	–0.81
SD	1.20	1.21	1.51	1.21	1.34	1.44	0.95	1.18	1.09	1.23	0.99
t-Paired	NS	NS	NS	NS	NS	0.046	0.040	NS	NS	NS	0.005
Females											
Mean	0.22	–0.31	–0.47	–0.05	–0.11	–0.14	–0.63	–0.53	–0.37	0.43	0.08
SD	0.99	1.13	0.99	1.23	1.10	0.90	0.95	0.70	1.06	1.20	0.83
t-Paired	NS	NS	NS	NS	NS	NS	0.017	0.008	NS	NS	NS
M vs. F	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.008

Length: right and left ear length (sa-sba); width: right and left ear width (pra-pa); W/L: right and left ear width to ear length ratio (pra-pa/ sa-sba × 100); area: right and left ear area (area of the polygon between pra, sa, pa, sba, t); angle: right and left angle of the auricle versus the facial midplane, computed as the angle between the t-pa line and the sagittal midplane passing through nasion and perpendicular to the ex_r-ex_l line; index: three-dimensional symmetry index. For each ear, the spatial position of the centre of gravity was computed from the *x*, *y*, *z* coordinates of pra, sa, pa, sba, t, and the distances of the same five landmarks from the relevant center of gravity calculated. The ten distances were summed. The differences between the positions of each pair (right and left) of landmarks were also assessed, and the sum of the five absolute (signless) differences obtained. The index was computed as 100 minus the percentage ratio between the sum of the differences and the sum of the distances. This index ranges between 100% (perfect symmetry) and 0% (no symmetry)
t-Paired: *p* value of Student's *t* tests for paired samples, 16 degrees of freedom for each sex; *NS* not significant ($p > 0.05$)
Comparison males vs. females, Student's *t* test for independent samples, 52 degrees of freedom
On average, patients with HED have smaller ears than reference subjects

affected than the younger one (Fig. 97.6). The brother and sister also had contrasting patterns of deviation from the norm, as well as the mother and her son, while more similar patterns were observed between the mother and her daughter (Fig. 97.7).

Clinical reports often indicate very similar general facial phenotypes between HED subjects, even from different ethnic groups and races (Ward and Bixler 1987; Ruhin et al. 2001; Skrinjaric et al. 2003). Nonetheless, when quantitative analyses are performed, variable patterns can be discovered, underlying the usefulness of a global anthropometric assessment. Indeed, a detailed quantitative assessment of the characteristics of a single part of the face found some variability even within a single family. Different expression of the involved genes may explain the variable phenotype.

To the scope, several hypotheses have been proposed: a global alteration of the migration of the neural crest cells, a more severe expression of the ED genes in all parts of the craniofacial district, a reduction in masticatory function (Ward and Bixler 1987; Escobar and Epker 1998; Ruhin et al. 2001; Johnson et al. 2002). Also, lyonization (the random inactivation of one the two X chromosomes occurring in somatic cells) may explain the variable pattern found between the two sisters (Fig. 97.6). Variable expressions of the original pathological entity classically characterize HED: patients with a more severe expression of the HED genes may have a greater involvement of facial bones. Nevertheless, in bone morphogenesis, a functional redundancy of the proteins defective in HED has already been hypothesized (Montonen et al. 1998), thus explaining the variable pattern of deviation from the norm found in the present subjects coming from the same family.

On average, ear dimensions appeared somewhat reduced in the analyzed HED subjects (negative mean *z*-scores in Table 97.3), but the statistical significance was attained only sporadically. In the 17 males, ear length and width were significantly ($p < 0.05$, Student's *t* tests for paired samples, 16 degrees of freedom) reduced only in the left side of the face; in the 17 females, only the left side ear width was significantly reduced as compared to the norm. This produced a different shape in this same

ear (significant reduction in the width-to-length ratio). In males, variations were also observed in ear position, with a somewhat larger sagittal angle of the auricle (approximately half standard deviation larger than the norm, not significant), and a smaller three-dimensional symmetry ($p < 0.005$). This last measurement was the only one with a sexual dimorphism in its deviation from the norm.

The present results confirm the preliminary data reported by Ferrario et al. (2004): apparently, ear dimensions and three-dimensional position are only minimally affected by ectodermal dysplasia. The contrasting findings reported by Ward and Bixler (1987) and Skrinjaric et al. (2003) may be effects of sample size, different age range, and different method of the already discussed genotypic and phenotypic variation in HED subjects.

A further comment should be made on age: both Ferrario et al. (2004) and Dellavia et al. (2008) found that the deviation from the norm of the facial soft tissues of HED subjects tended to lessen with age. Unfortunately, no other study analyzed the age-related patterns of soft tissue structures.

97.6 Longitudinal Studies in HED Patients

Indeed, longitudinal information on global facial growth (hard and soft tissues) in patients with HED is scarce and arises from case reports with medium-short time follow-ups, as recently reviewed by Dellavia et al. (2008). In a longitudinal cephalometric study performed in untreated children, Bondarets et al. (2002) found trends of craniofacial growth toward a marked Class III sagittal relationship of the jaws and an anterior growth rotation with time. No quantitative data on the three-dimensional arrangement of the facial soft tissues were provided.

In non-treated patients with HED, skeletal craniofacial deviations from the norm increased with advancing age (Johnson et al. 2002). In contrast, prosthodontic treatment seemed to emphasize growth normalization, with a higher facial balance after treatment (Ruhin et al. 2001); implant treated adult subjects were more similar to the norm than non-treated adults (Johnson et al. 2002).

In previous studies, facial convexity was also related to age: older patients were less different from the controls than younger patients (Ferrario et al. 2004). It has to be considered that adolescent and adult patients were all provided with some kind of dental prostheses, while this support was lacking for the children; soft tissue facial morphology is obviously expected to be modified by the dental prostheses in situ.

To assess the facial growth patterns in young HED patients, Dellavia et al. (2008) non-invasively monitored the variations in soft-tissue facial structures during childhood and adolescence. Twelve children aged 7 years were annually assessed up to 14 years of age, and their growth patterns were compared to those of normal children.

In all children with HED, the nose had a reduced growth, in good accord with previous reports (Fig. 97.8, all mean differential normalized growths were lower than 100%) (Ward and Bixler 1987; Saksena and Bixler 1990; Lexner et al. 2007). The upper facial third (forehead) grew more in adolescents with HED than in reference subjects, a finding that could be partially explained by the tendency to develop frontal bossing (Saksena and Bixler 1990; Tarjan et al. 2005). The lower lip also grew more in HED subjects than in their reference peers, in accordance with the characteristic aspect of everted lip described in previous investigations (Ferrario et al. 2004; Sforza et al. 2006). In contrast, the upper lip growth pattern was similar to the norm.

Maxillary and mandibular volumes in the HED patients had time-delayed growth peaks in both sexes, and especially in girls. During childhood, growth was initially slower, but a large increment was detected during adolescence. The peak development was shifted about 2 years later than in normal subjects. A pivotal role in this adjustment may be played by the eruption of permanent teeth. The analyzed ED

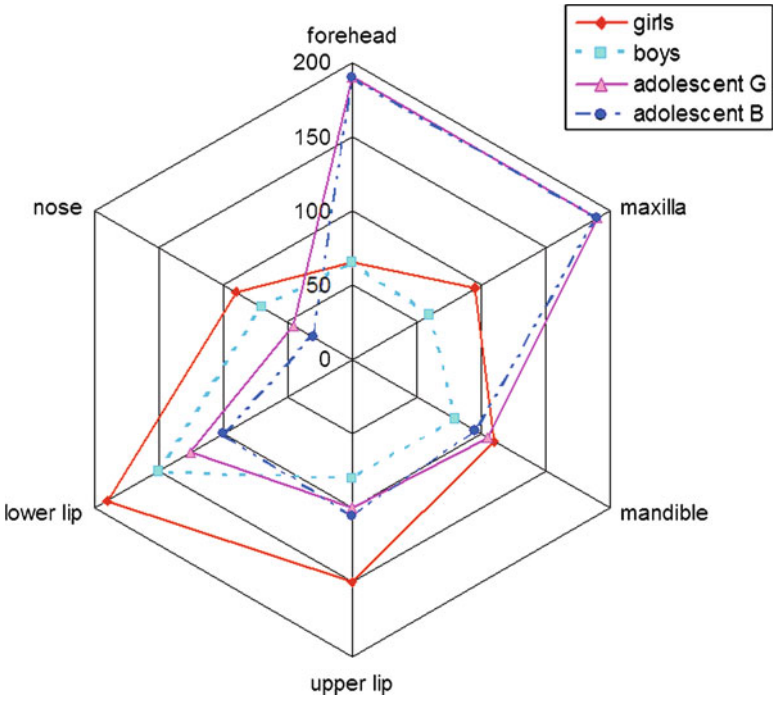

Fig. 97.8 Polar diagram showing the global differential normalized mean growth of soft-tissue facial volumes in hypohidrotic ectodermal dysplasia patients and in reference subjects of both sexes (males: continuous line; females: interrupted line) during childhood (computed between 7 and 10 years) and adolescence (computed between 11 and 14 years). 100% represents the normal mean growth of the reference children and adolescents; 50% represents a relatively reduced growth; 150% and 200% represent relatively larger growths. Origin of the axes (0%) represents a null growth. The various parts of the face have different growth potentials in children with hypohidrotic ectodermal dysplasia than in reference children

subjects presented with a variable number of missing teeth, and a significant correlation between number of maxillary missing permanent teeth and craniofacial dysmorphology has been suggested (Johnson et al. 2002; Ferrario et al. 2004). Reduced palatal dimensions were reported in boys with HED: the presence of teeth significantly influenced palatal characteristics (Dellavia et al. 2008).

The current results are only partially in accord with previous longitudinal studies (Bondarets et al. 2002), where a slightly retrognathic tendency of the maxilla, primarily related to the degree of hypodontia, was observed. The main difference between the two studies is that the children analyzed by Bondarets et al. (2002) did not receive orthodontic or prosthetic treatment, while almost all the HED subjects analyzed by Dellavia et al. (2008) wore removable prosthetic and orthodontic devices since 9 years of age. Subsequent stimuli to mandibular and maxillary growth can be hypothesized (Tarjan et al. 2005). Indeed, in children with HED prosthetic treatment has been recommended as early at 3 years of age to encourage a normal physiologic development and to improve masticatory efficiency (Tarjan et al. 2005).

Therefore, the modern perspectives of clinical management in patients suffering from ED are fully supported by the literature findings. In growing patients, an intermediate treatment with removable prostheses, orthopaedic devices, and temporary restorations will provide the best quality of life, and at the same time will prepare the skeletal and dental structures for the final therapy (Dellavia et al. 2008). Regular adjustments (approximately every year) and replacements of the prostheses should accomplish the growth of the jawbones (Suri et al. 2004). Removable appliances may also promote sagittal growth

of the mandible, thus bettering facial appearance and limiting subsequent major surgical interventions (Pigno et al. 1996; Tarjan et al. 2005). Speech therapy and physiotherapy of facial and masticatory muscles may also be recommended (Pigno et al. 1996; Kramer et al. 2007). At the end of skeletal growth, the final treatment may include orthognathic surgery, bone augmentation and dental implantology as necessary.

97.7 Conclusions

Diagnosis, treatment planning, and evaluation of results should all be based to a global, three-dimensional, quantitative assessment of the craniofacial characteristics of patients with HED. Both the hard- and the soft-tissue structures should be analyzed to provide a complete evaluation of any patient, and should be compared to those of healthy subjects of the same age, sex, race, and ethnic group (Ward and Bixler 1987; Saksena and Bixler 1990; Bondarets and McDonald 2000; Johnson et al. 2002).

Only further investigations, performed on larger numbers of subjects, may allow to better understand the complex phenomena that related genotype and phenotype in patients with HED. Additionally, longitudinal studies, performed with non-invasive data collections, may allow to follow the actual effects of oral rehabilitation in these patients, monitoring the various treatments and finding the best timing for each intervention.

97.8 Applications to Other Areas of Health and Disease

The quantitative assessment of those facial characteristics that differ the most from the norm serves not only for anthropometric and anatomical descriptions of a given disease or syndrome, but also for clinical applications. In a clinical approach, quantitative data support the qualitative description of facial alterations (Garn et al. 1984; Ward et al. 2000; Hammond et al. 2004), and may assist in the diagnosis of borderline patients or gene carriers (Saksena and Bixler 1990; Skrinjaric et al. 2003; Ward and Bixler 1987), especially for the less experienced clinical genetists.

In maxillo-facial, plastic, and reconstructive surgery, a quantitative approach is necessary to compare the outcome of different surgical procedures or intervention schedules, and it may also help in the identification of those facial areas susceptible to surgical intervention.

Quantitative assessments of suitable subjects can also offer unique possibilities to appraise the etiology of poorly understood clinical conditions, trying to isolate genetic from environmental factors.

For all these applications, the use of computerized image analyzers may allow to reduce time and costs, thus facilitating the screening of a larger number of persons even outside a clinical setting (Douglas et al. 2003).

Summary Points and Practical Methods

- The facial soft-tissue of subjects with HED can be successfully measured and monitored with non-invasive computerized anthropometry.
- Diagnosis, treatment planning, and evaluation of results should all be based on a global, three-dimensional, quantitative assessment of the craniofacial characteristics.
- Both the hard- and the soft-tissue structures should be analyzed to provide a complete evaluation

of any patient, and should be compared to those of healthy subjects of the same age, sex, race, and ethnic group.

- In children with HED, an early oral rehabilitation with suitable devices (removable prosthetic and orthopaedic appliances) seems to enhance the growth of structures of the middle and lower facial third.
- In growing patients with HED, a multidisciplinary intermediate treatment with removable prostheses, orthopaedic devices, and temporary restorations is mandatory.
- At the end of skeletal growth, the final treatment of HED patients may include orthognathic surgery, bone augmentation, and dental implantology as necessary.

Acknowledgments The precious and indispensable collaboration of all the analyzed subjects, their families, of the Associazione Nazionale Displasie Ectodermiche (ANDE, Italy). We are also deeply indebted to all the staff and students of our laboratory, who helped in data collection and analysis.

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Chapter 98
Anthropometric Indices of Facial Features in Down's Syndrome Subjects

Chiarella Sforza, Claudia Dellavia, Cristina Allievi, Davide G. Tommasi, and Virgilio F. Ferrario

Abstract Down's Syndrome (DS) is the most frequent live-born autosomal aneuploidy in humans, and it is characterized by a distinctive craniofacial phenotype. Qualitative reports and quantitative investigations comparing subjects with DS to normal subjects found modifications in head size (overall reduction) and shape (brachycephaly with a flattened occipital bone). The faces of subjects with DS are narrower, less deep, and shorter than normal faces, with a global anomalous relationship between individual measurements. In the upper part of the face, the interorbital width is decreased, the palpebral fissures are reduced with slanted eyelids, and the forehead is prominent with a depressed nasal bridge. The middle part of the face (maxillary region) is hypoplasic, with reduced vertical, lateral, and anteroposterior dimensions. Overall, the nose is significantly smaller; its vertical and anteroposterior dimensions are reduced, but its horizontal dimensions are increased. In DS subjects the nose is shorter and less protruding, but with larger nostrils, a flatter angle of alar slope, and a more acute nasal tip angle. The mandible is small, with more acute gonial angles, and a more prominent position. Overall, there is a tendency toward a skeletal Class III pattern; the prominent forehead and mandible, associated with midfacial hypoplasia, may result in a concave sagittal plane facial profile. In the horizontal plane, the face is less prominent. Mouth width is reduced, with a smaller lower lip and a larger upper lip, with increased vermilion area and height. The lips are prominent, with reduced nasolabial, interlabial (soft tissues), and interincisal (teeth) angles. There are alterations in ear dimensions (global reduction), position and shape, with a significant larger asymmetry than in normal subjects. The ears are usually more prominent from head surface in DS subjects than in normal subjects. Persons with DS also possess several alterations in the hard- and soft-tissue structures of the oral cavity (teeth and dental arches, palate, tongue, oral mucosa), with reduced hard tissue palatal dimensions.

In conclusion, the facial soft-tissue of subjects with Down' syndrome can be successfully measured and monitored with noninvasive computerized anthropometry. A global, three-dimensional, quantitative assessment of the craniofacial characteristics may help in clinical diagnosis.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_98,

Abbreviations

3D Three-dimensional
CVI Craniofacial variability index
DS Down's syndrome
SD Standard deviation

98.1 Introduction

In the human head and face, the skeleton, the muscles, the subcutaneous and cutaneous layers all combine together to form a complex structure. Its overall form (size, shape, and reciprocal arrangement of the parts) and function derive from a composite and coordinated pattern of development of separate cartilaginous, osseous, dental, and soft-tissue elements (Breitsprecher et al. 1999). Environmental stressors model and can even alter the genetically determined outline (Breitsprecher et al. 1999).

The correct assessment of this complex structure should be made with a comprehensive morphological and functional evaluation, aimed at a global assessment of all elements classically forming beauty: precision, symmetry, coordination and functional structure (Breitsprecher et al. 1999). The first elements to be considered are those describing the morphological structure that constitutes the base for function.

Facial phenotype can be modified in several genomic and chromosomal alterations, and often the specific phenotypic characteristics are used for clinical diagnosis. Down's syndrome (DS, MIM #190685; OMIM 2009) is the most frequent live-born autosomal aneuploidy in humans. The clinical entity is produced by the complete or partial trisomy of chromosome 21 (Desai 1997; Quintanilla et al. 2002; Roizen and Patternson 2003). The syndrome is characterized by morphological and functional abnormalities of body structures, from cellular organelles to multiorgan systems (Desai 1997; Roizen and Patternson 2003). Among the most constant features, there is a distinctive and immediately recognizable craniofacial phenotype (OMIM 2009) (Fig. 98.1).

In DS subjects, specific characteristics of the craniofacial phenotype can be identified even before birth, and the ultrasonographic assessment of their facial morphology is currently a useful diagnostic tool (Chitkara et al. 2002; Cicero et al. 2003; Minderer et al. 2003; Orlandi et al. 2003; Sonek 2003; Borenstein et al. 2008).

In contrast, the application of ultrasound for postnatal facial morphometrics is limited, and different instruments for three-dimensional (3D) imaging are in use, mainly divided into two categories: optical, noncontact instruments (laser scanners, 3D range-cameras, optoelectronic instruments, stereophotogrammetry, Moiré topography), and contact instruments (electromagnetic and electromechanical digitizers). Both kind of instruments are noninvasive, and can be safely used without any potential damage to the health of the subjects (Hammond et al. 2004; Sforza and Ferrario 2006; Maal et al. 2008). In particular, electromechanic digitizers have recently been used for the soft-tissue facial analysis of patients with DS (Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b), thus partially substituting conventional methods like classic, manual anthropometry (Farkas et al. 2001a, b, 2002a, b; Bagic and Verzak 2003). Additionally, conventional X-rays (cephalometry) have been used for the detection and measurement of these skeletal characteristics (Quintanilla et al 2002).

In the current chapter, the principal pre- and postnatal craniofacial characteristics of patients with DS, as shown by 3D imaging, classic anthropometry, and cephalometry, will be presented and discussed. Additionally, a further set of anthropometric data collected in DS subjects living in the community will be shown.

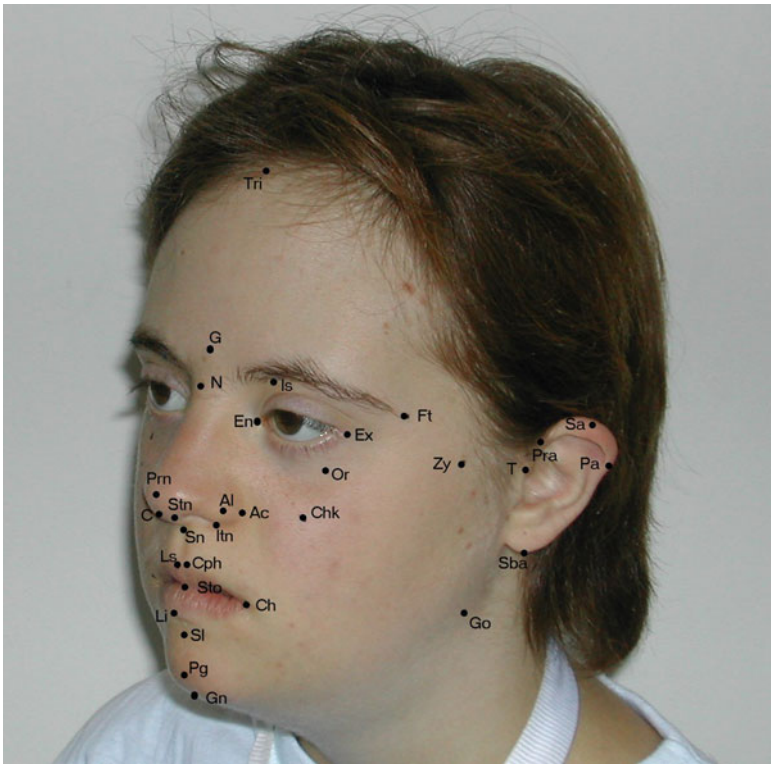

Fig. 98.1 Soft-tissue landmarks identified on the face of a young woman with Down syndrome. The image shows the set of 50 landmarks identified on the face of a woman with Down's syndrome

98.2 Facial Features in Down's Syndrome Subjects: Prenatal Characteristics

In the western world, prenatal diagnosis is widely used to detect several anomalies. Both invasive (e.g., amniocentesis and fetal chromosomal analysis) and noninvasive techniques (ultrasonographic morphological evaluations) are currently used. Pregnant women and their clinicians would prefer the use of less invasive and less potentially dangerous examinations (so-called "soft" assessments), at least for a first screening.

In particular, ultrasonography is one of the noninvasive techniques that can currently be used for imaging and measuring the craniofacial area in human subjects before birth. Ultrasound probes use acoustic waves in the Megahertz frequency domain, and can image both the skeletal surface and its soft-tissue cover. The method has no (currently) known invasiveness and biological hazards (at least at the commonly used intensities, frequencies, and scan durations, which are usually limited to 15 min each). Ultrasounds are widely used for prenatal, intrauterine imaging and diagnosis, also providing 3D reconstructions of fetal face and allowing for the quantitative analysis of several craniofacial features (Chitkara et al. 2002; Cicero et al. 2003; Minderer et al. 2003; Orlandi et al. 2003; Sonek 2003; Borenstein et al. 2008). The 3D reconstructions provided by the most recent instruments allow more refined measurements, permitting corrections when the best measurement plane has not been perfectly imaged (Borenstein et al. 2008).

One of the first morphological ultrasonographic markers of DS was an altered fetal nuchal translucency, associated with an increased thickness of the nuchal skinfold; this first assessment

was introduced at the beginning of the 1990s. Subsequently, several craniofacial characteristics were progressively coupled with DS in both the first and the second trimesters of pregnancy.

The most quoted symptoms in the literature are nasal bone absence or hypoplasia, a flatter facial profile, and altered ear size and shape (Chitkara et al. 2002; Cicero et al. 2003; Minderer et al. 2003; Orlandi et al. 2003; Sonek 2003; Borenstein et al. 2008).

Fetuses with trisomy 21 have a significantly larger incidence of nasal bone absence (delayed ossification) or hypoplasia than fetuses with a normal karyotype (Cicero et al. 2003; Minderer et al. 2003; Orlandi et al. 2003; Sonek 2003). The ultrasonographic findings have also been coupled with pathomorphological analyses, and these show that hypoplasia vs. normal development seems more indicative of DS than absence vs. presence of a detectable nasal bone (Minderer et al. 2003).

Postnatally, alterations in ear size, shape, and position had been frequently reported in persons with DS (Sforza et al. 2005b); alterations have also been found before birth (Chitkara et al. 2002; Cicero et al. 2003). Indeed, the prenatal developmental period of the ear is relatively long, spanning from the embryonic to the fetal age; also, its complex shape makes it particularly prone to disturbances. On average, fetuses with DS have smaller ears than fetuses with normal karyotype, and ear length and area have been proposed as additional morphological markers for ultrasound-based prenatal screening of aneuploidy (Chang et al. 2000; Chitkara et al. 2002).

More recently, Borenstein et al. (2008) reported the intrauterine measurement of the frontomaxillary facial angle, calculated between the upper surface of the palate and a line connecting the anterior part of the maxilla with the external surface of the forehead. In the fetuses with normal karyotype, this angle decreased linearly with increased fetal dimensions. In trisomy 21 fetuses, the angle was significantly wider than in chromosomally normal fetuses. The authors concluded that measurement of the frontomaxillary facial angle improved the performance of first-trimester screening for DS.

98.3 Facial Features in Down's Syndrome Subjects: Postnatal Characteristics

Several radiographic and anthropometric investigations have analyzed the craniofacial morphology in human subjects with DS (Farkas et al. 2001a, b, 2002a, b; Quintanilla et al. 2002; Bagic and Verzak 2003; Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b).

Qualitative reports and quantitative investigations comparing subjects with DS to normal subjects of the same sex, age and ethnic group found modifications in head size (overall reduction) and shape (brachycephaly with a flattened occipital bone). The faces of subjects with DS are narrower, less deep, and shorter than normal faces, with a global anomalous relationship between individual measurements (Sforza et al. 2005a). Indeed, the use of summary anthropometric indices (the mean *z*-score, that measures the average dimensional discrepancy between patients and a reference population; and its standard deviation, or craniofacial variability index) discriminates more than 89% of subjects with DS when compared to normal subjects (Sforza et al. 2005a).

In the upper part of the face, the interorbital width is decreased, the palpebral fissures are reduced with slanted eyelids and small skin folds at the inner corner of the eyes, and the forehead is prominent with a depressed nasal bridge.

The middle part of the face (maxillary region) is hypoplasic, with reduced vertical, lateral, and anteroposterior dimensions. In particular, considering the prenatal reports of nasal absence or hypoplasia in fetuses with DS, several researchers investigated the postnatal characteristics of the nose in detail. Overall, the nose is significantly smaller (volume, area) in subjects with DS than in the

reference subjects, and it has a different shape. The vertical (length of the nasal bridge, height of the nose) and anteroposterior (nasal tip protrusion, width of the nostrils) dimensions are reduced, but the horizontal dimensions (alar base width, superior and inferior widths of the nostrils) are increased (Farkas et al. 2001b; Tuxen et al. 2003; Ferrario et al. 2004a). Therefore, in DS subjects the nose is shorter and less protruding, but with larger nostrils, a flatter angle of alar slope, and a more acute nasal tip angle (Ferrario et al. 2004a). Also, the absence of nasal bones in adult subjects with DS has been reported (Tuxen et al. 2003).

The mandible is small, with more acute gonial angles, and a more prominent position. Overall, there is a tendency toward a skeletal Class III pattern; the prominent forehead and mandible, associated with midfacial hypoplasia, may result in a concave sagittal plane facial profile (Tuxen et al. 2003). In the horizontal plane, the face is less prominent (Ferrario et al. 2005).

Mouth width is reduced, with a smaller lower lip and a larger upper lip; the upper lip increment is particularly evident for the vermilion area and height. The lips are prominent, with reduced nasolabial, interlabial (soft tissues), and interincisal (teeth) angles (Farkas et al. 2001a, 2002b; Quintanilla et al. 2002; Tuxen et al. 2003; Ferrario et al. 2005).

There are alterations in ear dimensions (global reduction), position and shape, with a significant larger asymmetry than in normal subjects. In particular, ear length is reduced, ear width is often subnormal, and the ratio between ear length and face height is abnormal. Globally, ear area is reduced. Additionally, the ears are usually more prominent from head surface in DS subjects than in normal subjects (Desai 1997; Farkas et al. 2001a, b, 2002a, b; Quintanilla et al. 2002; Bagic and Verzak 2003; Roizen and Patterson 2003; Tuxen et al. 2003; Sforza et al. 2005b).

Nonpendulous ears (with a partially or totally adherent earlobe) are more frequent in DS subjects than in normal persons. DS subjects also can possess alterations in the ear cartilages, with a different morphology of the lateral surface of the auricle (Sforza et al. 2005b).

Some of the investigations on the facial phenotype of subjects with DS found some ethnic-related variation in the areas of major abnormalities, in particular as far as the nose and ears were concerned (Bagic and Verzak 2003; Farkas et al. 2001a, b; Cicero et al. 2003; Sonek 2003). By far, quantitative investigations on the facial morphology of Caucasian subjects with DS analyzed North American of European ancestry, Croatian, Spaniard and Italian people, but different methods were used (classic anthropometry, digital anthropometry and cephalometry), which makes comparisons difficult (Farkas et al. 2001a, b, 2002a, b; Quintanilla et al. 2002; Bagic and Verzak 2003; Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b).

Additionally, some studies mainly analyzed persons living in residential institutions (Bagic and Verzak 2003), while other investigations measured persons living in the community (Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b). Indeed, an increasing number of subjects with DS is living in the community (Roizen and Patterson 2003), and more detailed information on their facial characteristics may supply some information about the relationship between the global quality of life and craniofacial morphology. For instance, hypotonic facial muscles in subjects with DS (Desai 1997; Roizen and Patterson 2003) may modify soft tissue dimensions and positions in the lip area. Open mouth and everted lower lip are currently reported as a frequent feature for subjects with DS, but a better general muscular training and body fitness may result in improved orofacial conditions. Indeed, Sforza et al. (2004) measured a group of DS athletes who attended the "Special Olympics" games, and found less alterations in the mouth and lip area than expected: a better general muscular development (as it is expected in an athlete) may result in an improved orofacial health.

A further variation may derive from sex-related characteristics, even if most investigations did not find differences in the average deviation from the norm in DS men and women (Bagic and Verzak

2003; Ferrario et al. 2004a, 2005; Sforza et al. 2005a, b). Additionally, the effects of age on the deviation from the norm are still discussed. For instance, Ferrario et al. (2004a) and Sforza et al. (2005a) did not find age-related patterns in the facial structures; Quintanilla et al. (2002) and Bagic and Verzak (2003) reported age-related increments in the discrepancy in facial morphology; Farkas et al. (2002a, b) and Sforza et al. (2005b) found some improvements in facial morphology with advancing age. This aspect should be better clarified because the assessment of age-related variations in the altered craniofacial measurements can be used to monitor growth and development: subjects with DS often have altered postnatal growth rates (Farkas et al. 2002a b; Ferrario et al. 2005). A quantitative control of maturation may be used to find the best timing for reconstructive surgical intervention (Farkas et al. 2001a, 2002a).

98.4 Oral Features in Down's Syndrome Subjects

Together with a set of specific facial characteristics, persons with DS also posses several alterations in the hard- and soft-tissue structures of the oral cavity (teeth and dental arches, palate, tongue, oral mucosa) (Desai 1997; Quintanilla et al. 2002; Dellavia et al. 2007).

Persons with DS have xerostomia, with a reduction in salivary flow, which may result in alterations of the mucosal lining of the oral cavity, and an increased risk of periodontal disease (Desai 1997).

On average, hard tissue palatal dimensions are reduced in DS individuals than in control subjects (Desai 1997; Dellavia et al. 2007). The reduction in palatal size is in accord with the general reduction in craniofacial measurements, and it is often associated with a different shape: the hard- and soft-palate is narrower, shorter, but relatively higher (Dellavia et al. 2007).

The reduced dimensions of the oral cavity with dental crowding and posterior crossbite have often been cited as a cause of relative macroglossia in DS subjects, together with an actual enlargement of the tongue and muscular hypotonia (Desai 1997; Dellavia et al. 2007). Taken together, these conditions may lead to tongue and mandibular protrusion, and lastly to an open bite and a dental Class III malocclusion. A proinclination of the anterior mandibular teeth and a reduced interincisal angle are also common features in DS subjects (Quintanilla et al. 2002).

Patients with DS frequently have several dental morphological and numerical anomalies, with microdontia, crown variants, hypodontia and multiple congenitally missing teeth (Desai 1997). Eruption timing retardation of both the deciduous and the permanent dentitions have been reported (Dellavia et al. 2007; Quintanilla et al. 2002; Bagic and Verzak 2003), as well as hypoplasia and hypocalcification (Desai 1997). Also, short roots and unfavorable crown/ root ratio of incisor teeth may contribute to their mobility and subsequent tooth loss (Desai 1997).

Palatal dimensions are also related to the number of molar teeth: DS subjects with more molar teeth differ less from reference subjects, thus underlying the positive role of interdisciplinary dentofacial treatment (Dellavia et al. 2007). Indeed, early dental therapy, including arch expansion, tooth preservation, correction of impacted canines, may offer a significantly improved quality of life for aging DS patients (Desai 1997). Tooth preservation, and timely replacement of lost or congenitally absent teeth, would reduce the accelerated alveolar atrophy which makes dental prosthetic replacement more challenging (Dellavia et al. 2007). It is expected that subjects living with their families would receive a better oral care than institutionalized subjects, thus maintaining a better oral health and quality of life (Dellavia et al. 2009).

98.5 Selected Facial Features in DS Athletes ("Special Athletes")

The described facial phenotype of subjects with DS, both pre- and postnatally, pointed out that the ears and the nose are key parts of the specific characteristics of this syndrome. These two facial features were further analyzed in a group of 54 subjects (20 women, mean age 27.1 years, SD 7.2; 34 men, mean age 27.1 years, SD 9.1) with DS who were "special athletes" attending the Italian games of the Special Olympics in Fiuggi Frosinone (July 2003), and Rome (July 2004). Data were collected inside the "Special Smiles" program partly sponsored by Special Olympics. These "special athletes" were all living with their families, and had good health. Some facial measurements obtained on a subset of the present DS subjects were previously reported (Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b).

All the analyzed individuals, and their parents or legal guardians, were previously informed about the procedures, and signed an informed-consent form approved by the local ethics committee.

A set of 50 soft-tissue facial landmarks was marked on the face of each subject (Fig. 98.1) and the digital, 3D coordinates of the landmarks were obtained using an electromechanic digitizer (Sforza and Ferrario 2006). Using custom software, linear distances, angles, and areas were automatically computed from landmark coordinates (Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b). A detailed description of the methods used in our laboratory can be found in the chapter "Three-dimensional facial morphometry: from anthropometry to digital morphology" in this book.

Subjects covered a wide age range, and their facial data were converted into z-scores to allow an easier analysis and interpretation of results. Z-scores were obtained using data collected from a reference population (healthy subjects with normal karyotype and without craniofacial anomalies, previous trauma or surgery, matched for sex and age with the DS subjects). Each DS value was subtracted from its sex and age reference mean value, and divided by the relevant reference standard deviation. The z-scores are standardized measurements that quantify the distance of an individual from the reference population in terms of standard deviation; in other words, a z-score outside the ± 2 interval means that the measurement is smaller (or larger) than the reference value of two (or more) standard deviations.

98.5.1 Ear Morphometry in DS Athletes ("Special Athletes")

Several morphometric characteristics of the ears were measured: on each side, ear length and width, and the relevant ratio; ear area, ear angle versus the facial midplane, and ear 3D symmetry, as detailed by Sforza et al. (2005b).

In both sexes and for both sides of the face, all linear dimensions and areas measured on the ears were larger in the reference subjects than in the subjects with DS, with negative z-scores (Table 98.1). In men, size differences were associated with shape variations, with larger right and left ear width to ear length ratios in the subjects with DS than in the reference subjects. Variations were found also in the position of the auricle relative to the facial reference planes, with larger angles in both sexes and on both sides (positive z-scores, showing a more prominent auricle in DS subjects than in the reference subjects). The 3D symmetry index was larger in the reference subjects than in subjects with DS (larger asymmetry). All z-scores were not different between men and women (Student's t test for independent samples, $p > 0.05$ in all occasions), and pooled values were computed. Overall, all variations relative to the reference population were significant (Student's t test for

Table 98.1 3D ear morphometry in subjects with Down's syndrome as compared to their reference groups matched for sex, age and ethnicity

		Right-side ear					Left-side ear					3D symmetry
		Length	Width	W/L	Area	Angle	Length	Width	W/L	Area	Angle	Index
Males	Mean	–2.86	–1.96	0.36	–2.02	1.50	–2.87	–1.78	0.81	–1.88	0.86	–1.02
	SD	1.01	0.83	1.26	0.76	1.96	0.90	1.02	1.15	0.66	1.66	1.50
Females	Mean	–2.57	–1.96	0.06	–2.01	0.84	–2.98	–1.78	0.20	–1.95	0.88	–2.11
	SD	1.52	1.08	2.28	1.02	1.28	1.41	1.06	1.69	0.84	1.59	4.00
M vs. F	p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Pooled	Mean	–2.75	–1.96	0.24	–2.02	1.25	–2.91	–1.78	0.58	–1.90	0.87	–1.42
	SD	1.21	0.92	1.70	0.86	1.76	1.11	1.02	1.39	0.72	1.62	2.72
t-paired	*p*	0.001	0.001	NS	0.001	0.001	0.001	0.001	0.004	0.001	0.001	0.001

All values are *z*-scores [(DS subject value – reference mean)/reference standard deviation]

Length: right and left ear length (sa-sba); width: right and left ear width (pra-pa); W/L: right and left ear width to ear length ratio (pra-pa/sa-sba × 100); area: right and left ear area (area of the polygon between pra, sa, pa, sba, t); angle: right and left angle of the auricle versus the facial midplane, computed as the angle between the t-pa line and the sagittal midplane passing through nasion and perpendicular to the ex_r-ex_l line; index: 3D symmetry index. For each ear, the spatial position of the centre of gravity was computed from the *x*, *y*, *z* coordinates of pra, sa, pa, sba, t, and the distances of the same five landmarks from the relevant center of gravity calculated. The ten distances were summed up. The differences between the positions of each pair (right and left) of landmarks were also assessed, and the sum of the five absolute (signless) differences obtained. The index was computed as 100 minus the percentage ratio between the sum of the differences and the sum of the distances. This index ranges between 100% (perfect symmetry) and 0% (no symmetry)

Comparisons: males (M) vs. females (F), Student's t test for independent samples, 52 degrees of freedom; pooled: *p* value of Student's *t* tests for paired samples, 53 degrees of freedom; NS: not significant ($p > 0.05$)

Patients with Down's syndrome have smaller ears than reference people, with an increased asymmetry

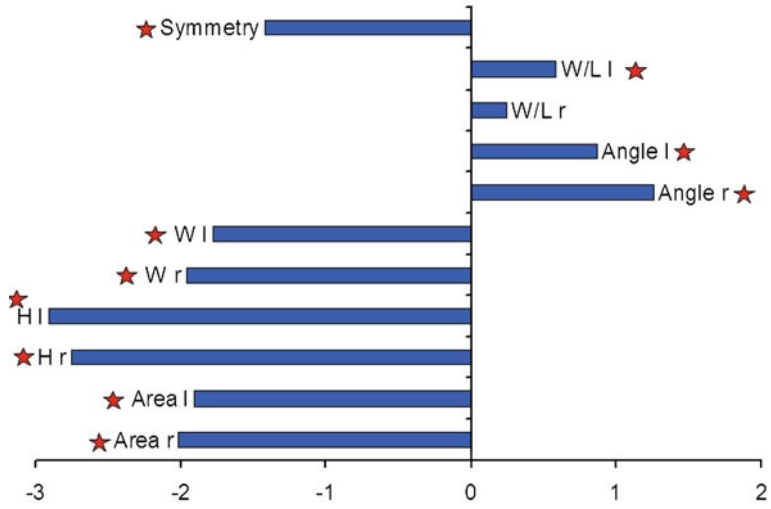

Fig. 98.2 Ear measurements smaller (lower than 0) or larger (larger than 0) in the analyzed Down's syndrome subjects than in the reference population. *X* axis shows the mean *z*-scores of the analyzed measurements. All *z*-scores are significantly different from zero (paired Student's *t*, $p < 0.05$, star) except the right side width-to-length ratio. The patients with Down's syndrome have smaller ears than reference people, with an increased asymmetry

paired samples), except the right side ear width to ear length ratio. Figure 98.2 shows the mean *z*-scores (men and women pooled) of the analyzed ear measurements that were smaller (lower than 0) or larger (larger than 0) in the analyzed DS subjects than in the reference population.

The present results confirm the reduction in ear size reported in the literature (Bagic and Verzak 2003; Chitkara et al. 2002; Farkas et al. 2002b; Sforza et al. 2005b), with mean values that were approximately 2 (ear width, ear area) or 3 SD (ear length) smaller than those found in the reference population (Fig. 98.2). A larger difference in ear length than in ear width was found also in our previous investigation (Sforza et al. 2005b) as well as by Farkas et al. (2002a). A contrasting finding was reported by Bagic and Verzak (2003). Indeed, in the subjects analyzed in the current chapter the *z*-score computed for the ear width to length ratio was not significantly different from 0 in the right side of the face. Differences in ethnicity (Bagic and Verzak 2003; Cicero et al. 2003; Farkas et al. 2001b, 2002a; Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b; Sonek 2003), as well as the intrinsic genotypic and phenotypic variability of DS subjects may be factors in these variations (Tuxen et al. 2003).

98.5.2 Facial Volumes in DS Athletes ("Special Athletes")

As detailed before, another clinically useful marker for ultrasound-based prenatal screening seems to be nasal bone absence or hypoplasia (Cicero et al. 2003; Minderer et al. 2003; Orlandi et al. 2003; Sonek 2003). This characteristic underdevelopment of the nasal complex is found also postnatally (Tuxen et al. 2003), and it is associated with hypoplasia of the middle third of the facial form (Bagic and Verzak 2003; Desai 1997; Farkas et al. 2001a, b, 2002a, b; Ferrario et al. 2004a, b, 2005; Quintanilla et al. 2002; Roizen and Patterson 2003; Sforza et al. 2004; Tuxen et al. 2003). Indeed, all the faces in DS subjects are reduced, and to best appreciate their facial volumetric variations (both as

Table 98.2 Facial volumes in subjects with Down's syndrome as compared to their reference groups matched for sex, age, and ethnicity

		Total	Forehead	Maxilla	Mandible	Total lip	Upper lip	Lower lip	Nose
Males	mean	–2.09	–1.22	–2.80	–1.10	–0.37	0.18	–0.86	–1.05
	SD	1.53	1.67	1.62	1.23	1.07	1.65	0.82	1.18
t-Paired	p	0.001	0.001	0.001	0.001	NS	NS	0.001	0.001
Females	mean	–1.88	–1.55	–2.93	–0.55	–0.68	0.01	–1.31	–0.68
	SD	1.07	1.45	1.19	0.93	0.84	1.08	0.70	0.98
t-Paired	p	0.001	0.001	0.001	0.018	0.002	NS	0.001	0.007
M vs. F	p	NS	NS	NS	NS	NS	NS	0.04	NS

All values are *z*-scores [(DS subject value – reference mean)/reference standard deviation]
t-Paired: *p* value of Student's *t* tests for paired samples, males: 33 degrees of freedom, females: 19 degrees of freedom; NS: not significant ($p > 0.05$)
Comparison males (M) vs. females (F), Student's *t* test for independent samples, 52 degrees of freedom
Patients with Down's syndrome have smaller facial volumes than reference people

absolute values and as percentages), several soft tissue facial volumes (total face; upper third/forehead; middle third/maxilla; lower third/mandible; total lip; upper and lower lip; nose) were computed and compared to data collected in reference subjects of the same sex, age, and ethnic group.

A general reduction of the volumes of all facial thirds was found in both sexes (almost all mean *z*-scores were negative, Table 98.2), with significant (Student's t for paired samples, $p < 0.02$) *z*-score values for all three facial thirds (forehead, maxilla, and mandible). The decrement was particularly evident in the maxillary region (Bagic and Verzak 2003; Desai 1997; Farkas et al. 2001a, b, 2002a, b; Ferrario et al. 2004a, b, 2005; Quintanilla et al. 2002; Roizen and Patterson 2003; Sforza et al. 2004; Tuxen et al. 2003), without sex-related differences (Student's t for independent samples, $p > 0.05$ for all facial volumes). In the same region, nose volume was significantly reduced, especially in males (Bagic and Verzak 2003; Farkas et al. 2001a; Ferrario et al. 2004b). In the lip and mouth region, some discrepancies were observed, with an opposite behavior of the volume of the upper (slightly – but not significantly – increased in men and unchanged in women) and lower (significantly decreased in both sexes, especially in women) lip. This finding parallels the modifications previously found for lip vermilion areas (Sforza et al. 2004), but partly contrast with investigations performed on Northern American DS subjects, where a reduction in the linear dimensions of the upper lip was found (Farkas et al. 2001a). Indeed, all the subjects analyzed in the present chapter had good anterior dental support, and modifications in the reciprocal positions of the upper and lower incisors were directly related to lip position (Dellavia et al. 2007, 2008, 2009; Quintanilla et al. 2002).

To better assess the differential variations in facial volumes in DS subjects, total lip and nose volumes were expressed as a fraction (1/1,000) of total facial volume (Fig. 98.3). In DS subjects, lip volume was approximately 7‰ of total facial volume (7‰ in DS women, 7.2‰ in DS men), a percentage slightly larger than in the reference population (6.4‰ in reference women, 6.3‰ in reference men). Within each sex, subjects with DS had also relatively larger nose volumes (in males, 7‰ in DS subjects, and 6.8‰ in reference subjects; in females, 6.4‰ in DS subjects, and 6.2‰ in reference subjects). Apparently, the general reduction in craniofacial configuration maintained relatively normal percentage dimensions for visceral structures of the digestive and respiratory systems (Roizen and Patterson 2003). Within these two structures, the volumetric distribution seemed to be a function of the genotype (Fig. 98.4), with relatively larger volumes for the upper lip in DS subjects (approx 33% of a total lip plus nose volume) than in reference subjects (approx 27–28%). In contrast, the percentage volume of the lower lip was larger in the reference subjects (21–23%) than in DS subjects (17–18%).

For both lips and nose, a sexual dimorphism was observed: noses were relatively larger in men than in women (both normal and DS men in Fig. 98.3, normal men in Fig. 98.4), lips were relatively

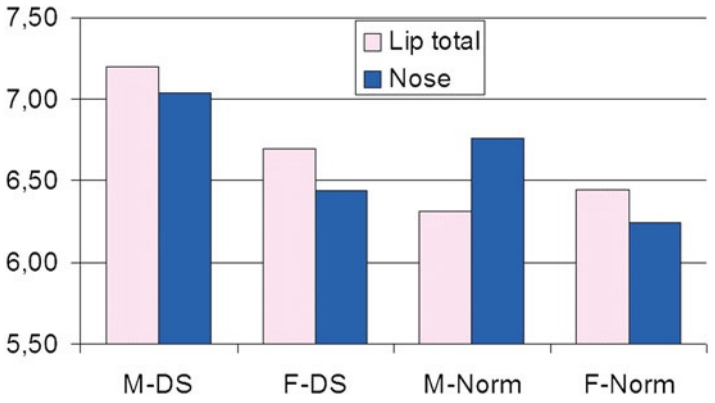

Fig. 98.3 Lip and nose volumes as a fraction (1/1,000) of total facial volume in the analyzed Down's syndrome (DS) subjects and in the reference population. In Down's syndrome subjects, lip and nose volumes as a percentage of facial volume are slightly larger than in the reference subjects

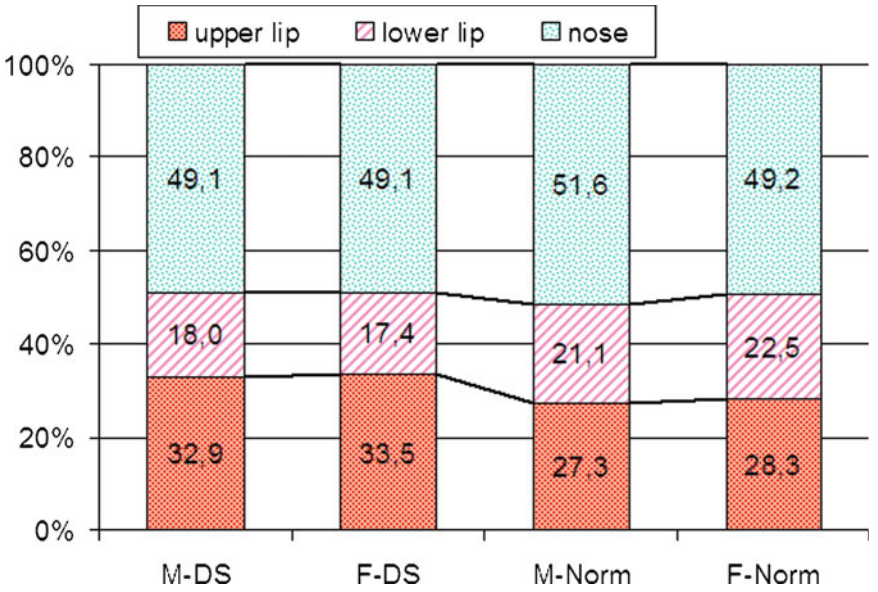

Fig. 98.4 Percentage upper and lower lip and nose volumes in the analyzed Down's syndrome (DS) subjects and in the reference population. All values are percentage of the total "lip plus nose" volume. Down's syndrome subjects have relatively larger volumes for the upper lip than reference subjects, while the reverse applies to the percentage volume of the lower lip

larger in women (total, upper and lower lip in normal women, Figs 98.3 and 98.4; upper lip in DS women, Fig. 98.4).

98.5.3 Global Facial Size and Harmony in DS Athletes ("Special Athletes")

To better investigate the global arrangement of facial features in DS subjects as compared to reference subjects, a set of facial measurements was selected, the relevant *z*-scores computed, and two summary

Table 98.3 Mean *z*-score and craniofacial variability index in subjects with Down's syndrome as compared to their reference groups matched for sex, age and ethnicity

	Mean *z*-score				CVI			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Males	–1.25	0.65	–2.71	–0.11	1.61	0.31	1.08	2.30
Females	–1.61	0.76	–3.01	–0.64	1.69	0.42	1.01	2.89

Patients with Down's syndrome have smaller faces than reference people, with an increased variability in facial dimensions

No significant differences between male and female subject data (Student's *t* test for independent samples, 52 degrees of freedom, $p > 0.05$)

CVI craniofacial variability index

values assessed (Sforza et al. 2005a): the mean *z*-score and the standard deviation of the *z*-scores. This last value, also called craniofacial variability index (CVI), provides a single assessment of the variability across the analyzed *z*-scores. In the current group of subjects with DS, 16 soft-tissue measurements were selected: five widths (skull base width, t_r-t_l; interocular width, en_r-en_l; biorbital width, ex_r-ex_l; width of the mandible, go_r-go_l; mouth width, ch_r-ch_l); six heights (forehead height, tr-n; face height, n-pg; nose height, n-sn; lower face height, sn-pg; right and left ear length, sa-sba), and five depths (upper face depth, n-t_m; mid face depth, sn-t_m; lower face depth, pg-t_m; right and left ear width, pra-pa).

Table 98.3 reports the descriptive statistics of the mean *z*-score and CVI (over 16 measurements) of the analyzed subjects. In the reference population matched for sex, age and ethnicity, the mean *z*-scores were all zero, with standard deviations ranging between 0.471 and 0.663. All the subjects with DS had negative mean *z*-scores: they had, on average, a smaller facial size than the normal individuals. In both sexes, the average mean *z*-scores were significantly different from 0 (Student's t test for paired samples, $p < 0.001$ in both occasions). No sex-related differences were found (Student's t test for independent samples, $p > 0.05$): the deviation from the norm was not dependent from sex. The reduction in facial size was outside the normal interval (mean ± 2 SD) in approximately the same percentage of men (18 of 34, 53%) and women (12 of 20, 60%).

In the reference population, the mean CVI ranged between 0.74 and 0.88, with standard deviations up to 0.209. Twenty-nine male and 15 female subjects with DS had a CVI larger than the normal interval, thus indicating a global disharmonious relationship between individual measurements. No significant sex differences were found ($p > 0.05$). Overall, 33 males and 17 females (93% of the total group of 54) fall outside of the quantitative definitions for normal facial size (*z*-score) and/or harmony (CVI), and only one male and three females had both values inside the normal intervals (Fig. 98.5). Ten females and 14 males (44% of the total) had both values outside the relevant normal intervals.

The diminished facial dimensions (negative mean *z*-score) confirm the findings on the facial volumes and ear region (Tables 98.1 and 98.2), and are in good accord with data in the literature (Bagic and Verzak 2003; Desai 1997; Farkas et al. 2001a, b, 2002a, b; Ferrario et al. 2004a, b; Quintanilla et al. 2002; Roizen and Patterson 2003; Sforza et al. 2005b; Tuxen et al. 2003). The variations in facial proportions (CVI values outside the normal intervals) are in accord with previous reports: Bagic and Verzak (2003) found a nonuniform reduction in facial dimensions, Farkas et al. (2001a, b, 2002a, b) observed different percentages of normal and abnormal measurements in the various parts of the face. Also, the variations in lip volumes (Fig. 98.4) are in good accord with the present results. Overall, the present results confirm the findings reported by Sforza et al. (2004, 2005b) for a subsample of the current subjects: persons with DS possess a smaller face than reference subjects, but the reductions in the different facial areas and in the three spatial planes are not uniform.

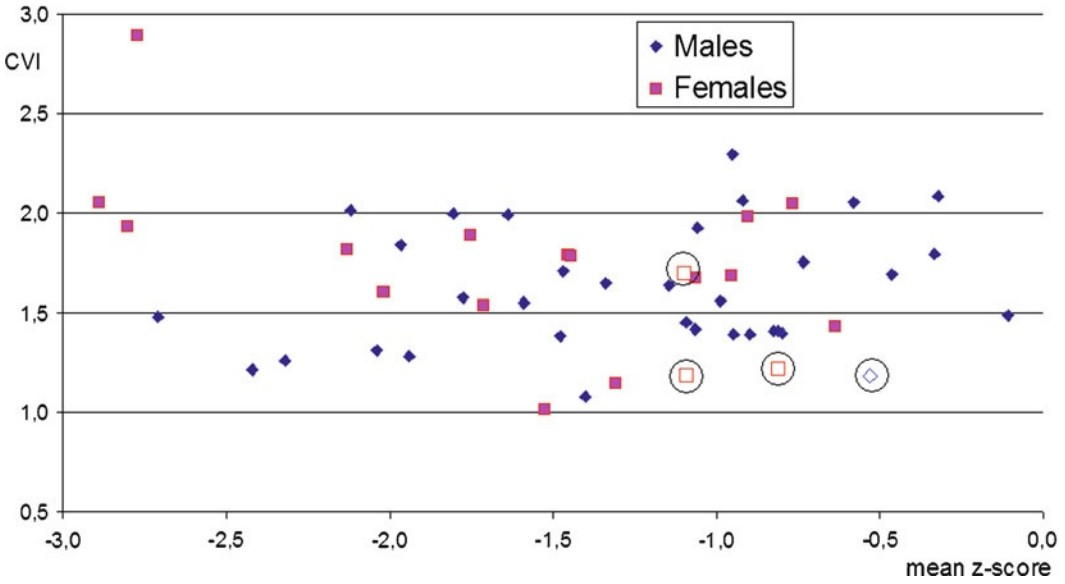

Fig. 98.5 Bivariate plot of mean *z*-score (*X* axis) and Craniofacial Variability Index (CVI, *Y* axis) in 54 subjects with Down's syndrome. Filled symbols: subjects with either *z*-score or CVI that exceed the normal range (mean ± 2SD) of individuals of the same age and sex; open symbols (also noted with an open circle): three women and one man with neither *z*-score or CVI that exceed the normal range (mean ± 2SD) of individuals of the same age and sex. Subjects with Down's syndrome possess a smaller face than reference subjects, but the reductions in the different facial areas and in the three spatial planes are not uniform. The mean *z*-score and Craniofacial Variability Index allow us to discriminate approximately 93% of subjects with Down syndrome when compared to normal subjects

These two indices (mean *z*-score and CVI) allowed discriminating approximately 93% of subjects with Down syndrome when compared to normal subjects (Fig. 98.5).

Current data confirm that the discrepancy of DS subjects from subjects with normal karyotype does not show a sexual dimorphism: the *z*-scores do not differ between male and females DS subjects (the only exception was lower lip volume in Table 98.2). As underlined before, this matter has not been analyzed in detail in previous studies, and only data from two laboratories were assessed separately for males and females: while Bagic and Verzak (2003) reported no sex-related differences, in our laboratory we found variations in some structures (Ferrario et al. 2004a; Sforza et al. 2004), and no differences in others (Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005b). In contrast, Farkas et al. (2001a, b, 2002a, b) reported only pooled values.

98.6 Conclusions

The assessment of the phenotype of DS patients should be based on a global, 3D, quantitative evaluation of all craniofacial characteristics (Table 98.4). Both the hard- (skeleton and teeth) and the soft-tissue structures should be analyzed to provide a complete evaluation of any patient, and should be compared to those of healthy subjects of the same age, sex, race and ethnic group.

Currently, more children and adults with DS are not being institutionalized and live in the community (Roizen and Patterson 2003), receiving more stimuli and sharing several aspects of life (like sport) with their coetaneous (Ferrario et al. 2004a, b, 2005; Sforza et al. 2004, 2005a, b). The effect of this improved quality of life of facial phenotype has not been investigated with sufficient detail.

Table 98.4 Features of patients with Down syndrome as compared to normal subjects

Prenatal	Nasal bone absence or hypoplasia
	Flat facial profile
	Reduced ear dimensions
Postnatal	
General	Reduction in head size
	Brachycephaly with a flattened occipital bone
	Concave sagittal plane facial profile
Upper facial third	Decreased interorbital width
	Reduced palpebral fissures with slanted eyelids
	Prominent forehead
	Depressed nasal bridge
Middle facial third	Maxillary hypoplasia
	Smaller, shorter and less protruding nose, but with larger nostrils
	Nearly normal nasal volume as a percentage of facial volume
Lower facial third	Reduced mandible with more acute gonial angles, and a more prominent position
	Tendency toward a skeletal Class III pattern
	Reduced mouth width, with prominent lips
Oral region	Xerostomia, reduced salivary flow
	Reduced hard tissue palatal dimensions
	Relative/absolute macroglossia
	Malocclusion (open bite, cross bite, incisal mandibular proinclination, Class III malocclusion)
	Dental morphological and numerical anomalies

The principal pre- and postnatal facial characteristics of patients with Down's Syndrome are listed

Preliminary studies indicate that DS subjects who live in their family and practice sports have better oral conditions than DS subjects living in institutions (Dellavia et al. 2007, 2009).

Additionally, longitudinal studies, performed with noninvasive data collections, are still lacking. For instance, the effects of better oral health care, teeth preservation and timely restoration of masticatory units, on soft tissue facial morphology should be quantified to monitor the treatment and find the best timing for each intervention.

98.7 Application to Other Areas of Health and Disease

Anthropometric and anatomical descriptions of a given disease or syndrome are always based on a combined qualitative and quantitative assessment of those facial characteristics that differ the most from the norm (Sforza and Ferrario 2006). The quantitative approach is particularly useful for clinical applications, allowing the direct comparison between different operators and clinical centers. In a clinical approach, quantitative data support the qualitative description of facial alterations (Hammond et al. 2004), and may assist in the diagnosis of borderline patients or gene carriers, especially for the less experienced clinical genetists.

Additionally, anthropometry may assist in the low-cost screening of neuro-developmental alterations that possess a specific facial morphology, like the fetal alcohol syndrome (Sforza and Ferrario 2006). A first discrimination among putative patients will reduce the costs for more complex examinations.

In those clinical and surgical specialties dealing with the face, a quantitative approach can more efficaciously compare the outcome of different medical, surgical, orthopedics, or orthodontic

procedures and intervention schedules (Dellavia et al. 2008, 2009), and it may also help in the identification of those facial areas susceptible of further improvement (Farkas et al. 2001a, b, 2002a, b).

For all these applications, the use of computerized image analyzers may allow us to reduce time and costs, thus facilitating the screening of a larger number of persons even outside a clinical setting.

Summary Points and Practical Methods

- The facial soft-tissue of subjects with Down's syndrome can be successfully measured and monitored with noninvasive computerized anthropometry.
- A global, 3D, quantitative assessment of the craniofacial characteristics may help in clinical diagnosis.
- Both the hard- and the soft-tissue structures should be analyzed to provide a complete evaluation of any patient, and should be compared to those of healthy subjects of the same age, sex, race and ethnic group.
- The principal facial prenatal markers of Down's syndrome, as assessed by intrauterine ultrasonography, are nasal bone absence or hypoplasia, a flat facial profile, and reduced ear size.
- The principal facial postnatal markers of Down's syndrome are overall reduction of head size, decreased interorbital width, reduced palpebral fissures with slanted eyelids, prominent forehead, depressed nasal bridge, hypoplasic maxillary and mandibular regions, and altered ear size and shape.
- In the oral region, subjects with Down's syndrome have a reduced mouth width, with prominent lips; reduced hard tissue palatal dimensions, with several dental anomalies.
- The effect of ethnic variations, as well as of sex and of physical activity, on the facial characteristics of subjects with Down's syndrome is still being debated. Overall, better general conditions seem to be related to lower alterations in the oral region.

Acknowledgements The precious and indispensable collaboration of all the analyzed subjects, their families, of the Italian Committee of the Special Olympics, is gratefully acknowledged. We are also deeply indebted to all the staff and students of our laboratory, who helped in data collection and analysis. Data collection in subjects with Down's syndrome was partly supported by Special Olympics Inc.

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Chapter 99
Sex Chromosome Aneuploidy and Anthropometry

Lise Aksglaede, Niels Erik Skakkebæk, and Anders Juul

Abstract Human growth is a highly complicated process influenced by genetic, hormonal, environmental, dietary, metabolic and socioeconomic factors. Although the interaction between sex steroids and the growth hormone (GH)-IGF-axis is of major importance in regulating growth, multiple genetic factors, including genes located on the sex chromosomes play independent roles.

Sex chromosome aneuploidy is the most common chromosome disorder in humans, with an incidence of 1 in 400 newborns. The most frequent type of aneuploidy involve the addition or deletion of an X or Y chromosome resulting in a 47,XXX, 45,X, 47,XXY or 47,XYY karyotype. The clinical and behavioural characteristics of these conditions are relatively well described in the literature, whereas, the addition of more than one extra sex chromosome is rare and relevant clinical information is limited.

Sex chromosome aneuploidies have a high but varying impact on normal growth, and disorders of growth may be the first or only symptom of an underlying genetic disorder. Interestingly, the presence of supernumerary sex chromosomes affects growth in a dimorphic pattern indicating that genes on the X and the Y chromosome affect height in a different manner.

Abbreviations

E2	Estradiol
FSH	Follicle stimulating hormone
KS	Klinefelter syndrome
LH	Luteinizing hormone
IGF-I	Insulin like growth factor I
IGFBP-3	Insulin like growth factor binding protein 3
SDS	Standard deviation score
SHOX	Short stature homeobox containing gene
SRY	Sex determining region of the Y chromosome
T	Testosterone

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_99,

99.1 Introduction

Human growth is a highly complicated process influenced by genetic, hormonal, environmental, dietary, metabolic and socioeconomic factors. Although the interaction between sex steroids and the growth hormone (GH)–IGF axis is of major importance in regulating growth, multiple genetic factors, especially genes located on the sex chromosomes, play independent roles.

Sex chromosome aneuploidy is the most common chromosome disorder in humans, with an incidence of 1 in 400 newborns. Aneuploidies most often originate from non-disjunction during meiosis and result in individuals with either supernumerary or subnumary sex chromosomes. It may be either maternally or paternally derived, although, in cases with poly Y, the additional Y chromosome must be of paternal origin, either generated by a paternal non-disjunction at meiosis II or by a post-zygotic mitotic error (Robinson and Jacobs 1999). The most frequent types of aneuploidy involve the addition or deletion of an X or a Y chromosome, resulting in a 47,XXX; 45,X; 47,XXY; or 47,XYY chromosome constitution. The clinical and behavioural characteristics of these conditions are relatively well described in the literature, whereas, the clinical phenotypes of individuals with the rare karyotypes that include more than one extra sex chromosome are less well described.

Klinefelter syndrome (KS) affects 1 in 660 newborn males (Bojesen et al. 2003), and it is known that approximately 80% of the cases are caused by the numerical chromosome aberration 47,XXY; the remaining have higher grade chromosome aneuploidies (e.g. 48, XXXY; 48,XXYY; and 49,XXXXY) or mosaicisms (e.g. 46,XY/47,XXY). Another, less frequent sex chromosome aneuploidy, the *SRY*-positive 46,XX male (also called de la Chapelle's syndrome), occurs with a prevalence of 1 in 20,000–25,000 males. These patients have some Y-chromosomal material including the *SRY* (sex-determining region of the Y chromosome) gene translocated to one of the X chromosomes and are therefore phenotypically males. The double Y syndrome (47,XYY) affects 1 in 1,000 males, whereas XXYY syndrome occurs in approximately 1 in 18,000 to 1 in 50,000 males.

In females, trisomy X (47,XXX) is the most frequent aneuploidy affecting 1 in 1,000 newborns (Jones 1997). Most of these children present with a normal phenotype at birth (Linden et al. 1988). The deletion of one X chromosome in a female occurs in 1 in 2,500 newborn girls and results in Turner syndrome with the 45,X karyotype.

A sex-chromosome aneuploidy may affect the patient at multiple organ levels. Though many individuals with sex chromosome variations can live functionally normal lives, others may experience physical, developmental, psychosocial, behavioural, and learning impairments. The natural history of these consequences is not completely elucidated, but one hypothesis in KS is that multiple genes on the extra X chromosome escape inactivation and thereby exert dosage effects. It is known that the phenotype of Klinefelter males progressively deviates from the normal, with the increasing number of extra X chromosomes present, whereas the Klinefelter males with mosaicism most often are less severely affected (Lanfranco et al. 2004). By contrast, the phenotypic effects of extra Y chromosomes appear not as severe as those of supernumerary X chromosomes. However, few studies on individuals with sex-chromosome tetrasomy and pentasomy have been conducted, and these have mostly been limited to case reports, and relevant clinical information is therefore limited. Additionally, the majority of the original studies on sex-chromosome aneuploidies were carried out in institutionalised populations of mentally retarded or psychotic adults, and more recent studies on unselected patients have pointed out that these early studies may be subject to ascertainment bias due to the highly selected material. However, no consistent clinical features or specific abnormalities in patients with sex-chromosome aneuploidy exist, and the diagnosis can only be made by karyotyping.

With the discovery of the sex-chromosome-related *SHOX* (Short Stature Homeobox containing) gene, which is located in the pseudoautosomal region 1 (PAR1) (Rao et al. 1997), a new perspective was added to the understanding of the regulation of growth. *SHOX* escapes X-inactivation and is highly expressed in growth plates of long bones, where it plays a role in bone growth and maturation (Rao et al. 1997; Munns et al. 2004). Subsequently, it has been clarified that *SHOX* has a dosage effect on adult height and that, while haploinsufficiency may lead to short stature, *SHOX* overdosage is implicated in tall stature (Rao et al. 1997). Accordingly, it has been suggested that the tall stature of individuals with supernumerary sex chromosomes is related to an overexpression of *SHOX*. Gene-dosage effects of a potential growth-control gene on the Y chromosome (*GCY*) has also been proposed and may also be involved in the additional height in sex-chromosome aberrations with an extra Y.

99.2 Sex Chromosome Aneuploidy and Growth

Representative growth curves for children with the most common sex-chromosome aberrations are illustrated in Figs. 99.1 and 99.2, and a summary of the existing data on anthropometric measures in these conditions is presented in Table 99.1.

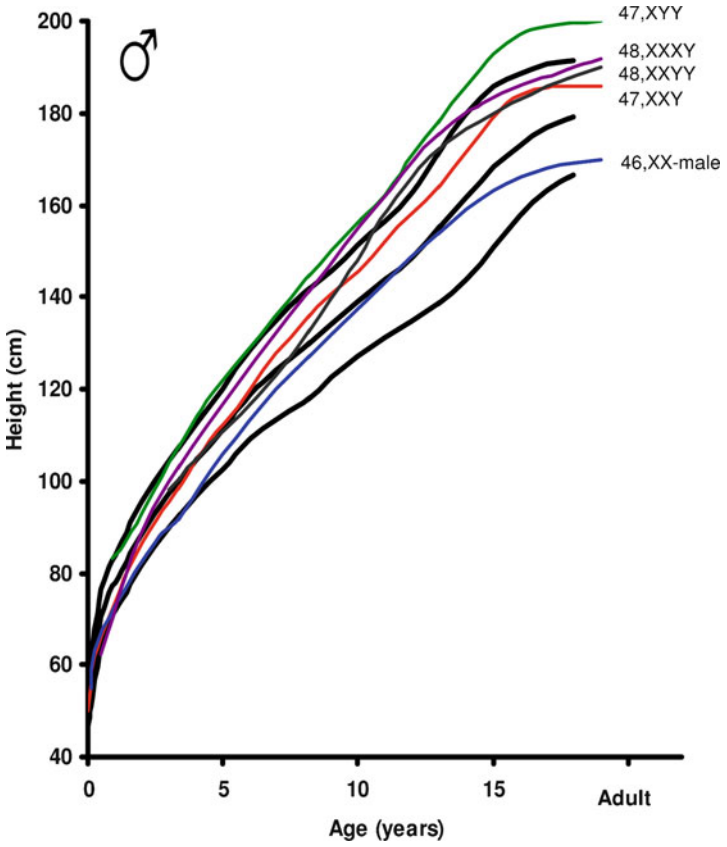

Fig. 99.1 Representative growth curves for boys with sex-chromosome aberrations. Wide lines represent mean +/-2SD in healthy Danish boys and adolescents.

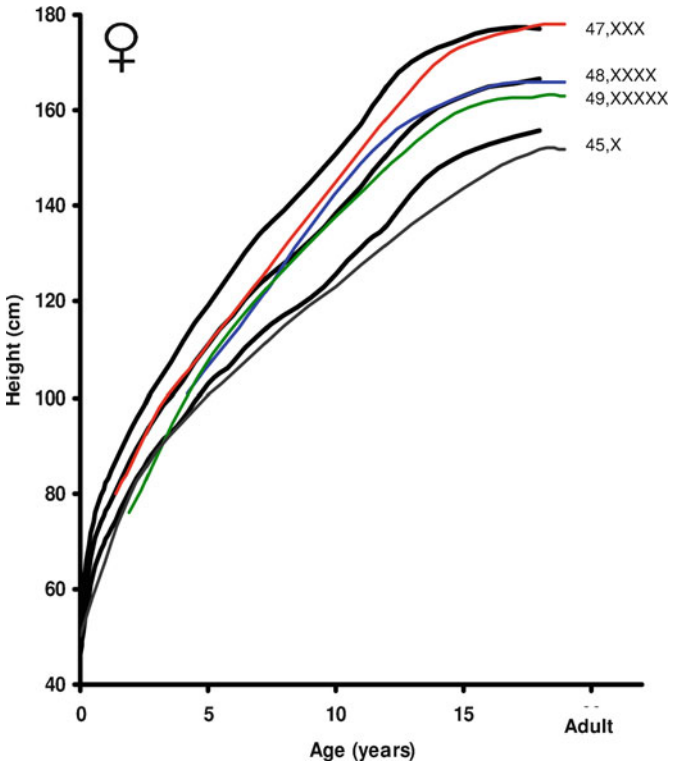

Fig. 99.2 Representative growth curves for girls with sex-chromosome aberrations. Wide lines represent mean +/-2SD in healthy Danish girls and adolescents.

Table 99.1 Anthropometric measures in sex chromosome aneuploidies

	Birth length		Birth weight		Head circumference		Final height		
	cm	SDS	Kg	SDS	cm	SDS	cm	SDS	Reference
46, XX-male	↓→				↓		↓		
	50.6	(–0.6)	3.14				170.6	[–1.3]	Vorona, 2007
							168.0	[–1.5]	Aksglaede, 2008
47, XXY	↑→		↓→		↓→		↑		
			3.16	(–0.34)			178.8	(+0.6)	Schibler, 1974
			3.05						Robinson, 1979
							182.1	[+0.5]	Varella, 1984
	50.7		3.23		34.5[a]		185.6	[+1.0]	Ratcliffe, 1985, 1991
							184.0	[+0.8]	Lanfranco, 2004
						(+0.6)			Zinn, 2005
						(–0.1)			Ross, 2005
							183.6	[+0.7]	Bojesen, 2006
							183.4	[+0.7]	Vorona, 2007
	51.8	(+0.2)	3.45				186.8	[+1.2]	Aksglaede, 2008
47, XYY	↑→		↑→		↑→		↑		
			3.33						Robinson, 1979
	51.5		3.39		35.2[a]		187.2	[+1.3]	Ratcliffe, 1985, 1991
	52.1	(+0.4)	3.32				197.3	[+2.9]	Aksglaede, 2008

(continued)

Table 99.1 (continued)

	Birth length		Birth weight		Head circumference		Final height		
	cm	SDS	Kg	SDS	cm	SDS	cm	SDS	Reference
48, XXYY				→				↑	
								(+2.2)	Tartaglia, 2008
48, XXXY								↑	
							190.0	[+1.8]	Ottesen, 2010
49, XXXXY								↓→	
45, X		↓		↓		→		↓	
	47.8	(–1.4)					146.9	[–3.7]	Varrela, 1984 Karlberg, 1991
47, XXX		↓		↓		↓			
	49.4		2.98						Robinson, 1979
			3.07		33.8[a]		164.8	[–0.3]	Ratcliffe, 1985, 1991
							177.8	[+2.1]	Ottesen, 2010
48, XXXX								↑→	
							166.0	↑ [0.1]	Ottesen,2010
49, XXXXX								↓	

[a] =head circumference at birth, SDS= standard deviation score, (SDS according to local reference), [SDS according to (Else Andersen, 1982)] ↑ =increased, → = no difference, ↓ = reduced compared to healthy subjects

99.3 47, XXY Klinefelter Syndrome

Patients with KS have been studied continuously since the syndrome was first characterised in 1942 by Harry F Klinefelter (Klinefelter 1942) and subsequently found to be caused by the presence of an extra X chromosome (Jacobs and Strong 1959). The 47,XXY male is characterised by small firm testes, gynaecomastia, eunuchoid body proportions, azoospermia, high levels of gonadotropins (FSH and LH) and low normal or subnormal levels of testosterone, learning disabilities and speech and language deficits (Paulsen et al. 1968). However, the phenotypic characteristics of KS are highly variable, and only approximately 25% of the cases are ever diagnosed (Bojesen et al. 2003).

99.3.1 Growth

Anthropometric studies in KS during infancy and childhood are somewhat inconsistent. Some studies find decreased birth length and weight and head circumference compared to controls, whereas others report normal stature at birth. Most studies find normal to increased growth during infancy and early childhood in these boys. Adult males with 47,XXY karyotype are taller than males with a normal karyotype, and their tallness is mainly caused by increased leg length.

In a study of 90 Klinefelter boys aged 2–17 years, height was becoming increasingly above normal with increasing age, whereas height velocity was above normal from 5 years of age. A significant tendency to disproportionately long legs during childhood was found. Head circumference was significantly reduced from birth and onwards, whereas bone age was on average 2SD below the normal until age eight, rising to near the mean by age 12 years (Stewart et al. 1982b).

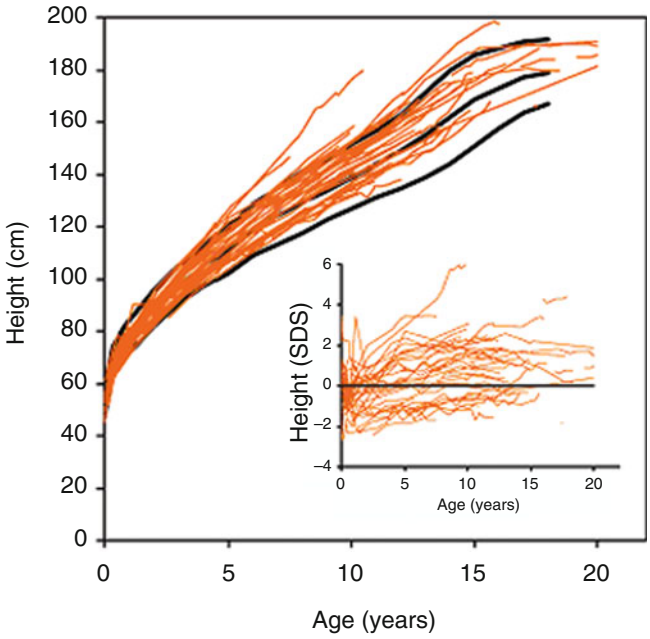

Fig. 99.3 Longitudinal growth curves in relation to chronological age in patients with 47,XXY Klinefelter syndrome. Inserted graph illustrates the height SDS in relation to age in these patients. *Lines* represent mean ±2 SD in healthy boys (Adapted from Aksglaede et al. 2008b. With permission. Copyright 2008, The Endocrine Society)

Robinson et al. reported unremarkable head circumference in 23 newborns with 47,XXY, whereas decreased head circumference was found in 40 boys above 4 years. The authors reported normal height in KS boys until the age of 3 years, whereas significantly fewer boys had a height percentile below 25 after the age of 3 years. These authors found low normal birth weight (Robinson et al. 1979).

Another 15 boys with 47,XXY were identified during the years 1964–1974 in The Denver Prospective Study, where 40,000 consecutive births at two Denver hospitals were screened by Barr-body analysis on the amniotic membranes obtained from their placentas (Robinson et al. 1990). Fourteen of these boys were followed until the age of 16–23 years. Mean height was at the 79th percentile, whereas mean weight was at the 50th percentile and head circumference at the 20th percentile at last follow-up.

A total of 23 47,XXY boys were followed from birth to adolescence in the Edinburgh Study of Growth and Development (Ratcliffe et al. 1990). These boys were diagnosed as part of a cytogenetics survey conducted during the years 1967 through 1979 where 34,380 consecutive infants were screened. At birth, the singleton XXY boys born at term were smaller than controls in weight, length and head circumference. During childhood, height velocity was significantly increased at all ages between 3 and 9 years. At 3 years of age, leg length was already proportionally increased and continued with a statistically significant increase present by age five. Standard deviation scores for head circumference were significantly reduced at all ages in this study (Ratcliffe et al. 1990).

Another study on growth in 87 males with Klinefelter syndrome found accelerated growth from early infancy through childhood and adolescence (Fig. 99.3). Height SDSs were higher than expected from the age of 6 years and onwards, and final height in adulthood was significantly increased as compared with healthy controls. Leg length was increased in these patients (Aksglaede et al. 2008b). Interestingly, these abnormal growth patterns were not reflected in the circulating levels of IGF-I (insulin-like growth factor) and IGFBP-3 (insulin-like growth factor binding protein), and the 47,XXY boys did not develop biochemical signs of hypogonadism until after puberty.

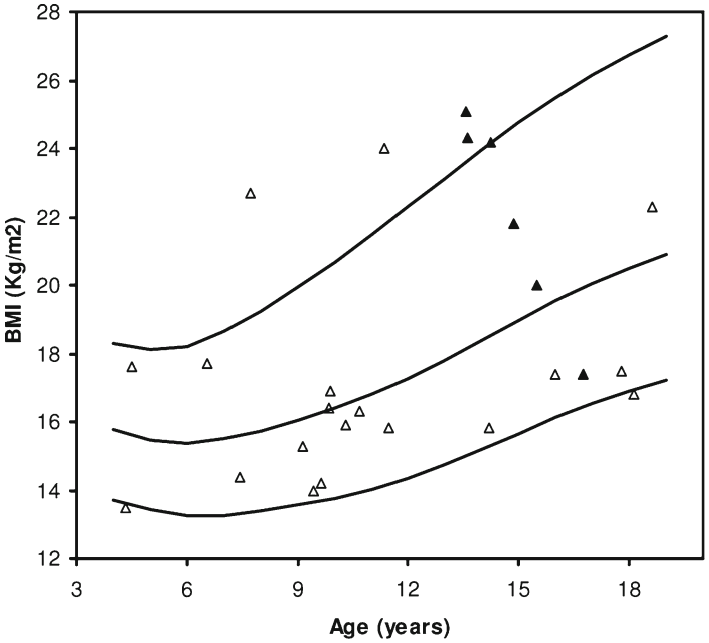

Fig. 99.4 BMI in relation to chronological age in boys with 47,XXY Klinefelter syndrome (*KS*). *Open triangles* indicate patients never treated with androgens and *solid triangles* indicate patients in androgen-substitution therapy. *Lines* represent mean and ±2 SD for healthy Danish boys and adolescents (Adapted by permission from BMJ Publishing Group Limited. Aksglaede et al. 2008a)

In the most recent multicentre study, median height SDS in 129 Klinefelter patients aged 27.7 (range 1.1–66.3 years) were +1.3 (range -1.8 to +4.9) (Ottesen et al. 2010). In this study, current height SDS was significantly ($p < 0.0001$) higher than target height SDS in 42 patients for whom parental heights were available.

In summary, patients with KS exhibit accelerated growth from early childhood, and, as a result, final height is significantly above normal. In addition, eunuchoid body proportions are a common feature in these patients. Head circumference is usually normal or slightly decreased at birth but below average in adulthood.

99.3.2 Body Composition

Increased deposits of body fat in KS patients from early childhood, evaluated by measuring subscapular and triceps skinfolds, have been reported (Ratcliffe 1982; Ratcliffe et al. 1990). Specifically, a tendency towards central obesity was observed in 75% of XXY boys from 6 years of age (Ratcliffe 1999).

In a study on whole-body DEXA scans in 24 children and adolescents with non-mosaic Klinefelter syndrome aged 4.3–18.6 years, a significantly increased body fat mass despite normal BMI and lean body mass was found, suggesting an unfavourable muscle/fat ratio to be present already in childhood (Figs. 99.4–99.6). This study included both androgen-substituted- and unsubstituted individuals, but there was no difference between treated and untreated patients (Aksglaede et al. 2008a).

In line with this, Bojesen et al. found significantly greater weight, BMI, waist circumference, total body fat and truncal fat in 71 adults (aged 35.0 years (range 19.0–66.2)) with KS compared with controls as evaluated by whole-body DEXA scan (Bojesen et al. 2006b).

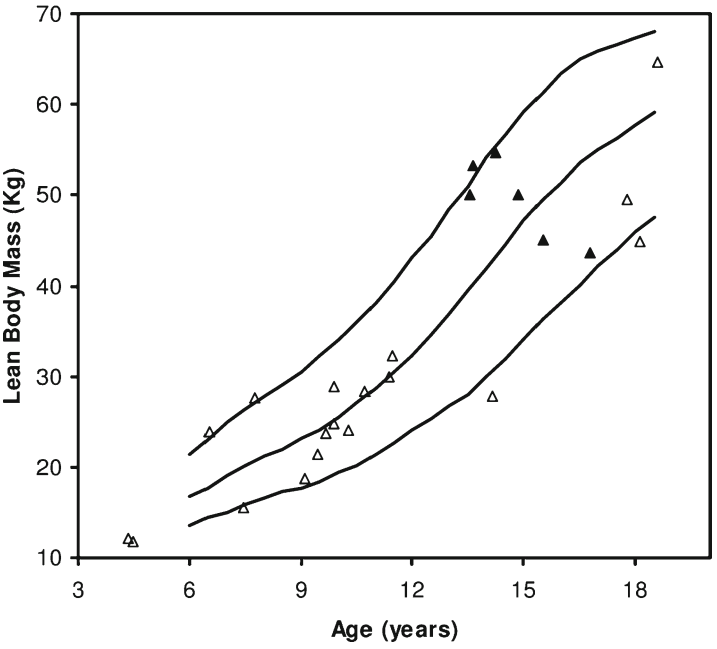

Fig. 99.5 Lean body mass in relation to chronological age in boys with 47,XXY Klinefelter syndrome (*KS*). *Open triangles* indicate patients never treated with androgens and *solid triangles* indicate patients in androgen-substitution therapy. *Lines* represent mean and ±2 SD for healthy Danish boys and adolescents (Adapted by permission from BMJ Publishing Group Limited. Aksglaede et al. 2008a)

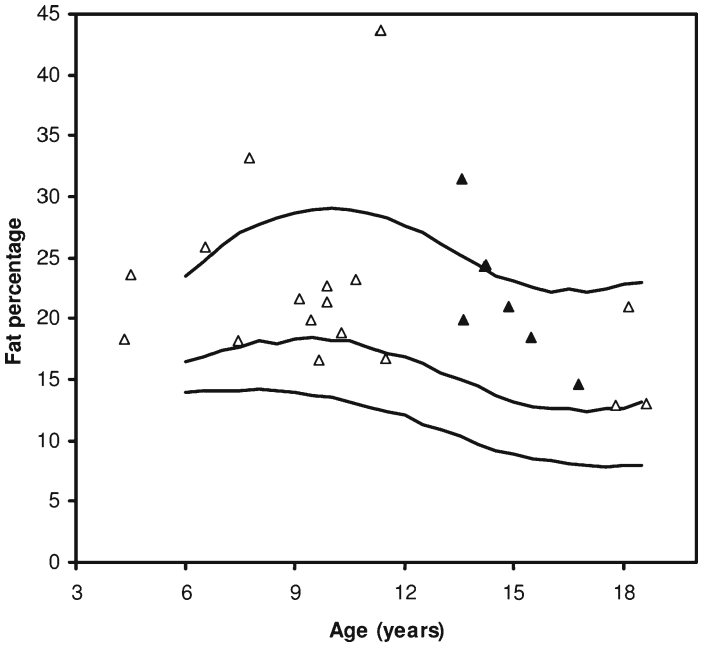

Fig. 99.6 Body fat percentage in relation to chronological age in boys with 47,XXY Klinefelter syndrome (*KS*). *Open triangles* indicate patients never treated with androgens and *solid triangles* indicate patients in androgen-substitution therapy. *Lines* represent mean and ±2 SD for healthy Danish boys and adolescents (Adapted by permission from BMJ Publishing Group Limited. Aksglaede et al. 2008a)

Thus, patients with KS present with increased body fat mass and an unfavourable muscle/fat ratio already from childhood and through adolescence.

99.4 48,XXYY

In addition to the characteristic physical features of Klinefelter syndrome (tall stature, hypogonadism and gynaecomastia), reports on patients with 48,XXYY have described hypertelorism, cubitus varus, pes planus, clubfoot, clinodactyly and scoliosis. Neurological problems, including seizures, intention tremor, hypotonia and tics have also been reported in multiple patients, along with occasional structural brain abnormalities including agenesis of the corpus callosum and frontoparietal cortical atrophy. Speech delays and motor delays with poor motor coordination are commonly described in the first 3 years of life. Although most cases reported in the literature describe some degree of cognitive disability or behavioural problems, a few reports describe adolescents with ''good social adjustment''.

99.4.1 Growth

In a study by Tartaglia et al. on 95 patients aged one to 55 years, who were diagnosed with a 48,XXYY karyotype, a significant increase in mean height SDS with age from +0.21 SDS in children less than 10 years of age (n = 25), to +1.06 SDS in the 11–19 age group (n = 35) and +2.18 SDS in the 20+ age group (n = 22) was found. Mean height of adult males was 192.4 cm (range 180.1–216 cm). Although mean BMI was stable across age groups in this study, there was considerable variation in body habitus within each age group, and individuals ranged from underweight to overweight. Thus, among the adults, 18.2% were underweight, while 31.8% were obese. Eighty-six percent (80/95) of the infants were born at term, with the average birth weight of term infants at 3,130 g (Tartaglia et al. 2008). In addition to tall stature, long leggedness and eunuchoid body proportions have been described (Sherman and Simpson 2003).

99.5 48,XXXY, 49,XXXXY

One study reported increased height with a height SDS of +1.8 (–2.0 to +3.2) in 48,XXXY (n = 9) but reduced height of –1.8 (–4.2 to – 0.1) in 49,XXXXY (n = 10) (Ottesen et al. 2010).

In summary, height deviates progressively from normal with increasing age in males with 48,XXYY karyotype, and final height is significantly above normal. By contrast, it seems that the presence of two extra X chromosomes affects height positively, whereas the addition of three extra X chromosomes affects height negatively. However, data on these latter patient categories are insufficient to draw firm conclusions.

99.6 *SRY*-Positive 46,XX Male

The *SRY*-positive 46,XX male has Y-chromosomal material including the *SRY* (sex-determining region of the Y) gene translocated to the distal tip of the short arm of the paternal X chromosome. Phenotypically, these patients are males and resemble the males with 47,XXY in many (hypogonadism, gynaecomastia and infertility), but not all, clinical aspects (growth).

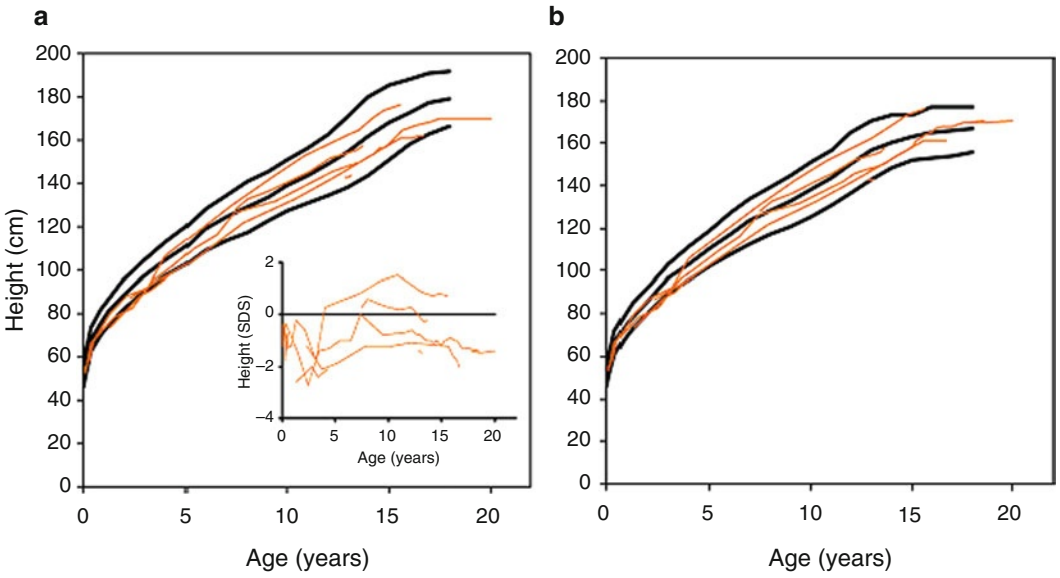

Fig. 99.7 Longitudinal growth curves in relation to chronological age in patients with *SRY*-positive 46,XX male syndrome. The *left panel* illustrates the growth curves in relation to growth in healthy boys, whereas, in the *right panel*, the growth curves are illustrated in relation to growth in healthy females. Inserted graph in A illustrates the height SDS in relation to age in these patients. *Wide Lines* represent mean ±2 SD in healthy boys (**a**) and in girls (**b**) (Adapted from Aksglaede et al. 2008b. With permission. Copyright 2008, The Endocrine Society)

99.6.1 Growth

Boys with *SRY*-positive 46,XX-male karyotypes are usually described as shorter than average. In a study of 14 46,XX males by Aksglaede et al., this was already evident in infancy where the height SDS were significantly reduced (Fig. 99.7a). Interestingly, when comparing these males with healthy females there was no difference (Fig. 99.7b). Final height of the adult males with *SRY*- positive 46,XX karyotype was decreased to a level equal to final height in females. These XX males had normal body proportions with normal sitting height/height ratios (Aksglaede et al. 2008b).

Vorona et al. studied 11 *SRY*-positive 46,XX males and found significantly reduced height and weight but no difference in BMI when comparing with 101 age-matched 47,XXY Klinefelter patients and 78 age-matched healthy males. In this study, the 46,XX males were also compared with a cohort of 157 age-matched healthy females, and no difference in height, weight or BMI was reported. The mean height of the *SRY*-positive 46,XX males was 170.6 cm, whereas mean height in patients with 47,XXY karyotype, healthy males and healthy females were 183.4, 180.7 and 168.9 cm, respectively (Vorona et al. 2007).

99.7 47,XYY

The karyotype 47,XYY is by far the most frequent and best characterised type of poly-Y complement, whereas trisomy and tetrasomy of the Y chromosome are much less frequent. The 47,XYY male has been described as tall, with an increased risk of learning difficulties but with a normal reproductive capacity except for the presence of Sertoli-cell-only syndrome, which has been described in 30% of boys with double-Y syndrome (Skakkebaek et al. 1973).

99.7.1 Growth

Birth weight and length and head circumference were normal in one study (Robinson et al. 1979), whereas these parameters were at or above the 97th percentile in another study (Geerts et al. 2003).

Stewart et al. found elevated growth velocity from early childhood (Stewart et al. 1982b), and, in line with this, several studies have reported increased height during childhood and through adolescence in 47,XYY males (Robinson et al. 1979; Stewart et al. 1982b; Varrela and Alvesalo 1985; Ratcliffe et al. 1990, 1992; Aksglaede et al. 2008b; Ottesen et al. 2010). One study found significantly ($p = 0.001$) higher final height than target height in 27 adults with 47,XYY (Ottesen et al. 2010).

Most studies on body proportions in 47,XYY have reported no difference as compared to normal males (Stewart et al. 1982b; Varrela and Alvesalo 1985; Ratcliffe et al. 1990). However, Stewart et al. found a slight, but non-significant increase in proportional leg length (Stewart et al. 1982b), and another longitudinal study reported slightly increased leg length around pubertal onset, but this difference was equalised in adolescence where the boys had normal sitting height/height ratios (Aksglaede et al. 2008b).

During childhood, head circumference and weight for height has been reported within normal limits (Stewart et al. 1982b).

In summary, *SRY*-positive 46,XX males present with impaired growth already in infancy, and final height is significantly below the height of healthy males but resembles the height of healthy females. By contrast, males with 47,XYY karyotype are significantly taller than healthy males, and final height in these patients usually exceeds final height of KS patients. In contrast to KS patients, the body proportions are within normal limits in both 46,XX males and 47,XYY males.

99.8 47,XXX

Girls with 47,XXX karyotype are usually normally developed at birth, and most cases have been discovered following a karyotype done as part of work-up of children with behavioural disorders. In accordance, learning disabilities and lower IQ scores are frequently seen (Otter et al. 2010). Most of the girls with 47,XXX karyotype have normal reproductive functions, including menstruation and fertility, although reports on delayed puberty and an increased incidence of premature ovarian failure exist (Otter et al. 2010).

99.8.1 Growth

Birth weight, length and head circumference in 47,XXX girls have been described as below average with respect to healthy girls (Robinson et al. 1979; Stewart et al. 1982a, b; Ratcliffe et al. 1990, 1994; Ratcliffe 1999). However, final height of triple-X girls usually exceeds that of controls, and their leg length in proportion to their overall height increases to a significant degree (Ratcliffe et al. 1994). Studies on skeletal maturation have revealed that bone age is about 1 SD below normal in early childhood (age 2–4 years) but well within normal limits by 7–10 years of age (Stewart et al. 1982b).

Sixteen 47,XXX girls were followed from birth to adolescence in the Edinburgh Study of Growth and Development (Ratcliffe et al. 1990). These girls were diagnosed as part of a cytogenetics survey conducted during the years 1967 through 1979, where 34,380 consecutive infants were screened. Twins and girls with a birth weight <2.5 kg were excluded from the data analyses. These girls had a birth weight,

length and head circumference significantly smaller than controls. During childhood, mean height velocity for the whole group did not differ from controls. However, looking at the individual growth curves, half the girls were below the 50th percentile, whereas the remaining were above that. The magnitude of the pubertal growth spurt in seven of these 16 girls did not differ from controls. However, age at onset of growth spurt and at peak height velocity was delayed in accordance with a 10-month delay in pubertal onset as assessed by Tanner stage B2. Sitting height/height ratio was reduced, indicating that the 47,XXX girls had proportionally long legs. The 47,XXX girls tended to be slim with a lower weight than height centile. Head circumference remained reduced throughout childhood and adolescence.

Another 11 girls with 47,XXX were identified during the years 1964–1974 in The Denver Prospective Study, where 40,000 consecutive births at two Denver hospitals were screened by Barr-body analysis on the amniotic membranes obtained from their placentas (Robinson et al. 1990). Ten of these girls were followed until early adulthood. At this time, height was at or above the 80th percentile in nine of ten and >95th percentile in five of these. Weights were within the normal range. Nine of ten had a head circumference at or below the 50th percentile, and five of these were at or below the 20th percentile.

Sixteen girls with 47,XXX karyotype were identified during the years 1967–1971 in seven Toronto Hospitals: The Toronto Study (Stewart et al. 1990). Six of these girls were followed annually until early adulthood. Height increased from the 55th percentile at age 2 years to the 85th percentile up to age nine. Height velocity was above the 50th percentile until age 12, and final height reached the 90th percentile, well above the midparental height, which was at the 48th percentile. In the early years, weight was below the 50th percentile, but rose above the 60th percentile later. Mean head circumference was consistently below the 50th percentile. Legs were significantly longer in comparison to sitting height. Arm span/height ratio was fairly constant between age 11 and 16 years.

Ottesen et al. found an increased median height SDS of +0.7 (–0.9 to +3.2) in 40 patients with 47,XXX. In a subgroup of 25 of these patients, where target height was available, current height SDS was significantly higher than target height SDS ($p = 0.009$) (Ottesen et al. 2010).

99.9 48, XXXX and 49,XXXXX

Very limited data on girls with 48,XXXX and 49,XXXXX karyotype exist. Ottesen et al. found slightly decreased height in 13 girls with 48,XXXX karyotype, whereas Jones et al. found normal to tall stature in these girls (Jones 1997; Ottesen et al. 2010). In line, median height SDS was –1.0 (–3.5 to –0.8) in 49,XXXXX, although only data from three girls were available (Ottesen et al. 2010).

In summary, girls with 47,XXX karyotype are usually small at birth, but end up with a final height above average for healthy females. In addition, these girls present with eunuchoid body proportions. By contrast, the presence of two or three extra X chromosomes may affect stature, but data on these patient categories are insufficient to draw any conclusions.

99.10 Applications to Other Areas of Health and Disease

The vast majority of studies on general health and disease in sex-chromosome aneuploidies have been conducted in patients with 47,XXY karyotype and 45,X Turner syndrome. Klinefelter syndrome has been associated with a significant 40–50% increase in mortality risk corresponding to a significantly reduced median survival of 2.1 years, in particular due to cardiovascular, infectious, neurological, pulmonary and urinary-tract diseases (Swerdlow et al. 2005; Bojesen et al. 2006a).

99.11 Metabolic Syndrome and Abdominal Fat

Truncal obesity has been related to the metabolic syndrome, which is defined as a clustering of insulin resistance and hyperinsulinaemia and is often associated with dyslipidaemia, hypertension, glucose intolerance or non-insulin-dependent diabetes mellitus and an increased risk of cardiovascular events. A fivefold increased risk of developing the metabolic syndrome in adults with KS compared to age-matched controls was found in a recent study where the strongest predictor for the metabolic syndrome was adiposity, especially truncal adiposity (Bojesen et al. 2006b). In this study on 71 adult patients with Klinefelter syndrome, Bojsen et al. found that all measures of insulin sensitivity and metabolic syndrome except blood pressure changed in a pathologic direction; fasting serum insulin and fasting plasma glucose were higher among the KS patients, whereas insulin sensitivity (HOMA2%S) was significantly reduced as compared with age-matched controls. Total cholesterol, LDL cholesterol and triglycerides were all significantly increased, and HDL cholesterol was significantly decreased in patients with KS. CRP and leptin levels were higher in Klinefelter syndrome patients, whereas levels of adiponectin and fructosamine were similar between the two groups. Using the NCEP/ATPIII criteria, significantly more Klinefelter syndrome patients (46%) than controls (9.9%) had metabolic syndrome. Furthermore, significantly more KS patients (9%) than controls (1.4%) had diabetic FPG levels, and significantly more patients (17%) than control subjects (3%) had impaired fasting glycaemia (Bojesen et al. 2006b).

99.12 Osteoporosis

Testosterone deficiency in otherwise healthy adult males is associated with a significant decrease in bone mineral density. Accordingly, it is well established that patients with KS have a high risk of developing ostopenia or even frank osteoporosis in young adulthood (Horowitz et al. 1992; Swerdlow et al. 2005; Bojesen et al. 2006a). It is, however, not clear whether the impaired bone density in these patients is a result of hypogonadism or a more complex genetic defect.

In a study on 24 children and adolescents with 47,XXY karyotype aged 11.0 years (range 4.3–18.6 years) bone mineralisation was examined. Eighteen of these patients (aged 10.1 years (range 4.3–18.6)) had never received sex-hormone therapy, whereas the remaining six (aged 14.6 years (range 13.6–16.8)) were treated with per oral testosterone undecanoate at the time of examination. Median lumbar BMD and BMC, whole-body BMC and BMD for age- as well as size-adjusted BMC were all within the normal ranges, indicating normal bone mineralisation in both treated and untreated subjects in this study (Fig. 99.8). Whole-body bone mineral content and lumbar mineral density were higher in the group of treated Klinefelter boys, although this did not reach statistical significance (Aksglaede et al. 2008a).

In adult Klinefelter patients, Kübler et al. found significantly lower bone mineral density in patients who had never received androgen replacement therapy or in whom treatment was instituted late (>the age of 20 years), whereas patients who started early androgen substitution (<20 years) had normal BMD (Kübler et al. 1992). In this study, patients never treated showed a significant positive correlation between BMD and serum T (Kübler et al. 1992). These data suggest that there is a critical time during development when adequate androgen levels are necessary for normal bone mineralisation. This may be due to an impaired androgen secretion at the critical stage of bone maturation during puberty so that subsequent therapy with androgen replacement may not be sufficient to restore normal bone mass.

In summary, bone mineralisation is normal in childhood and adolescence, whereas adult patients with KS have increased risk of developing osteopenia or osteoporosis.

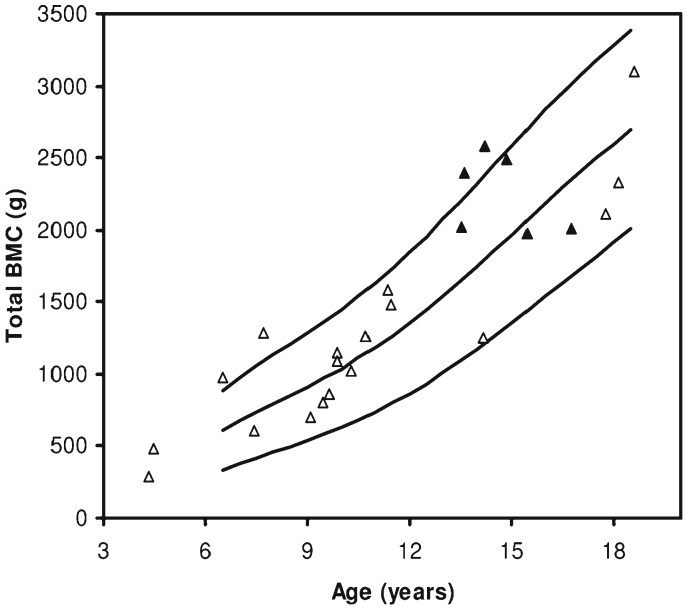

Fig. 99.8 Whole-body BMC in relation to chronological age in boys with 47,XXY Klinefelter syndrome. *Open triangles* indicate patients never treated with androgens and *solid triangles* indicate patients in androgen-substitution therapy. *Lines* represent mean and ±2 SD for healthy Danish boys and adolescents (Adapted by permission from BMJ Publishing Group Limited. Aksglaede et al. 2008a)

Summary Points

- Sex-chromosome aneuploidy is associated with physical, developmental, psychosocial, behavioural and learning impairments. However, the severity varies greatly.
- The phenotypic differences in sex-chromosome aberrations may result from gene-dosage effects of genes in the pseudoautosomal regions (PAR) of the X and Y chromosomes that escape X inactivation.
- Increased growth is a clinical hallmark in patients with polysomy X or Y.
- Patients with XYY and XXYY are taller than XXY.
- *SRY*-positive 46,XX males present with a growth pattern equal to female growth.
- The 47,XXY karyotype is associated with an increased risk of premature development of osteopenia or even frank osteoporosis.
- An unfavourable muscle/fat ratio is already present in patients with 47,XXY during childhood and adolescence.
- There is a five fold increased risk of developing the metabolic syndrome in adult 47,XXY, and the strongest predictor for the metabolic syndrome is adiposity, especially truncal adiposity.

Key Facts of Aneuploidy

- Sex-chromosome aneuploidy is defined as the addition or deletion of one or more X or Y chromosomes to a normal karyotype.
- It occurs during cell division and may be either paternally or maternally derived.
- It is the most common chromosome disorder in humans.
- The most frequent types of aneuploidies are 47,XXX; 45,X; 47,XXY; and 47,XYY.
- Some individuals with sex-chromosome variations can live functionally normal lives; others may experience physical, developmental, psychosocial, behavioural and learning impairments.

Key Facts of Klinefelter Syndrome

- Discovered in 1942 by Harry F Klinefelter.
- Defined by the presence of one or more extra X chromosomes (typically 47,XXY).
- Affects 1 in 660 newborn boys.
- Characterised by small testes, hypergonadotropic hypogonadism, infertility, tall stature and learning disabilities.

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Chapter 100
Anthropometric Indices in Turner Syndrome

Anna M. Kucharska

Abstract Turner syndrome (TS) is defined as the complex of characteristic physical features in a phenotypic female, caused by complete or partial X monosomy in some or all cell lines. It is a relatively common chromosomal aberration, but the variability of phenotypes among the patients is very large. In a majority of patients with Turner syndrome, one can expect short stature and infertility. Many of the characteristic features are detectable by physical examination, and anthropometric measurements are a valuable tool in the diagnostics and therapy in TS. In this chapter, the symptoms of Turner syndrome are introduced and their anthropometric aspects are pointed out. The relevance of anthropometric examination in the diagnostics and monitoring of therapy in Turner syndrome is described. A natural development of body constitution and composition is characterized according to several studies performed on children and adults. The alterations of anthropometric parameters during hormonal therapy are depicted. Anthropometric indices are shown as valuable markers of the effectiveness of growth hormone treatment, as well as markers of metabolic effects of growth hormone, sex steroids, and insulin sensitivity. The conditions for the appropriate anthropometric examination of the patient with Turner syndrome and evaluation of the appropriate measurements are described.

Abbreviations

BMI	Body mass index
FM	Fat mass
GH	Growth hormone
HOMAindex	Homeostatic model assessment- index
IGF-1	Insulin-like growth factor-1
LBM	Lean body mass
SDS	Standard deviation score
SHBG	Sex hormone binding globulin
SHOX	Short stature homeobox-containing gene
TS	Turner syndrome

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_100,

100.1 Introduction

Turner syndrome (Ullrich–Turner syndrome) is a relatively common chromosomal aberration causing characteristic physical features in girls, but the variability of phenotypes among the patients is very large. In the majority of patients with Turner syndrome, one can expect short stature and infertility. Other congenital anomalies are variable. Mental retardation is rare. Many of the characteristic features are detectable by a thorough physical examination. Anthropometric measurements are especially valuable in diagnostics, but anthropometric indices are also useful in monitoring of hormonal therapy and follow-up in patients with Turner syndrome.

100.1.1 Definition

Turner syndrome (TS) is defined as the complex of characteristic physical features in a phenotypic female caused by complete or partial X monosomy in some or all cell lines. Both criteria, a chromosomal aberration and physical symptoms are required for the diagnosis.

100.1.2 Frequency

The first definitive description of Turner syndrome was presented by O. Ullrich in 1930 and by H. Turner in 1938. It is a relatively common chromosomal disorder and its prevalence is approximately 1 in 2500 female live births (Saenger et al. 2001). This is much higher in early pregnancy. It has been estimated that as much as 1–2% conceptuses have a monosomy of X chromosome, but about 99% of them are spontaneously aborted (Gravholt et al. 1996).

100.1.3 Karyotypes

According to the available data from a classic karyotyping (a peripheral lymphocytes examination), approximately 50% of patients born with Turner syndrome have a monosomy of 45,X. Fifteen percent have a mosaicism for 45,X and one or more different cell lines. A majority of the rest (5–10% of TS patients) have an isochromosome Xq (a duplication of the long arm of one X chromosome, i(Xq)), or other structural disorders of a second X chromosome, for example a ring X chromosome (rX).

In the mosaicism, a percentage contribution of chromosomally different cell lines often varies in different tissues. Karyotypes of skin fibroblasts culture and of peripheral lymphocytes examination in the same individual often show different proportions of particular cell lines. Furthermore, mosaicism in patients with TS may be more frequent than was previously presumed. In the case of two different tissue examinations, approximately 80% of patients with monosomy 45, X in blood cells have mosaicism in skin fibroblasts (Held et al. 1992). In a small number of patients with TS material of Y chromosome may be present. Its presence can increase the risk of gonadoblastoma, which is recently estimated as approximately 7–10% (Gravholt et al. 2000).

100.1.4 Physical Features

The characteristics of Turner syndrome are dependent on the absence of some genes located on the second X chromosome. During a normal development, in 46,XX embryo, one X chromosome is inactivated shortly after a fertilization. Only the pseudoautosomal region of an X chromosome normally escapes this inactivation and two sets of genes are needed for its normal function. When only one set is present, the gene expression is impaired, and this phenomenon is known as the haploinsufficiency. The majority of genes involved in Turner syndrome are located on the short arm of the X chromosome, in the region Xp11.2–p22.1 (Zinn et al. 1998). In this region short stature homeobox-containing gene (SHOX) responsible for growth and genes responsible for normal development of lymphatic system are located.

Patients with Turner syndrome have variable manifestations of typical symptoms. The most common is short stature, in approximately 90% of patients. Webbed neck, cubitus valgus and lack of puberty are very characteristic for TS patients. These symptoms were described by H. Turner in his report on the syndrome. Many other features combined with this syndrome were found in the following years.

The most frequent manifestation of Turner syndrome, as mentioned above, is short stature and characteristic body proportions with a wide body, short legs, and relatively large hands and feet (Gravholt and Naeraa 1997). Gonadal failure occurs in approximately 90% of patients, and the majority of them has delayed or lack of spontaneous puberty. Nevertheless, 2–5% of patients have a chance of a normal pubertal development and fertility (Hovatta 1999). In a newborn or an infant, lymphatic edema of the hands and/or feet is very characteristic of Turner syndrome. Other typical features present in TS patients are: nuchal folds, low posterior hairline and nail abnormalities. Nails are hypoplastic, uplifted and hyperconvex. Multiple pigmented nevi are often present on the skin. Patients with TS have characteristic faces with epicanthal folds, hyperthelorism, low set ears, small mandible and high arched palate. Typical skeletal abnormalities for Turner syndrome are shortened fourth metacarpal bones (Fig. 100.1) and cubitus valgus. Scoliosis is more frequent than in normal population. A relatively common manifestation is recurrent, or chronic otitis media, and hearing disorders. Very characteristic are cardiac anomalies, especially left heart hypoplasia, coarctation of the aorta and bicuspid aortic valve. Cardiac manifestations occur in approximately 30% of patients with TS. Kidney anomalies are also more frequent in Turner syndrome girls than in the normal population. Typical malformations are horseshoe kidneys, malrotation of kidneys, other positional abnormalities, and aplasia or hypoplasia of the kidney. Most patients with TS have normal intelligence and only fewer than 10% of them have mild developmental delay. A detailed description of abnormalities characteristic of Turner syndrome is summarized in Table 100.1.

100.1.5 The Genotype–Phenotype Correlation

It has already been established that some symptoms are more characteristic for certain karyotypes in Turner syndrome. In the newborn with a pure monosomy of 45,X one can expect a congenital lymphedema of hands and/or feet. Mosaicism gives the patient a chance for a spontaneous puberty and fertility, especially in women with a mosaicism for 45,X/47,XXX (Sybert 2002). The isochromosome i(Xq) increases the risk for autoimmune diseases: hypothyroidism or bowel inflammatory disease (Elsheikh et al. 2002). A ring X chromosome (rX) is considered as associated with a mental retardation. Nevertheless the prediction of symptoms according to the classic karyotype in many cases is not completely reliable, because of a variable contribution of abnormal cell lines in different tissues and organs.

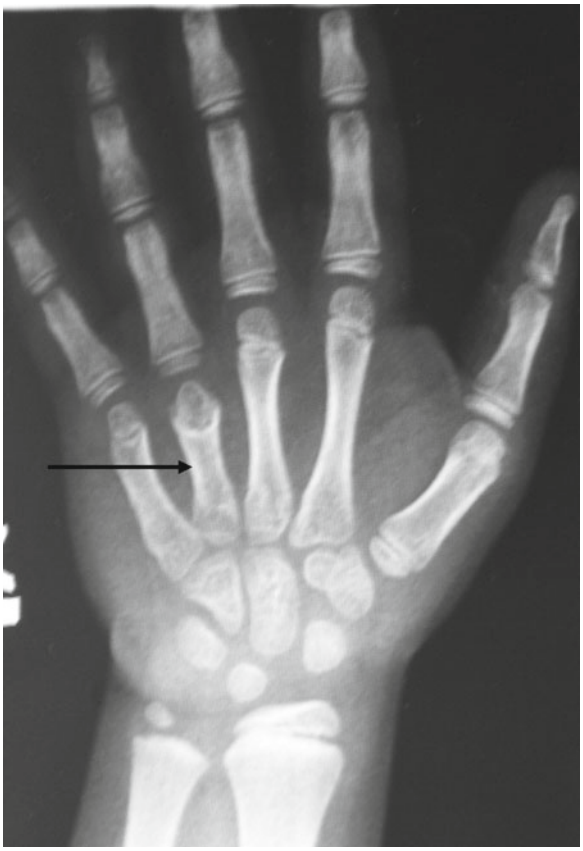

Fig. 100.1 Shortened fourth metacarpal bone in the patient with Turner syndrome

100.1.6 When Is Turner Syndrome Diagnosed?

Early diagnosis is made in 20–30% of patients soon after the birth, usually because of characteristic features: lymphedema of hands and/ or feet, or a webbed neck. The next 30% receive the diagnosis in midchildhood, due to the diagnostics of a short stature. The other 20–30% of patients are diagnosed as teenagers because of absent or delayed puberty. The remaining are diagnosed as adults -because of infertility, recurrent pregnancy loss, or secondary amenorrhea (Table 100.2).

100.1.7 Anthropometric Indices Useful in the Diagnosis of Turner Syndrome

Anthropometric indices may be very useful in the diagnosis of Turner syndrome, especially at midchildhood and adolescence. In any female with unexplained growth deficiency or delayed puberty the Turner syndrome should first be ruled out. The presence of other anthropometric features typical of TS, like obesity, shield-like chest, stocky build, relatively short legs, make the diagnosis very likely. Children with Turner syndrome have a characteristic pattern of body

Table 100.1 Abnormalities in patients with Turner syndrome

Growth and body building	Growth deficiency
	Short, webbed neck
	Broad chest
	Short legs
	Obesity
Skeletal manifestation	Cubitus valgus
	Shortened fourth metacarpals
	Scoliosis
Craniofacial manifestation	Flattened cranial base angle
	Marked reduction of posterior cranial base length
	Retrognathia
	Narrow maxilla
	High, arched palate
	Micrognathic mandible
	Crowded teeth
Sexual development disorders	Sexual infantilism
	Gonadal dysgenesis
	Hypoplastic nipples
Lymphatic system abnormalities	Lymphedema of hands and feet
Skin manifestation	Low posterior hairline
	Hyperconvex, uplifted nails
	Pigmented nevi
Ear abnormalities	Low set, dysplastic, rotated ears
	Otitis media
	Conductive/Sensorineural hearing impairment
Renal and urinary system abnormalities	Horseshoe kidney
	Malrotation of a kidney
	Duplication of collecting system
Cardiovascular anomalies	Left heart hypoplasia
	Coarctation of the aorta
	Bicuspid aortic valve
	Hypertension
Metabolic disorders	Glucose intolerance
Autoimmune and inflammatory disease	Hypothyroidism
	Celiac disease
	Iuvenile arthritis
	Inflammatory bowel disease
Mental development	Deficits in visuospatial organisation
	Nonverbal memory deficits
	Attention deficit hyperactivity disorder (ADHD)

proportions. The evaluation of the morphogram of the body is very helpful in the detection of typical changes. The standardization of measurement values should be calculated according to the data of a normal female population of the same ethnic origin. The evaluation of each parameter for chronological age and simultaneously for height age is very useful. The altered body proportions in TS girls seem to be more evident on morphograms calculated for height age (Table 100.3). (Compare the exemplary morphograms of the same, untreated girl, at the age of 8 years, standardized for chronological age (Fig. 100.2) and height age (Fig. 100.3)).

Reminder: a height age is the age for which the patient's height is on the 50th percentile.

Table 100.2 A typical causes of diagnosis of Turner syndrome at a different age

The age of diagnosis	Suspicious symptoms/the reason for karyotyping
Prenatal period	Fetus edema in USG
	Abnormal maternal triple screening/advanced maternal age
Newborn	Puffy hand and feet
	Webbed neck /redundant nuchal skin
	Hypoplastic left heart
	Coarctation of the aorta
Midchildhood	Short stature
Adolescence	Lack or delayed puberty
Adulthood	Secondary amenorrhea
	Infertility
	Recurrent miscarriages

Table 100.3 The comparison of anthropometric data standardized for chronological and height age in a patient with Turner syndrome. Additional data for Figs. 100.2 and 100.3

Antropometric parameters	SDS value normalized for chronological age	SDS value normalized for height age
Weight [SDS]	0.6	2.3
Height [SDS]	–1.9	0.0
Chest circumference [SDS]	1.5	3.0
Head circumference [SDS]	–0.4	0.1
Trunk length [SDS]	0.3	1.5
Leg length [SDS]	–3.0	–1.2
Biacromial diameter [SDS]	–1.1	0.3
Chest width [SDS]	1.0	2.3
Chest depth [SDS]	1.4	2.5
Biiliacal diameter [SDS]	–0.4	0.8
Upper arm circumference [SDS]	1.3	2.6
Arm length [SDS]	–2.4	1.1
Body mass index [SDS]	1.5	2.0

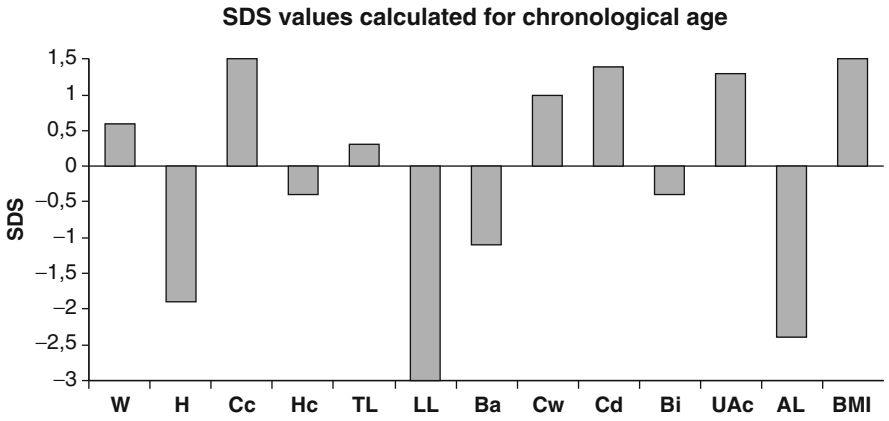

Fig. 100.2 An exemplary morphogram of the girl with Turner syndrome calculated for a chronological age. Weight (*W*); Height (*H*); Chest circumference (*Cc*); Head circumference (*Hc*); Trunk length (*TL*); Leg length (*LL*); Biacromial diameter (*Ba*); Chest width (*Cw*); Chest depth (*Cd*); Biiliacal diameter (*Bi*); Upper arm circumference (*UAc*); Arm length (*AL*); Body mass index (*BMI*); standard deviation score (*SDS*) normalized for healthy population

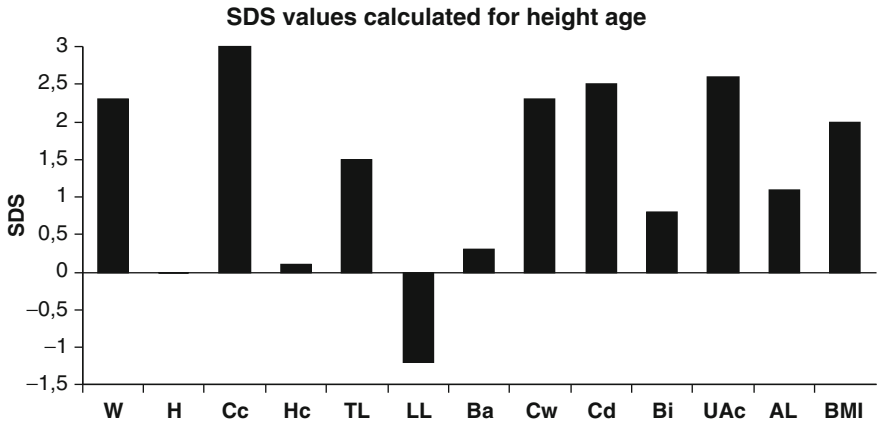

Fig. 100.3 An exemplary morphogram of the girl with Turner syndrome calculated for a height age. Weight (*W*); Height (*H*); Chest circumference (*Cc*); Head circumference (*Hc*); Trunk length (*TL*); Leg length (*LL*); Biacromial diameter (*Ba*); Chest width (*Cw*); Chest depth (*Cd*); Biiliacal diameter (*Bi*); Upper arm circumference (*UAc*); Arm length (*AL*); Body mass index (*BMI*); standard deviation score (*SDS*) normalized for healthy population

100.2 Natural Physical Development in Turner Syndrome

100.2.1 Height

Anthropometric data indicate that the final short stature in Turner syndrome is the result of the mild intrauterine retardation, slow growth during infancy and childhood, and lack of a pubertal spurt.

In a newborn with Turner syndrome the average birth size is lower by about 1 SDS (standard deviation score) (Ranke et al. 2002). During childhood the growth velocity is below 10th percentile for age. Approximately half of the patients with TS will have fallen below the fifth percentile even as soon as 2 years of age. The difference between TS children and healthy girls becomes greater at the age of puberty. Body height is the shortest measure in Turner girls, and the adult height deficiency in untreated patients is approximately 20 cm below the average for a normal female population, what corresponds with approximately –3.75 SDS. The final height values in TS women display distinct ethnic and geographic differences. For comparison, data from a multinational survey of adult height in Turner syndrome showed an average value of 144.3 ± 6.7 cm (Ranke et al. 1988), whereas in Scandinavian origin patients with TS the final height was 147.2 ± 7.1 cm (Karlberg Albertsson-Wikland 1995; Rongen Westerlaken et al. 1997), and in patients from Hungary was 140.8 ± 6.93 cm (Bösze et al. 1980). The differences according to karyotypes were not so strongly evident, but some studies suggest that patients with 46,X,delX(q) were significantly taller (Cohen et al. 1995).

100.2.2 Body Proportions

The body proportions in Turner girls, as well as in normal children, change with the age. This process is dependent on many factors. Among them, the most important seem to be hormonal factors: growth hormone, thyroid hormones, sex steroids secretion and function. The secretion of growth hormone in Turner syndrome is normal, but the production of gonadal steroids is impossible in the majority of patients. Furthermore, the sensitivity to growth hormone and sex steroids could be variable in Turner children. These factors lead to alterations of body constitution in TS patients.

Table 100.4 Key points of Anthropometric indices suggesting Turner syndrome

Height below 5th percentile for normal female population
Growth velocity below 10th percentile for the chronological age
Head circumference appropriate for a chronological age
Leg length [SDS] decreased more, than height [SDS]
A striking difference between height [SDS] and head circumference [SDS]

Data in several studies about the body proportions in Turner syndrome are not consistent. The first report considering adult patients showed that TS women without any growth- promoting treatment had reduced height with short extremities (Park 1977), but Varrela and coworkers did not find any significant alteration in body proportions (Varrela and Vinkka 1984). The next studies revealed that females with TS have growth deficiency along the longitudinal axis, and horizontal measurements are comparable to healthy female population. The body proportions were variable, but in shorter women the sitting height was taller. The same correlation was found in menstruating women (Gravholt and Naeraa 1997).

In conclusion: in adult women with Turner syndrome the height, sitting height, and arm-span may be reduced by 3–4 SDS. Size of hands and feet is usually reduced to a lesser extent. Biacromial and biiliacal diameter are comparable to the values in healthy women. Head circumference is equal to that in a reference population (Table 100.4).

According to anthropometric data, the significant difference between height SDS and head circumference SDS was proposed as an auxiliary marker diagnostic for Turner syndrome. Its usefulness was confirmed in children (Eggert et al. 1990) and also in adult patients with TS (Gravholt and Naeraa 1997). But it was not clearly established what amount of difference should be considered as significant.

The changes in body proportions in a TS patient before a final height achievement were investigated by the Dutch Growth Hormone Working Group (Rongen Westerlaken et al. 1993). According to their data, in early midchildhood the mean sitting height in TS children may be normal, but thereafter the trunk growth becomes slower, and at the age of 16 years is deviated from the normal mean value by –3.4 SDS. In the adulthood it achieves approximately –2.4 SDS. Similar changes were observed in leg length. It also decreased for the period between 3 and 12 years of life and from approximately –2.7 SDS at the age of 3 years down to –3.6 SDS and next increased to –2.5 SDS in adulthood. The ratio of the sitting height to the leg length was 3.2 SD above the normal mean value at the age of 3 years. Thereafter the ratio systematically rises to normal percentiles and reaches at the age of 15–18 years 0.6 SD, and again increases to 1.7 in adult patients with Turner syndrome. Similar results were reported by Gravholt and coworkers. Their study showed that the sitting height was approximately 10 cm below the averages, which corresponds to –3.69 SDS. The size of hands and feet was slightly smaller (to approximately –1.5 SDS). Arm-span was reduced almost exactly as much as height, to –2.9 SDS (Gravholt Gravholt and Naeraa 1997).

100.2.3 Body Composition in Turner Syndrome

Patients with Turner syndrome have a predisposition to obesity. Glucose metabolism is often altered in TS, and type 2 diabetes is seen frequently in adults, but insulin resistance has been reported as early as childhood (Caprio et al. 1991). Body mass index (BMI) and fat mass (FM) have been found to be higher in adult TS patients in comparison to age matched controls, total lean body mass (LBM) is inappropriately low. The body composition is altered in TS patients and displays characteristic

Table 100.5 Key points of body composition in Turner syndrome

BMI tends to be increased in Turner syndrome
Visceral FM is increased
Trunk and appendicular LBM is decreased
TS patients have higher content of body water (%) and lower resistance (Ω)
In adults visceral fat and hepatic adipose tissue is increased
FM correlates positively with HOMA-index, insulin and leptin
In adult TS women BMI below 25 kg/m^2 and a waist/hip ratio less, than 0.80 are recommended

regional differences: increased visceral fat mass (FM) and decreased trunk and appendicular lean body mass (LBM) (Ostberg et al. 2005; Gravholt et al. 2006) (Table 100.5).

In young TS girls BMI is close to normal, but after the 9th year of age, mean BMI SDS progressively increase in relation to unaffected age matched girls. After 12 years it remains greater than in normal population, but the next BMI gain becomes slower (Blackett et al. 2000; Gravholt et al. 2005).

Girls with Turner syndrome have a reduced amount of subcutaneous fat on limbs, and a normal amount of subcutaneous fat on the trunk (Hanaki et al. 1993). TS patients have higher content of body water (%) and lower resistance (Ω), measured by bioelectrical impedance (Gravholt and Naeraa 1997). No statistically significant difference in the body composition dependent on karyotypes was found.

100.3 Anthropometric Indices in Evaluation of the Therapy of Turner Syndrome

100.3.1 Anthropometric Markers of the Effectiveness of Growth Hormone Treatment

In the clinical picture of Turner syndrome the growth hormone (GH) deficiency does not exist, but there is a kind of tissue hyposensitivity to GH. Since 1980 it is well established that growth hormone treatment improves the final height in Turner patients and it became a standard of care for girls with TS in many countries worldwide. Initiation of GH therapy is recommended in girls with Turner syndrome, when the height drops below the fifth percentile of the normal female growth charts. If necessary the GH therapy should be started as early as 2 years of age. Below this age the effectiveness of GH treatment is limited. The effect of GH therapy is dependent on the dose and age at the start of therapy. Higher doses and earlier start of therapy are correlated with a better effect and a higher final height (Ranke et al. 2000). A final height after GH therapy in most patients is now 150 cm and more (The Canadian Growth Hormone Advisory Committee 2005).

Anthropometric examinations should be performed at intervals of 3–6 months during GH therapy. It is a good tool for the evaluation of the effectiveness of GH treatment and individualization of dosing. On the other hand the safety of GH therapy is controlled by insulin-like growth factor-1 (IGF-1) levels, which should be within the normal range. The prolonged exposure to elevated IGF-1 levels theoretically may cause potential long-term adverse effects. Growth hormone therapy should be continued until a satisfactory height has been achieved, or until the bone age is above 14 years and the patient's height has increased less than 2 cm for last 12 months (Bondy 2007).

The highly variable effectiveness of GH treatment in TS is not fully understood and the individualization of therapy allows to optimize the balance of costs and potential risk of therapy.

Table 100.6 Key points of Anthropometric predictors of a good effect of a GH treatment

The distance between the patient's present height [SDS] and mean parental height SDS
Body weight at the start of GH therapy
Height velocity during the first year of therapy
Leg length SDS increase similar or more than height SDS during GH therapy
Proportion upper to lower part of the body (the smaller the better)

Prediction models rise by analyzing data from the Kabi International Growth Study (KIGS; Pharmacia & Upjohn, Inc, International Growth Database) (Ranke et al. 2000). It revealed, that the strongest predictors, which positively correlate with the height velocity in the first year of GH treatment are: the weekly dose of GH and injections frequency, the difference between the patient's present height [SDS] and mean parental height in SDS, body weight, and additional oxandrolone therapy. Chronological age was negatively correlated with the height velocity (Ranke et al. 2000).

According to the authors own experience, the best predicting anthropometric marker of GH effectiveness is the reduction of leg length deficiency equal or higher, than the reduction of height deficiency during GH treatment (Kucharska et al. 2007). This observation is in agreement with the results of other authors. In the study of Gravholt and coworkers, shorter patients had relatively taller sitting height (Gravholt and Naeraa 1997). Similar results were reported by Rongen Westerlaken (Rongen Westerlaken et al. 1993). Their study showed that in Turner syndrome the ratio of sitting height and leg length was negatively correlated with statural height. In taller girls the ratio was lower, though one may also conclude that the proportion upper to lower part of the body is a valuable anthropometric marker of GH sensitivity.

100.3.2 Anthropometric Markers of Insulin Resistance

Total and regional FM correlates positively with homeostatic model assessment- index (HOMA-index), and levels of insulin and leptin. Other measures of body composition did not correlate with biochemical markers of insulin sensitivity.

100.3.3 Alterations of the Body Composition in Turner Syndrome During Hormonal Therapy

Among many factors that influence the low LBM and increased FM in Turner syndrome the most important are hormonal changes (GH/IGF-1 axis, insulin, estrogens and androgens). In patients with Turner syndrome the alterations of body composition with regional differences are due to resistance to the anabolic effect of GH and IGF-1, as well as insulin, testosterone and estradiol sensitivity. The fact that the effect of growth hormone is augmented by sex steroids is well known for years. Measurement of fat mass and lean body mass is much better in the precise evaluation of the alterations during hormonal treatment than BMI. BMI changes were found to be unaffected by GH treatment (Blackett et al. 2000). However the increase of LBM and decrease of FM are valuable markers of the metabolic effect of GH (Table 100.6).

Oxandrolone and estrogens also influence the body composition. In patients treated with oxandrolone, sex hormone binding globulin (SHBG) increases and correlates negatively with measures of adiposity (Gravholt et al. 2006).

Gonadal failure is one of the most common clinical features of Turner syndrome. The estrogen therapy should be introduced at the normal age of puberty, or as closely as possible. Recent data suggests that the replacement therapy started at the age of 12 does not disturb the positive effect of GH treatment on a final height in girls with Turner syndrome (van Pareren et al. 2003, Bondy 2007; Gravholt et al. 2005) and decreases fat accumulation in the liver (Ostberg et al. 2005).

100.4 Practical Methods and Techniques

100.4.1 Anthropometric Measures in Turner Syndrome

100.4.1.1 The Conditions of Appropriate Anthropometric Examination in Patients with Turner Syndrome

Patients should be measured in the morning, in underwear, and obviously barefoot by the Harpenden stadiometer. Three height measurements should be obtained, and the average value should be calculated. Sitting height measurement should be also obtained and leg length should be calculated by subtracting sitting height from standing height (Table 100.7).

Biacromial and biiliac diameters, head, hip, waist and upper arm circumferences characterize the body constitution in patients well. Skin folds measurements are useful in the evaluation of the body composition.

100.4.1.2 The Measurements Evaluation

Weight, height, BMI and other parameters, if possible, should be calculated in standard deviation score (SDS) on the basis of the local references of contemporary normal female population.

The growth charts specific for Turner syndrome of contemporary population are not available.

The best known growth curve for TS was prepared by Lyon approximately 30 years ago (Lyon 1985). The use of this historical data may not be valid for contemporary populations, because of growth acceleration. Nevertheless this growth chart can be useful in making a decision about the necessity of growth hormone testing in Turner girls, whose growth is not consistent with the expected for TS pattern.

Table 100.7 Key points of the anthropometric examination in Turner syndrome

Anthropometric parameters of TS individual should be evaluated according to the data of contemporary normal female population of the same ethnic origin
Morphograms are a valuable tool for the evaluation of a body constitution
Parameters of body proportions should be calculated for chronological age and height age
A reminder:
Height age = the age, for which the patient's present height is on the 50th percentile

A good practice is the preparation of morphograms in examined patients (see Figs. 100.2 and 100.3). The SDS values should be calculated according the references of normal female population of the same ethnic origin and prepared for chronological age and height age. It allows comparison between all parameters and characteristic alterations are easily detectable.

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Chapter 101
Polymorphisms in the Serotonin (5-Hydroxytryptamine (5-HT)) Type 2A Receptor (5-HTR2A) Gene, Other Related Genes and Anthropometry

Dolores Corella and Mercedes Sotos-Prieto

Abstract Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter, which helps to regulate many physiological processes such as sleep, appetite, eating disorders, thermoregulation, hormone secretion, mood, anxiety, etc. The serotonin and related genes, such as the 5-HT2A receptor gene (HTR2A), the 5-HT transporter gene (SLC6A4), the 5-HT2C receptor gene (HTR2C), or the 5-HT1A receptor (HTR1A) gene, are re-emerging as powerful candidates for studying the association between food intake and anthropometry. Variations in all of these genes need to be studied to better understand the effects of serotonin and its receptors on anthropometry. The most widely studied polymorphism is the −1438G>A (rs6311) in the regulatory region of the HTR2A. Despite the controversy in functional studies, it is suggested that the A allele is associated with decreased HTR2A expression. In epidemiologic studies, it has been reported that the A allele is associated with lower energy and macronutrient intake and, in association studies, with lower body mass index in obese subjects. Furthermore, a 44-bp insertion/deletion promoter region polymorphism (alleles L and S) in the serotonin transporter gene (SLC6A4) has been associated with greater body weight and obesity in those SS subjects. More controversy arises, however, regarding eating disorders. The −759C/T SNP in the HTR2C gene has been associated with weight changes after antipsychotic treatments. Patients with the −759T variant allele showed significantly less weight gain than those without the allele. These results, however, do not allow any definite conclusion to be drawn about the impact of genetic variation in the 5-HT-related genes on anthropometric variables and further studies are needed to gather more evidence on these associations.

Abbreviations

5-HT	5-hydroxytryptamine
5-HTTP	5-hydroxytryptophan
SLC6A4	Carrier family 6 neurotransmitter transporter, serotonin
HTTLPR	5-HTT gene–linked polymorphic region
VNTR	Variable number of tandem repeats
FTO	Fat mass and obesity associated
BMI	Body mass index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_101,

101.1 Introduction

Both increased energy intake and reduced physical activity have been major drivers of the current obesity epidemic. It has been estimated that, to return to the average weights of past decades in industrialized countries, the increased food intake would have to be reversed to about 500 cal a day for adults, or alternatively, similar results could be achieved by increasing physical activity by about 100 min (Swinburn et al. 2009). Although there are several ways to promote and increase physical activity (see the corresponding book chapters) with winning results, successful changes in food intake are more difficult to achieve. One of the reasons for this is the still incomplete knowledge that we have on the factors that determine food intake. Thus, one of the main lines of current research is the study of both genetic and environmental factors that influence food intake. This field is extremely complex because there are many processes involved, some of which are almost completely unknown, as is the case of the recently discovered fat mass and obesity-associated (FTO) gene that has now become the first gene to be regarded as a thoroughly replicated risk factor for obesity in dozens of epidemiological studies on different populations. Despite the fact that it has been consistently found in population studies that common variants in the first intron of the FTO gene define a risk allele predisposed to obesity, with homozygous subjects for this allele weighing approximately 3 kg more than homozygotes for the low-risk allele, the functional role of FTO in energy homeostasis remains elusive. Some studies have reported that the risk allele that confers a predisposition to obesity may play a role in the control of food intake and food choice, suggesting a link to a hyperphagic phenotype or a preference for energy-rich foods. However, the mechanisms behind this observation remain largely unknown.

Consistent results on the association between polymorphisms in the FTO gene and obesity-related measures in dozens of populations around the world have rekindled interest in investigating genes related to food intake. Among them, serotonin (5-hydroxytryptamine (5-HT))–related genes are re-emerging as powerful candidates. 5-HT is a monoamine neurotransmitter found in both the central and peripheral nervous systems, which contributes to the regulation of many physiological processes such as sleep, appetite, eating disorders, thermoregulation, pain perception, hormone secretion, mood, anxiety, and sexual behaviour. It is synthesized in the serotonergic neurons of the central nervous system and the enterochromaffin cells of the gastrointestinal tract (80–90% of the human body's total 5-HT), where it is used to regulate intestinal movements. Rapport et al discovered serotonin in 1948 while searching for vasoconstrictors causing hypertension and aptly named it for its presence in serum (sero) and its vasoactive properties (tonin). 5-HT is released into the synaptic junction and exerts its effect on specific receptors on the postsynaptic membranes. More details about biochemistry and physiology of 5-HT can be found in recent reviews (Jonnakuty and Grangnoli 2008; Garfield and Heisler 2009).

There are multiple genes related to the actions of 5-HT. The most important are the genes that codify for the different types of 5-HT receptors as well as the gene of the serotonin transporter. In this chapter, we will review the general functions of 5-HT related directly or indirectly with anthropometric measures, focusing on studies analyzing variations in the most important 5-HT-related genes. Taking into account the large number of variations reported, we will focus on the 5-HT receptor 2A (*HTR2A*) gene although some relevant variants in other genes will also be analyzed. To better understand the genetic concepts and association studies we also include a section on practical methods and techniques.

101.2 Biochemistry and Physiology of 5-HT and Its Receptors

Over 95% of 5-HT synthesis occurs in the enterochromaffin cells of the intestine and only a small fraction of total body serotonin is produced in the brain-stem neurons of the raphe nuclei. The precursor of 5-HT is the essential amino acid tryptophan (taken with the diet) that is converted into serotonin via a series of reactions (Fig. 101.1). First, the tryptophan is converted by tryptophan hydroxylase, which transfers the hydroxyl group to the benzyl ring of tryptophan, to 5-HTP (5-hydroxytryptophan). This reaction constitutes the rate-limiting step in serotonin synthesis. For this reaction, the cofactors oxygen and tetrahydropteridine are needed. The 5-HTP is converted into 5-HT by decarboxylation via the enzyme L-amino acid decarboxylase, together with the cofactors vitamin B6, B3, and magnesium. Serotonin synthesis in the central nervous system is influenced by the amount of plasma free tryptophan, which crosses the blood–brain barrier and competes with other neutral amino acids (aromatic amino acids) that have the same carrier. Serotonin degradation occurs in the intersynaptic space through the action of monoamino oxidase enzyme to form 5-hydroxyindole acetic acid (5-HIAA). Serotonin in the central nervous system is stored in secretory granules and released into a synapse. The removal of the neurotransmitter from the synaptic space occurs by re-uptake. The serotonin transporter (5-HTT, SERT, or SLC6A4) diminishes the function of 5-HT at its extracellular cognate receptor by removing 5-HT from outside the cell and bringing it back into a cell for metabolism via monoamino oxidase or vesicular repackaging.

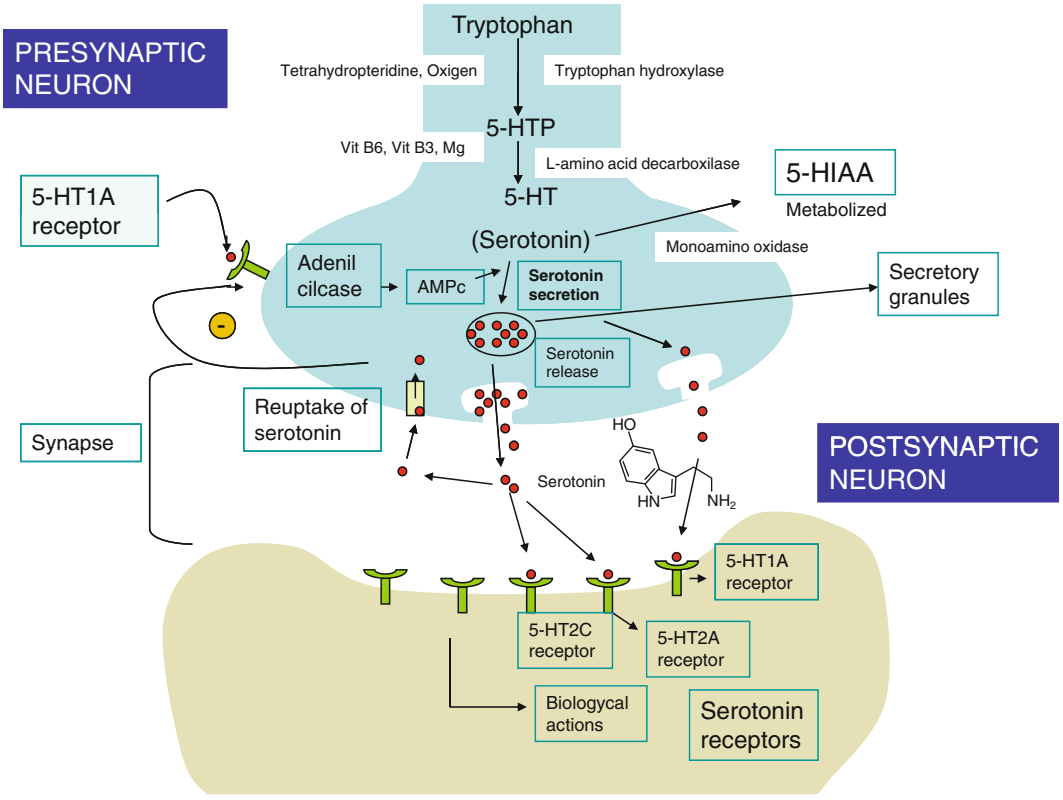

Fig. 101.1 Biosynthesis and metabolism of serotonin. Description of the serotonergic synapse, release and uptake of the serotonin. *5HTP:* 5-hydroxytryptophan, *5-HIAA:* 5-hydroxyindole acetic acid

Table 101.1 Families of the 5-HT receptors and main characteristics

Family	Main characteristics of the receptors
5-HT1	The 5-HT1 subfamily consists of 5 G-protein-coupled receptors (GPCRs), which are coupled to Gi/Go and mediate inhibitory neurotransmission. They include: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F. The 5-HT1A receptors are located at the presynaptic serotonergic neurons and postsynaptic nonserotonergic neurons and are the most widespread of all the 5-HT receptors. Studies carried out in mice showed a relation with increased anxiety and stress responses. Furthermore, the 5-HT1A receptors are associated with the opening of K^+ channels through a G-protein in the central nervous system and it is associated with the stimulation and inhibition of adenylcyclase.
5-HT2	The 5-HT2 subfamily consists of 3 GPCRs, which are coupled to Gq/G11 and mediate excitatory neurotransmission, including 5-HT2A, 5-HT2B, and 5-HT2C. The 5-HT2A is the main excitatory receptor subtype among the GPCRs. It was widely studied because it was the target of classic hallucinogens. Currently, the study of variations in the gene that codifies for this receptor has allowed its function to be linked to numerous disorders related with anthropometric variables. These associations will be detailed in the corresponding section. The 5-HT2B receptor has an important role in the regulation of cardiac structure and functions. The 5-HT2C receptor is rapidly regulated by 5-HT and it is important in the expression of anxiety, depression, and compulsive behaviours. Variations in its gene have also been widely studied and related to anthropometric variables.
5-HT3	This receptor is a member of the superfamily of ligand-gated ion channels. It consists of five subunits arranged around a central ion conducting pore. Its antagonists are used in the treatment of nausea and diarrhoea.
5-HT4	These receptors are GPCRs that stimulate cAMP production. They are located in the gastrointestinal tract, urinary bladder, heart, adrenal gland as well as the central nervous system and are involved in memory, cognition, feeding, respiratory control, and gastrointestinal motility.
5-HT5,5-HT6, 5-HT7	These receptors have been cloned in the last decade and more research is needed. 5-HT6 receptor could play a role in appetite and cognition as well as 5-HT5 in anxiety and motor control

At least seven different major families of receptors in the serotonin that mediate some of the effects of the serotonin (5-HT1-5-HT7) have been described. They are located both in the nervous system and peripheral organs. Furthermore, there are different subtypes in many of the major families of receptors. These have been divided into different families depending on their characteristics, such as, amino acid sequence, gene organization, and the system of signal transduction coupled to them (Hoyer et al. 1994). The main characteristics of each one are summarized in Table 101.1:

101.3 Serotonin Functions

5-HT has a wide range of physiological roles in the human body, involving various tissues (Jonnakuty and Grangnoli 2008; Garfield and Heisler 2009). The most directly related to anthropometry are the following:

- *Brain*: Serotonin is localized in the raphe nuclei of the brain stem where it is synthesized. As a central neurotransmitter, serotonin carries out an important role in the regulation of mood, sleep, body temperature, appetite and it is involved in numerous disturbances (anxiety, depression, headache, bipolar disturbance, etc). In terms of psychiatric disorders, there is compelling evidence on the implication of 5-HT in major depression, borderline depression (dysthymia) anxiety, obsessive–compulsive disorders, agoraphobia, etc. (Lowry et al. 2008). In general, too little brain 5-HT is linked to depression, anxiety, bulimia, bingeing, alcoholism, uncontrolled aggression, etc.

However, too much 5-HT may also be detrimental. 5-HT also controls appetite. The smell, sight, or expectation of food stimulates 5-HT release in the hypothalamus. As eating begins, 5-HT continues to increase until it registers in the hypothalamus as the experience of satiety. In comparison with other compounds that regulate food intake, 5-HT has been reported as more influential than other compounds. Generally, it has been demonstrated in animal models that the increase in 5-HT activity or availability will tend to reduce food intake, whereas decreasing 5-HT activity will tend to increase food intake. These changes are closely associated with changes in the concentrations of dopamine, another hypothalamic monoamine closely involved in the regulation of food intake. The pivotal role of central serotonin appetite is also strengthened by the evidence that drugs licensed to interfere with food intake in obese patients involve the serotonergic system.

- *Gastrointestinal tract*: Over 90–95% of peripheral serotonin is located in the enterochomaffin cells. By acting directly and via modulation of the enteric nervous system, 5-HT has numerous effects on the gastrointestinal tract. It is released in response to acetylcholine and increases internal motility. It also stimulates fluid secretion and provokes nausea and vomit by means of stimulating the sensory nerves in the stomach. Under normal conditions, 5-HT regulates the regular waves of gastrointestinal contractions that move food through the gastrointestinal tract. Underactivity or overactivity of the gut 5-HT system can produce symptoms of irritable bowel syndrome. The main gut disturbances in which 5-HT is involved are acute chemotherapy-induced nausea and vomiting. 5-HT also plays a role in the liver. In a diseased liver, 5-HT is involved in the progression of hepatic fibrosis and the pathogenesis of steatohepatitis.
- *Cardiovascular system*: Serotonin plays a role in vasoconstriction, vasodilatation, and vascular tone. Activation of the 5-HT1A receptor mediates central sympathoinhibition and bradycardia. In contrast, the 5-HT2A receptor mediates sympathoexcitation, which leads to a rise in blood pressure and tachycardia. In addition, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT4, and 5-HT7 are present in vascular smooth muscle cells and modulate contraction and relaxation of blood vessels. 5-HT4 receptor is also present in cardiac myocytes, through which serotonin mediates chronotropic and inotropic effects. Cardiovascular dysfunction is observed when serotonin signalling is altered or when a variation in serotonin concentration occurs. Recent studies have provided evidence that, in the absence of peripheral serotonin synthesis, blood serotonin (which is almost exclusively stored in platelets) is markedly reduced, and that this drop leads to heart failure.
- *Glucose metabolism*: There are some controversial results on how 5-HT participates in glucose metabolism. In some studies it has been found that serotonergic agents, used for reducing appetite and body weight, have unexpected effects on peripheral glucose homeostasis regardless of food intake and body weight. Some evidence suggests that 5-HT may increase blood glucose. However, there are other studies that suggest a hypoglycaemic effect, but the mechanisms are not well understood. It has been suggested in rat and human skeletal muscle studies that the 5-HT2A receptor may mediate the effect through which serotonin leads to rapid glucose uptake. A recent study involving polymorphisms in the 5-HT2A and 5-HT2C lends further support to the involvement of serotonin in glucose homeostasis and the risk of type 2 diabetes (Kring et al. 2009).

101.4 Practical Methods and Techniques

Research into 5-HT biochemistry and its functions has been greatly improved by studying the genetic variability in the main related genes. In humans, genetic analysis has evolved from the unmeasured genotype approach, carried out in affected families, to the direct assessment of DNA-sequence variability in unrelated or related individuals. The simplest type of polymorphism, known as

single-nucleotide polymorphism (SNP), results from a single base mutation that substitutes one base for another. Other types of genetic polymorphisms result from the insertion or deletion of a section of DNA, which include microsatellite repeat sequences and gross genetic losses and rearrangement. SNPs are scattered throughout the genome and are found in both coding and noncoding regions. Nucleotide substitutions occurring in protein-coding regions can also be classified as synonymous and non-synonymous according to their effect on the resulting protein. A substitution is synonymous if it causes no amino acid change, while a non-synonymous substitution results in alteration in the encoded amino acid. The latter type can be further classified into missense and nonsense mutations. A missense mutation results in amino acid changes due to the change of codon used, whereas a nonsense mutation results in a termination codon. SNPs occur with a very high frequency, with estimates ranging from about 1 in 1,000 bases to 1 in 100–300 bases. The candidate gene strategy, based on well-established biochemical studies, has facilitated the discovery of scores of single-nucleotide polymorphisms (SNP) that can be easily determined at low cost, providing the opportunity to study a large set of SNP combinations. Although the majority of genetic studies have focused on SNPs, variation in the human genome is not only present in the form of SNPs. Recently, large-scale copy-number variations that involve gains or losses of several kilobases of DNA have been reported to be common in the general population. The association of these genetic variations with the 5-HT functions and anthropometry remains to be investigated. Moreover, genomic technology is moving toward genome-wide association studies (GWAs) where various thousands of SNPs are measured at the same time. This approach has allowed the discovery of new genes related to several diseases, among them the above-mentioned FTO, and will also help to reveal new genes involved in the 5-HT biochemistry and functions.

The SNP or SNPs in the candidate gene are analyzed by different methods, which include the classic restriction fragment length polymorphism (RFLP) technique, or the more high-throughput techniques, based on fluorescent probes. Later, statistical analyses are carried out to assess the association between the measured anthropometric phenotype (height, weight, body mass index, obesity, waist circumference, total body fat, etc.) and the SNP. Codominant, dominant, or recessive models of inheritance are tested to establish the effects. In some studies, associated polymorphisms (in linkage disequilibrium) are analyzed together by haplotype analysis. Statistically significant associations between the SNPs and the anthropometric trait are obtained through these statistical analyses. However, a statistically significant association does not imply a causal association and several complementary methods are required. Replication of the observed associations in other independent populations is a common practice to increase the validity of associations. However, it is also important to distinguish between functional variants (i.e., altering an amino sequence or a transcription factor-binding element, etc) and nonfunctional SNPs. It has been suggested that before inclusion in an epidemiological study, every SNP used should undergo a thorough functional study (mainly in *in vitro* gene expression transcriptomic assays). However, as these *in vitro* data may be difficult to obtain, some researchers have proposed several bioinformatic tools to infer functionality. Recently, several simulation programs have been designed to predict whether a non-synonymous SNP is likely to have a functional effect on the phenotype or not. However, caution about these *in silico* predictions has also been advised. One of the problems with the results obtained from association studies using nonfunctional SNPs (that in some cases act as markers of the unknown functional variant) is their different degree of linkage disequilibrium with the true functional SNP among different populations. Thus, a nonfunctional variant may have a different impact on association studies depending on the linkage disequilibrium with the functional polymorphism, so contributing to the lack of replication.

Although in the recent decades, the vast majority of studies on the genetic effects of 5-HT-related genes variations have focused only on one or on a very few number of SNPs, currently the simultaneous determination of several of these SNPs has allowed us to discover some so-called gene–gene

interactions. In such situations, the effect of an SNP on an anthropometric phenotype is not independent but is modulated by the other SNP studied. These gene–gene interactions contribute to increasing the explained variability of the genotypic effect.

Nevertheless, when studying anthropometric traits, it should be borne in mind that these traits are very complex and that environmental (nongenetic) factors also play a crucial role. Although for many years diseases have been classified as either genetic or environmental, currently it is widely accepted that even the so-called single-gene disorders develop from the interaction of both genetic and environmental factors. Thus, new studies taking place in the field should incorporate this gene–environment interaction approach. For example, when studying the effect of an SNP on 5-HT effects, it should be of great interest to obtain information about the dietary intake of the individuals, as it is known that low-fat diets cause hormonal swings that can disrupt the balance of 5-HT in the brain. Without enough dietary fat, levels of 5-HT could be low and can result in several alterations. Thus, the combined effects of different amounts of dietary fat intake and SNPs in candidate genes should be studied to obtain more complete information. Further details about how to integrate genes and environment into the study of specific traits can be found in this review (Corella and Ordovas 2005).

Taking into account the vast number of SNPs described in the various 5-HT-related genes, we will focus more closely on the 5-HT2A receptor gene, which has been the gene most frequently linked to anthropometric variables. However, considering the importance of other SNPs in other 5-HT-related genes, we also included a brief review of the effects of these genes in order to obtain a more complete picture.

101.5 Description of the 5-HT2A Receptor Gene

The 5-HT2A receptor gene (*HTR2A*, formerly *HTR2*) was one of the first human 5-HT receptor genes to be cloned. It is located in chromosome 13q14–q21 and contains three exons separated by two introns spanning 20 kilobases (kb) (Chen et al. 1992). It seems to have two alternative promoters, with a silencer element just downstream of the second promoter element. Four transcription initiation sites have been described, with similar initiation sites found in mouse and rat homologues (Chen et al. 1992). The structure of this gene, including the promoter region, introns and exons, as well as the main SNPs is shown in Fig. 101.2. The 5-HT2A gene is involved in important brain functions and is implicated in the cause and treatment of psychiatric disorder. Thus, disruption of *Htr2a* signalling in mice reduced inhibition in conflict anxiety paradigms without affecting fear-conditioned and depression-related behaviour, which could indicate that the 5-HTR2A has a specific role in modulating conflict anxiety. Moreover, *HTR2A* has been a candidate gene for studying eating disorders because of its influence on food intake. Thus, pharmacological studies have demonstrated lower activity of the 5-HTR2A in individuals with bulimia nervosa.

Dozens of polymorphisms in the *HTR2A* gene have been described. Among them the -1438G>A, T25N, I197V, A447V, H452Y, 102T>C, and S421F coding and noncoding SNPs are the most analyzed. Table 101.2 shows SNPs in this gene as well as their minor allele frequency in different populations. The SNPs that have been most often studied in this gene are the non-synonymous or missense polymorphisms because of the high likelihood of a deleterious effect on protein structure and function. However, their impact in the HTR2A function has not been widely studied. Of particular interest are two common SNPs that are in almost complete linkage disequilibrium with each other: a variant close to the promoter region (–1438A>G) and a silent variant in exon 1 (102T>C). The –1438A>G SNP lies upstream of the promoter region of *HTR2A* and might affect expression by

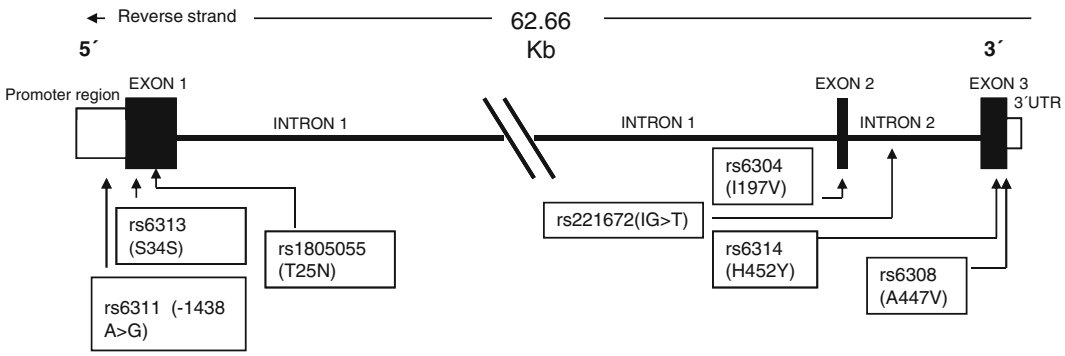

Fig. 101.2 Description of the HT2A receptor gene and location of some SNPs in the gene

Table 101.2 Variations in the *HTR2A* gene and allelic frequencies in different populations

				MAF (%)[a]		
SNP	N.S	Aa.S	Function	Eur	Asian	Afr
rs1805055	C>A	T25N	Missense Exon 1	3.3	0	0
rs6304	A>G	I197V	Missense Exon 2	0	0	5
rs6314	C>T	H452Y	Missense Exon 3	7.5	0	15.8
rs6308	C>T	A447V	Missense Exon 3	0.8	0	0
rs6313	C>T	S34S	Synonymous coding Exon 1	45	47.7	35
rs6311	-A>G	–	Regulatory region Promoter	45	46.5	37.5
rs221672	G>T	–	Intron 2	27.3	31.7	50.8
rs7997012	A>G	–		39.2	30	3.3
rs3742278	A>G	–	Intron 2	15.8	56.7	23.3
rs594242	C>G	–	Intron 2	17.8	2.2	12.5
rs1058576	C>G		Exon 3 Missense	0	0	0

[a]*MAF:* Minor allele frequency, data obtained from Hapmap. *N.S:* nuclear substitution, *Aa.S:* amino acid substitution; *Eur:* Europeans, *Afr:* African

altering promoter function. The functionality of this SNP has been investigated in various studies with conflicting results. Spurlock et al. (1998) carried out a functional analysis using a luciferase assay. Although basal promoter activity in both the A and G variants in the *HTR2A* was found, no significant differences in basal activity between those variants were noted in HeLa cells (epithelial cells derived from adenocarcinoma). Moreover, when promoter activity was induced by cAMP acid protein kinase C–dependent mechanisms, no differences were found. Five years later, Parsons et al. (2004) pointed out that one of the limitations of these assays carried out by Spurlock et al. (1998) to test the functionality of the –1438A>G SNP was that the constructs used did not take into consideration the more downstream promoter and employed only a single reporter gene vector. Taking into account the limitations of the work of Spurlock et al. (1998), Parsons et al. (2004) aimed to test the functionality of the –1438A>G SNP by employing an adequately designed expression system.

They tested the influence of a downstream enhancer in the construct design and employed three human cell lines (SH-SY5Y cells, epithelial cells derived from neuroblastoma; HeLa cells; and IMR-32 cells, fibroblast cells derived from neuroblastoma), using two reporter gene assays. They obtained very interesting results: the differences in expression of the A and G alleles were small in absence of the downstream enhancing element, while in the presence of the downstream enhancer large differences in expression between both variants were detected. Thus, the authors concluded that the *HTR2A* –1438A/G SNP might be a functional SNP in which the presence of the A allele significantly increases promoter activity in comparison with the G allele. However, this difference may be masked by some conditions related to the presence of transcription factors. Three years later, Myers et al. (2007) investigated several SNPs in the *HTR2A* gene promoter including the -1438A/G, -1420C/T, and -783A/G and carried out functional analyses using a luciferase reporter assay, as well as quantitative real-time polymerase chain reaction in a set of human fibroblast cell lines. Given that -783A/G and -1420C/T were in linkage disequilibrium with -1438A/G, they examined the promoter activity of putative haplotypes. In vitro reporter assays, using full promoter construct showed that the -1438A/G polymorphism, when expressed with the major allele at -1420 and -783 loci, did not significantly alter promoter activity. When the minor allele at -783 was expressed with the -1438A/G polymorphism, however, promoter activity was significantly altered. These results suggested possible gene–gene (epistasis) interactions between both variants and indicated the importance of determining the -783A/G SNP in epidemiological studies aimed at assessing the association between the -1438A/G polymorphism and phenotypical traits. Taken together, the G allele of the -1438 A>G polymorphism is supposed to reduce 5-HT2A receptor density or functional availability in the brain. This reduction seems more evident under certain genetic or epigenetic conditions.

101.6 Description of the 5-HT Transporter Gene

The serotonin transporter, also called *SCL6A4* (solute carrier family 6 neurotransmitter transporter, serotonin) (*5-HTT* or *SERT*), a sodium-dependent transporter located in presynaptic neuronal membranes, is a key determinant of brain 5-HT function as it controls 5-HT availability at postsynaptic receptors through high-affinity reuptake of released 5-HT into presynaptic terminals for metabolism via MAOA or vesicle repackaging. It allows neurons, platelets, and other cells to accumulate the chemical neurotransmitter serotonin. Some studies have shown that changes in serotonin transporter metabolism appear to be associated with many different phenomena, including alcoholism, obsessive–compulsive disorder, clinical depression, hypertension, and other diseases. The *SLC6A4* is found on chromosome 17 at location 17q11.1–q12 with 15 exons separated by 14 introns. Several genetics variations in this gene have been described. Table 101.3 shows several SNPs in this gene as well as their allelic frequencies in different populations. One that has been widely studied is the 44 bp insertion/deletion mutation in a region of the *SLC6A4* promoter (known as the 5-HTT gene–linked polymorphic region or 5-HTTLPR). Researchers commonly report it as having two functional alleles, a short (S) and a long (L) one, that correspond to the presence of 14- or 16-repeat units of a 20–23 bp incomplete repeats, but it can be subdivided further. Associated with this region are two SNPs, rs25531 and rs25532. Some *in vitro* studies have found that the long allele (LL) results in higher serotonin transporter mRNA transcription and increased 5-HT uptake in the brain compared to the SS or SL. Other SNPs that have been described in this gene are the STin2 (a variable number of tandem repeats (VNTR)) in the functional intron 2, which involves two major alleles (termed STin2.10 and STin2.12) that correspond to 10- or 12-repeat units of the 17bp VNTR, the G56A on the second exon and the I425V on the tenth exon.

Table 101.3 Variations in other serotonin-related genes and allelic frequencies in different populations

				MAF (%)[a]		
SNP	N.S	Aa.S	Function	Eur	Asian	Afr
Serotonin transporter						
rs25531	A>G		5´near gene	–	–	–
rs25532	C>T		5´near gene	20.5	0	3.6
rs56316081	G>A	V108I	Missense Exon 3	0	0	2.1
5HTTLPR	S>L		5´regulatory Functional	–	–	–
rs57098334 (STin2)	STin2.10>STin2.12'		Inton 2	–	–	–
rs28914832	A>C	I425L	Missense Exon 10	–	–	–
5-HT2C receptor gene						
rs3813929	-759C>T		5´near gene	17.4	14.4	9.3
rs6318	C>G	C23S	Missense Exon 4	15.8	3.3	46.6
rs3813928	-997A>G		Promotor region	22.5	14.4	9.1
rs498207	C>T		Promoter region	40	17.8	35.8
5-HT1A receptor gene						
rs6294	G>A	Y95V	Synonymous Exon 1	0	6.5	21.1
rs6295	C>G		5´near gene	–	–	–
rs1799921	A>G	I28V	Missense Exon1	–	–	–
rs1800044	G>T	R220L	Missense Exon 1	–	–	–
rs1799920	A>G	G22S	Missense Exon 1	–	–	–

[a]*MAF:* Minor allele frequency, data obtained from Hapmap. *N.S:* nuclear substitution, *Aa.S:* amino acid substitution; *Eur:* Europeans, *Afr:* African.
–: No data in hapmap

101.7 Description of the 5-HT2C Receptor Gene

The 5-HT2C receptor gene (*HT2RC*, formerly *HTR1C*) is located in Xq24. Its location makes haplotypic analysis difficult because of genetic heterogeneity between males and females. It was previously thought that it belonged to the '5-HT1-like' family; however, it exhibits considerable sequence homology with the 5-HT2A binding site and is coupled to the same second messenger system. It has six exons and five introns and spans approximately 1.4 kb. The *HT2RC* is a key contributor in controlling central dopamine functions and may play an important role in the aetiology of mental disorders. Yuan et al. (2000) screened the upstream region of the *HT2RC* gene and identified 3 SNPs (G>A at -995, C>T at -759, and C>T at -697) and a (GT)n dinucleotide repeat polymorphism at -1,027. They also carried out a luciferase reporter assay to test functionality and found significant differences between haplotypes. The haplotypes containing the minor alleles could be associated with higher transcription levels of the gene. Another widely studied SNP (rs6318) involves an amino acid change Cys23Ser. Table 101.3 summarizes some SNPs in the *HT2RC* indicating the minor allele frequency in different populations. Evidence shows that the antagonism of 5-HT2C receptor can result in higher food consumption while the 5-HT2C agonist could lead to

anorexic behaviour. The most relevant SNP regarding anthropometric studies is the -759C/T (rs3813929), which is associated with increased transcriptional levels of the *HT2RC* and may confer resistance to obesity and Type II diabetes.

101.7.1 Description of the 5-HT1A Receptor Gene

The 5-HT1A receptor is codified by the *HTR1A* gene. It is located at 5q11.2-q13. It is intronless and only has one exon. The HTR1A receptor plays a key role in regulating the activity of the serotonin system and mediates serotonin actions on mood and emotion. Presynaptic 5-HTR1A receptors are especially important as key effectors of a negative autoregulatory loop that inhibits the activity of serotonergic neurons. Studies carried out on receptor-deficient animal models showed behaviours related to increased anxiety and stress response. There are several human polymorphisms in this gene with different frequency depending on the population (Table 101.3). The most widely investigated SNPs are C-1019G (rs6295), C-1018G, Ile28Val (rs1799921), Arg219Leu (rs1800044), and Gly22Ser (rs1799920). Some of the other SNPs are Pro16Leu, Gly272Asp, and the synonymous polymorphism G294A (rs6294). These gene variants have been studied in relation to psychiatric disorders with no definitive results.

101.8 Associations Between the *HTR2A* Gene Variation and Phenotypes Related with Anthropometry

The most widely studied polymorphism in association studies is the -1438G>A (rs6311) in the regulatory region. This SNP is in complete linkage disequilibrium with the 102T>C SNP and occurs within the European population at a frequency of about 50%; this frequency, however, is lower in the Sub-Saharan African population (Table 101.2). Although several studies have examined the potential association between the -1438 A allele and a greater risk of anorexia, a few studies have also shown an association with direct anthropometric measures (such as weight, height, body mass index, obesity, waist to hip ratio, etc). As pointed out before, investigation on the functional effects of -1438 A/G showed that this SNP has the potential to modulate HTR2A promoter activity. However, results have been controversial and context dependent (gene–gene interactions of other modulations). In general, it has been shown that promoter activity was greater with the A allele than in the G allele (Parsons et al. 2004). In the following sections, we show the main associations of this SNP and others related with the above-described genes. We have grouped studies together depending on whether the examined phenotype involves anorexia or bulimia nervosa or other phenotypes such as body-mass index, obesity, etc.

101.8.1 Associations Between the -1438 G>A SNP in the HTR2A Gene and Eating Disorders (Anorexia Nervosa and Bulimia Nervosa)

Genetic research into eating disorders is of great importance in evaluating possible relationships between genetics and different eating disorder phenotypes. Serotonin reduces food intake and it could be involved in the aetiology of anorexia nervosa and weight regulation. In addition, drugs that

Table 101.4 Anthropometric characteristics in girls with anorexia nervosa and bulimia nervosa (From Vaz et al. 2003)

	ANr ($n = 48$)	ANp ($n = 20$)	BNp ($n = 90$)	BNnp ($n = 26$)
Age (years)	21.9 ± 6.8	23.2 ± 7.0	21.4 ± 3.3	22.3 ± 5.2
BMI (Kg/m^2)[a,b,c,d]	17.2 ± 1.7	16.5 ± 1.5	21.5 ± 2.3	22.0 ± 1.9
Waist (cm) [a,b,c,d]	60.5 ± 4.1	58.2 ± 4.1	67.9 ± 6.1	69.1 ± 4.9
Hip (cm)[a,b,c,d]	80.9 ± 6.2	78.1 ± 5.0	91.5 ± 7.4	91.4 ± 7.1
Waist-to-hip ratio	0.75 ± 0.04	0.75 ± 0.02	0.75 ± 0.05	0.76 ± 0.04
% fat [a,b,c,d]	15.5 ± 3.9	14.9 ± 3.1	22.8 ± 4.7	23.2 ± 6.3
Triceps skinfold [a,b,c,d]	9.3 ± 4.5	8.9 ± 3.0	15.4 ± 4.0	15.0 ± 4.7
Biceps skinfold[a,b,c,d]	4.7 ± 2.0	4.8 ± 2.5	8.5 ± 3.5	8.8 ± 4.0
Subscapular skinfold [a,b,c,d]	6.8 ± 2.0	6.3 ± 1.6	11.4 ± 4.1	11.4 ± 3.2
Suprailiac skinfold [a,b,c,d]	6.3 ± 3.0	5.3 ± 2.1	11.2 ± 9.9	12.2 ± 6.8

Significant differences $P = 0.0001$, a = ANr vs. BNp, b = ANr vs. BNnp, c = ANp vs. BNp, d = ANp vs. BNnp

ANr: Anorexia nervosa restrictive type, *ANp:* anorexia nervosa purgative type, *BNp:* bulimia nervosa purgative type, *BNnp:* bulimia nervosa no purgative type

increase serotonergic transmission exert anorectic activity. Furthermore, 5-HT genes have been targeted in the study of bulimia nervosa, as it has been shown that 5-HT functioning is disrupted in patients with bulimia nervosa. This gene is, therefore, a candidate for studying the genetics involved in eating disorders, weight, and other anthropometries measures.

Anorexia nervosa, a psychiatric illness and eating disorder, is characterized by extremely low body weight (18.5–19% of BMI is considered low weight) and body image distortion accompanied by an obsessive fear of gaining weight, while bulimia nervosa is characterized by recurrent binge eating, followed by compensatory behaviours. The criteria for diagnosing anorexia nervosa and bulimia nervosa are established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD). Anorexia nervosa is characterized by a refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to maintenance of body weight less than 85% of that expected). Furthermore, the DSM-IV-TR specifies two subtypes of anorexia nervosa: restricting type and binge-eating type or purging type; similarly, there are two types for bulimia nervosa: purging type and non-purging type. Although it is very difficult to establish general and specific anthropometric measures for these diseases, several studies have characterized their own samples mostly in women where the prevalence is higher. For instance, Vaz et al. 2003 showed different anthropometric measures between different subtypes of anorexia nervosa and bulimia nervosa, to investigate whether there could be changes in the nutritional status of the patients depending on the type of disease (Table 101.4).

The -1438G>A polymorphism has been implicated in many diseases such as schizophrenia, alcohol dependence, obesity, and seasonal affective disorder but also with anorexia nervosa and bulimia nervosa. Although there are some studies that have found an association between the A allele of the -1438 G>A polymorphism and this disorder, additional studies did not confirm such associations. Possible explanations for the inconsistency of these findings may include ethnic admixture, inadequate statistical power, and genetic and clinical heterogeneity. In Table 101.5, we summarize the main characteristics of the studies, analyzing the association of the polymorphism in the promoter region of the 5-HT2A receptor with anorexia nervosa and bulimia nervosa. It is suggested that the A allele of the -1438G>A polymorphism could be associated with restrictive behaviour and may be involved in lower caloric intake and body weight. Furthermore, different studies have shown that the A allele of this SNP is more frequent in anorexic patients than in controls and also in individuals with

Table 101.5 Association between -1438 G>A polymorphism and eating disorders (AN and BN), allelic frequencies and main outcomes of the studies

Author/year publication	Population characteristics	BMI (kg/m^2)	Allelic frequency	Phenotype association	Main outcomes
Ricca et al. (2002)	Italian 54 with BED (39.5 ± 13:76 y) 132 obese non-BED (43.3 ± 12:75 y) 148 AN (21.8 ± 4:0y) and 86 BN (23.8 ± 3:9y) 115 control (26.25 ± 6:1y)	ANr:13.8 ± 2.5 ANp:15.6 ± 2.1 BNp:20.2 ± 2.7 BED:38.5 ± 6.1 Obese:37.7 ± 4.9	BED: A: 0.50, G:0.49 Obese: A:0.51, G:0.48 AN: A:0.52, G:0,48 BN: A:0.53, G:0.46 Control: A:0.36, G:0.639	AN and BN	No significance differences in allelic distribution for BED and Obese non-BED while significance differences between AN and BN vs. C ($p < 0.0001$). Association of the A allele with AN and BN.
Rybakowski et al. (2006)	Polish (20.9 ± 1.6 y) 132 AN adolescent 93 controls	No data	AN: A: 0.65 G:0.35 Control A:0.56, G:0.43	AN	A statistical trend toward a higher frequency of the A allele of the –1438 A/G polymorphism in patients than in controls (64.9 vs. 56.7%, 2 test, $p = 0.08$). Significant association
Ando et al. (2001)	Japanese women 75 AN (24.4 ± 5.8y) 127 control	AN: onset of illness: 12.8 ± 2 Current mean: 15.7 ± 2.5	AN:A: 0.547, G:0.453 Control: A: 0.496; G:0.504	AN	No significant association between the 5-HT2A promoter polymorphism and AN. No allelic frequency differences AN vs. C ($P = 0.62$)
Bruce et al. (2005)	Canadian Caucasian women 33 BN (24.3 ± 6.4y) 28 NE (23.3 ± 5.7y)	BN: 21.8 ± 2.2 NE:22.2 ± 2.2	BN: A: 0.38, G:0.62 NE: A:0.43, G:0.57	BN	No significant association between BN and genotype ($P < 0.05$). Women with BN who were GG homozygotes on the -1438G/A SNP had increased impulsiveness and lower sensitivity to postsynaptic serotonin activation.
Fuentes et al. (2004)	Spanish 95 BN (NPAN and PAN) (21.6 ± 0.6 y)) 107 Control (32.1 ± 1y)	BN: 22.5 ± 0.5 C: 23.0 ± 0.3	BN A: 0.43, G: 0.57 Control: A: 0.41, G:0.59	BN	No significant difference in allelic distribution between patients with BN, either with or without previous AN episodes and controls ($P = 0.61$)
Gorwood et al. (2002)	Six European centres 316 AN (15.8 ± 3.42 y) 286 virtual controls*	No data	AN: A:0.40, G:0.60 Virtual controls: A: 0.43, G:0.57	AN	No evidence for heterogeneity of the A allele frequency between samples, either according to minimal-BMI ($P = 0.45$) or age at onset ($P = 0.12$). No direct role of the A
Rybakowski et al. (2003)	Polish 67 AN 114 healthy controls	No data	AN:A: 0.62, G:37.3 C: A: 0.64, G:0.36	AN	No significance differences between allelic distribution between AN and control.

[a] Virtual controls: controls derived from the nontransmitted alleles of the parents to the proband.

BED: Binge eating disorder, *NE:* normal eating, *AN:* anorexia nervosa, *ANr:* anorexia nervosa restrictive type, *ANp:* anorexia nervosa purgative type, *BN:* bulimia nervosa, *NPAN:* no previous anorexia nervosa episodes, PAN, previous anorexia nervosa bulimic patient group

bulimia compared to controls. Rybakowski et al. (2007) found that A allele was associated with personality traits, which are more typical of patients with restrictive anorexia. That may point to the A allele as a greater vulnerability factor in restrictive-type anorexia nervosa than in other subgroups of patients with anorexia. In addition, the A allele could be related to high levels of weight and shape concern, as well as greater general eating disorders (Ricca et al. 2004). A study that investigated whether the *5-HT2A* polymorphism could influence energy and nutrient intakes in adolescents showed that the A allele was significantly associated with lower energy and with total monounsaturated and saturated fat intakes (Herbeth et al. 2005). Also, this group had previously reported that this polymorphism could influence food and alcohol intakes in overweight adults. That could explain the serotoninergic action in food intake as well as in eating disorders. On the other hand, in bulimia nervosa a significant association between bulimia nervosa and the G allele has also been reported. Bruce et al. (2005) found that GG homozygotes in women with bulimia are characterized by increasing impulsiveness. Consistent with that, it is speculated that within individuals with active bulimia, the GG genotype may act as a phenotype modifier (increasing susceptibility to impulsiveness and dysregulation of serotonin when is activated by bulimia symptoms. Furthermore, functional activity of the *5-HT2A* promoter and 5-HT2A receptor activation appears lower for the G allele and higher for A allele. However, there are also studies that have found no association between bulimia and the -1438G>A polymorphism, probably due to the sample size of the studies.

101.8.2 Associations Between the -1438G>A SNP in the HTR2A Gene and Body Mass Index and Obesity

Although multiples studies have examined the potential association between the -1438 A allele and anorexia or bulimia, its association with body mass index and obesity risk has not been studied to the same extent.

Aubert et al. (2000), in unrelated overweight subjects (180 women, 96 men; BMI = 33.3 ± 4.8 kg/m^2) from Paris and from the Stanislas Family Study (31 women, 49 men; BMI = 29.6 ± 3.1 kg/m^2), found that in the whole overweight population, the A allele was associated with lower energy intake, and that this specific allele was more significant in the patient sample from Paris, which had a higher body mass index. These results were further supported by the findings of Herbeth et al. (2005) in 370 children and adolescents drawn from the Stanislas Family Study showing that the A allele was significantly associated with lower energy (GG (BMI: 19.2 ± 2.7 kg/m^2): 9.35 ± 2.70 MJ/day; GA (BMI: 19.5 ± 3.1 kg/m^2): 9.02 ± 2.17 MJ/d; AA (BMI: 19.1 ± 3.1 kg/m^2): 8.61 ± 2.17 MJ/d) and with total monounsaturated, and saturated fat intakes (expressed in g/d). Rosmond et al. (2002) examined the association between the -1438G/A SNP and obesity-related variables in 84 unrelated Swedish men. Homozygotes for the -1438G allele had, in comparison with -1438A/A subjects, higher body mass index (26.9 ± 4.3 vs. 25.1 ± 3.5 kg/m^2, $p = 0.017$ respectively), waist-to-hip ratio (0.96 ± 0.06 vs. 0.92 ± 0.06, $p = 0.015$ respectively), and abdominal sagittal diameter (23.6 ± 3.2 vs. 21.9 ± 3.4 cm, $p = 0.039$) (Table 101.6). Serum leptin, fasting insulin, fasting glucose, and serum lipids did not differ among genotypes. The authors suggested that an abnormal production rate of the *HTR2A* gene product might lead to the development of abdominal obesity.

We carried out a case–control study including 303 obesity cases and 606 controls paired by gender and age (Sorlí et al. 2008) (Table 101.6). In this sample of Spanish subjects, we did not find a significant association between the -1438G/A SNP and obesity (BMI ≥ 30 kg/m^2). However, as previous works suggested an increase in the effect of -1438G/A SNP in subjects with higher overweight, we carried out a subgroup analysis in obese and nonobese subjects. We found that in the obese group, AA subjects had a lower body mass index than G allele carriers (35.2 ± 5.3 kg/m^2 vs. 37.5 ± 7.8 kg/m^2;

Table 101.6 Antropometric values in different studies according to 5-HT2A-1438 G/A genotypes

	AA	AG	GG	
Rosmond et al. (2002)	(mean ± S.D)	(mean ± S.D)	(mean ± S.D)	*P*
Age (*n* (men):264: 51 years)				
BMI (kg/m^2)	25.1 ± 3.5	26.7 ± 4.0	26.9 ± 4.3	0.017
Waist to hip ratio	0.92 ± 0.06	0.94 ± 0.07	0.96 ± 0.06	0.015
Abdominal sagittal	21.9 ± 3.4	22.9 ± 3.8	23.6 ± 3.2	0.039
Herbeth et al. (2005)	**AA**	**AG**	**GG**	***P***
	(mean ± S.D)	**(mean ± S.D)**	**(mean ± S.D)**	
Age (years)(*n* = 370)	13.3 ± 2.6	13.6 ± 2.6	13.7 ± 2.7	
BMI (kg/m^2)	19.1 ± 3.1	19.5 ± 3.1	19.2 ± 2.7	0.797
Weight (kg)	48.9 ± 13.1	50.8 ± 13.5	49.4 ± 11.4	0.806
Height (cm)	158.6 ± 11.7	159.9 ± 11.8	159.1 ± 11.4	0.749
Sorlí et al. (2008)	**AA**	**AG + AA**		***P***
	(mean ± S.D)	**(mean ± S.D)**		
Age (case group, *n* = 606):45.6 ± 12.6 years				
BMI (kg/m^2)	35.2 ± 5.3	37.4 ± 7.8		0.039
Weight (kg)	92 ± 17	98 ± 23		0.068
Waist (cm)	105 ± 11	112 ± 17		0.011
Hip (cm)	115 ± 12	120 ± 17		0.066
Ying et al. (2009)	**AA**	**AG**	**GG**	***P***
	(mean ± S.D)	**(mean ± S.D)**	**(mean ± S.D)**	
Age (overweight group, *n* = 210; vales expressed only for men) 43 ± 7.31 years				
BMI (kg/m^2)	26.2 ± 2.0	29.1 ± 2.4	31.5 ± 3.2	0.043
Waist (cm)	93.9 ± 6.4	100.7 ± 8.5	105.3 ± 8.0	0.038
Hip (cm)	102.6 ± 5.9	102.3 ± 8.0	106.2 ± 6	0.102
Waist to hip ratio	0.93 ± 0.06	0.95 ± 0.06	0.98 ± 0.06	0.045

P = 0.039; Fig. 101.3). Likewise, significant differences were also obtained in waist perimeter, this being lower in AA subjects compared to G allele carriers (105 ± 11 cm vs. 112 ± 17 cm; *P* = 0.011; Fig. 101.4). These associations remained statistically significant even after multivariate adjustment for gender, age, origin, education, alcohol consumption, tobacco smoking, and physical activity (*P* = 0.029 and 0.01 for body-mass index and waist perimeter, respectively). Conversely, these associations were not observed in the nonobese control group (Figs. 101.3 and 101.4). In another study carried out on Spanish children, the authors did not find any significant association between the -1438G/A SNP and anthropometric variables. Our results supported the hypothesis of a greater influence of the -1438G>A polymorphism in the serotonergic system and anthropometric measurements in cases of greater BMI. Moreover, results from animal models demonstrate that obesity increases hypothalamic 5-HT2A receptor gene expression, and pharmacologic inactivation of 5-HT2A receptors inhibits overfeeding and obesity in mice (Nonogaki et al. 2006).

Ying et al. (2009) partially agreed with our findings. They studied 210 patients with overweight/obesity (27.9 ± 2.4 kg/m^2) and 216 unrelated healthy subjects (BMI: 22.6 ± 1.4 kg/m^2) and found that in overweight/obese men (BMI: 27.9 ± 2.4 kg/m^2), carriers of the G allele had statistically significant increased body mass index, waist circumference, waist-to-hip ratio, in comparison with patients carrying the A allele. However, the authors did not find significant difference between the -1438A>G genotype groups in overweight/obese women (Table 101.6).

Conversely, Kring et al. (2009), in a study carried out in obese men (*n* = 726) (BMI ≥ 30 kg/m^2) and in a randomly selected group of the same cohort of young men from Denmark, did not find any association between the 1438A>G SNP in the *HTR2A* gene and anthropometric variables (-1438G/A: BMI (kg/m^2): OR (95% CI) 1.01 [0.97–1.04], *p* = 0.70; Waist (cm): OR (95%CI):1.00[0.97–1.04], *p* = 0.81).

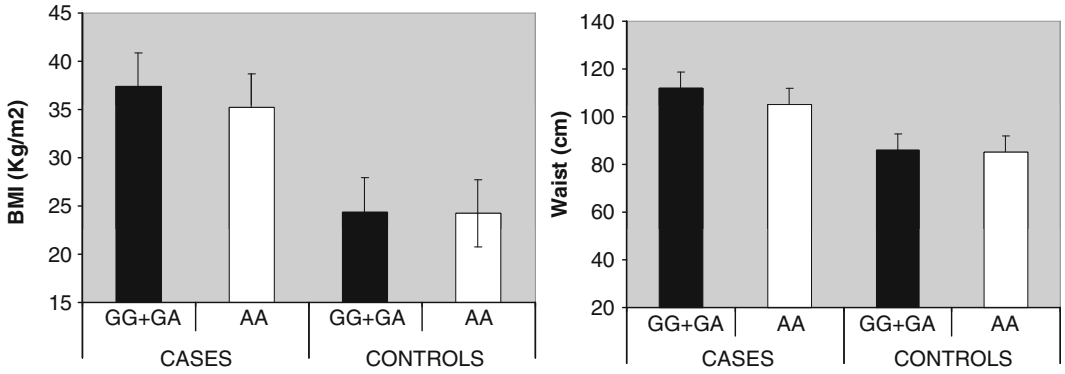

Fig. 101.3 Differences between case and controls BMI (kg/m^2) depending on the -1438G>A polymorphism in the serotonin 2A receptor gene. $^{*}P$ value for comparison between GG + AG and AA genotype for BMI (kg/m^2) in case subjects. $^{**}P$ value for comparison between GG + AG and AA genotype for BMI (kg/m^2) in control subjects

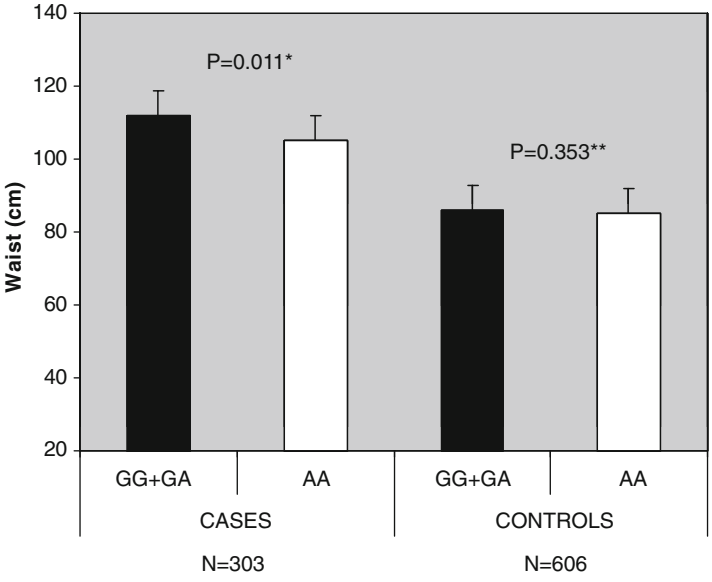

Fig. 101.4 Differences between case and controls waist circumference (cm) depending on the -1438G>A polymorphism in the serotonin 2A receptor gene. $^{*}P$ value for comparison between GG + AG and AA genotype for waist (cm) in case subjects. $^{**}P$ value for comparison between GG + AG and AA genotype for waist (cm) in control subjects

In general, association studies that have examined the effect of the 1438A>G SNP in the *HTR2A* gene on anthropometric measures have reported different results. The most replicated data suggest that the A variant allele is associated with a lower food intake (mainly in a recessive model) as well as with lower mean body mass index and waist circumference, but this association is only seen in subjects with higher BMI. These results could be supported by gene expression studies showing that the A allele was associated with lower receptor expression. However, these results do not allow us to draw any definite conclusion about the impact of the 1438A>G SNP in the *HTR2A* on obesity. Further studies are needed to provide more evidence on these associations.

101.9 Associations Between the SLC6A4 Gene Variation and Phenotypes Related with Anthropometry

The *SLC6A4* gene has also been studied in relation to eating disorders; however, the findings are still inconsistent. The variant that has been most studied is the functional length variation polymorphism (5-HTTLPR), which has functional implications. However, there is controversy over its association with bulimia nervosa. One study found that one or two copies of the short allele increased the risk sevenfold for bulimia, while subsequent studies did not find any association or even a higher frequency of long allele in women with bulimia and binge eating disorder. On the other hand, the short allele has been implicated in lowered dietary intake and decreased body mass index. Regarding anorexia nervosa, controversy over its association with this polymorphism in the promoter region is also expressed in different papers. In a study carried out by Matsushita et al. (2004), the short allele was related to lower dietary intake among subjects observed over 3 years or more, and the short allele frequency was significantly higher in those diagnosed with anorexia nervosa at eating disorder onset than in those diagnosed as anorexic later on, suggesting that the short allele might play some role in the development of anorexia among those with a prior eating disorder. However, Rybakowski et al. (2006) did not find a significant difference in the allelic frequency between anorexia nervosa patients and controls or personality dimension traits. This controversy could be due to the low samples size but also to uncertain diagnosis. Furthermore, a recent meta-analysis suggests the possibility that the L allele may be associated with obsessive–compulsive disorder in specific obsessive–compulsive disorder subgroups such as childhood-onset obsessive–compulsive disorder and in Caucasians (Bloch et al. 2008). Therefore, future research should continue to explore interaction effects in this SNP or other related ones by examining larger samples and also evaluating environmental factors that could be related to eating disorders.

Regarding the associations between the *SLC6A4* gene variation and obesity, recent results from animal studies have reported that depression-prone 5-HT transporter knockout (SERT(-/-)) rats had a strong increase (54%) in abdominal fat, in a sex-dependent way (observed in females but not in males), suggesting that SNPs associated with a decrease in the expression of the *SLC6A4* gene could confer a higher risk of increased abdominal fat formation in humans (Homberg et al. 2010). Some epidemiological studies analyzing the association between *SLC6A4* gene variation and anthropometric variables have reported results consistent with this hypothesis. Thus, one of the polymorphisms described in that gene consists of a 44-bp insertion/deletion in the promoter region yielding the so-called long (L) and short (S) alleles. In 1996, it was published that the short variant (S allele) reduces the transcriptional efficiency of the gene resulting in decreased 5-HT transporter expression in the neuron, a similar situation as that found in knockout (SERT(-/-)) rats. Sookoian et al. (2008) examined this polymorphism in a large sample of 1,329 adult men of European ancestry included in a population-based study in Argentina. They observed that the S allele was significantly associated with higher body mass index with codominant effects (LL: 25.4 ± 0.2, LS: 26.0 ± 0.1 and SS: 26.7 ± 0.2, $p < 0.0002$), and obtained a statistically significant odds ratio (OR) for obesity in SS carriers in comparison with LL carriers (OR and 95% confidence interval (CI): 1.32 and 1.01–1.85). These results, supporting the role of the LL genotype as a higher risk allele for obesity, were in agreement with a previous study undertaken by the same group in adolescents. These results are also in agreement with more than five studies in different populations showing a consistent association between the SS genotype and increased risk for depression. However, more studies and meta-analyses are needed to increase the evidence level.

101.10 Associations Between HTR2C Gene Variation and Phenotypes Related with Anthropometry

In 1995, Tecott et al observed that knockout mice for the *HTR2C* gene developed obesity. This gene has also been implicated in the regulation of feeding behaviour in animal models. However, the main role attributed to this gene is the modulation of weight gain in antipsychotic medications. The importance of the 5-HT system in psychiatric symptomatology and several side effects of antipsychotic drugs are well established. Weight gain is a frequently observed side effect of many antipsychotic treatments. Reynolds et al. (2003) investigated the influence of the –759C/T SNP in the *HTR2C* gene in weight changes in Chinese Han patients with first-episode schizophrenia after 6 weeks of clozapine treatment. The authors found that the patients with the –759T variant allele showed significantly less weight gain than those without (–759T allele (mean = 0.32 kg/m^2, SD = 0.68, vs. mean = 1.12 kg/m^2, SD = 0.88, $p < 0.05$). However, this study was undertaken in a small sample of patients and requires replication and further functional evidence. In this regard, gene-expression studies have reported controversial results. One of the most recent and complete studies assessed the activity of four promoter haplotypes expressed as luciferase constructs (Hill and Reynolds 2007). The presence of either -759T or -697C alleles reduced promoter activity, suggesting that resistance to weight gain in -759T patients may be mediated by reduced *HTR2C* gene expression. De Luca et al. (2007) carried out a meta-analysis of epidemiological studies investigating the influence of the -759C/T SNP in the *HTR2C* gene on weight gain after antipsychotic treatment. The authors identified 10 studies published between 2002 and 2005. The combined estimation showed a statistically significantly lower risk of weight gain associated with the -759T allele. However, there was evidence of significant heterogeneity among studies. Some further studies also supported this lower risk associated with the 759T allele, adding more evidence to this effect. More controversial is the association between this SNP and obesity in the absence of pharmacological treatment. Kring et al. (2009) studied the association between the -759C>T SNP and anthropometric and biochemical traits in Danish men. The authors did not find any association between this SNP and anthropometric variables. However, a significant association between the -759 T allele and impaired glucose tolerance and higher type 2 diabetes was found.

101.11 Associations Between *HTR1A* Gene Variation and Phenotypes Related with Anthropometry

Studies analyzing variations in the *HTR1A* have focused on major depressive disorder and other disorders (Savitz et al. 2009). The nexus between these disorders (including anxiety) and food intake and further obesity risk remains to be studied in well-powered and unbiased studies.

Summary Points

- Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter, which contributes to the regulation of many physiological processes such as sleep, appetite, eating disorders, thermoregulation, hormone secretion, mood, anxiety, etc., all of these processes being directly or indirectly associated with anthropometric measures.

- There are several genes related to 5-HT effects, among which the most important are: the 5-HT2A receptor gene (*HTR2A*) located at 13q14–q21, the 5-HT transporter gene (*SLC6A4*) located at 17q11.1–q12, the 5-HT2C receptor gene (*HTR2C*) located at Xq24, and the 5-HT1A receptor (*HTR1A*) gene, located at 5q11.2-q13.
- Several gene variations consisting of single-nucleotide polymorphisms (SNPs), insertion/deletion or tandem repeat variants have been described in all of these genes. The study of the association between genetic variations may help to better understand the effects of serotonin and its receptors on anthropometry.
- The most widely studied phenotypes related with anthropometry have been complex eating-related disorders including anorexia nervosa and bulimia, as well as direct anthropometric measurement such as body weight, waist circumference, height, body mass index, obesity, and percent of body fat.
- The most studied polymorphism is the -1438G>A (rs6311) in the regulatory region of the *HTR2A* that is in complete linkage disequilibrium with the 102T>C SNP. In epidemiologic studies, it has been reported that the A allele is associated with lower energy and macronutrient intake as well as with lower body mass index in obese subjects.
- Results from animal studies described that depression-prone 5-HT transporter knockout (SERT(-/-)) rats had a strong increase in abdominal fat, suggesting that SNPs, associated with a decrease in the expression of the *SLC6A4* gene, could confer a higher risk of increased abdominal fat formation in humans.
- In gene expression studies, a 44-bp insertion/deletion promoter region polymorphism (alleles L and S) was demonstrated to be functional with reduced expression in the S allele. Epidemiological studies have reported statistically significant body weight and higher obesity risk in SS subjects.
- The –759C/T SNP in the *HTR2C* gene has been associated with weight changes after antipsychotic treatments. It has been reported that patients with the –759T variant allele showed significantly less weight gain than those without the allele.
- However, these results do not allow us to draw any definite conclusion about the impact of genetic variation in the 5-HT-related genes on anthropometric variables and further studies are needed to provide more evidence on these associations.

Key Features

Table 101.7 Key points

– Genetic variation may play an important role in determining anthropometry. However, the identification of the candidate genes involved is still a work in progress. Among these, the serotonin (5-hydroxytryptamine (*5-HT*)) type 2A receptor (*5-HTR2A*) gene, and other serotoninergic genes have emerged as important candidates.
– Variations in the serotoninergic genes have been widely related to complex behavioral phenotypes such as anorexia and bulimia nervosa in addition to other psychiatric disorders. However, the evidence level is still low.
– Although some studies have found an association between the -1438G>A polymorphism in the regulatory region of the *HTR2A* gene and lower body mass index in obese subjects, more studies are needed to increase the consistency.
– To firmly establish the contribution of genetic variation in the serotoninergic genes to anthropometry, new studies including thousands of individuals and dozens of well selected functional genetic markers should be carried out. In addition, environmental modulations should be analyzed.

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Part XVI
Anthropometry in Cancer

Chapter 102
Anthropometry and Thyroid Cancer Risk

Cari Meinhold Kitahara and Amy Berrington de González

Abstract Thyroid cancer is a relatively rare malignancy, accounting for less than two percent of all cancer diagnoses, but the incidence of thyroid cancer has risen dramatically over the past thirty years in many parts of the world. This increase in thyroid cancer incidence has paralleled the shift in the distribution of body weight over the same period. However, the only established environmental risk factor for thyroid cancer is ionizing radiation, particularly in childhood and adolescence. Until recently, there were relatively few epidemiologic studies of the association between body size and thyroid cancer. Evidence from early case–control studies suggested that greater body mass index (BMI) may increase the risk of thyroid cancer in women, and recent case–control and prospective studies suggest a similar positive association for men. Several epidemiologic studies have also suggested that height is associated with an increased risk of thyroid cancer. Although little is understood about the potential underlying mechanisms for the associations of anthropometric factors with thyroid cancer risk, thyroid-stimulating hormones and iodine status may play a role. Future studies with information on central adiposity, obesity-related biomarkers, and weight at different ages may provide greater insight into the etiology of this malignancy.

Abbreviations

BMI	Body mass index
HR	Hazards ratio
OR	Odds ratio
RR	Relative risk
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_102,

102.1 Introduction

Thyroid cancer accounts for 1.3% of cancer diagnoses (approximately 141,000 incident cases) and 0.5% of cancer deaths (approximately 35,000 deaths) worldwide each year and is approximately three times more common in women compared to men (Parkin et al. 2005) (Table 102.1). Thyroid cancer is diagnosed at a relatively young age compared to other cancer types; for women the incidence peaks around age 50–54 and declines thereafter, while for men the incidence peaks much later, between ages 65 and 69 (SEER 2009). The main histological types are papillary, follicular, medullary, and anaplastic cancers, and each differ in terms of microscopic characteristics, incidence, prognosis, and, possibly, etiology. Of the cancers deriving from the follicular epithelium, papillary and follicular cancers are the most common, accounting for approximately 70% and 20% of all thyroid cancers, respectively, are well-differentiated, and have a very good prognosis, whereas anaplastic cancers account for less than 5% of all thyroid cancers, are non-differentiated, and have a much higher fatality rate; medullary cancers arise from the parafollicular cells of the epithelium (Ron and Schneider 2006). Although over 97% of thyroid cancer patients survive beyond 5 years after diagnosis (SEER 2009), the rapidly increasing number of incident cancers diagnosed worldwide over the past three decades has been cause for concern (Kilfoy et al. 2009). In the United States, particularly, the incidence has increased at a more rapid rate than any other cancer site, and thyroid cancer is now the seventh most common cancer in women (Enewold et al. 2009; Jemal et al. 2008).

One common explanation for these patterns is the more widespread use of sensitive diagnostic tools, which may detect very small papillary tumors of limited clinical significance (Parkin et al. 2005; Jemal et al. 2008). If improvements in detection were the sole explanation for the trends in thyroid cancer incidence, then a subsequent decrease in the incidence of larger tumors would be expected. However, larger and more advanced tumors have also increased in incidence during this time period, suggesting that environmental factors may also play a role in the rising number of thyroid cancer diagnoses over the past 30 years (Enewold et al. 2009).

Currently the only established environmental risk factor for thyroid cancer is exposure to ionizing radiation, particularly during childhood or adolescence (Ron and Schneider 2006). Consequences of the Chernobyl accident, for instance, included a steep increase in the number of papillary thyroid cancers diagnosed in Belarus and parts of Northeast Ukraine and Southwest Russia (Ron 2007). Greater knowledge on the health consequences of radiation has led to decrease in the use of radiation treatment for minor illnesses or conditions. Increases in medical radiation exposure including CT scans are unlikely to account for much of the increase in thyroid cancer risk, however (Berrington and Darby 2004).

Paralleling the rise in thyroid cancer incidence, an international 'epidemic' of obesity has been observed. In the United States, for instance, the proportion of obese adults increased from 15% to over 30% between 1980s and 2000s (Ogden et al. 2007). An adoption of 'western' behaviors, such as low physical activity and diets high in saturated fat and sugar, has certainly contributed to a shift in the distribution of body weight in less developed countries (Ogden et al. 2007). As the prevalence of obesity has increased worldwide, so has the importance of understanding its potential public health consequences and to identify individuals most at risk for obesity-related conditions.

In 2007, the World Cancer Research Fund/American Institute for Cancer Research published a review of the literature on obesity and cancer and concluded that there was convincing evidence of a causal association between obesity and cancers of the pancreas, colorectum, breast (postmenopausal), endometrium, and kidney, while "probable" and "limited" evidence existed in support of a causal relationship with gallbladder and liver cancers, respectively. The panel did not formally assess

Table 102.1 Key facts about thyroid cancer

1. Worldwide, there are approximately 141,000 new diagnoses and 35,000 deaths annually from thyroid cancer
2. The incidence of thyroid cancer, particularly papillary carcinoma, has increased in many countries worldwide since the 1970s. Recent studies suggest that this increase is not due entirely to improvements in detection or changes in diagnostic criteria
3. The prognosis for thyroid cancer is generally favorable. The 5-year survival is approximately 97%, and thyroid cancer incidence is approximately four-fold higher than thyroid cancer mortality
4. The female:male incidence ratio is typically 3:1. In the United States, thyroid cancer is now the seventh most common cancer in women and fifteenth most common cancer in men
5. The four main histological types (papillary, follicular, anaplastic, and medullary) differ in terms of microscopic characteristics, incidence, prognosis, and, possibly, etiology
6. The only established environmental risk factor for thyroid cancer is exposure to ionizing radiation, but iodine deficiency and a medical history of benign thyroid conditions, particularly goiter and thyroid nodules, are also consistently associated with thyroid cancer incidence

These key facts are based on the descriptive epidemiology and current information on the etiology of thyroid cancer

the level of evidence linking obesity with thyroid cancer risk, most likely due to the lack of prospective studies and a greater focus on more common cancer outcomes.

However, there is increasing evidence from epidemiologic studies in support of a role for anthropometric factors in thyroid carcinogenesis, particularly overall adiposity and height.

102.2 Observational Studies of Adiposity, Weight Gain, and Thyroid Cancer Risk

102.2.1 Case–Control Studies

Much of the evidence on the association between adiposity and thyroid cancer is based on results from case–control studies (Table 102.2). Some of these studies have also examined BMI or weight at different ages or periods in life (i.e., menarche), by age at diagnosis, and by sex, and all of these studies ascertained height and weight by self-report. However, if thyroid cancer patients experience disease-related weight loss or weight gain, or they tend to over- or under-report their height and weight compared to control participants, then the results from case–control studies may be biased estimates of the true relationship. Also, earlier case–control studies may have had limited power due to the lower prevalence of obesity.

In general, case–control studies have shown fairly consistent, though modest, positive associations between BMI and thyroid cancer risk (Fig. 102.1). An international pooled analysis, combining original data from 12 thyroid case–control studies, including 2,056 female and 417 male cases, showed an overall modest effect of BMI in women (highest versus lowest tertile, OR = 1.2, 95% CI: 1.10, 1.50, P-trend = 0.04) but no association in men (OR = 1.0, 95% CI: 0.80, 1.40, P-trend = 0.71) (Dal Maso et al. 2000). The results for women did not differ substantially by age at diagnosis or menopausal status. However, no association was observed with BMI in young adulthood (Dal Maso et al. 2000). A pooled case–control analysis restricted to medullary cancers ($n = 67$) showed a non-significant inverse association for BMI (highest vs. lowest tertile, OR = 0.65, 95% CI: 0.33, 1.28, P-trend = 0.23). More recently, a case–control study in New Caledonia found a positive association

Table 102.2 Case–control studies with information on anthropometric factors in relation to thyroid cancer risk, from the years 2000 through 2009

First author, year	Study period	Geographic location	No. cases/controls	Data collection (height/weight)	Adjustment factors
Dal Maso et al. (2000)*	Before 1998	USA, Japan, China, Sweden, Norway, Italy, Switzerland, Greece	M:417/965 F:2,056/3,358	Self-reported height and weight at age 17–20 and at diagnosis/pseudo-diagnosis	Age†, sex†, study†, A-bomb exposure and radiation dose (Japanese study)†, ethnicity (Hawaiin study)†, history of radiation
Guignard et al. (2007)	1993–1999	New Caledonia	M:39/58 F:293/354	Self-reported height and weight at diagnosis	Age†, sex†, year of diagnosis/reference, ethnic group, number of full-term pregnancies, miscarriages, irregular menstruations
Suzuki et al. (2008)	2001–2005	Japan	M:42/210 F:131/655	Self-reported height and weight at age 20 and at diagnosis	Age†, sex†, smoking, alcohol, family history of thyroid cancer, past history of thyroid diseases, total non-alcohol energy intake, hospital referral pattern, menopausal status, age at menarche, parity, hormonal replacement therapy
Brindel et al. 2009	1979–2004	French Polynesia	M:24/44 F:195/315	Self-reported height at interview and weight at age 18, 30, 40, 50, and at interview	Age†, sex†, height, ethnicity, education level, smoking, interviewer, radiation to head or neck for diagnosis before 15 years old, number of full-term pregnancies,

The case-control studies included in the table are the pooled analysis of 12 case-control studies Dal Maso et al. (2000), as indicated by the symbol *, which includes most case-control studies of anthropometric factors and thyroid cancer published prior to 2000, and three recent case-control studies not included in the pooled analysis. All studies collected height and weight information through self-report. As shown, these studies differed in terms of study period, geographical location, number of incident thyroid cancers, size of the study population, information available on body size, and covariates included in the analysis. The symbol † represents a matching factor

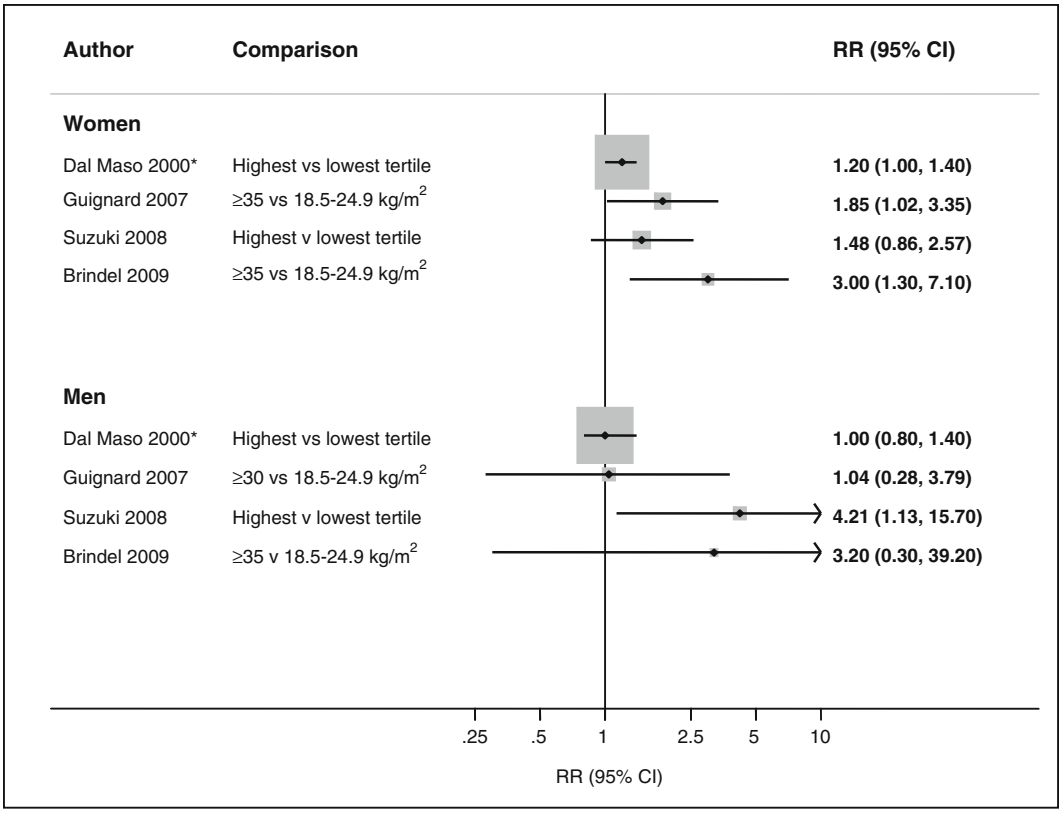

Fig. 102.1 Relative risks (RRs) of thyroid cancer according to highest versus lowest categories of body mass index (BMI) based on published data from case-control studies. The results are presented separately for women and men. In general, case–control studies have shown fairly consistent positive associations between BMI and thyroid cancer risk. While earlier studies showed stronger associations for women compared to men, more recent studies have also suggested a positive association in men. The * indicates the pooled case-control analysis (Dal Maso et al. 2009)

between BMI and thyroid cancer in women, particularly in women diagnosed over the age of 50 (≥35 vs. 18.5–24.99 kg/m^2, OR = 5.51, 95% CI: 1.49, 20.30); no clear associations were observed in men (Guignard et al. 2007).

Other recent case–control studies have suggested that the association may not be restricted to women (Suzuki et al. 2008; Brindel et al. 2009; Fig. 102.1). A Japanese case–control study found that BMI was positively associated with thyroid cancer risk in men only, particularly at younger ages, and greater weight both at age 20 and at diagnosis was associated with increasing risk in both men and women (Suzuki et al. 2008). Body surface area (calculated as (weight in kilograms)$^{0.425}$ × (height in meters)$^{0.725}$ × 0.7007184) was more strongly related to thyroid cancer risk in both men and women in this study, which suggests that BMI may not be the most appropriate measure of body fat in a Japanese population. A case–control study in French Polynesia showed clear associations between thyroid cancer risk and greater weight and BMI at age 18, 30, 40, and currently, both for men and women (Brindel et al. 2009). When the analysis was stratified by size of the tumor, it appeared that current weight and BMI were more strongly related to risk of smaller tumors, whereas weight and BMI at younger ages increased the risk of larger tumors. One possible explanation for this is that greater body size in young adulthood has a promotional effect on thyroid tumors, while thyroid cancers related to greater body size at older ages may result from greater surveillance and

detection. Although the number of thyroid cancers in these studies was small, particularly for men (Table 102.2), the latter two studies suggest that body size in both men and women and in early life and later adulthood may contribute to an increased risk of cancer.

102.2.2 Prospective Studies

Until recently, there have been few prospective studies on the association between obesity and thyroid cancer risk due to the relatively low incidence of thyroid cancer in the general population. These studies differ greatly in terms of size, geographic location, demographic characteristics, data collection, and information on important covariates (Table 102.3).

Although there are some inconsistencies, overall, the evidence is in support of a positive association between obesity and risk of thyroid cancer (Fig. 102.2). In a very large cohort of over two million Norwegian men and women, a positive association between obesity and thyroid cancer incidence was observed (BMI ≥ 30.0 vs. 18.5–24.9 kg/m^2: RR for women = 1.29, 95% CI: 1.13, 1.46; RR for men = 1.14, 95% CI: 0.82, 1.56) (Engeland et al. 2006). Positive dose–response associations were observed for well-differentiated thyroid cancers in women (RR for papillary cancer = 1.9, 95% CI: 1.01, 1.41, P-trend = 0.008; RR for follicular cancer = 1.63, 95% CI: 1.24, 2.15, P-trend = 0.002), but these associations were less clear in men (RR =1.11, 95% CI: 0.73, 1.69, P-trend = 0.05; RR = 1.66, 95% CI: 0.82, 3.37, P-trend = 0.05). The risk of anaplastic thyroid cancer increased with greater BMI, particularly in men (RR = 2.33, 95% CI: 0.88, 6.20, P-trend = 0.03). In contrast, an inverse association was observed in relation to medullary cancer, with the dose–response association being more evident in women (RR = 0.35, 95% CI: 0.16, 2.32, P-trend = 0.004). The Norwegian study had several strengths, including a large number of incident thyroid cancers in men and women (2,268 female and 778 male cases), nearly complete follow-up in the study area, and standardized measurements of height and weight. However, information on potential confounding factors, such as cigarette smoking and medical history of benign thyroid conditions, was not ascertained, potentially biasing these associations. A medical history of benign thyroid conditions, particularly of goiter or thyroid nodules, has been strongly related to the risk of thyroid cancer (Dal Maso et al. 2009). Also, weight gain is a common symptom of hypothyroidism, while weight loss is often observed in patients with hyperthyroidism (Fox et al. 2008). Current cigarette smoking is generally inversely related to both body weight and possibly also thyroid cancer risk (Mack et al. 2003), so inadequate control of smoking may bias the association between BMI and thyroid cancer risk in a positive direction.

A large prospective study of over 780,000 Korean men examined the relationship between obesity and risk of multiple cancers (Oh et al. 2005). In this study, BMI was associated with greater thyroid cancer risk (BMI 27.0–29.9 vs. 18.5–22.9 kg/m^2: RR = 2.23, 95% CI: 1.40, 3.55, P-trend <0.001). The magnitude of the association was the same after restricting the outcome to papillary thyroid carcinomas (RR = 2.23, 95% CI: 1.25, 3.99, P-trend <0.001). Based on these results and the prevalence of obesity in this cohort (defined as the standard cutoff in Asian populations, BMI ≥25 kg/m^2 (WHO 2000)), the population-attributable fractions of thyroid cancer from obesity were estimated to be 18% in the total population and 23% among never smokers alone.

Two large prospective studies, with 360,000 male Swedish construction workers (Samanic et al. 2006) and 204,964 men and women from San Francisco (Iribarren et al. 2001), showed no overall association between BMI and thyroid cancer risk. Considering that the Swedish cohort was relatively homogeneous in terms of socioeconomic status, it is unlikely that residual confounding by some poorly measured or unmeasured factor could account for the null results. The men were younger, on average, than men included in the Korean and Norwegian studies, but currently it is not

Table 102.3 Prospective cohort studies with information on anthropometric factors in relation to thyroid cancer risk, from the years 1997 to 2009

First author, year	Study period	Geographic location	Cohort	No. cases/study population	Data collection (height/weight)	Adjustment factors
Tulinius et al. (1997)	1968–1995	Iceland	Reykjavík Study	M:37/11,366 F:46/11,580	Measured height and weight at baseline	Age
Iribarren et al. (2001)	1964–1997	U.S. (San Francisco)	Kaiser Permanente Medical Care Program of Northern California (San Francisco or Oakland)	M: 73/94,549 F: 123/110,415	Measured height and weight at baseline and self-reported weight at age 20	Age, sex, race, education, smoking status, alcohol intake, self-reported personal history of hyperthyroidism, hypothyroidism, goiter, treatment of tonsils or neck region with X-rays, family history of thyroid disease, body mass index, weight gain, height, occupational exposures
Samanic et al. (2004)	1969–1996	U.S.	Veteran Affairs hospitals	M: 1,044/4,500,700	Discharge diagnosis of obesity (ICD8 = 277, ICD9 = 278.0)	Age, calendar year
Rapp et al. (2005)	1985–2002	Austria	Vorarlberg Health Monitoring and Promotion Program	M: unknown/67,447 F: 61/74,484	Measured height and weight at baseline	Age, smoking status, occupational group
Oh et al. (2005)	1992–2001	Korea	Korea National Health Insurance Corporation	M: 226/781,283	Measured height and weight at baseline	Age, smoking status, alcohol intake, regular exercise, family history of cancer, residence
Engeland et al. (2006)	1963–2003	Norway	Norwegian health surveys (linkage study)	M: 778/963,523 F: 2,268/1,037,424	Measured height and weight at baseline	Year of birth, age at measurement
Samanic et al. (2006)	1971–1999	Sweden	Swedish Foundation for Occupational Safety and Health of the Construction Industry	M: 171/362,552	Measured height and weight at baseline and follow-up examinations	Attained age, calendar year, smoking status
Sung et al. (2009)	1994–2003	Korea	Korea Medical Insurance Corporation (part of Korean National Health Insurance Corporation)	M: 43/449,214 F: 1,550/339,575	Measured height at baseline	Age, sex, body mass index, smoking, alcohol intake, regular exercise, monthly salary, occupation, area of residence, age at menarche, duration of breastfeeding, age at first child-birth, menopausal status, estrogen replacement, oral contraceptive use
Meinhold et al. (2010)	1983–2006	U.S.	U.S. Radiologic Technologists Study	M: 40/21,207 F: 242/69,506	Self-reported height and weight at baseline and during follow-up	Age, sex, birth year, smoking status, occupational and personal radiation exposure, history of benign thyroid conditions

The prospective studies included in the table had information on weight or height at entry into the study or hospital discharge records for obesity. As shown, these studies differed in terms of study period, geographical location, number of incident thyroid cancers, size of the study population, anthropometric information, and covariates included in the analysis

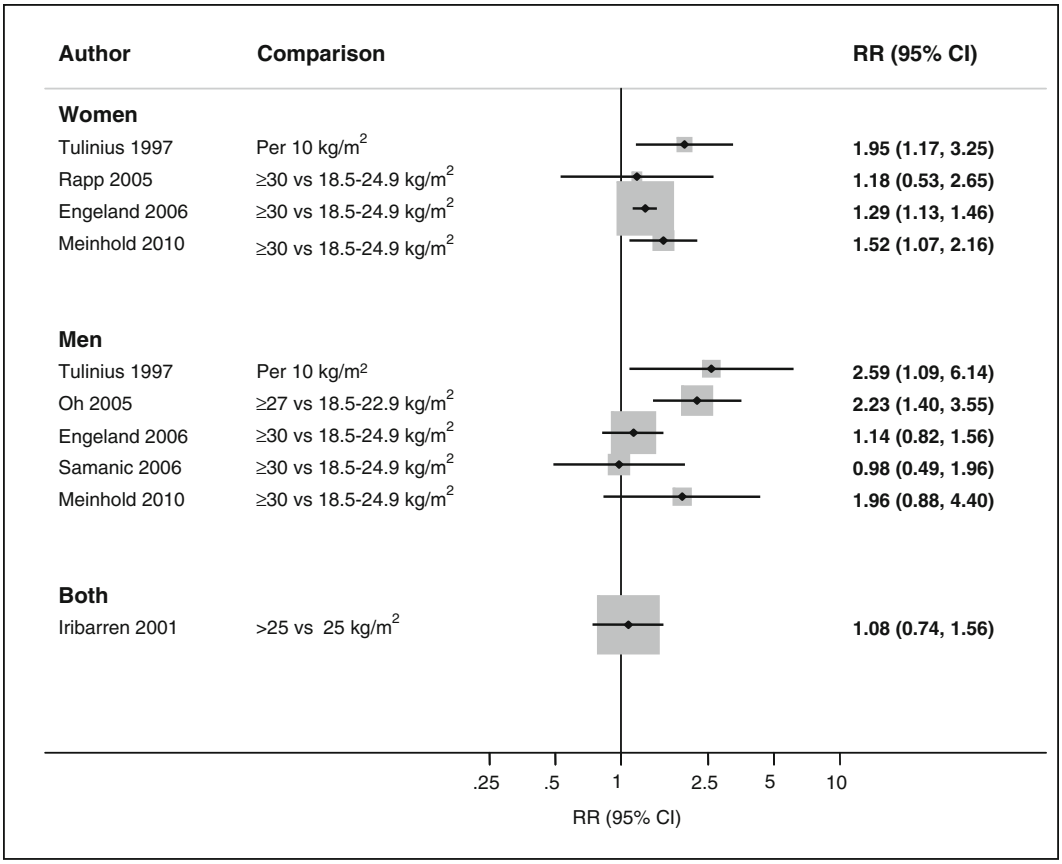

Fig. 102.2 Relative risks (RRs) of thyroid cancer according to highest versus lowest categories of body mass index (BMI) based on published data from prospective studies. The results are presented separately for women and men, where available. Although there are some inconsistencies, overall, the evidence is suggestive of a positive association between obesity and risk of thyroid cancer in both women and men

clear whether age modifies the association between body fat and thyroid cancer risk in men. The San Francisco study only compared participants with a BMI above or below 25 kg/m^2 and did not present results separately for each sex (Iribarren et al. 2001).

Two prospective studies had fewer than 100 incident thyroid cancer cases, limiting the interpretability of the results. One Icelandic study observed a relative risk of 1.1 (95% CI: 1.01, 1.20) for every 1-unit increase in BMI in men and 1.07 (95% CI: 1.02, 1.13) in women, but these results were only adjusted for age (Tulinius et al. 1997). Another small cohort did not show overall association between BMI and thyroid cancer in women, based on 61 incident cases; the number of male cases and the results for men were not presented (Rapp et al. 2005).

In a more recent prospective study of over 90,000 radiologic technologists in the United States, a positive association between BMI and thyroid cancer risk was observed for women (BMI ≥35.0 vs 18.5–24.9 kg/m^2: HR = 1.74, 95% CI: 1.03, 2.94, P-trend = 0.04) (Meinhold et al. 2010). The dose–response association was less clear in men (HR = 2.14, 95% CI: 0.60, 7.67, P-trend = 0.11); however, the number of thyroid cancers in the male participants was small (40 male vs. 242 female cases). Participants in this study were relatively young, with a mean age at entry of 43 for men and 39 for women. This study had information on established or potential thyroid cancer risk factors, including

personal and occupational exposure to ionizing radiation, medical history of benign thyroid conditions, cigarette smoking, and alcohol consumption. However, as this was an occupational group, the generalizability of these results may be limited.

One large prospective study used information from hospital discharge records to classify participants as being obese or nonobese (Samanic et al. 2004). Having a hospital discharge record for obesity was positively associated with thyroid cancer in a cohort of US veterans (RR for white men = 1.40, 95% CI: 1.09, 1.81; RR for black men = 1.92, 95% CI: 1.09, 3.40) (Samanic et al. 2004). However, some major limitations of this study included the potential for underestimation of obesity, as height and weight measurements were not available. Also, cancer diagnoses in this study were based only on inpatient records, and cancers diagnosed outside of the VA hospital system were not identified as cases. Additionally, obese patients may be under greater surveillance for other medical conditions than non-obese patients, which may have led to a greater detection of subclinical thyroid cancer in these individuals.

A recent systematic review and meta-analysis included five prospective observational studies of BMI and risk of thyroid cancer, not including the study using obesity discharge data from US veterans (Samanic et al. 2004) or the cohort in northern California (Iribarren et al. 2001). The pooled relative risk per 5 kg/m^2 increase in BMI was 1.33 (95% CI: 1.04, 1.69) for men and 1.14 (95% CI: 1.05, 1.22) for women (Renehan et al. 2008). The results from prospective studies suggest that the positive association is not restricted to women, as was observed in the pooled case–control study (Dal Maso et al. 2000).

102.3 Observational Studies of Other Anthropometric Measurements and Thyroid Cancer Risk

102.3.1 Weight Change and Thyroid Cancer

Several epidemiologic studies have examined the association of weight gain between young adulthood and middle-to-late ages with the risk of thyroid cancer. Weight gain was not associated with greater risk of thyroid cancer in the Japanese case–control study (Suzuki et al. 2008), the pooled case–control study (Dal Maso et al. 2000), or the large prospective study in San Francisco (>10 vs. ≤5 kg, RR = 0.88, 95% CI: 0.57, 1.38) (Iribarren et al. 2001). However, weight gain (highest attained weight except during pregnancy minus weight at menarche) was positively associated with thyroid cancer in a case–control study of Shanghai women under the age of 55 (≥19 vs. ≤9 kg, OR = 2.0, 95% CI: 1.1, 3.7) (Preston-Martin et al. 1993). Currently, it is not clear whether there is a relevant period in one's lifetime where weight change may have an important effect on thyroid cancer development. Studies with detailed information on weight at different ages and reproductive events (i.e., menarche, pregnancy, menopause, etc.) would be useful in investigating this relationship.

102.3.2 Body Fat Composition and Distribution

Body fat and lean body mass were examined in relation to thyroid cancer in the small Icelandic cohort, using information on height, weight, and femur condyl and radio ulnar measurements (Tulinius et al. 1997). A 1-unit increase in body fat was associated with a 2% increased risk of thyroid

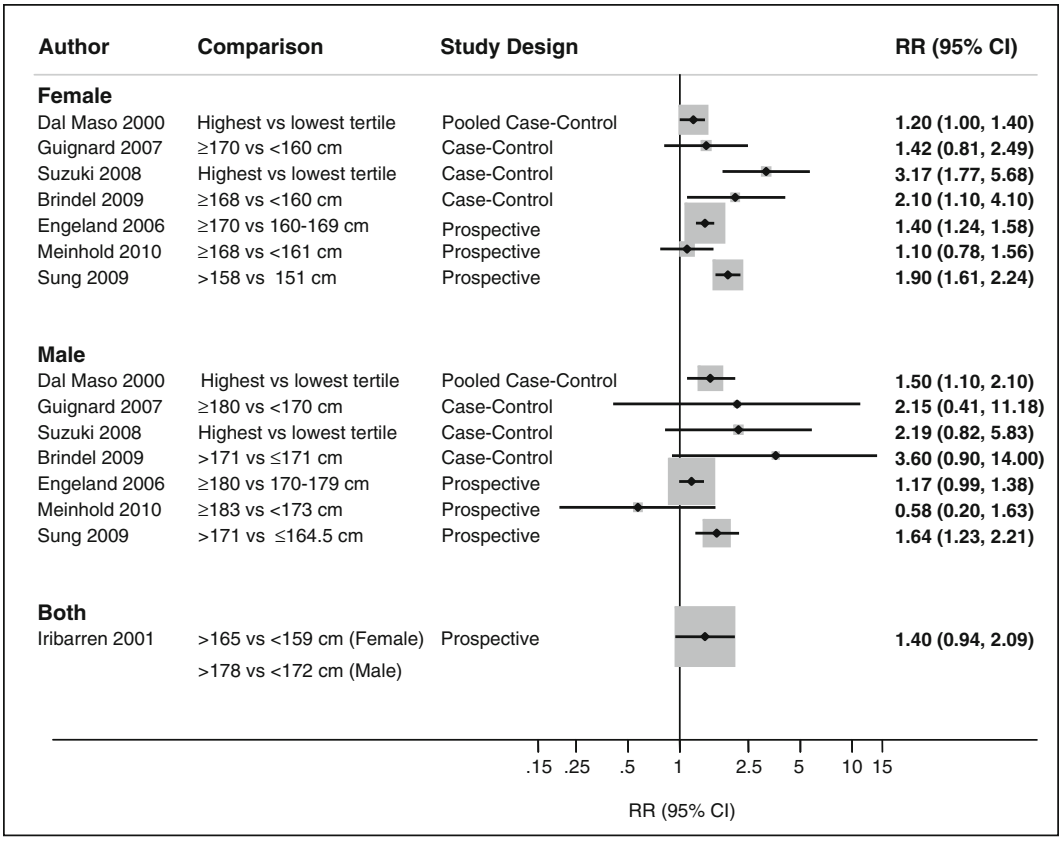

Fig. 102.3 Relative risks (RRs) of thyroid cancer according to highest versus lowest categories of height. The results are presented separately for women and men, where available. Evidence from epidemiologic studies suggests that greater height may increase the risk of thyroid cancer in both women and men, independently of body mass index

cancer in women (95% CI: 0.5–3.6%), but the results in men and for lean body mass in women were not presented, presumably due to lack of an association. As mentioned previously, the interpretation of these results is limited due to the small number of cases and the lack of adjustment for potential confounders other than age.

Currently, there is no evidence from published studies on the relationship between central adiposity and thyroid cancer risk. Epidemiologic studies with measurements for waist circumference or waist-to-hip ratio may provide some insight into potential biologic mechanisms underlying the associations for BMI, or overall adiposity, and thyroid cancer.

102.3.3 Height

Some evidence from these epidemiologic studies (Tables 102.2 and 102.3) suggests that greater height may increase the risk of thyroid cancer, independent of BMI (Fig. 102.3). In the international case–control pooling study, a positive association between height and total thyroid cancer was observed for both men (highest vs. lowest tertile, RR = 1.5, 95% CI: 1.1, 2.1) and women (highest vs. lowest tertile, RR = 1.2, 95% CI: 1.0, 1.4) (Dal Maso et al. 2000). Positive associations between

height and thyroid cancer were observed in two subsequent case–control studies (Suzuki et al. 2008; Brindel et al. 2009). A large study of Norwegian men and women showed a positive association between height and weight in both men (≥180 vs. 170–179 cm, RR = 1.2, 95% CI: 1.0, 1.4) and women (≥170 vs. 160–169 cm, RR = 1.4, 95% CI: 1.2, 1.6) (Engeland et al. 2006). In a large prospective study of Korean adults, every 5-cm increase in height was associated with an increased risk of thyroid cancer in men (HR = 1.16, 95% CI: 1.06, 1.28) and women (HR = 1.24, 95% CI: 1.18, 1.31) (Sung et al. 2009). A positive, but not significant, association was observed in the prospective study from San Francisco (Iribarren et al. 2001). However, no clear association was observed in a recent prospective study (Meinhold et al. 2010).

Positive associations between height and the risk of several other cancer sites, including colon, prostate, and breast have been consistently observed (Sung et al. 2009). The biological mechanisms whereby height may lead to cancer development have not been completely clarified, but it is possible that genes, growth factors, hormones, or other early environmental exposures in childhood and adolescence which contribute to skeletal growth may also have long-term health consequences (Sung et al. 2009); however the role of these factors in thyroid carcinogenesis is not well-understood (Dal Maso et al. 2009).

102.4 Strengths and Limitations of the Available Evidence

In contrast to nearly all of the prospective studies, which had direct measurements of height and weight, information on height and weight in the case–control studies were ascertained through self-report (Table 102.2). In addition to random variation, the results from these case–control studies may be influenced by systematic errors in self-reported height (often overestimated) or weight (often underestimated). Additionally, the same categories of BMI and other anthropometric factors were not always used across the case–control and prospective studies, making comparisons across studies slightly difficult.

The epidemiologic studies described above may not be representative of all the available evidence on the relationship between anthropometric factors and thyroid cancer risk. The strength of the results often influences whether or not researchers submit their work for publication (Olson et al. 2002). Evidence from published studies, therefore, may falsely support a positive association between these anthropometric factors and thyroid cancer risk. Publication bias may become less important in studies combining primary data from small, individual studies using meta-analytic or pooling techniques.

102.5 Biologic Mechanisms

Despite increasing evidence from epidemiologic studies that obesity increases the risk of thyroid cancer, potential biological mechanisms have not been well-described.

Thyroid stimulating hormone (TSH) is secreted from the pituitary gland to compensate for low levels of thyroid hormone, triiodothyronine (T_3) and thyroxine (T_4), and TSH levels are considered a more sensitive measure of thyroid function than thyroid hormones. TSH is a known thyroid growth factor which has been shown to regulate the growth and differentiation of thyroid cells in rodents (Hard 1998), and higher concentrations have been found in thyroid surgery patients with differentiated thyroid cancer compared to patients with benign thyroid disease (Haymart et al. 2008).

It is possible that these hormones are etiologically involved in human thyroid carcinogenesis, although epidemiologic studies directly examining the relationship between thyroid hormone or TSH levels and thyroid cancer are lacking.

Prospective studies examining TSH and its relation to potential thyroid cancer risk factors, particularly obesity, are needed to elucidate whether TSH is a cause or a consequence of these conditions. Thyroid hormones play a role in regulating resting energy expenditure, and may in turn influence the regulation of body weight (Kim 2008). Weight gain is a well-recognized symptom of hypothyroidism, a condition in which the levels of thyroid hormones are deficient, TSH levels are elevated, and the ability of the body to regulate metabolism and resting energy expenditure is impaired. The relationship between weight and thyroid function within a range of TSH considered to be normal, or euthyroid, is more controversial. For instance, it is unknown whether variation in thyroid function within normal range may result in weight change (i.e., through an influence on resting energy expenditure), or whether changes in weight lead to imbalances in thyroid hormones. Some cross-sectional and longitudinal studies show a positive dose–response association between BMI and TSH (Iacobellis et al. 2005; Fox et al. 2008). Increasing evidence from weight-loss intervention studies suggests that moderate-to-extreme weight loss may lead to normalization of TSH levels, and this association may be mediated by adipokines, such as leptin, which directly influence the hypothalamic-pituitary-thyroid axis (Kok et al. 2005).

Alternatively, adiposity may increase the risk of thyroid cancer through an influence on adult iodine requirements (Dal Maso et al. 2009). Given that excess or deficient iodine status may increase the risk of papillary and follicular thyroid cancer, respectively, iodine status could confound an association between BMI and thyroid cancer risk (Dal Maso et al. 2009). However, iodine intake is difficult to measure at the individual level, as iodine-containing foods, such as dairy, bread, and fish vary widely in iodine content depending on geographic region and processing and handling, and self-reported dietary intake is known to be captured with a great amount of variability.

102.6 Applications to Other Areas of Health and Disease

Thyroid cancer is just one of several diseases that may be more common in obese compared to normal-weight individuals. As the prevalence of obesity has risen dramatically over the past few decades in the United States and across the world, it has become increasingly important to study the potential public health consequences of this phenomenon. Gaps in the literature still remain, however. The incorporation of obesity-related biomarkers or more valid measurements of body fat, such as waist circumference or percent body fat, in epidemiologic studies may provide a more accurate picture about the health impact of obesity in the population.

102.7 Conclusion

Although thyroid cancer is a relatively uncommon malignancy, the incidence has been increasing for the past 30 years worldwide. Evidence from epidemiologic and experimental studies suggests that obesity may play a role. In early case-control studies, greater body size was associated with a higher risk of thyroid cancer in women but not men. However, more recent evidence from case–control and prospective studies indicates that overweight or obese men may also be at higher risk compared to normal-weight men. Several epidemiologic studies have observed a positive association between

height and risk of thyroid cancer. Little is understood about the biological pathways underlying the associations between anthropometric factors and thyroid cancer risk, though thyroid stimulating hormone and iodine status may play a role. Large prospective studies, particularly those with measurements of central adiposity or obesity-related biomarkers, may provide greater insight into thyroid cancer etiology. Additionally, data on tumor size would be useful to assess the possibility of over-detection of very small tumors in overweight or obese adults.

Summary Points

- There are few established risk factors for thyroid cancer, and most of these are non-modifiable.
- It has been hypothesized that obesity may be partly responsible for the increase in thyroid cancer incidence over the past three decades.
- Early case–control studies suggested that greater body size may increase the risk of thyroid cancer in women, but recent epidemiologic evidence indicates that overweight or obese men may also be at increased risk.
- Several epidemiologic studies have observed a positive association between height and risk of thyroid cancer.
- The biologic pathways underlying the associations between anthropometric factors and thyroid cancer risk are not well-understood.
- Epidemiologic studies with biomarkers related to obesity of more valid measures of body fat may provide greater insight into the etiology of this malignancy.

Acknowledgment This research was supported in part by the Intramural Research Program of the NIH and the National Cancer Institute.

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Chapter 103
Anthropometry and Ovarian Cancer: The Inflammation Connection

Julia B. Greer

Abstract Ovarian cancer affects over 200,000 women worldwide each year and has one of the highest case-fatality rates of any of the major cancers. Overweight and obesity have been associated with an increased risk of a variety of different illnesses and some types of cancer, in part, due to hormonal and metabolic factors that may drive tumorigenesis. Recent studies have demonstrated that obesity may play a role in ovarian carcinogenesis. Individuals who carry excess adipose tissue have been shown to have a characteristic state of systemic, low-grade inflammation. Many of the risk factors for ovarian cancer, including endometriosis, polycystic ovarian syndromes (PCOS), talc and asbestos exposure, and pelvic inflammatory disease (PID), have a recognized inflammatory component. Evidence linking obesity with an elevated risk of ovarian cancer, to date, has been conflicting; however, many prospective studies have shown that excess adiposity in young adulthood is related to both premenopausal and postmenopausal ovarian cancer risk. Other risk factors for ovarian cancer often affect women in their earlier, reproductive years; thus, the association between obesity in a woman's younger years and ovarian cancer is plausible. Moderate physical activity may be protective against ovarian cancer by decreasing estrogen levels, while vigorous activity may promote ovarian carcinogenesis via aberrations in androgen and progesterone levels. This chapter will review the traditional hypotheses of ovarian cancer—including incessant ovulation, gonadotropin stimulation, and the inflammatory hypothesis—and discuss the most relevant research on adiposity, diet and physical activity, and ovarian cancer risk. A brief overview of obesity and ovarian cancer survival is also included.

Abbreviations

BRCA	Breast cancer antigen gene
SEER	Surveillance Epidemiology End Results
PCOS	Polycystic ovarian syndrome
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
PID	Pelvic inflammatory disease
NSAIDS	Non-steroidal anti-inflammatory medications

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_103,

BMI	Body mass index
OR	Odds ratio
CI	Confidence interval
RR	Relative risk

103.1 Introduction

Ovarian cancer is the leading cause of death due to gynecological malignancies among women (Clarke-Pearson 2009). Approximately 140,000 women die of ovarian cancer in any given year and ovarian cancer is the seventh most common female cancer worldwide. Two thirds of women are over the age of 55 years, when they are diagnosed with ovarian cancer and more than two-thirds of cases, are diagnosed when the disease is advanced, either in state III or stage IV, and has progressed to involve the peritoneal cavity or other organs (Heintz et al. 2006). Figure 103.1 and Tables 103.1 and 103.2 display the staging of ovarian cancer as well as 5-year survival rates by stage and surgical outcomes. Epithelial ovarian cancer is the most common form of ovarian cancer and accounts for about 80–90% of all ovarian cancers, in comparison to germ cell or sex cord stromal tumors, which will not be covered in this chapter (Ness and Cottreau 1999). Invasive and noninvasive epithelial ovarian tumors have the same risk factors.

Ovarian cancer has been called "the silent killer" because it often lacks symptoms until it is in an advanced stage. Some women may experience characteristic symptoms prior to their diagnosis; however, these symptoms are rarely gynecological in nature and may be misleading (see Table 103.3). A large body of research has been devoted to trying to elucidate the etiology of this highly fatal cancer. Table 103.4 displays variables which have been recognized as positively or negatively influencing the likelihood of developing ovarian cancer. The factors which have been shown to be protective against developing ovarian cancer include parity (childbearing), oral contraceptive use, tubal ligation, hysterectomy, and prolonged breast feeding—especially if breastfeeding occurs frequently and without bottle supplementation (Clarke-Pearson 2009; Ness and Cottreau 1999). Risk factors for ovarian cancer include a lack of childbearing (nulliparity), family history of ovarian and/or breast cancer, inheritance of BRCA1 and BRCA2 mutations, infertility, endometriosis, talc use (i.e. talcum powder), asbestos exposure, polycystic ovarian syndrome, and hormone replacement therapy—particularly estrogen-only types of hormone replacement (Clarke-Pearson 2009; Ness and Cottreau 1999).

Evidence also suggests that obesity may contribute to ovarian carcinogenesis (Greer et al. 2006). A sizeable body of research has demonstrated that excess adiposity is associated with risk of cancer at several organ sites, including the colon, breast, pancreas, endometrium, esophagus, and kidney (Calle et al. 2003). The associations observed with the risk of these cancers may, in part, be explained by metabolic dysregulation of various hormones and growth factors that have potentially mitogenic effects (Bianchini et al. 2002). Mounting recent initiatives have also found that obesity and overweight are pro-inflammatory conditions, which may impact the risk of developing a variety of different illnesses, including some forms of cancer. This chapter will review the theories of ovarian carcinogenesis and focus on the interrelationship between obesity and the inflammatory hypothesis of ovarian cancer.

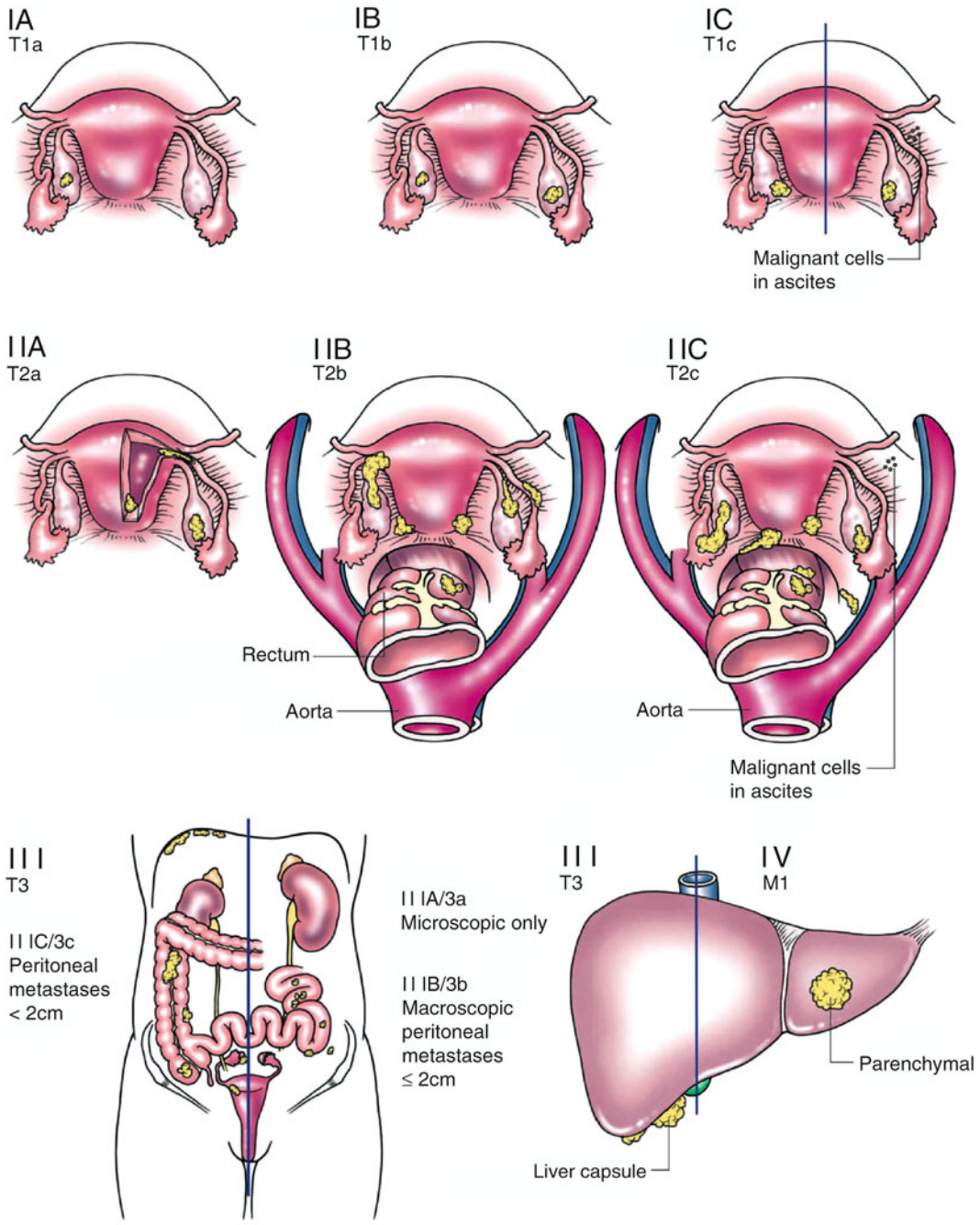

Fig. 103.1 Illustrated staging of ovarian cancer, reprinted with permission from (Heintz et al. 2006)

Table 103.1 Staging of ovarian cancer

Stage	Affected areas
Stage I	Cancer is confined to one or both ovaries. Tumor may be found on the surface of the ovary
IA	Tumor limited to one ovary
IB	Tumor in both ovaries
IC	Tumor limited to one or both ovaries with any of the following present: capsule ruptured, tumor on ovarian surface, malignant cells in ascites, or peritoneal washings
Stage II	Cancer involves one or both ovaries with extension into the pelvic region—it may be found in the uterus, fallopian tubes, bladder, sigmoid colon, or rectum. Few women are diagnosed at this stage
IIA	Tumor involves one or both ovaries with pelvic extension to uterus and/or fallopian tube(s)
IIB	Tumor involves one or both ovaries with pelvic extension to other pelvic tissues
IIC	Tumor involves one or both ovaries with pelvic extension (IIA or IIB) with malignant cells in ascites or peritoneal washings
Stage III	Cancer has spread beyond the pelvis to the abdominal wall or abdomen, small bowel, lymph nodes, or liver surface
IIIA	Tumor involves one or both ovaries with microscopically confirmed peritoneal spread beyond the pelvis
IIIB	Tumor involves one or both ovaries with macroscopic peritoneal spread beyond the pelvis 2 cm or fewer in greatest dimension
IIIC	Tumor involves one or both ovaries with a macroscopic peritoneal spread beyond the pelvis 2 cm or greater in greatest dimension and/or regional lymph node spread
Stage IV	Cancer has spread to distant organs including the liver, spleen, bones or lung

Table 103.2 Stage of ovarian cancer at diagnosis and 5-year survival rates, in percentages (Reprinted with permission from Clarke-Pearson 2009)

Stage	Patients with tumor stage at diagnosis	5-year survival rate (international)
Stage I	37	83–90
Stage II	8	65–71
Stage III	44	
IIIA	3	47
IIIB	5	42
IIIC	35	33
Outcome of initial surgery		
No residual tumor	NA	63
Residual disease		
Optimal debulking (<2 cm nodules)	NA	33
Suboptimal debulking (≥2 cm nodules)	NA	25
Stage IV	11	19

NA not applicable

Table 103.3 Frequent symptoms of ovarian cancer

Fatigue
Back pain
Urinary symptoms, such as urgency and frequency
Bloating, increasing abdominal girth
Abdominal or pelvic pain
Constipation

Table 103.4 Variables associated with increased or decreased risk of developing ovarian cancer

Increased risk	Decreased risk
Family history of breast, ovarian cancer	Childbearing (parity)
Known BRCA1 or BRCA2 germline mutation	Oral contraceptive use
Lack of childbearing (nulliparity)	Breastfeeding (of significant duration)
Endometriosis	Tubal ligation
Talc use/asbestos exposure	Hysterectomy
Polycystic ovarian syndrome (PCOS)	
Pelvic inflammatory disease (PID)	
Obesity, especially in youth	
Infertility	
Cigarette smoking (mucinous tumors)	

103.2 Hypotheses Concerning Ovarian Cancer Etiology

103.2.1 Incessant Ovulation

In 1971, Fathalla first suggested that consistent ovulation without pregnancy-induced rest periods contribute to neoplasia of the ovarian epithelium (Fathalla 1971). The incessant ovulation hypothesis of ovarian cancer posits that stromal epithelial clefts and inclusion cysts form following ovulation and undergo rapid proliferation during the 24 h that follow each ovulatory episode. This hypothesis hinges on the idea that repeated cell damage on the ovarian epithelium due to the effects of ovulation translates into an enhanced potential for ineffective DNA repair and/or inactivation of tumor suppressor genes and, subsequently drives mutagenesis (Ness and Cottreau 1999). Oral contraceptive use, parity, and breastfeeding decrease the risk of ovarian cancer by interrupting the long-standing and consistent ovarian ovulation process. However, weighted evidence of the actual quantitative decrease in risk due to interrupted ovulation is in greater magnitude than what would be inferred due only to the number of anovulatory months that a woman experiences with pregnancy or from taking oral contraceptives.

As Risch noted, ovulations typically occur over a period of at least 20 years (Risch 1998). On average, any given full-term pregnancy suppresses ovulation for perhaps a year, which amounts to, at most, 5% of the total number of ovulations. Even including a latency effect, this would correspond to only a 6% risk reduction, using SEER data. Epidemiologic studies demonstrate that among parous women, the reduction in risk for each pregnancy subsequent to the first is about 14–16%, an amount statistically inconsistent with the 5% for the number of suppressed ovulation. Each year of oral contraceptive use also suppresses ovulation at most for a year but the risk reduction for an additional year of use among ever users is only about 9%, which also is inconsistent with the reduction in risk that has been noted with pregnancy. Additional conflicting evidence for this hypothesis of ovarian cancer risk is seen in conditions such as polycystic ovarian syndrome (PCOS) and infertility (Ness and Cottreau 1999). Each of these conditions is associated with an *increased* risk of ovarian cancer although anovulation is a frequent characteristic of both; obese women are also more likely to be diagnosed with PCOS and often suffer fertility issue.

103.2.2 Gonadotropin Stimulation

The gonadotropins include luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH stimulates ovarian granulosa cells and incites follicular growth, while LH stimulates the theca cells

of the ovaries and its surge triggers ovulation. The gonadotropin hypothesis asserts that hormonal stimulation of ovarian epithelial cells, either on the surface of the ovary or within ovarian inclusion cysts, and possibly mediated through excessive gonadotropin secretion, contributes etiologically to ovarian carcinogenesis (Ness and Cottreau 1999). In 1983, Cramer and Welch published an important paper in which they noted that the ovarian epithelium repeatedly invaginates during a woman's life to form clefts and inclusion cysts (Cramer and Welch 1983). The authors suggested that under significant gonadotropin stimulation of the ovarian stromal cells and consequent activation by estrogen and/or estrogen precursors, the epithelium may proliferate and undergo malignant transformation. Cramer and Welch conclude that factors which influence systemic estrogen level regulation would also affect gonadotropin stimulation and, tangentially, the paracrine estrogenic milieu of the ovarian epithelium. The gonadotropin hypothesis is reflective of why pregnancy/parity and oral contraceptive use have been shown to be protective against ovarian cancer, since both may lower basal and peak gonadotropin stimulation and also suppress ovulation.

An extrapolation of this hypothesis is the theory that excess estrogenic stimulation increases ovarian cancer risk (Risch 1998). Estrogen is derived primarily from the ovaries, and to a lesser extent, from adipose tissue during a woman's premenopausal years; postmenopausally, estrogen is derived primarily from the aromatization of androgens to estrogen from visceral adipose tissue. Under this principle, obesity should contribute to postmenopausal ovarian cancer more than to premenopausal ovarian cancer because overweight and obese older women should create excess, endogenous estrogen via the aromatization of testosterone and other androgens to estrogen from their increased adiposity. In a meticulous review of hormonal factors and ovarian cancer, Risch describes the current research on hormonal theories of ovarian cancer and provides conclusive evidence for the role of androgens in promoting and progesterone in attenuating ovarian cancer risk (Risch 1998). As evidence, he notes that higher levels of androstenedione and dehydroepiandrosterone have been observed among women with ovarian cancer than controls, and that PCOS—which is characterized by elevated androstenedione and testosterone levels among women—is a well established risk factor for ovarian cancer. Additionally, he notes that pregnancy and childbearing have been shown to be associated with decreased risk of ovarian cancer, although pregnancy is a state in which women have greatly elevated levels of estrogen and progesterone; if estrogen is a risk factor for ovarian cancer, then pregnancy would be associated with increased, rather than decreased risk. He provides evidence of the apoptotic effects of progesterone, which attenuate and counteract estrogen's mitogenic effects. Although reiterating the body of Risch's research goes beyond the scope of this chapter, readers particularly interested in the hormonal etiology of ovarian cancer are referred to his article and encouraged to read it in depth (Risch 1998). Regardless of the myriad theories relating to hormonal risks of ovarian tumorigenesis, there have been limited numbers of studies of endogenous hormone levels and ovarian cancer. To date, no consistent evidence implicates steroid hormone levels in ovarian carcinogenesis.

103.2.3 Inflammation

The inflammatory hypothesis asserts that conditions involving local inflammation to the ovarian epithelium trigger cellular turnover and rapid proliferation, as well as a change in the cellular environment in which a chronic inflammatory response predominates (Ness and Cottreau 1999). States of chronic inflammation result in a concurrent shift in cytokine and chemokine balance that may foster an environment of genomic instability in addition to cellular regeneration, thereby potentiating the carcinogenic process. Asbestosis, talc exposure, endometriosis, and pelvic inflammatory disease

(PID) are all conditions in which a consistent and long standing state of local inflammation encompasses the ovarian epithelium; each of these conditions has been associated with a significantly elevated risk of developing ovarian cancer (Ness and Cottreau 1999; Brinton et al. 1997). Parallel findings are that tubal ligation and hysterectomy, each of which interrupts the pathway of inflammants to the ovaries, decrease the risk of developing ovarian cancer. Many studies have examined inflammatory variables and their relationship with ovarian cancer. For instance, the records of 20,686 women hospitalized with endometriosis during the period 1969–1983 were evaluated in a Swedish study by Brinton and colleagues (Brinton et al. 1997). The risk of ovarian cancer was found to be 4.2 times as high among subjects with a long standing history of ovarian endometriosis compared to age and period-specific incidence rates of the Swedish population.

Additional evidence supporting a role for inflammation in ovarian cancer risk was noted in a Canadian study conducted between 1989 and 1992 of 450 histologically verified new primary epithelial ovarian cancer cases in women ages 35–79 years and 564 randomly selected population controls (Risch and Howe 1995). In this study, cases were more likely than controls to report having had one or more episodes of PID. After making adjustments for age, parity, duration of oral contraceptive use, and other factors, the odds ratio (OR) was 1.53 [95% confidence interval (CI) = 1.10–2.13; $P = 0.012$] for women who reported having an episode of PID. Higher risk was present for women with recurrent PID (OR 1.88; 95% CI = 1.13–3.12; $P = 0.014$). The elevated risk associated with PID was observed particularly among women <60 years of age at interview (OR 1.60; 95% CI = 1.09–2.35; $P = 0.016$), for nulliparous women who had given birth to only one child (OR 2.40; 95% CI = 1.39–4.15; $P = 0.0017$), and for the small number of women who reported having an episode of PID prior to the age of 20 (OR 3.08; 95% CI = 1.17–8.13; $P = 0.023$).

103.3 Obesity, Inflammation, and Cancer

103.3.1 What Is Inflammation and How Might It Contribute to Carcinogenesis?

Inflammation is the multi-step, immune, and vascular response to tissue injury due to the effects of pathogens, irritants, and a variety of other noxious stimuli (Coussens and Werb 2002). Inflammation incites a synergistic network of chemical messengers, which establish and maintain a host response that is specifically designed to heal damaged tissue. Mobilized leukocytes and a family of modulating chemotactic cytokines activate downstream effector cells, establishing the natural evolution of the inflammatory response. Acute inflammatory responses are the primary systems by which wounds heal. Numerous mechanisms involved in the inflammatory response may contribute to neoplasia. In fact, each of the three hallmark steps involved in carcinogenesis—initiation, promotion, and progression—may be significantly influenced by the inflammatory process.

The cellular environment that characterizes inflammatory states supports the development of genomic aberrations and may help to initiate carcinogenesis. Free radicals are highly reactive atoms or groups of atoms with an unpaired electron that are generated by normal physiological processes including both the acute and chronic inflammatory states and are ubiquitous in the human body. Free radicals' effects may contribute to cancer initiation. Some free radicals can induce genetic alterations and posttranslational modifications of key, regulatory cancer-related proteins. Reactive oxygen and nitrogen intermediates, for instance, are capable of causing oxidative damage and nitration of DNA bases, which potentiate the frequency of the occurrence of DNA damage (Macarthur et al. 2004).

Table 103.5 Various types of cancers associated with inflammation

Malignancy	Inflammatory agent(s)
Bladder	Chronic urinary bladder catheterization, Schistosomiasis
Bronchial	Asthma, cigarette smoke, silica
Cervical, anogenital	Human papillomavirus
Cholangiocarcinoma	Chinese liver fluke
Colorectal	Inflammatory bowel disease (Crohn's, ulcerative colitis)
Esophageal	Barrett's metaplasia, gastroesophageal reflux
Gastric adenocarcinoma/MALT (mucosa-associated lymphoid tissue)	*Helicobacter pylori*-associated gastritis/ulcers
Hepatocellular	Hepatitis B and/or C
Kaposi's sarcoma	Human herpes virus type B, human immunodeficiency virus (HIV)
Mesothelioma	Asbestos
Nasopharyngeal	Epstein-Barr virus
Ovarian (epithelial)	Asbestos, talc, PID (pelvic inflammatory disease)
Pancreas	Chronic pancreatitis, hereditary pancreatitis
Prostate	Prostatitis
Vulvar	Lichen sclerosus

The inflammatory response also contributes to the growth of tumors. When tissues are injured, cells that have been depleted will expand and repopulate to achieve the numbers necessary for proper tissue or organ function. By extension of their role in tissue repair and replacement, inflammatory mediators may send survival and proliferative signals to normal as well as initiated cells, leading to the growth promotion of healthy tissues as well as dysplastic or neoplastic tissues (Coussens and Werb 2002).

In the majority of cases, the inflammatory response is a self-limiting event that resolves without complications. However, chronic inflammation is characterized by a shift in the cell types at the site of inflammation which can lead to lasting and deleterious health effects. Considerable evidence demonstrates that chronic inflammatory states may positively influence the development of cancer (Coussens and Werb 2002; Macarthur et al. 2004). Some of the known medical conditions and infectious agents with a recognized inflammatory component that are associated with increased cancer risks include *H. pylori* infection and gastric cancer, hepatitis B and hepatocellular cancer, chronic pancreatitis and pancreatic cancer, inflammatory bowel disease and colon cancer, and many others (as displayed in Table 103.5). Various types of tumors have been shown to over express cyclooxygenase-2 (COX-2), a modulatory molecule in inflammation and carcinogenesis which has been implicated in the positive regulation of growth and tumorigenesis. Some studies have also noted a protective effect of nonsteroidal anti-inflammatory medications (NSAIDs) on the risk of developing some forms of cancer (reviewed in Coussens and Werb 2002).

Epidemiologic evidence from both *in vivo* and *in vitro* studies has demonstrated that inflammation is an important component in the etiology of various cancers, including ovarian cancer. Although the incessant ovulation hypothesis often focuses on the interplay of hormonal factors and ovulation in carcinogenesis, the potentially mutagenic effect of ovulation may, in fact, be inflammation mediated. At the level of the ovarian follicle(s), ovulation may be characterized by a remarkable inflammatory process. A number of inflammatory mediators, including prostaglandins, leukotrienes, and vasoactive substances such as bradykinin are locally elevated during ovulation (Ness and Cottreau 1999). The rupture of follicles likely also involves a stage of tissue remodeling in which cell division and turnover rates are heightened, just as during inflammatory states.

103.3.2 Obesity: A Growing, Global Issue

Being overweight has become a public health issue of huge proportions. Obesity is defined as a body mass index (BMI) of ≥30 kg/m squared. Rates of both childhood and adult obesity in developed countries have been rising at an alarming rate. In February of 2001, the International Agency for Research on Cancer of the World Health Organization concluded that limiting weight gain during adult life, thereby avoiding overweight and obesity, reduces the risk of postmenopausal breast cancer and cancers of the colon, endometrium, kidney (renal cell), and adenocarcinoma of the esophagus (Vainio et al. 2002). In a 16-year prospective study of over 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment, members of this cohort who had a BMI of at least 40 had death rates from all cancers combined that were 52% higher (for men) and 62% higher (for women) than the rates in men and women of normal weight (Calle et al. 2003). In both men and women, BMI was also significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends of increasing risk with higher BMI values were observed for death from cancers of the stomach and prostate in men and for death from cancers of the breast, uterus, cervix, and ovary in women. Avoidance of weight gain thus seems to be an important factor for cancer prevention.

103.3.3 Obesity and Insulin Resistance: The Inflammation Connection

In part, associations of excess adiposity with cancer risk are explained by alterations in the metabolism of endogenous hormones—including sex steroids, insulin, and insulin-like growth factors—which can lead to distortion of the normal balance between cell proliferation, differentiation, and apoptosis (Bianchini et al. 2002). Although visceral adipose tissue was once viewed simply as a depot of fatty tissue and energy, recent research shows that it may also act as an active endocrine organ capable of undergoing hyperplastic changes (Hajer et al. 2008). Adipose tissue plays a central role in lipid and glucose metabolism, blood pressure maintenance, coagulation, as well as feeding behavior and satiety. Visceral adiposity also produces a variety of hormones and cytokines that are the main participants in the inflammatory process, including tumor necrosis factor-alpha, interleukin-6, adiponectin, leptin, resistin, and plasminogen activator inhibitor-1. A clustering of vascular risk factors including dyslipidemia, hypertension, and hyperglycemia, that has been observed among individuals who have an elevated proportion of visceral obesity is often referred to as metabolic syndrome (Baranova 2008). The most critical after-effect of the metabolic syndrome is low-level systemic inflammation supported by adipose-specific synthesis of active proinflammatory molecules. The factors secreted by adipocytes and stromal cells mediate increased peripheral insulin resistance and contribute to the development of the metabolic syndrome and a prediabetic state.

Obesity is associated with reduced glucose oxidation, increased lipid oxidation, hyperinsulinemia, and the development of clinical diabetes. Some studies have found that diabetes may increase the risk of neoplasia. Notably, a 16-year, prospective study that included over 1 million individuals (467,922 men and 588,321 women) who were free of cancer at baseline observed that diabetes was an independent predictor of mortality from cancer of the colon, pancreas, female breast, and, in men, of the liver and bladder (Coughlin et al. 2004). In the past decade, research on type II diabetes has found that inflammatory mediators may play a role in disease etiology. Some studies have shown that elevated levels of the inflammatory markers C-reactive protein and interleukin-6 are able to predict the development of type II diabetes in prospective cohort investigations (Pradhan et al. 2001). Most studies of diabetes and ovarian cancer risk have been inconclusive or have failed to show a significant association.

Risch's androgen hypothesis may come to play in ovarian cancer risk and obesity. Elevated BMI has been noted to be associated with increased free serum testosterone and decreased sex hormone binding globulin. Even without signs of androgenization among women, such as hirsutism or menstrual abnormalities, moderate levels of obesity have been correlated with women having increased quantities of both free and total serum testosterone (Risch 1998). In addition, due to the existence of low-grade, systemic inflammation, obese individuals have been observed to have higher circulating levels of the proinflammatory adipokines resistin and leptin, both of which have been correlated to increased insulin resistance (Baranova 2008). In general, obese individuals also have lower circulating levels of the anti-inflammatory adipokine, adiponectin (Baranova 2008); this adipokine profile favors sustained systemic inflammation, and creates an environment that supports the development of type II diabetes, fatty liver disease, atherosclerosis, and the promotion of some types of neoplasia. Increased levels of angiogenic factors such as vascular growth factors have also been noted in overweight and obese individuals (Silha et al. 2005), which may explain why obese individuals diagnosed with a number of different cancer types have decreased disease-free survival following initial treatment, worse prognosis, and greater risk of metastatic disease than lean individuals.

103.4 Obesity and Ovarian Cancer

103.4.1 Anthropometric Variables and Ovarian Cancer Risk

While the evidence has been conflicting, some studies support the relationship of anthropometric variables with ovarian cancer risk. Case-control studies of anthropometric variables and ovarian cancer risk suffer a number of limitations. Studies of current or recent weight and ovarian cancer risk may be biased by weight loss due to disease; studies of recalled, former weight may also be biased by underreporting. Additionally, among all studies, self-reported height and weight are more common than measured height and weight, which may further dilute findings. Nonetheless, each of these biases may steer results more towards the null. A 2005 study by Zhang and colleagues attempted to address the effects of disease on ovarian cancer risk (Zhang et al. 2005a). The study sample included 254 cases with histologically confirmed epithelial ovarian cancer and 652 controls. Information of adult height and weight at diagnosis, at 5 years before diagnosis and at age 21 years was recorded. Ovarian cancer risk was significantly increased with higher body weight and BMI at 5 years before diagnosis, but not at diagnosis. The adjusted ORs were 1.67 (95% CI = 1.04–2.67) for body weight >60 kg versus < or =50 kg and 1.75 (95% CI = 1.13–2.72) for BMI > or = 25.0 versus 18.5–21.9 at 5 years before diagnosis.

Due to the relative rarity of ovarian cancer, prospective studies may not be adequately powered to detect valid associations. Among prospective studies, some studies have found that a woman's risk of ovarian cancer might be more affected by her weight in youth rather than during adulthood. One large-scale, prospective study recruited a Norwegian cohort of approximately 1.1 million women, aged 14–74 years, who were measured and evaluated between 1963 and 1999 (Engeland et al. 2003). The cohort was followed for an average of 25 years through linkage to population-based cancer and death registries. Results indicated that women who were overweight or obese in adolescence or young adulthood had an increased risk of ovarian cancer; women with a very high BMI in adolescence had a relative risk of 1.56 (95% CI = 1.04 - 2.32) compared with women with average BMI. No such association was seen in older women (see Tables 103.6 and 103.7). This finding is especially valuable in light of the growing epidemic of obesity among children and adolescents in developed countries.

Other studies have found that obesity is only related to ovarian cancer in selected situations or among particular cohorts of women. For instance, Table 103.8 shows the results of a prospective

Table 103.6 Relative risk of ovarian cancer with 95% confidence intervals (95% CI) by age at measurement from Cox regression analysis by body mass index (BMI), adjusted for birth cohort (Engeland et al. 2003)

	BMI, kg/m^2			
Age at measurement, years	<18.5 RR (95% CI)	18.5–24.9 RR (95% CI)	25.0–29.9 RR (95% CI)	≥30.0 RR (95% CI)
20–29	0.97 (0.71–1.33)	1.00 (referent)	1.02 (0.83–1.25)	1.45 (1.02–2.04)
30–39	1.00 (0.69–1.45)	1.00 (referent)	1.00 (0.88–1.13)	1.07 (0.87–1.31)
40–49	1.44 (1.03–2.01)	1.00 (referent)	0.87 (0.79–0.95)	0.96 (0.85–1.10)
50–59	0.72 (0.39–1.35)	1.00 (referent)	1.00 (0.90–1.11)	0.99 (0.88–1.12)
60–69	1.61 (0.92–2.80)	1.00 (referent)	1.04 (0.90–1.20)	0.94 (0.79–1.12)
70–74	0.52 (0.07–3.78)	1.00 (referent)	1.02 (0.72–1.44)	0.79 (0.52–1.21)

Table 103.7 Relative risk of ovarian cancer with 95% confidence intervals (95% CI) from Cox regression analysis, adjusted for age at measurement and birth cohort, according to body mass index (BMI) and height (Engeland et al. 2003)

Variable	Relative risk (95% CI)	Test for linear trend[a]
Adolescent measurement BMI[b]		
Low	1.19 (0.85–1.67)	
Medium	1.00 (referent)	
High	1.43 (1.00–2.04)	
Very high	1.56 (1.04–2.32)	
Adolescent measurement BMI, kg/m^2		$P = .15$
<18.5	1.09 (0.92–1.30)	
18.5–24.9	1.00 (referent)	
25.0–29.9	0.96 (0.91–1.01)	
≥30.0	0.98 (0.92–1.05)	
Height, cm		$P < .001$
<150	0.98 (0.82–1.16)	
150–154	0.87 (0.79–0.95)	
155–159	0.96 (0.90–1.02)	
160–164	1.00 (referent)	
165–169	1.08 (1.01–1.14)	
170–174	1.15 (1.06–1.25)	
≥175	1.29 (1.11–1.51)	

[a] BMI and height, respectively, were included as continuous variables

[b] Defined by percentiles in a U.S. reference population: low (<25th), medium (25th–74th), high (75th–84th), and very high (≥85th)

study of 94,525 U.S. women who were followed for 7 years demonstrated that there was an elevated risk of ovarian cancer among obese compared to normal weight women, but only among those women who never used hormone replacement therapy (multivariable relative risk 1.83, 95% CI = 1.18–2.84) (Leitzmann et al. 2009). A recent meta-analysis by Schouten and colleagues was composed only of prospective studies and evaluated anthropometric variables and ovarian cancer risk (Schouten et al. 2008). Results of this study demonstrate that, while height was associated positively with risk of ovarian cancer, the only pooled finding concerning adiposity was that elevated BMI was associated with an increased risk of premenopausal ovarian cancer. A shown in Tables 103.9 and 103.10, in our own work evaluating a population-based study of 763 ovarian cancer cases and 1348 healthy controls in the U.S., we found that high weight and BMI in early adulthood, as well as weight gain since adolescence, were associated with an elevated risk of ovarian cancer, but particularly among nulliparous women (Greer et al. 2006)

Table 103.8 Relative risk of ovarian cancer in relation to BMI at baseline in all women and in subgroups of women as defined by selected reproductive variables (Leitzmann et al. 2009)

		BMI at baseline, kb/m^2		*P* value for test	
Variable	<25.0	25.0–29.9	≥30.0	Of trend	Of interaction
All women					
Person-years	291,801	206,936	139,773		
No. of cases	141	86	76		
Age adjusted RR (95% CI)	1.0	0.85 (0.65–1.11)	1.14 (0.86–1.51)	.45	
Multivariate RR (95% CI)[a]	1.0	0.89 (0.69–1.18)	1.26 (0.94–1.68)	.16	
Menopausal hormone use					
Never use					
No. of cases	39	43	43		
Multivariate RR (95% CI)	1.0	1.39 (0.89–2.14)	1.83 (1.18–2.84)	.007	
Ever use					
No. of cases	102	43	33		
Multivariate RR (95% CI)[a]	1.0	0.68 (0.48–0.98)	0.96 (0.65–1.43)	.53	.02
Hysterectomy					
No					
No. of cases	110	61	53		
Multivariate RR (95% CI)	1.0	0.85 (0.62–1.17)	1.19 (0.85–1.66)	.42	
Yes					
No. of cases	31	25	23		
Multivariate RR (95% CI)[a]	1.0	1.04 (0.62–1.77)	1.49 (0.87–2.58)	.16	.72
Combination of menopausal hormone use and hysterectomy					
Never used menopausal hormones					
No hysterectomy					
No. of cases	37	35	36		
Multivariate RR (95% CI)	1.0	1.24 (0.78–1.97)	1.74 (1.09–2.76)	.02	
Hysterectomy					
No. of cases	2	8	7		
Multivariate RR (95% CI)[a]	1.0	3.83 (0.82–18.01)	3.81 (0.79–18.34)	.13	
Ever used menopausal hormones					
No hysterectomy					
No. of cases	73	26	17		
Multivariate RR (95% CI)	1.0	0.62 (0.39–0.97)	0.77 (0.45–1.31)	.15	
Hysterectomy					
No. of cases	29	17	16		
Multivariate RR (95% CI)[a]	1.0	0.82 (0.45–1.40)	1.34 (0.73–2.48)	.41	.55
Family history of ovarian cancer					
No					
No. of cases	119	81	67		
Multivariate RR (95% CI)	1.0	1.02 (0.77–1.36)	1.36 (1.00–1.86)	.06	
Yes					
No. of cases	22	5	9		
Multivariate RR (95% CI)[a]	1.0	0.29 (0.11–0.77)	0.74 (0.34–1.62)	.31	.02

95% CI 95 percent confidence interval; *BMI* body mass index; *RR* relative risk

[a]The multivariate model used person-time as the underlying time metric and included the following covariates: age, race/ethnicity (white/non-white), family history of ovarian cancer, family history of breast cancer, duration of oral contraceptive use, menopausal hormone therapy, and physical activity

Table 103.9 Adjusted odds ratios and 95% confidence intervals for height, weight, and body mass index at various life periods for all women in the SHARE study (Greer et al. 2006)

	All women ($N = 2110$)				
		Cases	Controls	Adjusted OR[a]	95% CI
Height, cm					
Quartile 1	<157.7	179	379	1.00	
Quartile 2	157.5–162.6	231	376	1.26	0.98–1.62
Quartile 3	162.7–167.6	92	177	1.07	0.78–1.48
Quartile 4	>167.6	260	416 *trend P.16*	1.26	0.98–1.61
Recent weight, kg					
Quartile 1	<57.6	170	339	1.00	
Quartile 2	57.6–65.3	207	373	1.13	0.87–1.46
Quartile 3	65.4–76.5	200	324	1.31	1.00–1.72
Quartile 4	>76.5	185	312 *trend P.04*	1.29	0.98–1.70
Weight at age 18					
Quartile 1	<49.5	192	401	1.00	
Quartile 2	49.5–54.0	210	395	1.07	0.83–1.37
Quartile 3	54.1–58.5	168	267	1.32	1.01–1.74
Quartile 4	>58.5	189	283 *trend P.006*	1.29	1.06–1.80
Recent BMI					
Quartile 1	<21.8	173	330	1.00	
Quartile 2	21.8–24.6	196	341	1.10	0.85–1.44
Quartile 3	24.7–28.7	192	339	1.14	0.87–1.49
Quartile 4	>28.7	201	338 *trend P.12*	1.24	0.95–1.63
BMI at age 18					
Quartile 1	<18.7	189	350	1.00	
Quartile 2	18.7–20.2	165	348	0.92	0.70–1.20
Quartile 3	20.3–21.9	197	310	1.22	0.94–1.59
Quartile 4	>22.0	208	338 *trend P.07*	1.18	0.91–1.53
Weight change, recent-age 18					
Quartile 1	<4.5	144	300	1.00	
Quartile 2	4.5–11.2	257	400	1.35	1.03–1.75
Quartile 3	11.3–20.2	176	337	1.14	0.86–1.52
Quartile 4	>20.2	182	309 *trend P.11*	1.38	1.04–1.85
BMI change, recent–age 18					
Quartile 1	<1.7	191	335	1.00	
Quartile 2	1.7–4.1	192	337	1.00	0.77–1.30
Quartile 3	4.2–7.5	185	339	0.99	0.76–1.29
Quartile 4	>7.5	191	335 *trend P.49*	1.11	0.85–1.46

BMI body mass index; *CI* confidence interval; *OR* odds ratio

[a] Adjusted for age, race (white, other), number of live births, family history of ovarian cancer, tubal ligation, and oral contraceptive use (ever, never)

103.4.2 Physical Activity and Ovarian Cancer Risk

There is a strong correlation between lack of physical activity and obesity. Physical activity has been shown to decrease adiposity, increase lean muscle mass, and improve glucose and lipid profiles. Physical activity decreases postmenopausal endogenous estrogen levels, which have been correlated to the relationship of increasing physical activity levels and diminished risks of breast and endometrial cancers among older women. The association between physical activity and ovarian cancer is

Table 103.10 Adjusted odds ratios and 95% confidence intervals for height, weight, and body mass index (BMI) at various life periods for nulliparous women only in the SHARE study (Greer et al. 2006)

	Nulliparous women ($N = 406$)			
	Cases	Controls	Adjusted OR*	95% CI
Height, cm				
Quartile 1	55	32	1.00	
Quartile 2	63	60	0.59	0.33–1.04
Quartile 3	40	19	1.31	0.64–2.70
Quartile 4	77	60 trend P.99	0.79	0.45–1.39
Recent weight, kg				
Quartile 1	47	53	1.00	
Quartile 2	66	48	1.30	0.74–2.27
Quartile 3	62	35	1.80	1.00–3.24
Quartile 4	60	35 *trend P.03*	1.78	0.99–3.23
Weight at age 18				
Quartile 1	48	52	1.00	
Quartile 2	62	44	1.39	0.79–2.45
Quartile 3	58	19	3.31	1.69–6.46
Quartile 4	65	55 *trend P.26*	1.22	0.70–2.10
Recent BMI				
Quartile 1	45	55	1.00	
Quartile 2	66	48	1.60	0.92–2.79
Quartile 3	55	37	1.67	0.92–3.02
Quartile 4	69	31 *trend P.003*	2.53	1.39–4.61
BMI at age 18				
Quartile 1	42	47	1.00	
Quartile 2	54	34	1.72	0.93–3.17
Quartile 3	66	34	2.19	1.20–4.00
Quartile 4	71	55 *trend P.26*	1.40	0.80–2.45
Weight change, recent–age 18				
Quartile 1	44	61	1.00	
Quartile 2	86	55	2.14	1.26–3.64
Quartile 3	53	35	1.81	0.98–3.34
Quartile 4	50	19 *trend P.001*	3.73	1.88–7.42
BMI change, recent–age 18				
Quartile 1	59	62	1.00	
Quartile 2	62	50	1.30	0.77–2.20
Quartile 3	59	37	1.53	0.86–2.75
Quartile 4	53	21 *trend P.003*	2.67	1.40–5.11

BMI body mass index; *CI* confidence interval; *OR* odds ratio

[a]Adjusted for age, race (white/other), family history of ovarian cancer, tubal ligation, and oral contraceptive use (ever/never)

less well defined. For example, in a population-based case-control study (767 histologically-verified cases and 1367 healthy controls) of women 20–69 years of age, leisure-time physical activity was significantly associated with reduced occurrence of ovarian cancer ($P = .01$) (Cottreau et al. 2000). After adjusting for age, parity, oral contraceptive use, tubal ligation, family history of ovarian cancer, race, and BMI, women who reported the highest level of activity had an OR of 0.73 (95% CI = 0.56–0.94) for ovarian cancer compared with women who reported the lowest level s of physical activity. When the authors analyzed the relationship by various recalled time periods during life, the odds ratios for the highest versus the lowest category of activity at ages 14–17, 18–21, 22–29, 30–39, 40–49, and >50 years ranged from 0.64 to 0.78.

However, other studies have noted that frequent and vigorous physical activity may actually *increase* the risk of ovarian cancer. For instance, during a 16-year follow-up (from 1980 to 1996), 1.2 million person-years were accrued by 92,825 cohort members 377 cases of epithelial ovarian cancer were confirmed in a prospective study known as the Nurses' Health Study (Bertone et al. 2001). Recreational physical activity was quantified in hours of duration, as well as intensity level. Compared with inactive women, participants reporting higher activity in terms of metabolic equivalent task hours (MET hours) were at greater risk of ovarian cancer (Relative Risk [RR] for 20 to <30 MET hours/week = 1.84 [95% CI = 1.12–3.02]; RR for >30 MET hours/week = 1.27 [95% CI = 0.75–2.14]). These findings are plausible, because known hormone and ovulatory function changes are a frequent consequence of vigorous athletic training. Running may increase levels of androgens, prolactin, and gonadotropins and levels of some androgens remain elevated even hours after a long race (Mathur et al. 1986). Even moderate amounts of aerobic exercise may have effects on female reproductive function, such as altered luteal progesterone levels, which would not be suspected from menstrual patterns alone (Risch 1998).

103.4.3 Dietary Variables and Ovarian Cancer

An unhealthy diet can contribute to the risk of cancer, either directly by ingesting known carcinogens (such as high-heat cooked meats that contain heterocyclic amines and polyaromatic hydrocarbons) or indirectly, by the promotion of overweight and obesity. Among the Women's Health Initiative Dietary Modification Randomized Controlled Trial of over 48,000 post-menopausal women, a lowfat diet was shown to be protective against ovarian cancer and decreased risk by about 40% (Prentice et al. 2007). Other studies, both prospective and case-control in design, have found increased risk of ovarian cancer to be correlated with eggs, cholesterol, saturated fat, and other dietary nutrients. Decreased risks have been noted in some studies to be related most consistently to intake of various types of fruits, whole grains and vegetables, particularly leafy greens and cruciferous vegetables. In all, however, too few consistent findings have been made to establish any clear guidelines for dietary intake and ovarian cancer risk other than those that have been established for general health and well being; in other words, eat a variety of foods, but limit intake of calorie-dense foods and increase intake of fiber and nutrient-rich foods, such as fruits and vegetables.

103.4.4 Obesity and Ovarian Cancer Prognosis: Outcomes and Survival

Obesity is known to be a negative prognostic factor for a number of cancers, including breast and endometrial cancer. Shortened overall and disease-free survival have been found in obese cancer patients when compared to normal weight cancer patients, especially among patients with advanced disease (i.e. Stage III or IV) (Pavelka et al. 2006). To date, findings relating to obesity and survival in ovarian cancer patients have been limited and contradictory. One recent study of 214 patients with histopathologically confirmed invasive epithelial ovarian cancer who were recruited in 1999–2000 observed reduced survival among patients with BMI > or = 25 kg/m(2) at 5 years before diagnosis (P = 0.001) (Zhang et al. 2005b). Compared to nonobese individuals, obese individuals have longer operative times, greater likelihood of wound breakdown and elevated intraoperative blood loss (Matthews et al. 2009). Obese individuals also tend to be more difficult to manage in terms of

anesthesia; their greater number of common medical comorbidities may also contribute to notably elevated rates of perioperative and/or morbidity and mortality among obese individuals (Matthews et al. 2009). Nonetheless, many studies have not shown a significant difference in survival rates for obese versus nonobese women with ovarian cancer, given similar rates of optimal surgical debulking. Another issue to contend with in evaluating the research conducted on survival relates to chemotherapy dosage. In some instances, the calculation of chemotherapy dosing might be based on ideal body weight, rather than actual body weight, which may result in less-than-therapeutic dosing among women of greater weight or BMI.

103.5 Conclusions

103.5.1 Applications to Other Areas of Health and Disease

In studying many types of cancer, relevant risk factors, including anthropometric variables, such as height, weight, and BMI, should be evaluated at early life stages to accurately assess cancer risk, not just in the years closest to cancer diagnosis. Individuals who are predisposed to certain types of cancers, such as those with germline mutations that are known to cause recognized cancer syndromes, should especially be counseled on diet, exercise, and weight loss and/or maintenance. For breast and ovarian cancers, it would be especially valuable to examine the risk of being obese in young women who carry BRCA mutations, as this is the cohort with the greatest known relative lifetime cancer risk. Data collected on study participants should accurately assess known inflammatory conditions, including pathogens, as well as noninfectious causes of chronic inflammation, in order to discern whether obesity is additive or multiplicative in terms of specific cancer risks. Prospective studies that examine obesity and other lifestyle-related risk factors, including cigarette smoking, alcohol consumption and, for women, reproductive choices, are warranted to accurately evaluate the impact of obesity on the etiology and risk of various types of cancer. Many of the previously performed studies may not be adequately powered to detect weak associations or interactive effects.

Summary Points

(Key points that relate anthropometric variables with ovarian cancer risk are provided in Table 103.11).

- There is an increasing awareness that obesity plays a contributory role in numerous pathologies, including ovarian carcinogenesis.
- Obese individuals have been found to experience a constant, low-grade state of systemic inflammation which may contribute to tumorigenesis.
- The initiation, promotion, and expansion of tumors may be influenced by numerous components that function in the inflammatory response—and these effects are accentuated for individuals carrying excess adiposity.
- High BMI in early adulthood may be particularly associated with an increased risk of developing ovarian cancer.
- Ideally, large-scale, prospective studies that recruit and evaluate young women who can be followed into late adulthood would be most valuable in studying the effects of anthropometric, lifestyle and reproductive variables on the risk of developing cancers with a recognized hormonal influence, such as ovarian cancer.

Table 103.11 Key points that relate anthropometric variables to ovarian cancer risk

Some, but not all, studies have noted that obesity may increase the risk of ovarian cancer
Much of the evidence indicates that obesity in young adulthood is especially associated with elevated ovarian cancer risk
• Having an elevated BMI at age 18 has been shown to increase the risk of either/both premenopausal and postmenopausal ovarian cancer
• This relationship is plausible, because other risk or protective factors appear to have the greatest influence in women's younger years
• Excess adiposity may influence the development of ovarian cancer due the systemic effects of low grade, constant inflammation, as well as by its effects on hormonal levels, especially the excess of estrogens and androgens and the deficits in progesterone levels
The effects of physical activity on the risk of ovarian cancer are as yet undetermined
• Some studies have shown that moderate to vigorous physical activity may decrease risk
• Other studies have demonstrated that activity, particularly vigorous physical activity, is associated with elevated risk of ovarian cancer
• Either relationship makes sense, given that physical activity lowers estrogen levels while increasing levels of androgens; even moderate activity may alter luteal progesterone levels

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Chapter 104
Anthropometry and Breast Cancer Risk

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Abstract Anthropometric factors are among the few risk factors for breast cancer that are potentially modifiable. As such, many studies have attempted to characterize the relationship between body size and breast cancer risk. Although there is much variability between studies with regard to the nature and the magnitude of such risk factor relationships, most studies indicate some association between body size and breast cancer risk. In particular, there is evidence of an increased breast cancer risk in postmenopausal women who are overweight or obese, particularly among nonusers of menopausal hormone therapy. Conversely, studies in premenopausal women suggest a weak inverse association between adult weight and breast cancer risk. Risk factor relationships have also been noted with measures of fat distribution and weight change in adulthood, with similar distinctions in associations by menopausal status. While most studies have focused on measures of body size in adulthood, a growing literature suggests that body size in early life is also relevant to breast cancer risk. Regardless of the anthropometric measure of interest, there are several methodological issues to consider in assessing these relationships, which can impact study findings and comparisons across studies. In particular, using self-reported anthropometric measures is problematic if women are biased in reporting their body size or have problems with recall, however, it may not always be possible or preferable to collect physical measurements of body size. Variability in population characteristics, study design, protocols for data collection, and the way anthropometric data are handled in analyses all contribute to variability in study findings.

Abbreviations

BMI	Body mass index
cm	Centimeters
ER	Estrogen receptor
HRT	Menopausal hormone replacement therapy
kg	Kilograms
m	Meters
PR	Progesterone receptor
WHR	Waist-to-hip ratio

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_104,

104.1 Introduction

Breast cancer is the most commonly diagnosed malignancy among women worldwide, with more than one million cases diagnosed each year (Bray et al. 2004). While mortality rates from breast cancer have declined in recent decades and survival rates have improved in most countries, breast cancer remains a leading cause of cancer death in women (Bray et al. 2004) (Table 104.1). Consistent with the high burden of breast cancer, particularly in more developed countries, an extensive literature has been devoted to exploring the etiology of this disease. Still, it is estimated that established breast cancer risk factors explain less than 50% of all incident disease (Madigan et al. 1995).

Epidemiologic studies implicate a role of genetics, reproductive history, and environmental and lifestyle factors in the development of breast cancer. Given that few established risk factors for breast cancer are potentially modifiable, the role of anthropometric factors in breast cancer etiology is of particular public health importance. A large number of prior studies have noted associations between weight, weight change, body mass index, height, and abdominal adiposity and breast cancer risk. Most studies have focused on measures of adult body size and shape, although evidence also exists to suggest associations between measures of body size and shape from childhood or adolescence and risk of breast cancer in adulthood. Regardless of the timing or measure of interest, there are substantial methodological complexities that studies must account for in exploring anthropometric risk factors for breast cancer, and many potential sources of bias.

Here we broadly summarize what is known about anthropometric factors in relation to breast cancer risk, as well as some of the methodological issues that complicate the study of anthropometric risk factors in breast cancer studies.

104.2 Adult Body Size

Studies of anthropometric risk factors for breast cancer have focused primarily on measures of body size in adulthood. Adult weight, body mass index (BMI), abdominal adiposity, weight change, and height have all been implicated as risk factors for the development of breast cancer. The magnitude and

Table 104.1 Key facts about breast cancer

1. Breast cancer is the most commonly diagnosed cancer among women worldwide, with greater than one million women diagnosed each year.
2. Breast cancer can be diagnosed in men and women and at almost any age, but greater than 95% of all breast cancers are diagnosed in women aged 40 years and older.
3. Incidence rates for breast cancer vary geographically and, within countries, between racial/ethnic groups. Rates are highest in developed countries among non-Hispanic white women.
4. Through screening mammography, it is possible to detect breast cancer at an early stage before the tumor has spread and before the onset of disease symptoms.
5. Breast cancer is the second leading cause of cancer death among women, contributing to almost half a million deaths each year.
6. Survival from breast cancer is generally favorable, especially when diagnosed at an early stage: in developed countries, 5-year survival is close to 90%.
7. Inherited genetic mutations are thought to be responsible for 5–10% of all breast cancers.
8. In addition to genetic factors, many other risk factors for breast cancer are things that women cannot easily change; the age at which a woman starts and stops her menstrual periods, her pregnancy history, and the density of her breasts all impact breast cancer risk.

This table lists key facts about breast cancer including the global burden of breast cancer, the populations most impacted, information about detection and survival, and nonmodifiable risk factors for disease

directionality of associations between these measures and breast cancer risk, however, vary considerably between studies. Much of this variability is likely attributable to differences in methodology and study population characteristics. Still, the lack of consistency in observed associations does contribute to some uncertainty about the true association between adult body size and breast cancer risk.

104.2.1 Weight and Body Mass Index (BMI)

Adult weight, typically adjusted for adult height (i.e., BMI) has long been considered a risk factor for breast cancer. Repeated studies have noted that this relationship between weight in adulthood and breast cancer risk is a complex one, likely involving multiple biological pathways. In particular, the majority of studies assessing this risk factor relationship have demonstrated important differences in associations by menopausal status: a weak inverse association in premenopausal women has been demonstrated by several studies, while studies in postmenopausal women suggest an increased breast cancer risk in overweight and obese women (Table 104.2).

In a pooled analysis of seven large prospective studies, van den Brandt et al. (2000) found that a 10 kilogram (kg) increase in weight was associated with a 10% reduction in risk of premenopausal breast cancer and a 6% increase in risk of postmenopausal breast cancer. Similarly, an increase in BMI of 4 kg/meters $(m)^2$ was associated with an 11% reduction in risk and a 7% increase in risk among premenopausal and postmenopausal women, respectively (van den Brandt et al. 2000). However, associations between weight and breast cancer risk may not follow a linear trend. For example, the previously mentioned pooled analysis noted that the reduced risk of premenopausal breast cancer associated with elevated BMI was limited primarily to women with a BMI of at least 31 kg/m^2 and the increased risk of postmenopausal breast cancer did not increase further past a BMI of 28 kg/m^2 (van den Brandt et al. 2000).

Studies that are able to stratify analyses in postmenopausal women according to the use of menopausal hormone replacement therapy (HRT) suggest that the positive association between BMI and postmenopausal breast cancer risk is limited to women who are not users of HRT (van den Brandt et al. 2000; Morimoto et al. 2002; Lahmann et al. 2004). In postmenopausal users of HRT, the association between BMI and breast cancer risk more closely resembles the weak inverse association observed in premenopausal women. This marked contrast in associations with BMI across menopausal status and HRT use is consistent with the theory that BMI or weight influences breast cancer risk through an effect on hormone levels. Briefly, given that adipose tissue is the primary source of endogenous estrogens in postmenopausal women, elevated BMI or weight contributes to elevated levels of endogenous estrogens, which, in turn, contribute to an increased risk of breast cancer (Lorincz and Sukumar 2006). In HRT users, however, circulating hormone levels are driven primarily by exogenous estrogens from HRT, masking the effect of increased endogenous estrogen from adipose tissue. Mechanisms behind the inverse association between BMI or weight and premenopausal breast cancer have not been well described (Lorincz and Sukumar 2006).

In the context of most breast cancer studies, weight and BMI are ascertained either through self-report or physical measurements. Some concerns about validity arise when using self-reported weight given the tendency for women, particularly overweight and obese women, to underreport their weight (Elgar and Stewart 2008). Somewhat less pronounced is the tendency for overestimation in self-report of adult height (Elgar and Stewart 2008). When considered in combination, bias in self-reported weight and height can lead to considerable bias in the estimation of BMI: one nationally representative survey conducted in Canada estimated that measures of BMI calculated from self-reported height and weight were, on average, 1.31 kg/m^2 units lower than BMI calculated

Table 104.2 Summary of cited studies on adult BMI (kg/m^2) and breast cancer risk

Author (year)	Study design (location)	Study period	Breast cancer cases	Method of data ascertainment	Comparison categories	Relative risk estimate (95% confidence interval)
Premenopausal women						
Huang et al. (1997)	Prospective cohort (USA)	1976–1992	1,000	Self-report (collected biennially during follow-up)	Whole number cut-points: >31.0 vs. ≤20.0	0.62 (0.45–0.86)
Coates et al. (1999)	Case-control (USA)	1990–1992	1,590	Physical measurement	Quintiles: ≥30.4 vs. <21.6	0.69 (0.54–0.88)
van den Brandt et al. (2000)	Pooled prospective studies (USA, Europe, Canada)	1976–1993	703	Self-report (3 studies); physical measurements (1 study)	Whole number cut-points: ≥33 vs. <21	0.58 (0.34–1.00)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	474	Physical measurement (baseline interview)	Quintiles: ≥28.8 vs. <21.6	0.82 (0.59–1.14)
Weiderpass et al. (2004)	Prospective cohort (Europe)	1991–1999	716	Self-report (collected at baseline)	WHO cut-points: ≥30.0 vs. 20.0–24.9	0.66 (0.40–1.07)
Postmenopausal women (overall)						
Huang et al. (1997)	Prospective cohort (USA)	1976–1992	1,517	Self-report (collected biennially during follow-up)	Whole number cut-points: >31.0 vs. ≤20.0	1.13 (0.87–1.46)
Magnusson et al. (1998)	Case-control (Sweden)	1993–1995	2,904	Self-report (1 year prior to data collection)	Quintiles: ≥28.3 vs. <22.2	1.65 (1.40–1.95)
van den Brandt et al. (2000)	Pooled prospective studies (USA, Europe, Canada)	1976–1993	3,208	Self-report (6 studies); physical measurement (1 study)	Whole number cut-points: ≥33 vs. <21	1.27 (1.03–1.55)
Postmenopausal women (no HRT use)						
Huang et al. (1997)	Prospective cohort (USA)	1976–1992	N/A	Self-report (collected biennially during follow-up)	Whole number cut-points: >31.0 vs. ≤20.0	1.59 (1.09–2.32)
van den Brandt et al. (2000)	Pooled prospective studies (USA, Europe, Canada)	1976–1993	N/A	Self-report (5 studies); physical measurement (1 study)	Continuous: per 4 kg/m^2 increase	1.09 (1.04–1.14)

Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	315	Physical measurement (baseline interview)	Quintiles: >31.1 vs. ≤22.6	2.52 (1.62–3.93)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	911	Physical measurement (baseline interview)	Quintiles: ≥28.8 vs. <21.6	1.36 (1.06–1.75)
Postmenopausal women (HRT users)						
van den Brandt et al. (2000)	Pooled prospective studies (USA, Europe, Canada)	1976–1993	N/A	Self-report (5 studies); physical measurement (1 study)	Continuous: per 4 kg/m^2 increase	1.04 (0.92–1.18)
Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	704	Physical measurement (baseline interview)	Quintiles: >31.1 vs. ≤22.6	0.96 (0.73–1.27)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	494	Physical measurement (baseline interview)	Quintiles: ≥28.8 vs. <21.6	0.71 (0.50–1.01)

This table summarizes key studies cited in the text examining the association between adult weight and breast cancer risk in premenopausal and postmenopausal women. Postmenopausal women who are obese or overweight are at an increased risk of developing breast cancer, particularly if they are not users of HRT, while studies in premenopausal women suggest a slightly reduced risk of breast cancer associated with overweight and obesity

BMI body mass index, *HRT* hormone replacement therapy, *kg* kilograms, *m* meters, *WHO* World Health Organization

from measured height and weight (Elgar and Stewart 2008). For this reason, the use of physical measurements for weight may be preferable in some settings. However, in retrospective studies where measurements must be taken subsequent to breast cancer diagnosis, measured weight is likely to have been influenced by the progression of disease and by breast cancer treatment; in such settings, self-report of weight prior to breast cancer diagnosis may be more appropriate even if it is associated with some degree of bias.

Studies assessing the association between weight or BMI and breast cancer risk must also consider the influence of body size on the performance of breast cancer screening. Prior studies have reported that women who are overweight or obese are less likely to seek out routine breast cancer screening and, among those who do receive screening, the performance of screening may be influenced by the fattiness of the breast (Kerlikowske et al. 2008). As a result, overweight and obese women may be underrepresented in case populations, especially populations of early stage disease, in breast cancer studies.

104.2.2 Abdominal Adiposity

The distribution of adipose tissue, not just the amount, has also been implicated as a risk factor for the development of breast cancer. Specifically, evidence suggests that increased abdominal fat deposition is associated with an increased breast cancer risk. Studies assessing the association between abdominal adiposity and breast cancer risk have focused primarily on three measures: waist circumference, hip circumference, and the ratio of waist-to-hip circumference (WHR) (Table 104.3).

With respect to the relationship between WHR and breast cancer risk, evidence is most consistent in indicating a positive association among postmenopausal women (Huang et al. 1999; Friedenreich 2001; Connolly et al. 2002; Morimoto et al. 2002). Positive associations have also been noted among premenopausal women, but with less consistency (Friedenreich 2001; Connolly et al. 2002). In a meta-analysis of studies on the relationship between WHR and breast cancer risk, 9 of 11 studies reported an increased risk among women in the highest versus lowest category of WHR, with relative risk estimates ranging from a 1.1-fold to 8.2-fold increased risk in postmenopausal women and a 1.2-fold to 7.8-fold increased risk in premenopausal women in the highest versus lowest WHR category (Connolly et al. 2002). As with BMI, some studies have suggested that the association between WHR and postmenopausal breast cancer risk is limited to women who are not users of HRT (Huang et al. 1999; Morimoto et al. 2002), which could imply an underlying hormonal mechanism of action.

Fewer studies have reported on associations between breast cancer risk and the two component measures of WHR (i.e., waist circumference and hip circumference). However, studies assessing associations between these component measures and breast cancer risk suggest that waist circumference (Huang et al. 1999; Morimoto et al. 2002) and hip circumference (Morimoto et al. 2002; Lahmann et al. 2004) may be stronger predictors of breast cancer risk when considered individually than when considered in combination as WHR.

Although waist circumference, hip circumference, and WHR are all highly correlated with BMI (Huang et al. 1999), associations between these measures and breast cancer risk appear to persist after adjusting for BMI and certain dietary measures (Huang et al. 1999; Connolly et al. 2002; Morimoto et al. 2002). This suggests that associations between these body size measures and breast cancer risk are not simply reflections of an association between overall obesity and breast cancer risk. Central adiposity, measured most directly by waist circumference, may be particularly relevant

Table 104.3 Summary of cited studies on abdominal adiposity and breast cancer risk

Author (year)	Study design (location)	Study period	Breast cancer cases	Measure of interest	Comparison categories	Relative risk estimate (95% confidence interval)
Premenopausal women						
Huang et al. (1999)	Prospective cohort (USA)	1986–1994	197		Quintiles:	
				Waist circumference	36.0–55.0 in vs. 15.0–27.9 in	1.74 (0.74–4.07)
				Hip circumference	43.0–65.0 in vs. 20.0–36.9 in	0.56 (0.26–1.21)
				Waist-to-hip ratio	≥0.84 vs. <0.73	1.43 (0.86–2.37)
Connolly et al. (2002)	Meta-Analysis	N/A			"High" vs. "Low" categories:	
			2,999	Waist-to-hip ratio	Case-control studies	2.07 (1.15–3.73)
			523	Waist-to-hip ratio	Cohort studies	1.44 (1.01–2.04)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	474		Quintiles:	
				Waist circumference	≥89.3 cm vs. <71.0 cm	1.81 (1.11–2.97)
				Hip circumference	≥108.0 cm vs. <94.0 cm	1.70 (1.05–2.77)
				Waist-to-hip ratio	≥0.847 vs. <0.736	1.05 (0.74–1.50)
Postmenopausal women (overall)						
Huang et al. (1999)	Prospective cohort (USA)	1986–1994	840		Quintiles:	
				Waist circumference	36.0–55.0 in vs. 15.0–27.9 in	1.26 (0.88–1.81)
				Hip circumference	43.0–65.0 in vs. 20.0–36.9 in	1.07 (0.76–1.51)
				Waist-to-hip ratio	≥0.84 vs. <0.73	1.22 (0.96–1.55)
Connolly et al. (2002)	Meta-Analysis	N/A			"High" vs. "Low"	
			3,570	Waist-to-hip ratio	categories: Case-control	1.75 (1.07–2.87)
			2,711		studies	1.21 (0.99–1.48)
					Cohort studies	
Postmenopausal women (no HRT use)						
Huang et al. (1999)	Prospective cohort (USA)	1986–1994	322		Quintiles:	
				Waist circumference	36.0–55.0 in vs. 15.0–27.9 in	1.50 (0.98–2.29)
				Hip circumference	43.0–65.0 in vs. 20.0–36.9 in	1.83 (1.12–2.99)
Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	319		Quintiles:	
				Waist circumference	>95 cm vs. ≤73 cm	1.99 (1.31–3.02)
				Hip circumference	>113 cm vs. ≤95.5 cm	2.43 (1.58–3.73)
				Waist-to-hip ratio	>0.86 vs. ≤0.74	1.33 (0.88–2.01)

(continued)

Table 104.3 (continued)

Author (year)	Study design (location)	Study period	Breast cancer cases	Measure of interest	Comparison categories	Relative risk estimate (95% confidence interval)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	911		Quintiles:	
				Waist circumference	≥89.3 cm vs. <71.0 cm	1.21 (0.87–1.67)
				Hip circumference	>108.0 cm vs. <94.0 cm	1.56 (1.12–2.17)
				Waist-to-hip ratio	≥0.847 vs. <0.736	0.94 (0.74–1.21)
Postmenopausal women (HRT users)						
Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	708		Quintiles:	
				Waist circumference	>95 cm vs. ≤73 cm	0.89 (0.68–1.18)
				Hip circumference	>113 cm vs. ≤95.5 cm	0.82 (0.63–1.08)
				Waist-to-hip ratio	>0.86 vs. ≤0.74	0.95 (0.72–1.25)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	494		Quintiles:	
				Waist circumference	≥89.3 cm vs. <71.0 cm	0.68 (0.41–1.12)
				Hip circumference	>108.0 cm vs. <94.0 cm	1.02 (0.61–1.69)
				Waist-to-hip ratio	≥0.847 vs. <0.736	0.85 (0.60–1.20)

This table summarizes key studies cited in the text examining the association between measures of abdominal adiposity and breast cancer risk in premenopausal and postmenopausal women. Evidence suggests that increased abdominal fat deposition is associated with an increased breast cancer risk
HRT hormone replacement therapy, *cm* centimeters, *in* inches

to breast cancer risk given that upper abdominal (i.e., visceral) fat has a higher production rate of free estradiol and a lower concentration of sex hormone binding globulin than peripheral fat (Huang et al. 1999; Friedenreich 2001).

Certain methodological issues should be considered when interpreting the results of epidemiologic studies assessing the relationship between central adiposity and breast cancer risk. While the majority of studies obtain physical measurements for waist and hip circumference as part of an in-person interview protocol, there is considerable variability in the protocols used for collecting these measurements (Connolly et al. 2002). For example, some studies measure waist circumference at the narrowest part of the trunk while others take measurements at the umbilicus or at some specified distance above the umbilicus. Although any measurement error is not likely vary with disease status, the possible effect of measurement error should be considered in any interpretation of these measures. Measures of WHR are particularly subject to measurement error given that this variable incorporates two sources of measurement error (i.e., from waist circumference and from hip circumference). Additionally, given that there are no clinically relevant cut-points for categorizing waist circumference, hip circumference, or WHR, measures classified as "high" or "low" in one study may not be so-classified in another study. This lack of consistency in category cut-points complicates the comparison of findings across studies.

104.2.3 Weight Change

In a review published by the International Agency for Research on Cancer, adult weight gain was cited as the measure of body size most consistently associated with breast cancer risk in postmenopausal women (Vainio and Bianchini 2002). Several studies have suggested that weight change is more strongly associated with breast cancer risk than recent weight or BMI, and several have noted associations with weight change even in the absence of any association between weight or BMI and breast cancer risk (Friedenreich 2001) (Table 104.4).

As with weight and BMI, associations between weight change and breast cancer risk differ according to menopausal status and, among postmenopausal women, according to the use of HRT (Morimoto et al. 2002; Lahmann et al. 2005; Eliassen et al. 2006). In one prospective analysis using data from the Nurses' Health Study in the United States, postmenopausal women who had gained at least 25 kg since age 18 years experienced a 1.4-fold increased risk of breast cancer relative to women whose recent weight was within 2 kg of their weight at age 18; when stratifying estimates according to HRT use, a 25 kg weight gain since age 18 was associated with a 1.9-fold increased risk in women who had never used HRT compared to a 1.2-fold increased risk in current or former users of HRT (Eliassen et al. 2006). Weight gain after the onset of menopause was not significantly associated with an increased breast cancer risk in this study population, regardless of HRT use status, although other studies have observed an increased risk with an increase in BMI late in adulthood (Morimoto et al. 2002). Some, but not all studies have reported an opposite effect of weight loss on postmenopausal breast cancer risk (Friedenreich 2001; Lahmann et al. 2005; Eliassen et al. 2006). Evidence of an association between weight change and breast cancer risk in premenopausal women is more limited. The majority of studies in premenopausal women report a null or nonsignificant inverse association between weight gain and breast cancer risk (Coates et al. 1999; Weiderpass et al. 2004; Lahmann et al. 2005). A relationship between weight loss or BMI reduction since early adulthood and breast cancer risk has not been observed in premenopausal women (Coates et al. 1999; Weiderpass et al. 2004; Lahmann et al. 2005).

While the literature is relatively consistent in reporting associations between weight change and breast cancer risk, there is substantial heterogeneity across studies in terms of how weight change is

Table 104.4 Summary of cited studies on adult weight gain and breast cancer risk

Author (year)	Study design (location)	Study period	Breast cancer cases	Weight/BMI change time period	Method of data ascertainment	Comparison categories	Relative risk estimate (95% confidence interval)
Premenopausal women							
Huang et al. (1997)	Prospective cohort (USA)	1976–1992	1,000	Age 18–present	Self-report	Weight loss/gain ≤2 kg vs. gain >25 kg	0.74 (0.54–1.03)
Coates et al. (1999)	Case-control (USA)	1990–1992	1,590	Age 20–present	Self-report (age 20)/ physical measurement (present)	Weight loss/gain ≤2 kg vs. gain ≥21 kg	0.72 (0.54–0.95)
Lahmann et al. (2005)	Prospective cohort (Europe)	1992–2000	254	Age 20–present	Self-report (age 20)/ physical measurement (baseline)	Weight loss/gain ≤2 kg vs. gain >20 kg	0.87 (0.51–1.49)
Weiderpass et al. (2004)	Prospective cohort (Europe)	1991–1999	680	Age 18–present	Self-report	BMI gain 0–1.4 kg/m^2 vs. gain >4.0 kg/m^2	0.95 (0.72–1.25)
Postmenopausal women (overall)							
Magnusson et al. (1998)	Case-control (Sweden)	1993–1995	2,331	Age 18–present	Self-report	Weight gain 0–9.5 kg vs. gain ≥30 kg	1.45 (1.13–1.86)
Eliassen et al. (2006)	Prospective cohort (USA)	1976–2002	4,393	Age 18–present	Self-report	Weight loss/gain ≤2 kg vs. gain ≥25 kg	1.45 (1.27–1.66)
			2,376	Menopause–present	Self-report	Weight loss/gain ≤2 kg vs. gain ≥10 kg	1.18 (1.03–1.35)
Postmenopausal women (no HRT use)							
Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	311	Age 18–present	Self-report (age 18)/ physical measurement (baseline)	BMI change ≤0 kg/m^2 vs. gain >9.7 kg/m^2	1.92 (1.07–3.43)
			314	Age 50–present	Self-report (age 50)/ physical measurement (baseline)	BMI change ≤0 kg/m^2 vs. gain >4.0 kg/m^2	1.45 (0.98–2.15)
Lahmann et al. (2005)	Prospective cohort (Europe)	1992–2000	626	Age 20–present	Self-report (age 20)/ physical measurement (baseline)	Weight loss/gain ≤2 kg vs. gain >20 kg	1.52 (1.08–2.13)
Eliassen et al. (2006)	Prospective cohort (USA)	1976–2002	1,394	Age 18–present	Self-report	Weight loss/gain ≤2 kg vs. gain ≥25 kg	1.98 (1.55–2.53)
			876	Menopause–present	Self-report	Weight loss/gain ≤2 kg vs. gain ≥10 kg	1.19 (0.94–1.50)

Postmenopausal women (HRT users)							
Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	692	Age 18–present	Self-report (age 18)/ physical measurement (baseline)	BMI change ≤0 kg/m^2 vs. gain >9.7 kg/m^2	1.36 (0.94–1.97)
			699	Age 50–present	Self-report (age 50)/ physical measurement (baseline)	BMI change ≤0 kg/m^2 vs. gain >4.0 kg/m^2	0.90 (0.68–1.17)
Lahmann et al. (2005)	Prospective cohort (Europe)	1992–2000	456	Age 20–present	Self-report (age 20)/ physical measurement (baseline)	Weight loss/gain ≤2 kg vs. gain >20 kg	0.95 (0.32–1.38)
Eliassen et al. (2006)	Prospective cohort (USA)	1976–2002	2,687	Age 18–present	Self-report	Weight loss/gain ≤2 kg vs. gain ≥25 kg	1.20 (1.01–1.43)
			1,379	Menopause–present	Self-report	Weight loss/gain ≤2 kg vs. gain ≥10 kg	1.15 (0.96–1.38)

This table summarizes key studies cited in the text examining the association between adult weight gain and breast cancer risk in premenopausal and postmenopausal women. Adult weight gain is consistently associated with breast cancer risk in postmenopausal women, but no real relationship between weight change and breast cancer risk has been observed in premenopausal women

BMI body mass index; *HRT* hormone replacement therapy; *kg* kilograms

defined. Some studies consider changes in weight while others measure changes in BMI. The ages between which these changes are measured also vary: some studies consider the difference between weight or BMI at age 18 or 20 and recent weight, while other focus on weight or BMI change within a more recent time period (e.g., since age 50, since menopause, or since age 30). Differences in the time frame over which weight or BMI changes are defined are particularly important to consider when comparing results across studies, since changes over different time periods may influence breast cancer risk through different biological mechanisms. It is possible that weight changes during periods of hormonal transition, such as pregnancy or menopause, may be particularly relevant given that the breast is more susceptible to carcinogenic insult during these time periods (Friedenreich 2001). Recent weight gain could function as a promoter of breast cancer growth; however, studies assessing the relationship between recent weight changes and breast cancer risk must consider the possibility that the disease itself could have an impact on body weight and BMI rather than vice versa.

As in studies of adult weight and BMI, studies measuring weight change must consider the potential for bias and measurement error when collecting measures of recent and historical weight. In addition to these complexities, there are important limitations inherent to breast cancer studies that define weight change as the difference between two weight or BMI measures at two points in time. Calculating weight change in this manner may not capture the full range of change during adulthood if weight or BMI fluctuates within this time period. Such measurements also fail to capture information on the rate or trajectory of weight change (e.g., whether the weight change occurred gradually beginning at age 18 or occurred rapidly within recent years). Few studies have assessed the possible relationship between weight cycling and breast cancer risk, but it is possible that patterns of weight change and not just the magnitude of change may be important.

104.2.4 Height

Existing studies indicate that women who are tall in stature experience a slightly increased risk of breast cancer relative to shorter women. This modest positive association between adult height and breast cancer risk has been noted by repeated studies in diverse study populations, although not all studies support an association (Table 104.5). While the biological basis for an influence of height on breast cancer risk is not well understood, it has been suggested that adult height is a reflection of childhood energy intake and the number of ductal stem cells in the breast that develop *in utero* (Friedenreich 2001). Thus, an association between breast cancer risk and the height a woman attains in adulthood may actually implicate a role of early life exposures in breast cancer development.

Most epidemiologic studies assessing the association between height and breast cancer risk have separately assessed associations in premenopausal and postmenopausal women. Although studies are relatively consistent in noting an association between height and breast cancer risk among postmenopausal women, evidence is weaker and less consistent in premenopausal women. In a pooled analysis of seven large prospective studies, a 5-cm increase in height was associated with a 2% nonsignificant increase in risk of premenopausal breast cancer (van den Brandt et al. 2000). The same increase in height was associated with a statistically significant 7% increase in breast cancer risk among postmenopausal women (van den Brandt et al. 2000). Studies examining adult height as a categorical rather than a continuous variable, however, suggest that height may not be linearly associated with breast cancer risk (van den Brandt et al. 2000; Lahmann et al. 2004). For example, one large prospective study noted a 1.3-fold increased risk of premenopausal breast cancer and a 1.4-fold increased risk of postmenopausal disease among women in the highest versus lowest quartile of height, but found no evidence of a trend (Lahmann et al. 2004).

Table 104.5 Summary of cited studies on adult height and breast cancer risk

Author (year)	Study design (location)	Study period	Breast cancer cases	Method of data ascertainment	Comparison categories	Relative risk estimate (95% confidence interval)
Premenopausal women						
van den Brandt et al. (2000)	Pooled prospective studies (USA, Europe, Canada)	1976–1993	703	Self-report (3 studies); physical measurements (1 study)	A priori cut-points:	
					≥175 cm vs. <160 cm	1.42 (0.95–2.12)
					Linear (5-cm increase):	1.02 (0.96–1.10)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	474	Physical measurement (baseline interview)	Quintiles:	
					≥167.7 cm vs. <156.0 cm	1.33 (0.96–1.84)
					Linear (1-cm increase):	1.01 (1.00–1.03)
Weiderpass et al. (2004)	Prospective cohort (Europe)	1991–1999	716	Self-report (collected at baseline)	A priori cut-points:	
					≥175 cm vs. 165–169 cm	0.91 (0.67–1.23)
					Linear (1-cm increase):	1.02 (1.00–1.03)
Postmenopausal women						
Magnusson et al. (1998)	Case-control (Sweden)	1993–1995	2,803	Self-report (1 year prior to data collection)	A priori cut-points:	
					≥175 cm vs. <160 cm	1.08 (0.79–1.49)
van den Brandt et al. (2000)	Pooled prospective studies (USA, Europe, Canada)	1976–1993	3,208	Self-report (6 studies); physical measurement (1 study)	Whole number cut-points :	
					≥175 cm vs. <160 cm	1.28 (0.94–1.76)
					Linear (5-cm increase):	1.07 (1.03–1.12)
Morimoto et al. (2002)	Prospective cohort (USA)	1993–2000	1,024	Physical measurement (baseline interview)	Quintiles:	
					>167.0 cm vs. ≤156.4 cm	1.27 (1.00–1.62)
Lahmann et al. (2004)	Prospective cohort (Europe)	1992–2000	1,402	Physical measurement (baseline interview)	Quintiles:	
					≥167.7 cm vs. <156.0 cm	1.40 (1.16–1.69)
					Linear (1-cm increase):	1.02 (1.01–1.03)

This table summarizes key studies cited in the text examining the association between adult height and breast cancer risk, indicating a weakly positive association in premenopausal and postmenopausal women

cm centimeters

A small but increasing literature suggests that the age at which a woman first reaches her adult height could also be associated with breast cancer risk. Initial reports indicated as much as a 30% reduced risk of breast cancer in young women who reached their adult height at age 18 years or older relative to women who reached their adult height at age 13 or younger (Li et al. 1997). Subsequent studies have reported similar associations in older women, but indicate that the role of this factor may be restricted to certain subtypes of disease (Beaber et al. 2008). While a woman's age at maximum height is not itself an anthropometric measure, evidence of an association between this factor and breast cancer risk highlights the importance of considering patterns of growth and the timing of growth in the context of breast cancer risk.

As with weight and BMI, information on adult height in epidemiologic studies of breast cancer is typically collected in the form of either physical measurements or self-report. Studies assessing the validity of self-reported height indicate a high level of concordance with measured values overall; however, there is a tendency for women to slightly overestimate their height (Elgar and Stewart 2008). Any such bias in the reporting of height is not likely to differ between breast cancer cases and women without breast cancer, still the potential for misclassification must be considered in interpreting associations between height and breast cancer risk in studies relying on self-report. The use of physical measurements for height avoids the potential for bias in self-report, but it is not always feasible to directly measure the height of study participants. Finally, as with previously discussed measures, comparisons across studies of the relationship between height and breast cancer risk must take into consideration the fact that categorical cut-points (e.g., quartiles of height) tend to differ in different study populations and settings.

104.3 Body Size in Early Life

The process through which breast cancer develops from a single cancerous cell to a detectable tumor is thought to occur over a period of several years. Therefore, exposures measured at the time of breast cancer diagnosis may not reflect the environment under which that cancer first began to develop. The most etiologically relevant time period may instead be many years prior to breast cancer diagnosis. Thus, with respect to anthropometry, it is plausible that body size in early adulthood and childhood could be relevant to a woman's breast cancer risk. There are considerable methodological complexities to studying the association between early life body size and breast cancer risk. Still, existing epidemiologic studies of these potential associations suggest an important role of body size prior to adulthood.

104.3.1 Birth Weight and Birth Size

Motivated by the hypothesis that *in utero* exposures to circulating estrogens and other hormones could influence a woman's risk of developing breast cancer in adulthood, birth size has been examined in relation to breast cancer risk (dos Santos Silva et al. 2008). Birth weight and, to a lesser extent, birth length, head circumference, and ponderal index (i.e., weight in kg/height in m^3) have now been examined as breast cancer risk factors in a number of studies.

Modest positive associations between adult breast cancer risk and birth weight, birth length, and head circumference at birth were noted in a large meta-analysis of published and unpublished data (dos Santos Silva et al. 2008). Based on measurements taken from birth records, a 500 g increase in birth

weight was associated with a 6% increase in breast cancer risk, however, this association disappeared after adjusting for birth length and head circumference. The strongest independent association was noted with respect to birth length: women who were at least 51 cm in length at birth had a 17% increased risk of breast cancer relative to women who were 49 cm in length. After adjusting for birth weight and head circumference, a 2-cm increase in birth length was associated with a 9% increase in breast cancer risk. As with birth weight, a positive association between head circumference at birth and breast cancer risk was noted but did not persist after adjusting for other measures of birth size. Associations did not differ substantially with age and were only slightly attenuated after adjusting for maternal height, adult height, and adult BMI.

Studies examining associations between birth weight, birth length, head circumference at birth, and breast cancer risk typically rely on measurements abstracted from birth records. The use of birth records is generally preferable over self-report given that women may have considerable difficulty recalling these measurements with accuracy. Still, some reports have noted considerable interobserver variability in measurements from birth records, particularly birth length (Johnson et al. 1997). In studies that do rely on self-report, problems with recall are not likely to differ between women with and without breast cancer, but are still likely to impact study findings. In the previously mentioned meta-analysis, a positive association between birth weight and adult breast cancer risk was noted when based on data taken directly from the birth record, but no association was noted when relying on self-report or maternal report; statistical heterogeneity between studies was largely accounted for by differences in the source of birth weight data (dos Santos Silva et al. 2008). Therefore, the source of birth size data must be considered when interpreting and comparing findings across studies.

104.3.2 Body Size in Childhood and Adolescence

As with adult body size, the possible relationship between overweight and obesity in childhood and adolescence and breast cancer risk is of growing public health significance. Still, relatively few studies have explored associations between breast cancer risk and body size in childhood or adolescence. Studies that have examined such anthropometric risk factors have varied, not only in their findings but also in their methodologies. While some studies rely on self-report for obtaining height and weight measures at specific ages, others rely on measurements abstracted from medical records or school records, and still others use comparative measures and visual aides to help women approximate their past body shape or fatness.

Overall, studies in premenopausal women suggest a modest inverse association between body size during childhood or adolescence and subsequent breast cancer risk (Huang et al. 1997; Berkey et al. 1999; Weiderpass et al. 2004). A lower risk of postmenopausal breast cancer in women who were obese during adolescence has also been noted by some, but not all studies (Huang et al. 1997; Magnusson et al. 1998; Berkey et al. 1999). In an analysis of data from the Nurses' Health Study, women who reported a BMI greater than 25 kg/m^2 at age 18 years had a 0.6-fold lower risk of breast cancer prior to menopause and a 0.7-fold lower risk of breast cancer after menopause as compared to women with a BMI of 18.2 kg/m^2 or lower at age 18 (Huang et al. 1997). Information on body size at ages 5 and 10 years was also collected from this study population using a 9-level silhouette scale (Stunkard et al. 1983) (Figure 104.1): women were asked to identify the body silhouette (i.e., somatotype) that most closely corresponded with their recalled shape at these ages. Using this methodology, women who identified with the largest somatotype at age 10 had a reduced risk of breast cancer relative to women who identified with the thinnest somatotype, regardless of menopausal status

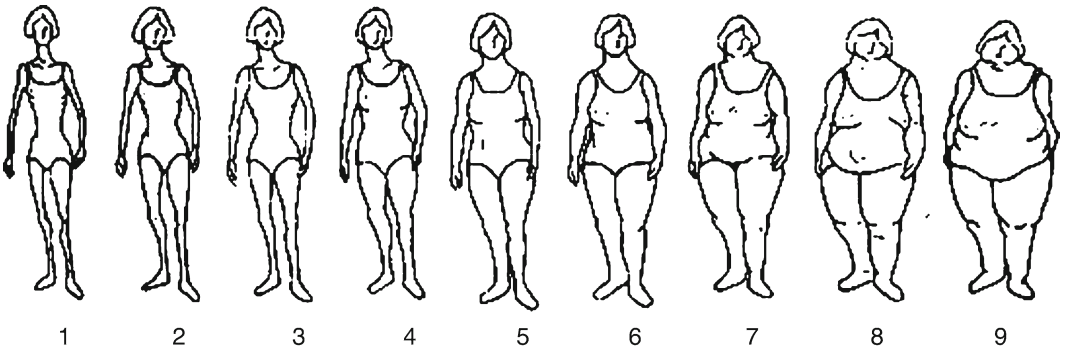

Fig. 104.1 Female body somatotype scale (Reprinted from Stunkard et al. (1983) with permission). Female body somatotype scales such as this, reprinted from Stunkard et al. (1983) with permission, are frequently used as visual aides in recalling past body size

(Berkey et al. 1999), however, a woman's somatotype at age 5 years was not associated with breast cancer risk. Consistent with these findings, other studies have reported a 30% lower breast cancer risk in premenopausal women who perceived themselves to have been fatter than other girls at age 7 years (as compared to women with an average body size at that age) (Weiderpass et al. 2004), and a significant trend of decreasing postmenopausal breast cancer risk with increasing somatotype size at age 7 (Magnusson et al. 1998). In another analysis using data on height and weight from school records, women in the lowest quintile of BMI at age 7 and at age 15 had a significantly higher breast cancer risk than women in the highest BMI quintile at these ages (Hilakivi-Clarke et al. 2001).

More so than with other anthropometric measures, there are considerable complexities in obtaining body size measurements from childhood and adolescence. Prospective collection of physical measurements for height and weight at young ages is unrealistic since any breast cancer study collecting such measurements would require a prohibitively long study follow-up. While a small number of studies have been able to use historical measurements of height and weight from medical and/or school records, such data sources are rare. The majority of studies instead rely on self-reported measures for past height and weight, although this approach is associated with considerable measurement error. Validation studies have suggested that using somatotype drawings to help women approximate their past body shape allows for a reasonably accurate assessment of body fatness at young ages (Must et al. 1993). Other studies approximate gradients of adolescent body size by asking women to recall how their body size at certain ages compared to that of their peers at that age. Each of these approaches to ascertaining body size carry advantages and limitations, and the choice of methodology should be considered when evaluating study results or comparing results across studies. Similarly, the timing of body size measures is important given that measures prior to the onset of puberty (e.g., age 5) could influence breast cancer risk in a manner different from measures during or after the onset of puberty (e.g., age 15).

104.4 Sources of Heterogeneity

As can be inferred from the literature cited throughout this chapter, there is substantial heterogeneity among studies of anthropometry and breast cancer risk. Some differences between studies result from differences in methodologies, but it is also plausible that the role of anthropometric risk factors may differ between populations. Specifically, associations between anthropometric factors and breast

cancer risk may differ with population characteristics (e.g., menopausal status, race/ethnicity), as well as certain tumor characteristics (e.g., hormone receptor status, histology). Studies that stratify analyses according to these characteristics provide the most sensitive estimation of risk factor associations. It is important to keep in mind potential sources of heterogeneity when interpreting the results of any given study.

104.4.1 Population Characteristics

As previously detailed, most studies of anthropometric risk factors for breast cancer assess associations separately for premenopausal and postmenopausal women and, among postmenopausal women, according to use of HRT. Given considerable evidence that the role of anthropometric risk factors varies with menopausal status and HRT use, it is plausible that the biological mechanisms through which anthropometric factors influence breast cancer risk differ with respect to these characteristics. Assessing associations in premenopausal women separately from postmenopausal women also allows for the likely possibility that the relative impact of anthropometric factors on breast cancer risk varies with menopausal status. Similarly, the role and impact of body size on breast cancer risk may vary with race/ethnicity. Fewer studies have addressed this potential source of heterogeneity, but those that have suggest considerable variability in associations with anthropometric factors. In a recent analysis of Hispanic white and non-Hispanic white women conducted in the southwestern United States, adult height and BMI were associated with premenopausal and postmenopausal breast cancer risk, but only among non-Hispanic women (Slattery et al. 2007). Thus, the racial/ethnic composition and age distribution of the study population can have an impact on observed associations between body size and breast cancer risk.

104.4.2 Tumor Characteristics

In light of increasing evidence that breast cancer is a biologically heterogeneous disease, the relationship between anthropometric factors and disease risk is likely to differ for distinct biological subtypes of breast tumors. That is, because different kinds of breast tumors are thought to arise through different pathways, anthropometric factors may differentially influence a woman's risk of developing certain kinds of breast tumors. Studies that are able to separate breast cancer cases into biologically distinct case groups provide some evidence that adult body size is most strongly associated with risk of hormone receptor-positive breast cancer. In a recent meta-analysis, women in the highest category of BMI had a significantly lower risk of premenopausal estrogen receptor (ER) positive/progesterone receptor (PR) positive breast cancer (odds ratio = 0.80), and a significantly higher risk of postmenopausal ER-positive/PR-positive breast cancer (odds ratio = 1.89); however, no such associations were noted with respect to risk of ER-negative/PR-negative breast cancer (odds ratio = 1.03 and 1.17 for premenopausal and postmenopausal women, respectively) (Suzuki et al. 2009). On a related note, studies evaluating risk factor relationships for different molecular subtypes of breast cancer have suggested that body size, particularly in postmenopausal women, is most strongly associated with risk of basal-like and luminal A subtypes of breast cancer (Millikan et al. 2008). Although less pronounced, differences have also been noted by studies stratifying case groups according to tumor histology (Li et al. 2006).

104.5 Summary of Methodological Considerations

Many methodological considerations impact the study design, data collection, and data analysis phases of epidemiologic studies investigating anthropometric risk factors for breast cancer. Considerations include the choice of different measures of body size (e.g., waist circumference versus WHR for characterizing central adiposity), different methods for measuring body size (e.g., self-reported versus measured weight), and the choice of analytic approach (e.g., linear versus quartile categorization of continuous measures). Several of these issues have been described above in relation to specific measures, but most relate more generally to the study of anthropometry and breast cancer risk.

As previously described, a wide variety of anthropometric measures have been studied as possible risk factors for the development of breast cancer – from measures of adult body size and fat distribution, to changes in body size, and body size early in life. Given that these different measures could plausibly impact a woman's risk of breast cancer through different mechanisms, the choice of which measure(s) to ascertain and over which time period should be largely determined by the scientific hypothesis of interest. However, even though the biological mechanisms through which the measures discussed here influence breast cancer risk may be distinct, most of these measures are highly correlated. For example, in an analysis using data from the Women's Health Initiative Observational Study (WHI-OS,) a woman's recent BMI was highly correlated with her reported change in BMI since age 18, her waist circumference, and her hip circumference (Pearson correlation coefficients = 0.9, 0.8, and 0.8, respectively) (Morimoto et al. 2002). Therefore, in order to assess the independent effects of any given measure of body size it is typically necessary to collect information on a variety of related measures.

For any given measure of body size, there may be multiple possible methods for data collection. Different methods carry different advantages and limitations, which must be weighed in the context of a study's design and objectives. With respect to measures of recent body size, the choice between using self-report versus physical measurements generally depends on the timing of data collection (i.e., prior to breast cancer diagnosis or at some interval following diagnosis) and the study interview protocol (i.e., in-person interview, telephone interview, or self-completed survey). Studies that rely on self-reported measurements of body size must consider the potential for bias in reporting, while studies that rely on physical measurements must consider that body weight and central adiposity are likely to be influenced by breast cancer progression and treatment. Studies examining the role of body size in the more distant past must typically rely on self-report and, as such, face considerable problems with recall. Although any bias or errors in recall are not likely to differ between women with breast cancer and women without, such bias may have an appreciable impact on study findings. The use of somatotype drawings is one approach to aiding recall of body size in the distant past, but reporting of body size under this approach is more subjective. While measurement error is almost guaranteed in any study of anthropometric risk factors for breast cancer, the source, nature, and magnitude of that measurement error is largely dependent on the manner in which anthropometric data are collected.

Once anthropometric data have been collected, the way in which those data are analyzed also presents an important methodological consideration. Given evidence that the relationships between measures of body size and breast cancer risk may not be linear, most studies assess anthropometric risk factors for breast cancer as categorical variables. However, with the exception of adult BMI category cut-points recommended by the World Health Organization (i.e., underweight: <18.5 kg/m^2, normal weight: 18.5–24.9 kg/m^2, overweight: ≥25 kg/m^2, obese: ≥30 kg/m^2), there are no standard

categorical cut-points for analyzing anthropometric measures. In the absence of standardized category cut-points, continuous measures, such as height, weight, and waist circumference are typically analyzed in tertiles, quartiles, or quintiles. While convenient, categorizing variables in this manner makes it difficult to draw comparisons across studies: since the range and distribution of body size measures varies between study populations, the tertile, quartile, and quintile distributions also vary. For example, in comparing two large prospective studies with data on breast cancer incidence and recent BMI, the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Women's Health Initiative Observational Study (WHI-OS), both analyzed BMI as a categorical variable using the quintile distribution of BMI to generate category cut-points: in the EPIC study, women with a BMI less than 21.6 kg/m^2 and women with a BMI of at least 28.8 kg/m^2 were grouped into the lowest and highest quintiles, respectively (Lahmann et al. 2004), while in the WHI-OS the cut-points for the lowest and highest quintiles were equal to 22.6 and 31.1 kg/m^2, respectively (Morimoto et al. 2002). Thus, comparisons of breast cancer risk in the highest versus lowest category of an anthropometric measure may not be entirely comparable across studies. Additionally, because there is no biological basis for categorizing continuous anthropometric measures according to tertiles, quartiles, or quintiles, the use of such cut-points may obscure true patterns of increasing or decreasing breast cancer risk with body size, especially if the true relationship involves some threshold effect. In the absence of biological evidence to inform category cut-points for analyzing measures of body size and standardized cut-points, there is substantial variability between studies in terms of how measures of body size are handled in data analysis.

In spite of considerable methodological complexities, epidemiologic studies have now clearly demonstrated a link between anthropometry and breast cancer risk. However, such complexities do contribute to uncertainty about the exact nature of the relationship between anthropometric factors and breast cancer risk.

Summary Points

- Postmenopausal women who are obese or overweight are at an increased risk of developing breast cancer, particularly if they are not users of HRT. Studies in premenopausal women suggest a slightly reduced risk of breast cancer associated with overweight and obesity.
- The distribution of fatty tissue, not just the amount, may also be a risk factor for breast cancer. Evidence suggests that increased abdominal fat deposition is associated with an increased breast cancer risk.
- Adult weight gain is the anthropometric measure most consistently associated with breast cancer risk in postmenopausal women, although no consistent relationship between weight change and breast cancer risk has been observed in premenopausal women.
- Women who are tall in stature experience a slightly increased risk of breast cancer relative to shorter women.
- Increasing evidence suggests that body size in early life is associated with breast cancer risk. While there is considerable variability between studies, women with a short birth length and women with larger than average body size in adolescence may have a slightly lower risk of breast cancer.
- Most epidemiologic studies of breast cancer rely on participant self-report for ascertaining body size. Using self-reported measures can lead to bias if women are biased in reporting their body size or have problems with recall. However, it is not always possible or even preferable to collect physical measurements.

- Associations between many measures of body size and breast cancer risk differ greatly by menopausal status and HRT use. The relationship between anthropometric factors and breast cancer risk may also differ for different subtypes of breast cancer.
- Studies assessing the relationship between anthropometric factors and breast cancer risk vary widely in their study design, protocols for data collection, and the way anthropometric data are handled in analyses. All of these differences contribute to variability in study findings.

Acknowledgments This publication was supported by grant number T32 CA09168 from the National Institutes of Health (NIH). Its contents are solely the responsibility of the author and do not necessarily represent the official views of the National Cancer Institute, NIH.

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Chapter 105
Anthropometric Parameters in Hospitalized Elderly Patients with Cancer

E. Paillaud, B. Campillo, E. Alonso, and P.N. Bories

Abstract The prevalence of malnutrition in hospitalized elderly patients >70 years is estimated to be between 50% and 70% and is considered as one of the criteria of frailty in this population. On the other hand, malnutrition is common in patients with advanced cancer and is a poor prognostic factor; as such it should be detected as soon as possible. Therefore, the assessment of nutritional status is an essential element of therapeutic strategy in geriatric oncology and includes the determination of anthropometric parameters, biological data and measure of food intake. The most widely used anthropometrics measures in cancer are body mass index (BMI) and weight loss, with a prevalence of malnutrition varying between 20% and 70%, depending on threshold values reported (BMI<20 or 21, weight loss <5 or 10%). In elderly patients as in other adults, the impairment of these parameters is mainly determined by the localization of the tumor and the stage of the disease, with a higher prevalence of malnutrition occurring in digestive tract tumors and in advanced cancers. Aging per se does not represent a risk factor for malnutrition. However, elderly patients are at high risk of altering their nutritional status in terms of muscular mass as well as fat mass during the course of hospitalization. This calls for a specific nutritional intervention in geriatric oncology.

Abbreviations

BMI	Body mass index
CC	Calf circumference
HAS	High authority of health
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
MNA	Mini nutritional assessment
TST	Triceps skinfold thickness
10th perc	10th percentile

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_105,

105.1 Introduction

The terms "older persons," "elderly people," and similar words generally refer, in the international literature, to the age group ≥65 years (Yancik 1997). This age break, somewhat arbitrary, is associated with the retirement age. There is an increasing tendency to use age 70+ or 80+ years in reference to the elderly in geriatric medicine. In France, the age threshold of 70 years has been proposed by the French institution HAS, High Authority for Health, to define the elderly population. The number of elderly people over 65 years in the industrialized world is steadily increasing and, at that time in France, represented 16.2% of the population (Beaumel and Vatan 2008). Approximately 25% of individuals aged 80 years will become centenarians. With the increase of the aged population, there is an increase in prevalence of health problems (Fried et al. 1999). The prevalence of malnutrition in hospitalized elderly patients over 70 years of age is high and may vary from 30% to 70%, according to several surveys conducted in Europe (Constans et al. 1992; Paillaud et al. 2000; Mowe and Bohmer 1991; Kyle et al. 2002; Potter et al. 1995; Persson et al. 2002). Malnutrition is considered as one of the criteria of frailty in older patients (Xue et al. 2008). The nutritional status of older persons is influenced by many factors including underlying diseases. Cancer is one of the diseases that frequently alters nutritional status; in addition, its incidence increases with age. Epidemiological data indicate that, in France, 30% of cancers and 48% of deaths attributable to cancer occurred after the age of 75 years (Belot et al. 2008). In advanced stages of the disease, malnutrition can progress to cachexia, characterized by the loss of adipose tissue and skeletal muscle mass. The causes of cancer cachexia include hypercatabolic activity related to interactions between host- and tumor-derived factors including pro-inflammatory cytokines, anorexia, and intake inability (Tisdale 2004). Malnutrition in cancer patients reduces the body's defense against infectious diseases. It is associated with a poorer response to treatment, shorter survival, and a reduced quality of life (Andreyev et al. 1998; Dewys et al. 1980). For these reasons, malnutrition should be prevented or detected as early as possible and clinical practice in geriatric oncology includes routine nutritional screening of elderly patients at risk of malnutrition and assessment of nutrition status at the time of hospitalization (Balducci and Extermann 2000). The assessment of nutritional status includes several markers: anthropometric measures, dietary intake, and serum protein profile. Two anthropometric parameters are often used to identify a cancer patient at risk of malnutrition: weight loss and body mass index. Other anthropometric variables can be used to make a complete assessment of nutritional status, which may highlight more discrete changes during hospitalization. Two questions arise regularly in geriatric oncology:

1. Is age a risk factor for malnutrition in cancer patients?
2. Is cancer associated with more extensive changes in nutritional status than other diseases occurring in the elderly?

105.2 Practical Methods and Techniques of Nutritional Assessment in Geriatric Oncology

Anthropometric parameters include weight, weight changes expressed as percent of initial body mass, body mass index (weight[kg]/height^2[m^2]), skinfold thicknesses, and mid-arm circumference (Table 105.1). The most widely used anthropometric parameter is body mass index (BMI). The World Health Organization categorizes underweight as BMI <18.5 and normal weight as 18.5–24.9. In elderly patients, the cutoff used to define malnutrition differs among studies and varies from 20 to 22. The threshold value usually used corresponds to the 10th percentile of data

Table 105.1 Anthropometric parameters usually used in elderly patients for malnutrition diagnosis

Anthropometric parameters	Threshold value for malnutrition diagnosis in elderly	Threshold value for severe malnutrition diagnosis
Weight loss (%)		
HAS criteria*	≥5% within 1 month ≥10% within 6 months	≥10% within 1 month ≥15% within 6 months
BMI (kg/m^2)	<10th perc	
70–74 years (F/M)**	<21.7/<21.8	
75–79 years (F/M)**	<21.9/<21.2	
>80 years (F/M)**	<19.7/<21.8	
HAS criteria*	<21	<18
Arm circumference (cm)	<10th perc	
75–79 years (F/M)**	<25.3/<26.9	
>80 years (F/M)**	<23.1/<24.9	
Triceps Skinfold (mm)	<10th perc	
75–79 years (F/M)**	<12/<6.9	
>80 years (F/M)**	<10.2/<6.1	
Muscle arm circumference (cm)	<10th perc	
75–79 years (F/M)**	<20.5/<23.7	
>80 years (F/M)**	<19.7/<22.0	
Mini Nutritional Assessment	<17 points	

This table lists the parameters measured to diagnose moderate or severe malnutrition. The threshold values given are those defined by the French National Authority for Health* and the 10th percentiles of anthropometric measures** assessed in a French healthy elderly population (Delarue et al. 1994). The Mini Nutritional Assessment is a global score including anthropometric parameters, which are body mass index (BMI), weight loss over the last 3 months, mid-arm muscle circumference, and calf circumference (Vellas et al. 2006).
10th perc 10th percentile of a nationally specific anthropometric reference data, *HAS criteria* French National Authority for Health criteria for undernutrition diagnosis in the elderly, *BMI* body mass index

assessed in a population of healthy elderly. However, such anthropometric reference values in the elderly are scarce and only a few national anthropometric reference percentiles for elderly populations have been published (Delarue et al. 1994). The use of these tables derived from a healthy population can be controversial because the definition of healthy in the elderly is not consensual. Moreover, BMI may be unreliable in the presence of overt fluid retention (edema or ascitis) and may not identify significant unintentional weight loss, if used as a single assessment. Nevertheless, BMI correlates strongly with mid-arm muscle circumference and tricipital skinfold thickness in elderly cancer patients and shows the highest sensitivity for detecting severe malnutrition (Table 105.2) (Campillo et al. 2004). Reliable measurement of height can be difficult in the elderly hospitalized patients because of postural changes and unsteadiness. Furthermore, cumulative height loss between 30 and 80 years averages about 5 cm for men and 8 cm for women. This height loss would account for an artifactual increase in body mass index of approximately 1.4 kg/m^2 for men and 2.6 kg/m^2 for women (Sorkin et al. 1999). For these reasons, it could be of interest to use the self-reported height or use Chumlea's formulae to estimate height from the heel–knee height (Chumlea and Guo 1992).

A loss of more than 10% of the usual body weight suggests malnutrition. Ideally, the reference weight should be obtained from an earlier medical record. If this is not available, the usual self-reported body weight may be used. In case of acute illness, the body weight must have been measured before the onset of the disorder. Factors that may influence the interpretation of the result, such as dehydration or edema, should be taken into account. Nevertheless, weight loss can be difficult to determine in elderly people with cognitive disorders because the self-reported weight often cannot

Table 105.2 Value of BMI in the detection of malnutrition (Campillo et al. 2004)

	Diagnosis of malnutrition (%) according to:	Sensitivity (%) of BMI <20 to detect	Specificity (%) of BMI <20 to detect
BMI < 20	38.6		
MAMC < 5th or 10th perc	44.7	65.8	81.8
TST < 5th or 10th perc	20.0	64.7	66.2
MAMC and TST < 5th or 10th perc	11.8	62.2	86.5
MAMC or TST < 5th or 10th perc	52.9	80.0	65.3

This table shows the sensitivity and specificity of BMI<20 to detect malnutrition in comparison to other anthropometric parameters. Anthropometric parameters were measured within 48 h of admission in 91 patients (mean age ± SD = 66.7 ± 12.7 years) with advanced cancer of various organs. The prevalence of malnutrition was assessed by low BMI, low MAMC, low TST, and the association of low MAMC or TST, whereas severe malnutrition was diagnosed on the basis of low MAMC and TST. The sensitivity and specificity of BMI < 20 to detect moderate or severe malnutrition varied between 62% and 86%. This parameter showed a high specificity for the detection of severe malnutrition in cancer patients.

BMI body mass index, *MAMC* mid-arm muscle circumference, *TST* triceps skinfold thickness, *5th or 10th perc* 10th percentile of a nationally specific anthropometric reference data

be used. Skinfold thickness can be measured with standardized calipers, but this requires technical skill. Several different sites can be used: subscapular, suprailiac, biceps, triceps, thigh, and calf. Finally, all these anthropometric indicators are simple and inexpensive to obtain, but have to be interpreted in the light of age, gender, and ethnicity.

To improve the assessment of malnutrition in elderly, the Mini Nutritional Assessment (MNA) was developed in home-care programs, nursing homes, and hospitals (Vellas et al. 2006). The MNA is a multidimensional tool, which combines anthropometric measurements, global assessment, dietary assessment, and subjective assessment. The anthropometric variables used in MNA are weight loss over the last 3 months, BMI, mid-arm muscle circumference (MAMC), and calf circumference (CC).

According to the recommendations of the High Authority for Health in France (HAS) (HAS 2007), the diagnosis of malnutrition is based on the presence of one or more of the following criteria: weight loss ≥5% in 1 month or ≥10% in 6 months, body mass index <21, serum albumin concentrations <35 g/l, and global MNA score <17.

105.3 Prevalence of Malnutrition in Hospitalized Elderly Patients with Cancer

Modification of the nutritional status is a frequent complication in patients with cancer. The nutritional status can be affected either directly by the malignant process, by side effects of treatment (surgery, chemotherapy, and radiotherapy), or by psychological factors. There are very few studies concerning exclusively elderly cancer patients. Table 105.3 reports the nutritional studies of hospitalized cancer patients with mean age of 60 years or more. The most widely used anthropometrics measures in cancer are body mass index (BMI) and weight loss, with a prevalence of malnutrition varying between 20% and 70%, depending on threshold values reported (BMI<20 or 21, weight loss <5 or 10%). The body weight or BMI, measured once, can have a limited capacity to effectively detect patients at nutritional risk in breast and prostate cancer (Toliusiene and Lesauskaite 2004) because preexisting overweight may mask the beginning of the deterioration of the nutritional status. In order to tackle nutritional deterioration, it is important to gather objective data on nutritional status and its evolution throughout the course of the cancer. Other anthropometrics measures, such as

Table 105.3 Prevalence of malnutrition in elderly patients with cancer

References	Age (year) Number of patients	Cancer	Anthropometric parameters used for diagnosis	Prevalence of malnutrition (%)
Sarhill et al. (2003) USA	Mean age = 61 years n = 352 In-patients	Advanced metastatic cancer	Weight loss ≥10% BMI <18.5 MAMC <15th perc TST<25th perc	71 23 30 51
Campillo et al. (2004) France	Mean age = 68 years n = 91 In-patients	Advanced cancer	BMI <20 MAMC <10th per TST <10th per	38.6 44.7 20
Toliusiene and Lesauskaite (2004) Lithuania	Mean age = 72 years n = 40 In-patients	Advanced prostate cancer	Weight loss >3 kg MNA<17	39.5 10
Paillaud et al. (2006) France	>70 years (n = 43) ≤70 years (n = 45) In-patients	Locally advanced or metastatic tumors	Weight loss ≥10% >70 years ≤70 years BMI <20 >70 years ≤70 years	 71 82 44 49
Hurria et al. (2007) USA	Mean age = 76 years n = 245 Out-patients	Solid tumors at different stages	BMI < 22 Weight loss > 5%	20 26
Bories et al. (2008) France	>70 years n = 178 In-patients	Solid tumors at different stages	BMI < 21 Weight loss ≥ 10% MNA < 17	24.9 17.5 26.6
Girre et al. (2008) France	Mean age = 79 years n = 105 Out-patients	Solid tumors at different stages with 61% of breast cancer	Weight loss > 10% BMI < 21 21–23 >23	7.7 26 19 54

This table lists the nutritional studies of cancer elderly in-patients published in peer review journals. We reported mean age, number of patients, cancer localization, nutritional parameters used, and prevalence of malnutrition. The most widely used anthropometrics measures in cancer are body mass index (BMI) and weight loss, with a prevalence of malnutrition varying between 20% and 70%, depending on threshold values reported.
BMI Body mass index, *TST* Triceps skinfold thickness, *MAMC* Mid-arm muscle circumference, *MNA* Mini Nutritional Assessment

MAMC or TST, reflect the body composition changes that may occur during the disease. It is the loss of the fat-free mass that is responsible for the reduced functional status, increased mortality, and other negative outcomes associated with malnutrition (Tchekmedyian et al. 1992). The prevalence of malnutrition also varied according to the tumor site, disease stage, and the type of treatment used. One factor which most heavily influenced the nutritional status is the tumor site (Table 105.4). Patients with pancreatic, gastric, or esophagus cancer appear to have highest prevalence of weight loss, whereas those with breast or prostate cancer have the lowest ones.

105.4 Influence of Age

At admission, nutritional status is similarly altered in elderly and in other adults: aging per se does not represent a risk factor for malnutrition in cancer (Table 105.5) (Paillaud et al. 2006). However, during the course of hospitalization, elderly patients suffer from a greater loss of both fat and muscular mass

Table 105.4 Influence of the tumor type on the prevalence of malnutrition

	Dewys WD* 1998 *n* = 3,047	Nourissat et al.** 2007 *n* = 477
Type of tumor: *n* (%)		
Gastric	52 (38%)	8 (89%)
Esophagus		7 (78%)
Pancreas	29 (26%)	4 (58%)
Lung	154 (15%)	21 (31%)
Colon	46 (14%)	37 (36%)
Ovary		5 (25%)
Prostate	8 (10%)	4 (17%)
Lymphoma	29 (10%)	
Sarcoma	13 (7%)	
Breast	17 (6%)	13 (10%)
Acute Leukemia	5 (4%)	

This table lists the two international studies showing the prevalence of malnutrition according to tumor type. Malnutrition was assessed on the basis of weight loss >* or ≥** 10% in the previous 6 months. The prevalence of malnutrition was higher in patients with digestive tract cancer

Table 105.5 Comparison of nutritional status in cancer patients according to age (Paillaud et al. 2006)

	>70 years (*n* = 45)	<70 years (*n* = 43)	Statistical significance
Age (year)	77 ± 0.7	55.3 ± 1.2	
Gender (M/F)	20/25	24/19	$P < 0.0001$
Tumor type:			
Digest/hemato/solid	7/24/14	10/7/26	
Weight (kg)	56.6 ± 1.8	58.1 ± 1.8	
Weight loss (%)	16.1 ± 1.4	17.0 ± 1.4	
BMI (kg/m²)	21.4 ± 0.6	20.7 ± 0.6	
MAC (cm)	25.8 ± 0.7	25.7 ± 0.7	
TST (mm)	12.6 ± 0.9	13.3 ± 1.0	
MAMC (cm)	21.8 ± 0.6	21.5 ± 0.5	

This table shows the comparison of nutritional status in cancer patients according to age. Two groups of hospitalized patients with advanced cancer were defined according to age: an elderly group (>70 years) and a younger group (<70 years). Their nutritional status was assessed by different anthropometric parameters. Data are given as mean ± SEM. Means between groups were compared using the unpaired Student's *t* test. Anthropometric values did not differ between the two groups.
BMI body mass index, *MAC* mid-arm circumference, *TST* triceps skinfold thickness, *MAMC* mid-arm muscle circumference

(Table 105.6). This is partly explained by: (1) a lower spontaneous oral intake, compared with younger patients and (2) an intake below the recommended value for healthy, sedentary, elderly people. This higher risk for elderly patients calls for a specific nutritional strategy during hospitalization.

105.5 Comparison With Other Types of Disease

Cancer is associated with a more extensive modification of nutritional status than other diseases occurring in the elderly. Table 105.7 (personal data) compares anthropometric data in elderly cancer patients with those operated on for osteoarthritis, or those hospitalized for neurological or cardiac

Table 105.6 Changes in anthropometric parameters after a 2-month hospitalization in cancer patients, according to age (Paillaud et al. 2006)

	>70 years (n = 13)			<70 years (n = 9)		
	Day 0	Day 60	p	Day 0	Day 60	p*
BMI (kg/m²)	20.5 ± 1.5	20.3 ± 1.5		20.0 ± 1.7	19.9 ± 1.5	
MAC (cm)	25.7 ± 1.4	24.2 ± 1.0	< 0.03	27.0 ± 2.0	27.4 ± 1.7	
TST (mm)	11.5 ± 1.3	9.9 ± 1.0	< 0.03	15.2 ± 2.9	16.4 ± 2.8	
MAMC (cm)	22.1 ± 1.1	21.1 ± 0.8	0.085	22.2 ± 1.3	22.2 ± 0.9	
Fat mass (%)	25.4 ± 1.7	23.6 ± 1.4	< 0.05	28.5 ± 2.5	30.0 ± 2.6	

*not available, not significant

This table shows the changes in anthropometric parameters during the course of hospitalization in cancer patients according to age. Two groups of hospitalized patients with advanced cancer were defined according to age and were nutritionally assessed upon admission (day 0) and 2 months after (day 60) by measurement of anthropometric parameters. Data are given as mean ± SEM. Comparison of means between Day 0 and Day 60 using the paired Student's t test. MAC, TST, and fat mass decreased in the elderly patients after a 2-month hospitalization.
BMI body mass index, *MAC* mid-arm circumference, *TST* triceps skinfold thickness, *MAMC* mid-arm muscle circumference

Table 105.7 Comparison of anthropometric parameters between elderly hospitalized patients with cancer and those operated on for hip fracture or osteoarthritis or hospitalized for medical disorders (personal data)

Groups	Surgical (prosthesis for osteoarthrosis) n = 33	Medicine n = 44	Hip fracture n = 51	Cancer n = 47	p
Age (years)	74.7 ± 5.1	82.9 ± 8.2	83.0 ± 8.2	77.7 ± 5.4	$<10^{-4}$
Gender (H/F) (n)	15/18	9/35	10/41	10/27	0.009
MNA-sf	10.3 ± 3.1	5.7 ± 2.1	5.7 ± 2.4	5.1 ± 2.0	$<10^{-4}$
Weight (kg)	75.0 ± 17.9	60.0 ± 15.2	55.8 ± 11.3	56.3 ± 12.0	$<10^{-4}$
BMI (kg/m²)	28.1 ± 6.2	24.0 ± 5.6	21.8 ± 4.2	21.4 ± 4.2	$<10^{-4}$
MAC (cm)	31.0 ± 4.1	27.5 ± 4.8	25.6 ± 3.3	25.8 ± 4.7	$<10^{-4}$
TST (mm)	16.3 ± 8.0	11.1 ± 6.1	9.9 ± 3.8	12.5 ± 5.8	$<10^{-4}$
BST (mm)	7.2 ± 4.4	5.2 ± 4.1	3.9 ± 2.6	4.8 ± 4.6	0.003
Dietary intake (kcal/day)	1884 ± 326	1599 ± 422	1507 ± 461	1117 ± 657	$<10^{-4}$
Dietary intake (kcal/kg/day)	26.3 ± 6.8	27.9 ± 9.8	27.7 ± 8.3	22.8 ± 13.4	0.054

Four groups of hospitalized patients over 70 years were defined according to the cause of hospitalization. They were nutritionally assessed by measurement of anthropometric parameters and dietary intake. Data are given as mean ± SEM. Means between groups were compared using the ANOVA test. All data differed significantly among the four groups, with the most impaired values observed in patients with cancer and hip fracture.
MNA-sf mini-nutritional assessment-short form, *BMI* body mass index, *MAC* mid-arm circumference, *TST* triceps skinfold thickness, *BST* biceps skinfold thickness

diseases, or those operated on for hip fracture. Nutritional status is similarly compromised in the cancer and hip-fracture groups. These two geriatric populations are at particular risk of malnutrition and should be nutritionally evaluated upon admission and during hospitalization, and if necessary, should benefit from nutritional support.

Summary Points

- Clinical practice in geriatric oncology includes routine nutritional screening of elderly patients at risk of malnutrition and assessment of nutrition status at the time of hospitalization (Table 105.8).
- The most widely used anthropometric parameters are BMI and weight loss.

- The prevalence of malnutrition assessed by weight loss or BMI on hospital admission is not higher in elderly patients with cancer than in younger ones.
- During the course of hospitalization, anthropometric parameters decrease in elderly persons with advanced cancer resulting in a more impaired nutritional status in comparison with that of younger persons.
- Two elderly hospitalized populations are at particular risk of malnutrition: patients operated for hip fracture and cancer patients. These groups require increased surveillance.

Key Points

Table 105.8 Key points of malnutrition in hospitalized elderly patients with cancer

Key points
The number of elderly people in the industrialized world is steadily increasing and is associated with an increased prevalence of health problems.
The prevalence of malnutrition in hospitalized patients >70 years is between 30% and 70%.
More than 30% of cancers occur in patients aged >70 years.
Malnutrition is a poor prognostic factor and should be detected in cancer patients.
Elderly cancer patients are usually nutritionally assessed by means of BMI and percent weight loss.
The prevalence of malnutrition is similarly high in hospitalized elderly and in other adult patients with advanced cancer on admission (≥50%).
Elderly patients are at high risk of altering their nutritional status during the course of hospitalization.

This table lists the key facts of malnutrition in elderly patients with cancer including the tools to measure it

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Chapter 106
Body Weight and Body Surface Area in Chemotherapy

Dominique Levêque

Abstract In oncology, dosing of anticancer drugs in adult patients is mostly adjusted to estimated body surface area or more rarely to body weight. When compared with a fixed (or flat) dose which is the rule in other therapeutic areas, this approach is a complication necessitating calculations that can lead to prescription and administration errors. Dosing according to body surface area or to body weight is based on the intuitive belief that the variability in drug exposure (ie, the capacities of the organism to clear a drug) is related to body size in adults. Dose normalization to body size is assumed to decrease the interindividual pharmacokinetic and pharmacodynamic variability and in turn, to optimize clinical outcomes. Unfortunately, this approach is mostly empirical and is rarely validated before approval of the anticancer drug. Theoritically, body size-based dosing should only be used if it has been demonstrated that it constitutes a significant factor affecting clinical variability. Numerous studies have shown that dosing according to body surface area or body weight did not significantly affect drug exposure variability. It has never been proved that body size was a covariable of pharmacokinetics and pharmacodynamics of anticancer agents in adults patients. Although the use of body surface area has been discouraged during clinical development, this practice remains the rule particularly for conventional agents. For few agents, alternative methods of dosing optimization include the integration of phenotypic or genotypic factors.

Abbreviations

AUC	Area under the concentration-time curve
BSA	Body surface area
CV	Coefficient of variation

106.1 Introduction

In pharmacotherapy, drugs are generally given to adult patients at a fixed (or flat) dose, independently of the size of the body, at least because it is more convenient. By contrast, in oncology, dosing of anticancer agents is traditionally adjusted according to estimated body surface area or, more

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_106,

Table 106.1 Key features of anticancer chemotherapy

1. Chemotherapy is one of the modalities (besides surgery and radiotherapy) of anticancer treatment.
2. In oncology, chemotherapy defines the use of drugs (called anticancer agents or antineoplastic agents) that eradicate cancer cells.
3. Anticancer agents are mainly given intravenously and in combination.
4. Most of the anticancer agents are very toxic because they also destroy healthy cells (lack of selectivity).
5. Side effects of chemotherapy (digestive, hematologic, and infectious) may be prevented or treated by supportive care products.

This table lists the key facts of anticancer chemotherapy including the definition, the lack of selectivity, and the management of side effects

Table 106.2 Classes of drugs used in the treatment of cancer (referred to as chemotherapy)

Class	Clinical use	Route of administration
Conventional cytotoxic agents	All types of cancer	Mostly parenteral, oral
Hormonotherapy	Hormone-dependent tumors (breast and prostate cancer)	Mostly oral, parenteral
Monoclonal antibodies	Selected types of cancer (those expressing the target antigen)	Parenteral
«Targeted therapies» (enzyme inhibitors)	Selected types of cancer (those expressing deregulated enzyme activity)	Mostly oral, parenteral

This table lists the various types of drugs used in the treatment of cancer including the conventional cytotoxic agents, hormonotherapy, the monoclonal antibodies, and the "targeted therapies"

rarely, to body weight. In a general way, dosing based on body size is mostly used in pediatrics in relation with development and maturation of children.

Anticancer agents, also referred as chemotherapy (Tables 106.1 and 106.2), are known to have a low therapeutic index. This means that for most of them, the therapeutic dose is very close to the maximal tolerated or toxic dose. The activity of a drug (therapeutic or toxic) depends on its concentration at the site of action (pharmacodynamic relationship), which generally is the reflection of its fate in plasma after administration (pharmacokinetics) (Table 106.3). For a given dose, interindividual variability in drug exposure (pharmacokinetic variability) may occur, leading to severe side effects or insufficient anticancer activity (pharmacodynamic variability). Adjustment of dosing according to body surface area or body weight is based on the intuitive belief that the variability in drug exposure (i.e., the capacities of the organism to clear a drug) is related to body size in adults. Consequently, it is assumed that this approach decreases the pharmacokinetic variability and, hence, optimizes the exposure to anticancer agents and the therapeutic activity.

For 20 years, numerous critics have raised concerns on the dosing of anticancer agents adjusted to body size in adults. Currently, this practice remains the standard in adult oncology, but alternative approaches, in particular, genetic, are emerging. This chapter will present the principles and the limitations of the dosing of anticancer agents based on body size in adult patients.

106.2 Background

In 1958, Donald Pinkel suggested to use body surface area instead of body weight in the dosing of anticancer agents (Pinkel 1958). This was based on the observation that, for some anticancer agents (in fact, the few that were available at that time: methotrexate, mechlorethamine, 6 mercaptopurine,

Table 106.3 Key facts of pharmacokinetics and pharmacodynamics

1. Pharmacokinetics describes the behavior of drugs in the body after administration.
2. Drug disposition in the organism generally follows three steps (absorption, distribution, and elimination that include metabolism and/or excretion).
3. These processes may be quantified by parameters (pharmacokinetic parameters) estimated from the plasma drug concentration versus time curve.
4. The area under the plasma drug concentration versus time curve (AUC) defines the exposure of the organism to the drug.
5. Absorption relates the fate of the drug from the administration site to the blood (it does not apply to the intravenous or intra-arterial route). The process is characterized by the plasma concentration peak, the time for plasma concentration peak, and the absolute bioavailability.
6. Bioavailability is the fraction of the administrated dose which reaches the general circulation (i.e., available for the therapeutic effect).
7. Elimination corresponds to the irreversible loss of the drug from the body. The drug may be eliminated by metabolism (biotransformed in an inactive metabolite) and/or excreted via the bile in the feces or in the urine. These processes involve metabolizing enzymes and sometimes drug transporters that mediate active transcellular passage.
8. The elimination parameters are the total clearance (capacity of the body to clear the drug), which is calculated by dividing the amount of the drug in the body by the area under the plasma drug concentration versus time curve (AUC), and the terminal half-life (time over which the plasma concentration of the drug decreases by half).
9. Pharmacokinetics is also characterized by the intra- and interindividual variability of parameters. For a given dose, the extent of absorption (for example, bioavailability for an oral agent) or the rate of elimination may greatly vary among patients.
10. These variations of plasma concentrations may affect the clinical outcomes (tolerance and therapeutic effect). The relation between drug concentrations and clinical effects is called pharmacodynamics (i.e., the study of the impact of pharmacokinetic variability on the drug effects).

This table lists the key facts of pharmacokinetics and pharmacodynamics including the different steps of drug disposition in the organism, the area under the plasma drug concentration versus time curve (AUC), the corresponding parameters, and the impact of pharmacokinetic variability (pharmacodynamics)

actinomycin D, and thiotepa), the therapeutic dosages were comparable in humans and small laboratory animals (mice, rats, and hamsters) when related to body surface area and not to body weight. At the end of the fifties, body surface area arose as a criterion of drug dosage because it was estimated to correlate with physiologic functions. Since then, and without any scientific validation, drug dosage normalized to body surface area was used in phase I clinical trials (first administration of a drug in humans) and was included in the official labeling (or summary of the product characteristics) of almost all marketed anticancer agents.

Currently, this practice is relatively specific to oncology and, besides anticancer agents, also concerns supportive care products, such as some hematopoietic growth factors, antifungal agents, or antidotes (drugs used to prevent or cure symptoms related to the disease or to the toxicity of the anticancer treatments). Sometimes, this approach appears irrational (and rather confusing) within a class of anticancer agents, such as the therapeutic monoclonal antibodies. Monoclonal antibodies display comparable pharmacokinetic behaviors (limited distribution in the body and very low clearance), but are used either at a fixed dose or at a dose based on body weight or body surface area (Table 106.4). This heterogeneity may even be observed for a single drug, such as rituximab. Rituximab, a monoclonal antibody that specifically targets lymphocytes, is bizarrely given at a dose adjusted to body surface area in the treatment of cancer (375 mg/m² in non-Hodgkin lymphoma and 500 mg/m² in chronic lymphocytic leukemia) and at a fixed dose (1 g) in rheumatoid arthritis, a systemic non-cancerous inflammatory disease. Similarly, dacarbazine is a conventional agent whose dosing is based on body weight when administered as monotherapy and on body surface area when combined with another anticancer agent.

Table 106.4 Heterogeneity of dosing expression of monoclonal antibodies used in the treatment of cancer

Therapeutic monoclonal antibody	Expression of dosing
Rituximab	Body-surface-area-based; fixed dose in non cancerous diseases
Alemtuzumab	Fixed dose
Trastuzumab	Body-weight-based
Cetuximab	Body-surface area-based
Panitumumab	Body-weight-based
Bevacizumab	Body-surface area-based
Ibritumomab tiuxetan (coupled with a radioisotope)	Radioactive dose
Gemtuzumab ozogamicin	Body-weight-based

This table lists the various expressions of dosing of anticancer therapeutic monoclonal antibodies including the use of body surface area, body weight, the fixed dose, and the radioactive dose

However, fixed dosing tends to be used with recent anticancer agents and particularly the so-called «targeted therapies». Contrasting with conventional agents, the research of which is primarily based on the killing of tumoral cells in vitro, «targeted agents» interact with a relative specificity with predefined physiological or tumoral determinants (enzymes, such as kinases, in a general way). Currently, all approved «targeted therapies» in the European Union (gefitinib, erlotinib, sunitinib, sorafenib, imatinib, dasatinib, nilotinib, lapatinib, pazopanib, everolimus, and temsirolimus) are administrated at a fixed dose in adult patients. This is probably due to their low toxicity profile when compared with conventional agents and to their oral administration (except temsirolimus given by intravenous injection). Oral, fixed dosing is far more convenient than that adjusted to body size. In fact, and unless a liquid oral formulation is available, accurate adjustment to body size is not possible with solid forms (tablets or capsules).

106.3 Practical Considerations

Practically, and when compared with the fixed dose, body-size-based dosing is a complication necessitating calculations that can generate prescription, preparation, and administration errors (medication errors). The oncologist estimates body size area of the patient (in m^2) using weight and height and then calculates the dose by referring to the approved dosage expressed by m^2 (that mentioned in the official labeling). For example, for a patient of 1.66 m^2, the dose of rituximab to be administered is 375 mg/m^2 (approved dosage) × 1.66 m^2 = 622.5 mg (Table 106.5). Then, the pharmacist analyzes the order (in particular, checks the estimation of body surface area and the corresponding dosage) and delivers the product using the available dosage presentations, generally ready to be administered. Most of the anticancer agents are parenteral drugs and their preparation is generally performed in hospital pharmacies. For rituximab, the dose (622.5 mg) is prepared using the 100 mg and 500 mg marketed presentations. Hence, preparation of a dose of an intravenous form adjusted to body size may lead to wastage associated with significant financial consequences, given the prohibitive cost of anticancer agents.

Regarding oral anticancer agents (besides «targeted therapies»), dosing can also be complicated for the physician and the patient. For example, the recommended treatment schedule for capecitabine (a conventional agent used in breast and gastro-intestinal cancers) includes nine levels of dosing (i.e., the number of pills to be taken), depending on the body surface area of the patient.

Table 106.5 Practical considerations of drug dosing based on body surface area: an example using an adult patient treated by the therapeutic monoclonal antibody rituximab

Oncologist	Estimates body surface area of the patient using body weight and height: 1.66 m²
	Calculates the administrated dose: approved dosage of rituximab (375 mg/m²) × 1.66 m² = 622.5 mg
Pharmacist	Analyzes the prescription: checks the body surface area estimation and the corresponding dose
	Prepares the dose ready to be administered intravenously (622.5 mg) using the available marketed presentations of rituximab (100 and 500 mg)

This table lists the practical considerations followed by the oncologist and the pharmacist regarding the treatment of an adult patient with the monoclonal antibody rituximab

106.4 Limitations of Body-Size-Based Dosing

Scientifically, body-size-based dosing appears mostly either unjustified (i.e., not better than fixed dosing) or unvalidated (not proven that it is better than fixed dosing). In fact, body surface area or body weight should only be used if it has been demonstrated that size constitutes a significant factor affecting pharmacokinetic and pharmacodynamic (clinical) variability. When compared to fixed dosing, administration of anticancer drugs adjusted to body weight or body surface area should lead to the improvement of therapeutic outcomes (optimized antitumoral response and decreased toxicity).

Since 1990, numerous papers have been published highlighting the lack of relationship between body surface area and the elimination parameters (clearance) of anticancer agents (Grochow et al. 1990; Reilly and Workman 1993; Gurney 1996; Ratain 1998; Sawyer and Ratain 2001; Miller 2002; Newell 2002; Egorin 2003; Levêque 2007; Mathijssen et al. 2007). For most anticancer agents, including the recent monoclonal antibodies, body size is not a factor that significantly affects drug disposition in the organism or decreases exposure variability. It is not really a surprise because the physiological activities of the two main organs involved in the elimination of drugs (the kidneys and the liver) are not correlated to body size in adults. In addition, the variation of body surface area in adult patients is weak (15%) when compared with pharmacokinetic variability of anticancer agents (25–50%). It has to be stated that, in oncology, the dosage of anticancer agents is often tailored to the patient's clinical response. The standard dose is decreased in case of inacceptable toxicity or sometimes increased if the therapeutic response is judged insufficient. Curiously, these dosing modifications that may be significant (20–50%) remain based on body size (e.g., from 100 to 75 mg/m²). In all, estimated body surface area or body weight has not been shown to significantly correlate with pharmacokinetic or pharmacodynamic variability of numerous anticancer drugs. In other words, several anticancer agents could be administered at a fixed dose in adult patients because interindividual variability persists on using body-size-calculated dosing.

Some trials have compared body surface area dosing with fixed dosing of anticancer drugs in adult patients in terms of pharmacokinetic variability and clinical outcomes (Table 106.6). Variation in pharmacokinetics and toxicity was found to be similar in patients receiving irinotecan, an intravenous drug used for the treatment of colorectal cancer, either at fixed dose (600 mg, 26 patients) or adjusted to body surface area (350 mg/m², 47 patients) (De Jong et al. 2004). The coefficients of variation of irinotecan clearance were around 25% in both groups. Thus, flat fixed dosing of irinotecan did not major pharmacokinetic variability nor hematological toxicity. Paclitaxel is an intravenous conventional agent given in the treatment of lung, ovary, and breast cancer. Paclitaxel pharmacokinetics have been studied in 12 patients who received the anticancer agent both at a fixed dose (300 mg) and at a dose based on body surface area (175 mg/m²) in a randomized

Table 106.6 Features of clinical trials comparing body surface area dosing and fixed dosing of anticancer agents in adult patients

Anticancer drug	Method of dosing	Pharmacokinetic variability	Clinical outcomes	Reference
Irinotecan	Body surface area-based	16.7% (CV of AUC)		
	Fixed dose	29.9% (CV of AUC)	No difference in toxicity	De Jong et al. (2004)
Paclitaxel	Body-surface area-based	25.1% (CV of clearance)		
	Fixed dose	25.9% (CV of clearance)	No difference in toxicity	Miller et al. (2004)

This table lists the features of trials that have compared body surface area dosing and fixed dosing of irinotecan and paclitaxel, in terms of pharmacokinetic variability and clinical outcomes. CV, coefficient of variation; AUC, area under the concentration–time curve

Table 106.7 Expression of dosage of 148 investigational anticancer agents in 225 adult phase I trials reported at major oncology meetings in the years 2005 and 2006 (Levêque et al. 2008)

	Fixed dose (%)	Body-surface area-based (%)	Body-weight-based (%)
All trials	40.4	44	13.8
Trials with conventional agents	1.3	96	2.7
Trials with "targeted therapies"	78.5	16.4	2.7

This table lists the various expressions of dosage of investigational agents including conventional drugs and "targeted" therapies

crossover design (Miller et al. 2004). Exposures to paclitaxel determined by the area under the plasma concentrations–time curve (AUC) were comparable with the two dosing approaches and no difference in terms of hematological toxicity appeared. The variability was higher with flat fixed dosing compared with the traditional body-surface-area-based dosing (29.9% vs. 16.7%), but without clinical consequences (toxicity). These two a posteriori studies (i.e., undergone after drug approval) show that fixed dosing is not detrimental in terms of clinical impact when compared to body-surface-area-based dosing.

Consequently, in 2002, the abandonment of the use of body surface area in dosing of new agents in phase I studies was recommended by some authors (Baker et al. 2002). To see if these recommendations were effectively implemented, a survey assessed the expression of dosage of 148 investigational anticancer agents in 225 adult phase I trials reported at major oncology meetings in the years 2005 and 2006 (Levêque 2008). Dosages were still adjusted to body surface area and body weight in 44% and 13.8% of all trials. Only 91 studies (40.4%) exhibited a fixed dose (Table 106.7). Regarding the type of anticancer drug, virtually all trials (96%) involving conventional agents used body-surface-area-based dosing, whereas the majority of studies (78.5%) of targeted anticancer agents used a fixed dose, perhaps in relation with their low toxicity (when compared with cytotoxics) and to the fact that they were primarily oral drugs. Thus, recommendations were not really followed, particularly for conventional agents.

106.5 Alternative Approaches of Dosing Optimization

Fixed dosing is the simplest way to administer a medication until other factors or covariables are identified that significantly improve patient care. As discussed earlier, body size is not a factor that optimizes anticancer drug dosing in adult patients since it does not significantly decrease drug exposure

Table 106.8 Alternative approaches of dosing optimization of anticancer agents

Method	Advantage	Limits
Genotypic: identify genetic variants associated with pharmacokinetic/pharmacodynamic variability	Optimization a priori	Applies to very few drugs Partly explains pharmacokinetic/pharmacodynamic variability Still used as body-size dosing
Phenotypic: adjusting drug dosage according to elimination capacities of the patient	Validated by clinical trials	Applies to very few drugs Still used as body-size dosing
Physiologic: adjusting drug dosage according to the renal function of the patient	Not based on body size	Only applies to carboplatin

This table lists the alternative methods of dosing of anticancer agents including the genotypic, phenotypic, and physiologic approaches

variability and, in turn, does not affect clinical outcomes. The search for the causes underlying pharmacokinetic variability has led to the exploration of genetic or phenotypic factors as potential means to improve the dosing schedules of anticancer agents (Table 106.8).

Drug disposition in the organism (absorption, distribution, and elimination) is controlled by molecular determinants, such as metabolizing enzymes and transporters. Pharmacokinetic variability may be related to variations in the expression of these determinants. One cause of variation is genetic, due to polymorphisms that affect (in general decrease) the activities of enzymes or transporters. Regarding drug dosing, identification of patients with genetic variants (genotyping) before the initiation of treatment can avoid serious side effects related to defective elimination or decreased therapeutic activity due to insufficient anabolic formation of the active entity. Currently, only four anticancer agents (mercaptopurine, thioguanine, irinotecan, and tamoxifen to a lesser extent) are administered by dosing optimization based on genotyping (Walko and McLeod 2009). All of these are mentioned in the package inserts of three products (mercaptopurine, thioguanine, and irinotecan), at least in USA. For example, a dose reduction of irinotecan is recommended in patients with decreased activity of UGT1A1, an enzyme involved in the elimination of the anticancer agent, in relation to the gene variant *UGT1A1*28.* However, as mentioned in the official labeling of irinotecan (Camptosar® in the USA), the precise dose reduction is not known. To avoid excessive toxicity, dosage is reduced by 25% in homozygote patients with the gene variant *UGT1A1*28*, but is still based on body surface area. In addition, dose individualization based on genotyping of one determinant appears far from optimal. In fact, variability in irinotecan disposition and toxicity is multifactorial, involving both genetic and non-genetic factors, such as sex (Mathijssen 2009). Overall, dosing adjustment based on genotyping does not appear good enough for irinotecan and remains related to body size.

The variability of enzyme activity may also be extra genetic, as with fluorouracil, a drug characterized by a high and variable metabolic elimination when given by continuous venous infusion. Differences in fluorouracil exposure affect clinical outcomes (efficacy and tolerance). Fluorouracil dosing may be individualized based on the capacities of elimination of the patient that can be determined before treatment with a test dose or during treatment by measuring plasma concentrations (Gamelin et al. 2008). However, and like the genotypic approach, this phenotypic method of dosing still used body surface area.

Drug dosing may be adjusted to renal function, as in the case of carboplatin, whose elimination is highly related to the glomerular filtration rate (Calvert et al. 1989). Variations in elimination (i.e., in renal function) affect the tolerance (mainly hematological) of the drug. Carboplatin is the rare anticancer agent whose dosing is not based on body surface area but on the renal function of the patient.

106.6 Applications to Other Areas of Health and Disease

Besides chemotherapy, questioning the use of body size in the dosing of drugs in adult patients may apply to other therapeutic areas, such as anti-infective agents or drugs used in the treatment of autoimmune diseases. Avoiding dose calculation based on the weight or the body surface area of the patient may limit errors of prescription, dispensation, and administration.

106.7 Conclusion

Dosing of anticancer drugs is adjusted to body surface area or body weight, although it has never been proven that this practice leads to improvement of therapeutic outcomes in adult patients when compared to fixed dosing. Numerous marketed anticancer agents could be administered at a fixed dose, but, unfortunately, it is improbable that their official labelings will change. For oral agents, some simplifications may occur, as for capecitabine, which has recently been tested using a flat dosing (Traina et al. 2008). Regarding investigational agents, fixed dosing could be used until it is demonstrated that body size or another variable (genotypic, phenotypic) is a significant factor of clinical variability. Fixed dosing has at least the potential to reduce medication errors and perhaps to limit the wastage of costly products. Novel approaches of dosing improvement are emerging, but currently concern very few agents.

Summary Points

- The particularity of anticancer drug dosing is that it is to be adjusted according to body surface area or body weight in adult patients.
- When compared with a fixed (or flat) dose, this approach is a complication necessitating calculations that can lead to prescription and administration errors.
- Dosing according to body size should be used if it leads to improvement of therapeutic outcomes, when compared with a fixed dose.
- Dosing according to body size in oncology is mostly empirical and is very rarely validated, a priori.
- Variation in body surface area is weak in adult patients when compared with pharmacokinetic variability.
- Numerous studies have shown that dosing according to body surface area or body weight did not significantly affect drug exposure variability. It has never been proved that body size was a covariable of pharmacokinetics and pharmacodynamics of anticancer agents in adult patients.
- Although the use of body surface area has been discouraged during clinical development, this practice remains the rule particularly for conventional agents.
- For a few agents, alternative approaches of dosing optimization include the integration of phenotypic or genotypic factors.

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Part XVII
Anthropometry in Exercise and Sport Activities

Chapter 107
The Meaning of Muscle Mass for Health, Disease, and Strength Exercises

Roberto Carlos Burini and Nailza Maestá

Abstract Skeletal muscle is the largest organ of the mature body having major contributions to endogenous amino acid supply, insulin-dependent glucose removal and total body energy expenditure. Muscle mass is a determinant of metabolic homeostasis, physical strength and daily living activities. Higher lean mass equates to higher nutritional reserve and strength whereas lower muscle mass (sarcopenia) is a major contributor to disability and increased mortality. The definition of sarcopenia is arbitrary and its diagnosis is dependent on the methodology of muscle mass assessment, reference groups and cut off points. Methods used to assess muscle mass such as anthropometry, BIA or DXA are unable to distinguish aqueous and non aqueous components of the muscle mass whereas this is accomplished with the more expensive CT or MRI. Data are referred as kg of muscle mass, % of the body mass or correcting either appendicular or total muscle mass for height (kg/m^2). The most used data comes from either DXA or BIA assessment in male and female populations of Rosseta, New Mexico (NM Elder Health Survey) and NHANES III studies with cut off points at −2 SD for both genders. There is no cut off for hypertrophic-muscle mass. There are also no consensual criteria for defining sarcopenic-obesity or the fat frailty, the worse condition with regard to the difficulties of performing physical tasks. For this purpose muscle mass must be associated with some type of functional test (strength and power) to assess muscle quality. This chapter highlights the roles of muscle mass, its measurements and variations in health and diseases, and the lack of data for correctly interpreting muscle mass and function in the presence of obesity and strength exercises.

Abbreviations

AIDS	Acquired immune deficiency syndrome
ASM	Appendicular skeletal muscle mass
BIA	Bioelectrical impedance
CT	Computerized tomography
DXA	Dual X-ray absorptiometry
MRI	Magnetic resonance imaging
NHANES	National Health and Nutrition Examination Survey

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_107,

SD	Standard deviation
SMI	Skeletal mass index
US	United States of America
VO_2 max	Maximum aerobic capacity
WC	Waist circumference

107.1 Introduction

107.1.1 Skeletal Muscle Role in Health

Skeletal muscle is the largest organ in the mature human body and the major reservoir of free amino acids, which are mobilized for the immune response in many diseases, or stressful events, or both (Evans 1997). It is also the most responsible for the insulin-dependent glucose removal from plasma and is the major contributor to whole-body energy expenditure (Elia 1992). As a major determinant of physical strength, the loss of lean mass is thought to be a major contributor to functional decline and disability (Janssen et al 2004a, b).

Multiple independent studies have so far reported that all-cause mortality and body mass index (BMI) show a U-shaped association in men and women: namely that, whereas there is a significant increase in all-cause mortality among persons with a BMI higher than approximately 25 kg/m^2, persons with a BMI lower than approximately 20 kg/m^2 also show increased mortality, even after adjusting for possible confounding factors.

Epidemiological cross-sectional studies have documented associations between low skeletal mass and physical disability (Baumgartner et al 1998; Janssen et al 2004a) or low physical performance. Subjects in the lowest quartile of cross-sectional thigh area had a higher risk (1.90 for men and 1.68 for women) of developing mobility disability than those in the highest quartile (Visser et al. 2005).

There is a positive association between muscle mass and strength and in improving functional performance and reduced disability (Rolland et al. 2008). Muscle strength is associated with lower mortality. The relationship between muscle mass and strength is linear, whereas the relationship between physical performance (such as walking speed) and muscle mass is curvilinear (Newman et al. 2006). Muscle strength is related to muscle mass, but the ability to perform activities of daily life also relies on other physiological characteristics, such as flexibility, coordination, praxis, and balance (Rolland et al. 2008).

Human skeletal muscle is dependent on genetic predisposition, exercise, nutrition, and the hormonal–inflammatory state. A decrease of muscle mass with aging results in sarcopenia, whereas an increase of fat mass results in obesity. Each of these conditions is believed to contribute, at least in part, to difficulties with physical function and increased levels of physical disability (Baumgartner et al. 1998).

Approximately 60% of fat-free mass is muscle and about 75% of muscle mass is appendicular (Morley 2008).

The control of skeletal muscle size is tightly regulated by the synergy between hypertrophy (anabolic) and atrophy (catabolic) processes (Leger et al. 2006). The quantity of protein in skeletal muscle is maintained by a continuous repair process, which involves both protein breakdown and synthesis. The total mass of skeletal muscle is determined by the balance between protein synthesis and protein breakdown (Miyazaki et al. 2008). Skeletal muscle is highly adaptable and can change its structural and functional properties in response to physiological simulation (Miyazaki et al. 2008).

Muscle inactivity, which can occur with immobilization and microgravity, causes muscle atrophy (Miyazaki et al. 2008). After the age of 40, skeletal muscle is lost at a rate of approximately 5% per decade. In the elderly, the muscle protein synthesis rate is reduced by 30% (Rolland et al. 2008).

With aging, there is a decrease in both muscle fiber size and number, with a greater loss of type II and an increase in hybrid type I and II fibers (Reeves et al. 2006). The loss of muscle mass is greater in the legs than in the arms, but the loss of muscle quality in the elderly seems more significant in the arms for men compared to women, whereas loss of muscle quality in the leg seems similar in men and women (Lynch et al. 1999).

Men and women present different trajectories in the decline in skeletal muscle with aging; men have a gradual decline, whereas women tend to have a sudden drop in muscle mass and function following menopause (Rolland et al. 2008).

It is well known that aging is associated with decreased functional capacity, free-fat mass, bone mass, maximal heart rate, and other factors that greatly increase the risk of chronic disease and reduced independence later in life (Evans 1997). VO_2 max declines at the rate of 3–8% per decade after 30 years of age, but, adjusted for muscle mass, VO_2 max no longer declines. This suggests that loss of muscle mass is a significant contributor to fatigue and decreased endurance (Rolland et al. 2008).

The large, and supposedly involuntary, loss of muscle tissue in the elderly is considered responsible in part for the age-related decline in functional capacity. Fatty infiltration of skeletal muscle common in the elderly is associated with reduced strength and functional status (Rolland et al. 2008).

After 50 years of age, muscle mass is reported to decline at an annual rate of approximately 1–2%, but strength declines at 1.5% per year and accelerates to as much as 3% per year after age 60 (Evans 1997). These rates are higher in sedentary individuals and twice as high in men compared to women (Gallagher et al. 1997). Age-related loss of skeletal mass, strength, and function ultimately causes about 15% of persons 65–75 years of age and 50% of persons >85 years of age to require assistance with daily living activities (Rolland et al. 2008).

Human skeletal muscle hypertrophy occurs with an increase in functional demands, seen with resistance training and with functional electrical stimulation after spinal cord injury and in the elderly following surgery (Leger et al. 2006). Increased muscle activity attributable to a resistance-exercise- and functional overload induces skeletal muscle hypertrophy (Miyazaki et al. 2008). High-intensity resistance training (above 60% of the one repetition maximum) causes large increases in strength and significant increases in muscle size (Evans 1997).

107.1.2 The Importance of Muscle Loss

In 1931, Critchley noted that, with aging, there was a loss of muscle mass, which was most noticeable in the hands and feet (Critchley 1931). This age-related loss of muscle mass was later called sarcopenia (from the Greek: sarx for flesh and penia for loss) by Irving Rosenberg (Rosenberg 1997).

Whereas originally sarcopenia was considered to be a generalized loss of muscle, it is now more conventionally used to describe a level of muscle loss substantially more than that seen in normal young persons. Sarcopenia is one of the four major causes of weight loss. The others are anorexia, cachexia, and dehydration (Morley 2008).

Sarcopenia is different from starvation and cachexia, which are also associated with loss of muscle mass but whose causes and therapeutic approaches are different. During starvation, protein–energy deficiency results in a loss of fat and muscle mass (Morley 2008), but these are reversible with

Table 107.1 Complications relative to loss of lean body mass (Demling 2006. Reproduction permission requested)

Lean body mass (% loss of total)	Complications (related to lost lean mass)	Associated mortality (%)
10	Impaired immunity and increased infection	10
20	Decreased healing, weakness, and infection	30
30	Too weak to sit, pressure sores, pneumonia, and no healing	50
40	Death, usually from pneumonia	100

replenishment. Cachexia results in both fat and muscle mass loss, but it accompanies chronic disease (Rolland et al. 2008). This progressive muscular abnormality, which affects several anabolic and catabolic systems and results in a progressive catabolic state, is a devastating condition seen after musculoskeletal trauma, catabolic diseases such as cancer, diabetes, sepsis, chronic obstructive pulmonary disease, chronic heart failure and AIDS denervation, neuromuscular disorders such as Duchenne muscular dystrophy and myotrophic lateral sclerosis, and critical illness myopathy (Leger et al. 2006).

Cachetic patients usually die from either opportunistic infections or wound-healing failure, both of which are related to the decrease of lean body mass (Table 107.1).

Sarcopenia is attributable to an imbalance between protein synthesis and degradation, or between apoptosis and the regeneration process, or both. However, sarcopenia is thought to mainly reflect an age-related decrease in the synthesis of muscle protein rather than an excess catabolic process associated with disease or from a reduced caloric intake, although some have hypothesized that low-grade, chronic inflammation with increased protein degradation may contribute (Rolland et al. 2008).

Lifestyle behaviors leading to sarcopenia are physical inactivity, smoking, and poor diet. The risk factors are age-related changes in hormones and cytokine levels. Postulated mechanisms are alterations in muscle protein turnover, muscle tissue remodeling, the loss of alpha motor neurons, and muscle cell recruitment apoptosis (Baumgartner and Waters 2006).

Causes of sarcopenia are: impaired muscle capacity to regenerate (deficiency in satellite cells and protein turnover alterations); increased oxidative stress; loss of motoneurons; reorganizations of neuromuscular junction disturbances of the endocrine system; deteriorization of the immune system; and development of a chronic inflammatory state (Combaret et al. 2009).

Sarcopenia has become an important area of clinical research because it is considered to be an important contributor to the age-related loss of physical function. Age-related muscle loss is a prevalent condition associated with disability and mortality. Sarcopenia plays a predominant role in the etiology and pathogenesis of frailty, which is highly predictive of adverse events, such as hospitalization, associated morbidity and disability, and mortality (Rantanen 2003).

Sarcopenia is assumed to be a major component in the development of frailty to the degree that the International Academy of Nutrition and Aging Screen for Frailty (IANA) definition for frailty is strongly related to sarcopenia (Abellan van Kan et al. 2008; Baumgartner et al. 1998). This condition is approximately twice as common as frailty (Morley et al. 2005). In USA, it is estimated that there are roughly 3.6 million persons with frailty (Morley 2008). It results in a decrease in muscular strength and endurance (Rosenberg 1997) and is strongly associated with disability (Janssen et al. 2004b) with a cost of approximately $ 18.5 billion or 15% of the total healthcare expenditure in USA (Janssen et al. 2004a, b). These costs will escalate as the population older than 65 years grows from 13% (1977) to 17% in 2020, and to 21% in 2040 (U.S. Census Bureau 2000).

Higher BMI is a risk factor for loss of muscle mass in postmenopausal women, as an excess accumulation of fatty acids around the muscle fibers may interfere with their functioning (Rolland et al. 2009) and thereby reduce muscle quality (muscle strength adjusted for muscle size). The age-related

increase in fat mass generally precedes the loss of muscle mass (Baumgartner and Waters 2006), but the reverse is also true. The loss of muscle mass results in lower physical activity, which, in turn, results in reduced energy expenditure, fat gain, and obesity (Rolland et al. 2009).

An increase of fat mass may be more predictive of self-reported disability, functional limitation, and poor physical performance than a decrease of muscle mass (Rolland et al. 2009). It has been recognized that persons who lose muscle, but remain obese, are at very high risk of disability and mortality (Baumgartner et al. 2004). This condition is called "obese sarcopenia" or "fat frail." In addition, when muscle contains large amounts of fat, there is an increased likelihood of poor outcomes, a condition termed myosteatosis (Rolland et al. 2008).

It has been hypothesized that sarcopenic obesity is associated with increased fatty infiltration of muscle (Baumgartner et al. 2004). Contractility, motor unit recruitment, or muscle metabolism decreases in the presence of fat infiltration (Rolland et al. 2008).

Sarcopenic obesity is the worst condition with regard to the difficulties of performing physical tasks that require strength (Rolland et al. 2009). Sarcopenia may only affect physical performance and function in the presence of increased fat mass. Furthermore, the occurrence of obesity and sarcopenia together has been reported to be a much more pejorative condition in the development of physical disabilities than either sarcopenia or obesity alone (Baumgartner et al. 2004). Sarcopenic obesity has been reported to predict the onset of disability more accurately than either sarcopenia or obesity alone.

While it is recognized that the factors that cause strength loss are different from those resulting in muscle loss (Rolland et al. 2009), sarcopenia usually results in a decline in strength and power, leading to frailty and disability. Metabolic syndrome and diabetes are associated with a decline in muscle strength and increased falls and hip fractures (Morley 2008).

In postmenopausal women, sarcopenia is not associated with physical difficulties, in the absence of obesity. However, in the presence of obesity, sarcopenia tends to render some physical functions more difficult (Rolland et al. 2009).

Janssen described severe sarcopenia (defined using BIA) as being only a modest independent risk factor for the development of physical disability. During the eight-year follow-up, the risk of developing disability was only 1.27 times higher for subjects with severe sarcopenia and the risk was not statistically significant in moderate sarcopenia (Janssen 2006).

In the elderly, the benefit of higher muscle mass in obese individuals offsets the associated cardiovascular risk factors, and low muscle mass is associated with decreased survival rates following acute illness and with a doubled risk of nosocomial infection in the care of the elderly (Rolland et al. 2008). The amount of lean mass in the obese is low compared to their total body weight and predicts functional limitation. High muscle mass may act as a nutritional reserve during a medical event and extremely high muscle mass may, in part, explain the lower rate of death in certain obese elderly (Rolland et al. 2008).

107.1.3 Skeletal Muscle Mass Measurements

Body composition methodology has changed considerably during the past two decades from underwater weighing to the availability of fan-beam DXA machines that can quantify muscle, bone, and fat mass in a few minutes. This period has also seen the introduction of very precise bone-tissue measurement methods, such as magnetic resonance imaging, and somewhat less precise techniques, such as bioelectrical impedance (Rolland et al. 2008).

Methods used to measure muscle mass are outlined in Table 107.2.

Table 107.2 Methods to estimate muscle mass (Reproduced with permission from Morley 2008)

Approach	Problems	Cost
DEXA	Cannot distinguish muscle from organ protein; problem when abdominal fat is present	$$$
Bioelectrical Impedance	Problems with hydration status	$$
Anthropometry	Operator-dependent crude approximation	$
Urinary creatine/Creatinine	Physical activity	$
	Non-muscle sources	
	Renal clearance	
CT or MRI	Cross-sectional	$$$$
Neutron Activation	Cannot distinguish muscle from organ protein	$$$
	Limited availability	

DEXA Dual energy X-ray absorptiometry; *CT* computerized tomography; *MRI* magnetic resonance imaging

Methods used to assess muscle mass, such as anthropometry, BIA, or DXA, are unable to distinguish aqueous and nonaqueous components of the muscle mass. Theoretically, this can be accomplished with CT or MRI (Rolland et al. 2008). DXA has limited ability to distinguish water retention of fat tissue infiltration within muscle. Kim et al. (2004) estimated that fatty infiltration of muscle can inflate skeletal muscle mass estimates from DXA by 1–8%. However, Chen et al. (2007) and others (Kim et al. 2004) reported strong correlations ($r > 0.94$) between DXA and MRI measures of skeletal muscle mass, indicating that this increasingly available method is useful for cross-sectional studies and screening.

Most studies measure appendicular muscle mass and adjust for height. Heymsfield et al. have summed the muscle mass of the four limbs from DXA scans as appendicular skeletal muscle mass (ASM), and defined a skeletal muscle mass index (SMI) as ASM/height^2 (kg/m^2) (Heymsfield et al. 1990).

All definitions of sarcopenia are arbitrary and open to criticism. An operational definition needs to differentiate those with sarcopenia from those not affected, and needs to define standards and be applicable across populations (Rolland et al. 2008).

The trigger to screen for sarcopenia should be a loss of muscle mass of 5% or greater, over a year or less (Morley 2008).

Calf circumference is regularly correlated to muscle mass, but this correlation is low and makes calf circumference a poor screening tool for sarcopenia (Rolland et al. 2003).

Sarcopenia was based on appendicular skeletal muscle mass measurements (Heymsfield et al. 1990), which correspond to the sum of the two upper and lower limb muscular masses in kilograms.

Individuals with an SMI two standard deviations below the mean SMI of a middle-aged reference male and female population from the Rosetta Study (Gallagher et al. 1997) were defined as gender-specific cutoff points for sarcopenia. Later, sarcopenia severity was divided into grade I (-1 SD) and grade II (-2 SD) among different populations using DXA (Baumgartner et al. 1998; Gallagher et al. 1997) as the method for skeletal muscle mass assessment (Table 107.3). This definition has been used by several authors (Baumgartner et al. 1998; Rolland et al. 2003).

The NHANES III study (Janssen et al. 2004a) (Table 107.4) used BIA methodology similar to our studies (Table 107.5) and has different resulting figures.

The Botucatu follow-up study (Mexa-se pró-saúde) is a prospective dynamic cohort study designed to evaluate the role of diet and physical activity on the occurrence of metabolic syndrome, its components, and comorbidities. All the participants were over 35 years, living in the urban area

Table 107.3 Skeletal mass index distribution in studied populations

		Skeletal mass index (kg/m²)				
		–2 SD	–1 SD	Mean	+1 SD	+2 SD
Rosseta study (kg/m²) (Gallagher et al. 1997)	Male	6.4	7.5	8.6	9.7	10.8
	Female	5.5	6.4	7.3	8.2	9.1
NMEHS (kg/m²) (Baumgartner et al. 1998)	Male	6.3	7.0	7.7	8.4	9.1
	Female	4.5	5.2	5.9	6.6	7.3

SD Standard deviation; *NMEHS* New Mexico Elder Health Survey; *kg* kilograms; *m* meters

Table 107.4 Muscle mass distribution using bioelectrical impedance (BIA) (Janssen et al. 2004a)

		Skeletal mass index (kg/m²)				
		–2 SD	–1 SD	Mean	+1 SD	+2 SD
Male	≤ 40 years (n = 3116)	22.5	29.4	33.6	37.8	42.0
	≥ 60 years (n = 2225)	21.3	25.5	29.7	33.9	38.1
Female	≤ 40 years (n = 3298)	15.6	18.6	21.6	24.6	27.6
	≥ 60 years (n = 2285)	11.5	14.7	17.9	21.1	24.3

SD Standard deviation; *kg* kilograms; *m* meters

Table 107.5 Muscle mass distributions using bioelectrical impedance (BIA) in a sample of subjects clinically selected (2004–2008) for a lifestyle modification program[a], including physical exercises (Botucatu, SP, Brazil)

		Skeletal mass index (kg/m²)				
		–2 SD	–1 SD	Mean	+1 SD	+2 SD
Male	<60 years (n = 93)	24.0	28.1	32.1	36.2	40.2
	≥60 years (n = 49)	20.6	25.3	30.0	39.8	39.5
Female	<60 years (n = 343)	14.3	17.3	20.3	23.3	26.3
	≥ 60 years (n = 147)	12.1	15.1	18.2	21.2	24.2

SD Standard deviation; *kg* kilograms; *m* meters
[a] See details in the text

of Botucatu (a city located in the midwest of São Paulo state (Brazil), which has a population of 120,800 (2007)). The participants were clinically evaluated following a maximum exercise test on the treadmill, along with nutrition, biochemistry, and other fitness assessments.

107.1.4 Diagnosis and Prevalence of Sarcopenia

By using different methods and references, sarcopenia was found to range from 5% to 13% in persons aged 60–70 years of age and from 11% to 50% in persons over 80 years of age (Baumgartner et al. 1998; Morley 2008). After the age of 60, the prevalence of moderate and severe sarcopenia has been estimated to be 53% and 11% in men and 22% and 9% in women, respectively (Janssen et al. 2004a, b).

The prevalence of sarcopenia estimated based on a bioelectric impedance equation from the New Mexico Elder Health Survey was 20% in men between the age of 70 and 75 years and about 50% in those over 80 years. Among women in the same age ranges, it was 25% and 40%, respectively (Baumgartner et al 1998). In a later study, by estimating sarcopenia based on dual energy X-ray

Table 107.6 Prevalence of sarcopenia in studies using bioelectrical impedance (BIA)

Studies	Gender (*n*)	Prevalence of sarcopenia – % (*n*)		
		Grade I	Grade II	Total
NHANES III (Janssen et al. 2004a)	Male (2,223)	53.1 (1,130)	11.2 (249)	64.3 (1,429)
	Female (2,276)	21.9 (498)	9.4 (214)	31.3 (712)
Botucatu's study	Male (58)	65.5 (38)	5.2 (3)	70.7 (41)
	Female (170)	21.2 (36)	3.5 (6)	24.7 (42)

NHANES III National Health and Nutrition Examination Survey III; Botucatu's study: using data from Table 107.5.

absorptiometry (DXA), it ranged from 8.8% in women and 13.5% in men aged 60–69 years, and up to 16% in women and 25% in men older than 80 years (Rolland et al. 2008).

Still based on the Baumgartner index, sarcopenia was detected in 10% of the female population 70 years of age and older in the French European Patient Information and Documentation Systems Study (EPIDOS Study), with cutoff points derived from a different reference group (from the Baumgartner's) (Rolland et al. 2008).

Using a similar definition (–2 SD) in the population based on NHANES III, 35% of the elderly had a moderate degree of sarcopenia and 10% a severe degree (Janssen et al. 2004a). In the Botucatu study, the prevalence of sarcopenia was twice as high in males as in females at similar ages (Table 107.6). By using yet another definition, 6–15% of persons over 65 years of age had sarcopenia (Rolland et al. 2008).

The large variability in sarcopenia prevalence is related to the differences in measurement and the cutoff points used to define it (Morley 2008).

One reason for the divergent prevalence of sarcopenia within and between groups is due in part to the changes in assessing muscle mass that have occurred over the past 20 years, and the fact that studies used different measures of relative muscle mass, reference groups, and cutoff points. Therefore, it is difficult to compare prevalence estimates among studies (Rolland et al. 2008). The recognition of the need for a consensus operational definition of sarcopenia occurred in 1995 (Chumlea et al. 1995). The best reference data set should include measurements that are correlated with and can discriminate sarcopenia and have a broad ethnic racial and age representation (Rolland et al. 2008).

Moreover, most obese adults have increased muscle mass in addition to a high fat mass, but a low muscle mass in relation to their total body weight (Newman et al. 2003), whereas the thin elderly have a high proportion of muscle mass in relation to their total body weight. Thus, the skeletal muscle mass index potentially misclassifies the obese elderly with a high SMI and mobility and functional limitations and the thin elderly with a low SMI and none or few mobility or functional limitations. Thus, Baumgartner's original estimates were adjusted for body fatness (Baumgartner et al. 1998).

There are no consensual criteria for defining sarcopenic obesity. One can create a continuous sarcopenic obesity index by adjusting muscle mass for weight or fat mass using a regression-based approach (Newman et al. 2003). Waist circumference instead of fat mass or percentage fat can be used to define obesity for sarcopenic obesity studies (Castaneda and Janssen 2005).

The approach in cross-classifying subjects by SMI and a measure of adiposity, however, is distinctly different in that it combines the joint effects of sarcopenia and obesity in a single categorical variable. From a statistical point of view, it makes little difference when studying associations of sarcopenia with other outcomes, whether adjustment for fat mass or body mass is made using a priori adjustment to the index or by regression adjustment during analysis (Rolland et al. 2008).

Table 107.7 Distribution of the skeletal muscle mass index obtained by BIA and waist circumference in a sample of subjects clinically selected (2004–2008) for a lifestyle modification program, including physical exercises (Botucatu, SP, Brazil)

		Skeletal muscle mass index			
Waist circumference	Gender	<P25 *n*(%)	P25–P75 *n*(%)	>P75 *n*(%)	Total
< P25	Male	18 (46)	21 (25)	2 (5)	41
	Female	59 (43)	69 (26)	9 (6)	137
P25–P75	Male	19 (49)	44 (53)	19 (45)	82
	Female	69 (50)	145 (54)	58 (41)	272
> P75	Male	2 (5)	18 (22)	21 (50)	41
	Female	10 (7)	54 (20)	75 (53)	139
Total	Male	39	83	42	164
	Female	138	268	142	548

The data used were calculated from Table 107.5

By crossing the quartile distribution of the Table 107.5 data with similar distribution of waist circumference (WC), we came to an arbitrarily classification of sarcopenic obese (SMI < P25/WC > P75), which was 5% (males) and 7% (females) (Table 107.7).

Skeletal muscle mass adjusted for both height and body weight and not height alone is a significant predictor of mobility limitation in a large sample of elderly men and women (Newman et al. 2003). Rather than adjusting statistically, Janssen et al (2002) used muscle mass relative to weight rather than stature. In a later study, Baumgartner cross-classified subjects by SMI and percent body fat and reported that associated disability was strongest in those who were both sarcopenic and obese. Newman et al (2003) used a residual method to adjust muscle mass for fat mass in addition to height and found that this index had stronger associations with lower-extremity functional limitation and disability than sarcopenia defined by SMI alone (Rolland et al. 2008).

By using data from NHANES III, in addition to operating curves, to determine the sex-specific skeletal mass cutoff point for physical disability risk, women whose SMI was below 5.75 kg/m^2 muscle mass had an increased risk for physical disability (OR = 3.31, 95% CI; 191–5.73) as were those whose SMI was below 8.5 kg/m^2 (OR: 4.71, 95% CI; 2.28–9.74). It is important to note that, in this study, total skeletal mass was predicted using a bioelectrical impedance equation (Janssen et al. 2004a). These new cutoff points were closely similar to those first proposed by Baumgartner et al (1998).

Differences among studies regarding the strength of associations of various definitions of sarcopenia with functional status are a function of the methods used to define functional status or disability and their sensitivity and precision (Rolland et al. 2008).

The main effect from a loss of muscle mass is reduced muscle strength, which is an important factor to consider in defining sarcopenia. The loss of muscle quality, also an important component of the definition of sarcopenia, supposes an assessment of both muscle strength and muscle mass (Rolland et al. 2008) (Fig. 107.1).

The Jamar dynamometer for grip strength is a simple estimation of total muscle strength (Rantanen et al. 2003), but is not useful for those with hand arthritis (Morley 2008). Leg muscle strength, assessed as maximal lower extremity muscle strength or power, is a good measure of functional status and is strongly associated with measures of mobility, but it is only properly measured with a dynamometer by a trained technician (Overend et al. 1992).

Lower limb strength and/or power can be measured by walking speed or stair climbing. The use of the Cybex and similar machines is useful for research, but requires expensive equipment and technical skill (Morley 2008).

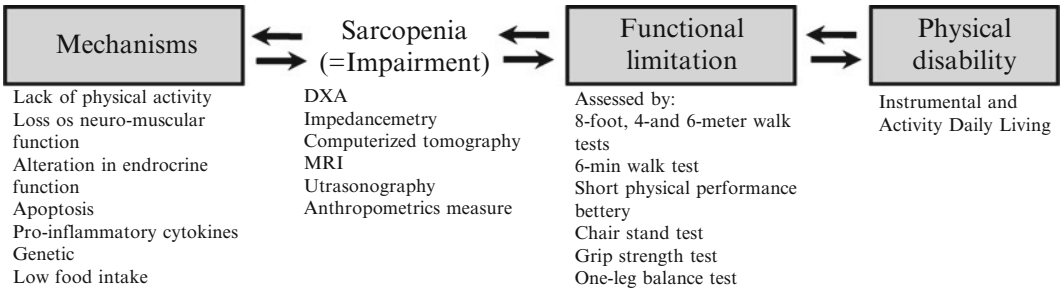

Fig. 107.1 Sarcopenia and the disability process (Reproduced with permission from Rolland et al. 2008)

Aging changes fiber patterns and this results in the slowing of twitch contraction time and a slowing of maximum shortening speed. For these reasons, it is important to measure muscle strength and power as well as mass (Morley 2008). Muscle power is defined as muscle work being either strength multiplied by speed or muscle strength multiplied by distance divided by distance. Muscle power declines with aging at a higher rate than muscle strength (Rolland et al. 2008).

Muscle power is more strongly related to functional limitation than muscle mass or muscle strength (Rolland et al. 2008). Muscle power includes muscle contraction speed and a measure of muscle quality, in addition to muscle strength (Morley 2008).

Muscle mass is strongly correlated to muscle strength and power but the same amount of muscle mass is able to produce different levels of strength and power. Thus, which measures of muscle strength should be used to define sarcopenia is unclear at this time, considering available data (Rolland et al. 2008).

Ultrasonic studies have shown that changes in tendons with alterations in pensation angles play an important role in the ability to generate power (Narici and Maganaris 2006). Electromyography can be used to determine loss in motor units; it should be recognized that loss of executive function interacts with sarcopenia to produce falls (Morley 2008).

107.1.5 Muscle Mass Gain and Sarcopenia Treatment

Behavioral treatments, such as exercise, increase muscle mass and strength; pharmacologic treatments, such as growth hormone, increase mass without a significant change in strength (Rolland et al. 2008).

The diagnosis of hypertrophic skeletal muscle still lacks cutoff points. By using the distribution of the data seen in Table 107.7, we could estimate that 5% of the males and 6% of females have higher SMI and lower WC values. Considering sarcopenia (mean-2SD) values and using hypertrophy as mean + 2SD, Table 107.5 shows us the equivalent muscle mass >39.5 kg for males and ≥24.2 kg for females, when both are over 60 years.

Treating sarcopenia by improving muscle strength or muscle power is more effective clinically for disability or mobility than increasing muscle mass. However, increasing muscle mass is more important for other outcomes, such as protein stores or thermogenesis (Rolland et al. 2008).

Skeletal muscle grows predominately in a hypertrophic manner after birth. This occurs by increasing myofibrillar diameter and length because of predominant protein synthesis over protein

breakdown. Protein synthesis is influenced positively by muscle contraction, growth factors, and leucine. Muscle protein synthesis is enhanced by anabolic factors, such as insulin, glucose, creatine, branched chain amino acids (BCAA), and glutamine, acting on cell hydration (Rivas et al. 2008).

Sarcopenia and poor performance in the elderly are associated with birth weight in both males and females, independent of adult weight and height (Yliharsila et al. 2007), and has a significant heritable component.

Potential candidate genes determining muscle strength (Rolland et al. 2008):

(a) Candidate genes for lower extremity muscle strength: the gene growth/differentiation factor 8 (GDF8), cyclin-dependent kinase inhibitor 1A (CDKN1A), and myogenic differentiation antigen 1 (Myod 1).
(b) Genes strongly related to muscle strength: the genes in the myostatin pathway including cyclin-dependent kinase 2 (CDK2), retinoblastoma (RB1), and insulin-like growth factor 1 (IGF-1).
(c) Genes related to loss of muscle power as well as muscle quality during adulthood: namely, lower quadriceps strength values – ciliary neurotrophic factor gene variant (CNTF A allele); and arm and leg strength (especially women) – IGF-2 genotype.
(d) Genes that influence knee extensor peak power in response to strength training: the actinin alpha 3 (ACNT 3) R577X genotype; and the angiotensin-converting enzyme (ACE) gene.
(e) Genes that may be associated with muscle strength: polymorphisms in the vitamin D receptor (VDR); genes associated with sarcopenia in elderly men; genes associated with muscle strength and body composition in postmenopausal women; and genes associated with muscle strength in older women.

107.2 Applications to Other Areas of Health and Disease

Muscle mass quantification is a suitable index for metabolic homeostasis (amino acids, glucose, and free fatty acid metabolism), human kinetics, and strength. Hence, it is important for nutritional and metabolic areas of health as well as for orthopedic and trauma areas. As a major bed of body oxygen and blood, skeletal muscle mass is important for cardio-respiratory systems and aerobic fitness. Skeletal muscle hypertrophy occurs with an increase in functional demands, such as resistance training or functional overload, which cause large increases in muscle size and strength – major goals of weight lifters and bodybuilders.

Summary Points

- Men and women present different trajectories in the decline of skeletal muscle with aging; men have a gradual decline, whereas women have a sudden drop following menopause.
- Loss of muscle is a significant contributor to fatigue, decreased endurance, and functional disability. Fatty infiltration of skeletal muscle is commonly associated with reduced strength and functional status.
- There is a positive association between muscle mass and strength and this relation is linear, whereas the relationship between physical performance and muscle mass is curvilinear.
- Skeletal muscle atrophy is attributable to an imbalance between protein synthesis and degradation, or between apoptosis and regeneration processes, or both.

- Lifestyle behaviors leading to skeletal muscle loss are physical inactivity, smoking, poor diet, and inflammatory states.
- Sarcopenia is considered a generalized loss of muscle at a level substantially higher than normal young persons.
- The loss of muscle mass results in lower physical activity, lower energy expenditure, fat gain, obesity, muscle fatty acid infiltration, and insulin resistance in a condition called obese sarcopenia, with poor outcomes.
- Human skeletal muscle is dependent on genetic predisposition, resistance exercises, nutrition, and hormonal and inflammatory states, by controlling the balance between hypertrophy (myofibrilar protein synthesis) and atrophy (protein breakdown).
- Human skeletal muscle hypertrophy occurs with an increase in functional demands seen with resistance training and with functional electrical stimulation after spinal cord injury.
- Behavioral treatments, such as exercise, increase muscle mass and strength; pharmacologic treatments (by hormones) increase mass without a significant change in strength.

Key Features

Table 107.8 Key facts on anthropometric measurements of muscle mass and health, diseases, and strength exercises.

1. Muscle mass is a determinant of nutritional reserves, metabolic homeostasis, and physical strength and related abilities. Lower muscle mass is a risk factor for functional disabilities (frailty) and increased mortality
2. The methodology to measure skeletal muscle mass has changed considerably in sensitivity, specificity, and cost. All definitions of either higher or lower muscle mass are arbitrary and open to criticism. Their large variability is related to the differences in measurement, reference groups, and cutoff points
3. Skeletal mass index is a single index used for the sum of the muscle mass of the four limbs
4. For defining sarcopenic obesity (or fat frail), muscle mass must be associated with some functional test (strength and power). Measuring muscle mass in the presence of muscle fat infiltration (myosteatosis) has been criticized

Acknowledgments To the graduate students Damiana T. Pierine and Rodrigo Minoru Manda for their collaborative work in organizing the domestic data and editing the manuscript.

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Chapter 108
Exercise, Nutrition, and Anthropometry of Bone Development in Term and Preterm Infants

Ita Litmanovitz and Alon Eliakim

Abstract The physiology of bone mass accretion in the early postnatal life has been studied extensively due to the development of reliable, precise, and noninvasive methods for bone mass assessments. Most of the studies address bone development in very low birth weight preterm infants. Given that the period of greatest bone mineral accretion in utero occurs during the last trimester of pregnancy and that it is very difficult to match bone requirements in the postnatal extra-uterine environment, metabolic bone disease remains relatively common in preterm infants. At birth, both bone mineral density measured by dual X-ray (DEXA) absorptiometry and bone strength measured by quantitative ultrasound measurements of bone speed of sound (SOS) were found to be significantly lower in preterm compared to infants born at term, with a strong correlation between tibial SOS and gestational age. Moreover, longitudinal studies demonstrated a decrease in bone mineralization by DEXA and in bone strength determined by bone SOS during the 1st weeks of post-natal life, emphasizing the importance of the intra-uterine environment for bone development. Interestingly, postnatal catch-up of bone strength in premature infants occurs only when the stress and the inflammatory state, which accompanies the early postnatal life of preterm infants, is reduced.

There is conflicting data regarding the beneficial effect of enriched post discharge formula (PDF) on bone metabolism. Enriched PDF, at least until corrected age of 40 weeks, was found beneficial for bone development, but there is still no convincing evidence to support its beneficial effect after this period.

There is mounting evidence to support the notion that assisted exercise (passive, range of motion, and flexion and extension with gentle compression of the large joints) attenuates the natural decrease of bone strength or even increase bone mineralization in premature infants. The mechanism for these beneficial bone effects is not clear; however, it may involve exercise-induced increase in bone formation, leptin, and insulin-like growth factor-I level. Whether the positive bone effects are related to the range of motion exercise per se, or whether the assisted exercise regimen leads to increased overall daily movement in preterm infants in not known. The optimal exercise regimen for this unique population also needs to be determined.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_108,

Abbreviations

AGA	Appropriate for gestational age
BMC	Bone mineral content
BMD	Bone mineral density
DEXA	Dual energy x-ray absorptiometry
FBM	Fat body mass
IDM	Infants of diabetic mothers
IGF-1	Insulin-like growth factor-I
IL-6	Interleukin-6
LBM	Lean body mass
NICU	Neonatal Intensive Care Unit
PDF	Post-discharge formula
QUS	Quantitative ultrasound
SGA	Small for gestational age
SOS	Speed of sound
TF	Term formula
VLBW	Very low birth weight

108.1 Introduction

In healthy newborns, lean (predominately muscle), fat, and bone tissues, the key components of body mass, increase rapidly. The pattern of this increase is profoundly altered by premature birth. Although little is known about the mechanisms that control the early postnatal development of muscle, fat, and bone, there is mounting evidence that the factors regulating body composition among these compartments are distinct and lead to different rates of growth. In addition, in the case of muscle and fat tissues, for example, growth may be antagonistic (e.g., exercise-induced increase in muscle mass associated with decrease in fat mass). By contrast, in the case of muscle and bone, growth of the two tissues is usually synergistic.

Body composition is difficult to study in premature babies largely because of the limited tools appropriate for this fragile population. Recently, the use of three distinct techniques was shown to be useful to determine body composition in premature babies: (1) dual energy X-ray absorptiometry (DEXA), which measures lean, fat, and bone tissue for the whole organism and for specific anatomic regions, (2) limb ultrasound (LUS), which quantifies regional muscle and fat mass (Pereira-da-Silva et al. 1999), and (3) quantitative bone ultrasonography (QUS), which is related to bone strength (Littner et al. 2003).

Over the past two decades, overall birth rates have been steadily declining in the USA. However, the incidence of preterm birth (infants born at less than 37 weeks of gestation) increased and about 12% of infants in the USA are born prematurely. Furthermore, advances in perinatal care, such as the increased use of assisted ventilation in the delivery room and surfactant therapy, have improved the chances for survival of low-gestational-age and low-birth-weight infants. The rising incidence of preterm births, coupled with their improved survival as a result of highly evolving technologies, has placed increased need to address other diseases of prematurity that develop later in the neonatal period, such as osteopenia of prematurity.

Metabolic bone disease is relatively common in preterm infants because the period of greatest bone mineral accretion occurs during the last trimester of pregnancy, and because this is difficult to match

in the postnatal extrauterine environment. In addition, preterm morbidity, such as bronchopulmonary dysplasia, the use of steroid and diuretic treatment, and the common need for total parenteral nutrition further predispose preterm infants to osteopenia. Moreover, the common practice in the majority of Neonatal Intensive Care Units (NICUs) involves minimal handling, which may potentially increase the rates of osteopenia. Clinical osteopenia occurs usually in the 6–12 postnatal week and can cause fractures in up to 10% of very low birth weight (VLBW) infants. Currently, the diagnosis of neonatal bone disorders is based primarily on biochemical evaluation of serum alkaline phosphatase and radiological evidence of osteopenia and/or fractures, and, in rare cases, on measurements of bone mineralization by dual-photon X-ray absorptiometry (DEXA).

There is substantial evidence demonstrating the utility of quantitative ultrasound (QUS) measurement of bone speed of sound (SOS), which has become a viable alternative to assessing bone strength in infants (Littner et al. 2003), children (Eliakim et al. 2001), and adults (Njeh et al. 2001). We have previously shown that gestational age, birth weight, nutritional modifications, and assisted exercise influence measurements of bone SOS by QUS and bone strength in preterm infants (Nemet et al. 2001). In the present chapter, we aimed to summarize the available scientific information regarding the deleterious and beneficial effects of gestational age, body weight, nutrition, and assisted exercise on body composition and bone strength in term and preterm infants, and comment on the possible use of these techniques for monitoring the level and the therapeutic effect of osteopenia of prematurity.

108.2 Practical Method and Technique

108.2.1 Dual-Photon X-ray Absorptiometry

Two beams of relatively high and low energy levels are used to estimate total body mineral content (BMC) and bone mineral density (BMD). In the past, the accuracy of DEXA in small animals and human infants was questioned. In poorly mineralized bones, BMC may be underestimated, and, in small subjects, fat mass may be overestimated. However, with correctional equations (Rigo et al. 1988) and the development of the faster fan-beam scans, DEXA was found to be valid, reliable, and accurate in small animals. DEXA is now widely accepted as a reliable and accurate measure of body composition in infants and is currently considered the gold standard for bone mass measurements. However, the use of DEXA in the clinical setting is very limited by its relatively high cost and by the need to transport the patient to the device, making it unfeasible for very small or sick preterm infants (i.e., infants who are at the highest risk of developing metabolic bone disease).

108.2.2 Quantitative Ultrasound Measurements on Bone Speed of Sound

This method is based on the concept that the propagation of sound waves through a medium depends upon its physical properties. The denser the medium, the faster the sound waves propagate. Bone SOS is also influenced by other bone properties, such as cortical thickness, elasticity, and microarchitecture, providing a better picture of bone strength (Foldes et al. 1995). QUS is a relatively inexpensive, portable, and noninvasive method that involves no ionizing radiation and has been shown to correlate accurately with measurements by DEXA (Kang et al. 1999). A modest but significant correlation was found between bone quantitative ultrasound and both total body and regional

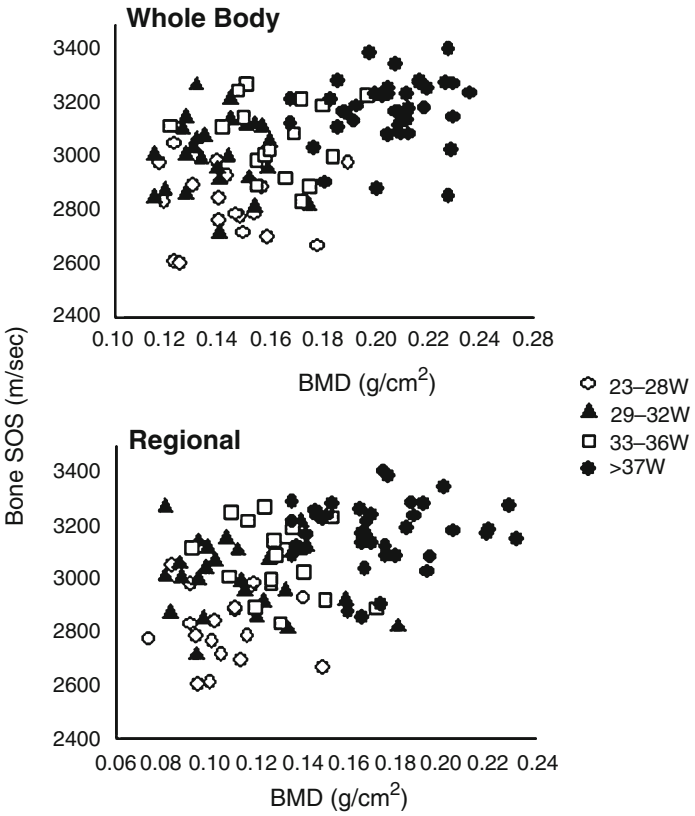

Fig. 108.1 Comparison of bone quantitative ultrasound with both whole-body bone mineral density (*BMD*) by dual-energy X-ray absorptiometry (*DEXA*) and regional DEXA by gestational age. Significant correlations were found between bone quantitative ultrasound and both whole-body BMD by DEXA (*upper panel*) and regional DEXA-derived BMD (*lower panel*)

Table 108.1 Key features of bone SOS

1. Quantitative ultrasound measurements of bone SOS determine bone strength.
2. The method is based on the concept that the propagation of sound waves through a medium depends upon its physical properties.
3. The denser the medium, the faster the sound waves propagate.
4. Bone SOS is influenced by bone density and by other bone properties, such as cortical bone thickness, elasticity, and architecture.
5. This method determines both quantitative and qualitative bone properties.
6. The method is non-invasive and involves no ionizing radiation.

This table lists the key facts of bone SOS measurements of bone strength and the rationale and advantages of the technique
SOS speed of sound

DEXA-derived BMD (whole body, $r = 0.48$; regional $r = 0.45$, Ahmad et al. 2009) (Fig. 108.1). Clearly, the two modalities measure different but related properties of bone in the newborn. While DEXA measures quantitative aspects of BMD, bone QUS is also influenced by qualitative factors that contribute to bone strength, such as bone elasticity, microarchitecture, and fatigue damage. Thus, although the two modalities are not interchangeable, a complementary use of both methods may better reflect "true" bone strength (Table 108.1).

108.3 The Effect of Gestational Age and Birth Weight

Both BMD measured by DEXA and bone strength measured by QUS were found to be significantly lower in preterm compared to term infants (Nemet et al. 2001; Littner et al. 2003; Ahmad et al. 2009). Figure 108.2 demonstrates significant strong correlation between tibial SOS and gestational age ($r = 0.78$, $p < 0.0005$) (Nemet et al. 2001). SOS was found to be much more closely correlated with gestational age than with birth weight, suggesting that maturity might be a more important determinant of bone development than birth weight (Littner et al. 2003).

Several studies examined the effect of birth weight on bone development, focusing on infants of diabetic mothers (IDM) born large for gestational age compared to infants born appropriate for gestational age (AGA). BMC measured by single photon absorptiometry and DEXA was found either decreased (Mimouni et al. 1988) or unaltered (Lapillonne et al. 1997) in IDM. Interestingly, infants of mothers with poorly controlled diabetes (especially during the first trimester of pregnancy) had significantly higher birth weight and reduced BMC (Mimouni et al. 1988). More recently, our group demonstrated significantly decreased tibial bone SOS in IDM compared to controls (Regev et al. 2004). The reduced bone SOS in the IDM group was not related to either postnatal hypoglycemia or maternal hemoglobin A1c levels when used as indices of poor glycemic control during pregnancy. However, there was an inverse correlation between birth weight and bone SOS. A possible mechanism for the decrease in bone strength in IDM is the reduced intrauterine mobility that correlates with the increased body weight of these infants.

A negative relationship between size at birth and bone SOS was also described in small for gestational age (SGA) infants. Opposite to large for gestational age infants, SGA infants have higher bone SOS than AGA controls (Littner et al. 2005). Given that BMD is reported to be low in these infants, the authors speculated that intrauterine growth restriction may affect BMD and bone protein matrix in opposite directions.

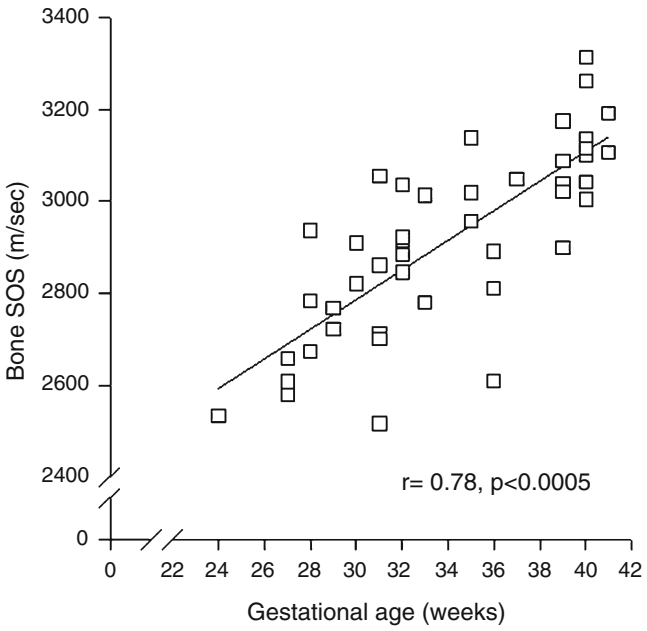

Fig. 108.2 Cross-sectional relationship between tibial speed of sound (*SOS*) and gestational age. Significant strong correlation is shown between the tibial SOS and gestational age

108.4 Postnatal Bone Strength Development

Several studies have shown by single- and dual-photon absorptiometry that VLBW premature infants, compared to a reference population at term, had a considerably lower BMC. Despite an overall growth after birth and during the 1st weeks of life, there was a relative decrease in BMC and progressive decrease in BMD in VLBW infants, indicating a disorder of formation or remodeling of the cortical bone. Similarly, we demonstrated a decrease in bone strength of VLBW preterm infants, determined by measurements of bone SOS during the 1st weeks of life (Litmanovitz et al. 2004; Eliakim et al. 2009). Tibial SOS was also significantly lower in premature infants who reached corrected age of full term (Nemet et al. 2001). The results emphasize, once more, the advantage of intrauterine growth for bone development compared to the standard care in NICU, and that, despite the major advances in neonatal intensive care and adequate nutrition, there is a significant decrease in bone strength during early postnatal life that could result from both quantitative and/or qualitative impairments of bone metabolism.

The relatively large sample size that was evaluated allowed us to determine bone SOS levels at different corrected ages and postnatal ages (Eliakim et al. 2009). The levels may now serve as reference values for the unique population of preterm infants (Fig. 108.3). Interestingly, bone SOS was increased in a small subgroup of the VLBW preterm infants. The bone SOS of this group at birth was significantly lower compared to the majority of preterm infants, who demonstrated a decrease in

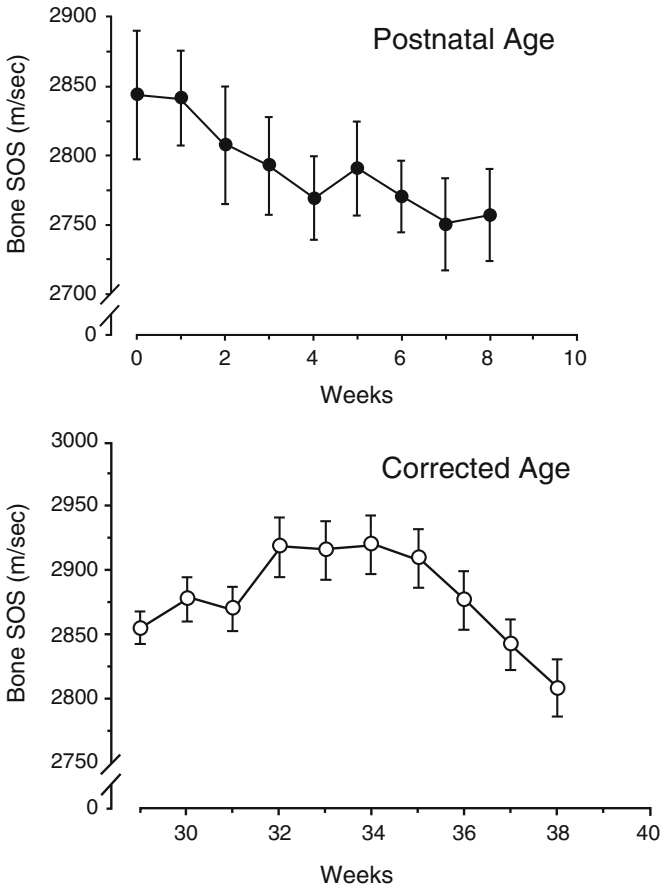

Fig. 108.3 Bone speed of sound (*SOS*) in preterm infants. Levels of bone SOS are expressed according to postnatal age (*upper panel*) and corrected age (*lower panel*)

bone SOS during the follow-up period. There were no significant differences in bone SOS between the groups at discharge from the NICU (in fact, bone SOS was even higher in the bone gainers). Moreover, evaluation of all the study participants revealed that there was a significant inverse correlation between bone SOS at birth and changes in bone SOS during the follow-up period. Therefore, the results suggest that the after-birth "catch-up phenomenon" is not limited only to body weight, body length, and head circumference, but may exist for bone strength as well.

As we previously published, during the 1st weeks of life, there is a significant increase in circulating growth factors and a significant decrease in circulating inflammatory markers in VLBW preterm infants. Of note is that circulating growth factors were higher and inflammatory cytokines were lower in preterm infants whose bone SOS increased during the study follow-up. However, only the difference in circulating interleukin-6 (IL-6) levels reached statistical significance (Ahmad et al. 2007). These results suggest that increases in bone strength in premature infants occur only when stress and inflammatory state, which accompany the early postnatal life of preterm infants, are reduced. These phenomena are not unique only for preterm infants. Recent studies demonstrate that there is an independent link between inflammatory mediators and growth, and that optimal growth occurs when the action of anabolic factors, such as insulin-like growth factor-I (IGF-I), mitigate the actions of stress-related inflammatory factors such as IL-6. In children with chronic inflammatory diseases, such as systemic juvenile idiopathic arthritis, inflammatory bowel disease, AIDS, and cystic fibrosis, high IL-6 levels are also associated with low IGF-I levels and growth restriction.

Recently, Ahmad et al. (2009) performed a prospective, cross-sectional, observational study in preterm and term infants and compared multimodal measurements of body composition, including limb ultrasound, bone QUS, and DEXA (Table 108.2). They used the postmenstrual age to compare AGA infants of different degrees of maturity. Considering that only the most premature group (born at 23–28 weeks) had a postmenstrual age equivalent to term at the time of discharge, they could compare them to the term infants and found that this group of preterm infants reaching term had significantly lower body weight, length, head circumference, muscle, fat cross-sectional areas, bone SOS, whole body and regional lean body mass (LBM), fat body mass (FBM), and BMD compared to term-born infants. However, similar to previous observation, these infants maintained LBM to FBM proportions similar to term infants. Interestingly, in the two other preterm group of infants (born at 28–32 and 33–36 weeks), who were discharged earlier from the NICU and did not reach term, fat percentage was lower and, thus, the ratio of LBM to FBM was higher. This is consistent with the fact that, during fetal life, premature infants appear to follow a similar pattern with an earlier accretion of LBM, followed by accumulation of FBM. Therefore, preterm infants who did not reach term mainly gained LBM, whereas those reaching term before discharge gained both LBM and FBM.

Limb ultrasound estimates of cross-sectional areas of lean and fat tissues in the leg region were remarkably correlated with regional and whole-body estimates of fat-free mass and fat obtained by DEXA and were significantly lower in preterm infants (Fig. 108.4). The results suggest the potential usefulness of muscle ultrasound as an investigative tool for studying aspects of body composition in preterm infants.

108.5 The Effect of Post-Discharge Nutrition

Increased risk of osteopenia in VLBW infants is attributed to limited accretion of bone mass in utero and to a greater need for bone nutrients. Despite the remarkable advances in nutritional support during hospitalization, at term, VLBW infants have considerably lower BMC and lower bone strength than term-born infants (Nemet et al. 2001; Ahmad et al. 2009).

Table 108.2 Body composition measurements in term and preterm infants

	23-28 weeks (n=20)	29-32 week (n=26)	33-36 weeks (n=17)	37-42 weeks (n=39)
Ultrasound measurements				
Muscle area (cm^2)	5.4*	4.8	2.7	6.6
	(4.9,5.9)	(4.6,5.1)	(2.2,3.2)	(6.2,7.0)
Fat area (cm^2)	3.7*	2.8	2.7	4.3
	(3.2,4.3)	(2.5,3)	(1.9,4.8)	(4.1,4.6)
Bone SOS (m/s)	2797.4*	3003.9	2470.3	3168.4
	(2720.4,2874.4)	(2949.8,3058)	(2267.2,2673.4)	(3129.0,3207.9)
Whole-body DEXA measurements				
LBM (g)	2556.9*	2251.0	2250.4	3162.8
	(2374.2,2739.6)	(2152.8,2349.1)	(2098.7,2402.1)	(3033.7,3291.8)
FBM (g)	345.6*	142.0	177.3	417.6
	(240.3,450.9)	(114.9,169.1)	(112.1,242.5)	(357,478.2)
BMD (g/cm^3)	0.145*	0.139	0.161	0.204
	(0.135,0.154)	(0.133,0.145)	(0.152,0.170)	(0.199,0.210)
Apparent BMD	0.314*	0.308	0.352	0.405
	(0.298,0.330)	(0.297,0.320)	(0.339,0.367)	(0.396,0.414)
BMC (g/cm)	43.0*	35.3	42.6	72.5
	(37.2,48.8)	(32.7,38.0)	(37.6,47.6)	(68.3,76.7)
Fat (%)	11.1	5.7	6.8	11.2
	(8.8,13.5)	(4.8,6.6)	(4.8,8.7)	(9.9,12.5)
Regional DEXA measurements				
LBM (g)	52.2*	47.1	52.2	74.4
	(45.7,58.7)	(43.7,50.5)	(45.3,59)	(70.3,78.4)
FBM (g)	13.9*	6.9	8.1	19.0
	(9.6,18.2)	(5.4,8.4)	(5.2,10.9)	(16.0,22.0)
BMD (g/cm^3)	0.106*	0.113	0.128	0.172
	(0.098,0.115)	(0.103,0.123)	(0.119,0.138)	(0.164,0.180)
Apparent BMD	0.231*	0.249	0.280	0.340
	(0.216,0.246)	(0.230,0.269)	(0.262,0.299)	(0.325,0.355)
BMC (g/cm)	1.2*	1.2	1.5	2.7
	(1.0,1.4)	(1.0,1.3)	(1.3,1.7)	(2.5,2.8)
Fat (%)	19.0	12.1	12.1	19.2
	(15.7,22.4)	(10.0,14.3)	(9.1,15.1)	(16.8,21.7)

This table lists the body composition measurements of term and preterm infants using ultrasound, whole-body DEXA, and regional DEXA measurements, showing significant difference between term and preterm infants born at 28–32 weeks reaching term (marked by *)

SOS speed of sound; *LBM* lean body mass; *FBM* fat body mass; *BMC* bone mineral content; *BMD* bone mineral density; *DEXA* dual-energy X-ray absorptiometry

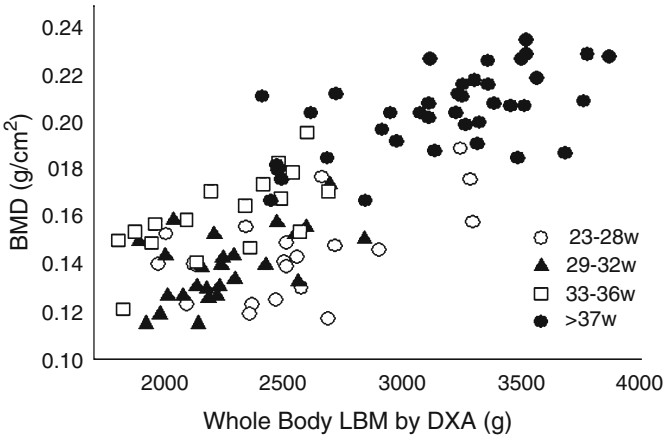

Fig. 108.4 Relationship between bone mineral density (*BMD*) and dual-energy-X-ray-absorptiometry (*DEXA*)-derived measurements of whole-body lean body mass (*LBM*) by gestational age. Significant correlation is shown between BMD and whole-body LBM by DEXA

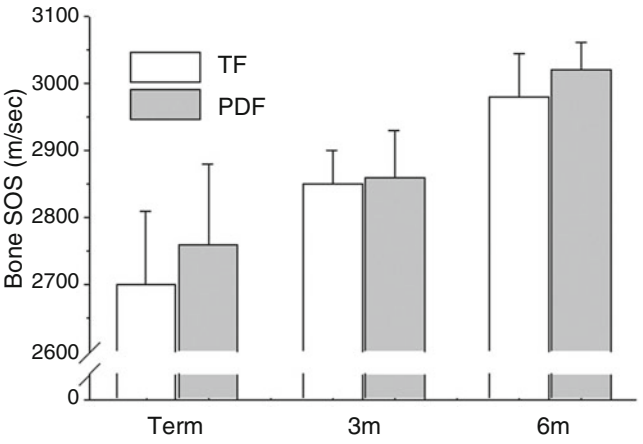

Fig. 108.5 Bone speed of sound (*SOS*) in very low birth weight (*VLBW*) infants fed enriched post-discharge formula (*PDF*) and regular term formula (*TF*). There is increased bone SOS in both groups, with no significant advantage for enriched PDF or TF

Avila-Diaz et al. (2001) found that preterm infants who were fed with human milk had lower BMC compared to full-term infants at 6 months. Helin et al (1985) reported a reduction in BMC up to 16 years of age in preterm infants who were fed by regular term formula (TF) after discharge; however, no information was provided on the source of early diet. Bishop et al. (1993) suggested that the use of enriched post-discharge formula (PDF), containing high concentrations of calories, minerals, vitamins, and trace elements enhances skeletal growth and bone mineralization of preterm infants. By contrast, two other studies, assessing body composition with DEXA, found no significant difference in bone area, bone mineral mass, BMD, or BMC between infants fed PDF or regular TF (Cooke et al. 2001; De Curtis et al. 2002).

We recently measured the effect of different formulas on preterm infants' bone strength and demonstrated that tibial bone SOS of VLBW infants increased progressively during the first 6 months post term, with no significant advantage for enriched PDF or TF (Fig. 108.5) (Litmanovitz et al. 2007a). The study differed from previous studies by the nutritional design (randomization to PDF or TF only after corrected age of full term) and by the method of evaluation of bone metabolism (QUS and bone turnover markers). The study was the first to assess the effect of diet intervention by the quantitative ultrasound technique, which, as noted earlier, in addition to quantitative measures, also assesses qualitative factors that contribute to bone strength. This is important because the increase in bone mass is not always accompanied by increase in bone strength, which is functionally the most important bone property. The finding that feeding after 40 weeks with nutrient-enriched PDF had no beneficial effect on bone SOS suggests the possibility that both quantitative and qualitative bone properties and overall bone strength were not affected by the enriched diet (Litmanovitz et al. 2007a).

Interestingly, at 3 months post term, the measurements of bone SOS in both groups were already comparable to that of a reference value of full-term infants (Zadik et al. 2003). A rapid phase of mineral accretion between 40 and 60 weeks post conception was also demonstrated among preterm infants who were fed standard neonatal formula. It was related to the consumption of higher volume that compensated for the increased need of these infants. Overall, it was suggested that the relative osteopenia observed in preterm infants resolves relatively early after discharge from the hospital.

In conclusion, special PDF with high contents of protein, minerals, and trace elements is mandatory, at least until a post-conceptual age of 40 weeks. There is still no convincing evidence to support the beneficial effect of its longer use for bone metabolism and development. Continued growth monitoring is required to adapt feeding choices to the needs of individual infants, to avoid underfeeding or overfeeding, and to monitor for signs of osteopenia.

108.6 The Effect of Exercise

Physical activity stimulates bone formation and increases BMD. This may be particularly important for premature infants because, during the prolonged hospitalization in the NICU (i.e., in small incubators and cradles), their standard care involves minimal sensory and/or tactile stimulation. Thus, it was suggested that the limited physical activity of hospitalized premature infants can play an important role in the development of bone demineralization and osteopenia. Therefore, in order to avoid that, efforts should be made to understand the mechanisms that link physical activity and bone metabolism in preterm infants, and to develop strategies to increase physical activity in this unique population.

There is mounting evidence to support the concept of the functional "bone–muscle unit" in which muscle activity can stimulate bone growth through mechanoreceptors and through the activity of hormones, such as IGF-I, which influence both muscle and bone. By contrast, absent or poor fetal movement is associated with impaired bone mineralization. Consistent with that, Gomez et al. (2007) found that bone was profoundly abnormal and poorly mineralized in fetal Myod-Myf5-deficient mice that lack striated muscle and have no functioning "bone–muscle unit" or in utero mechanical loading through muscle activity.

Spontaneous postnatal physical activity affects bone strength. The effect of reduced, spontaneous, unilateral limb movements on bone strength assessed by QUS measurements of bone SOS was evaluated in premature infants (Eliakim et al. 2002a). The relative unilateral reduced mobility was the result of a contralateral intracranial insult. Compared to unaffected legs, tibial bone SOS was significantly decreased in the legs with reduced spontaneous movements. By contrast, when spontaneous body movements in healthy control premature infants were normal and symmetrical, both legs had similar SOS. This indicates the important role of daily physical activity for bone strength even in the neonatal period. Moreover, the type of physical activity that premature infants usually perform is mainly spontaneous and is characterized by antigravity and flexion and extension movements and not by the classical weight-bearing activity. Our results suggest that even this modest type of daily activity can increase bone strength in this unique population.

Attempts to measure the effects of assisted exercise (which is also termed "kinesthetic stimulation" by a number of investigators) in human infants were first reported by White and Labarba (1976), who studied 12 (six control) preterm infants born at 34 weeks and showed significant increases in body weight in the treatment group after a 10-day intervention beginning on the second day of life. In 1995, Moyer-Mileur et al. studied the effects of a single daily session of passive range of motion movement with gentle compression of the upper and lower limbs in 13 intervention and 13 control preterm infants (born at 28 weeks). The intervention started at an average postnatal age of 2 weeks and lasted 4 weeks, and, compared to a group of control preterm infants, there was a significant increase in body weight by 33% and in BMD (measured by single-photon absorptiometry) by 34% in the exercise group. Later, the same group of investigators repeated this study using DEXA and corroborated their original observations in 16 intervention and 16 control preterm infants. The authors concluded that, when premature infants perform daily physical activity, in addition to the consumption of the recommended energy and nutrient intake, bone mass accretion is similar to the increase in bone indices in utero during the last trimester (Moyer-Mileur et al. 2000). This enhancement of bone mass by physical activity was not accompanied by changes in circulating levels of calcium, phosphate, alkaline phosphatase, parathyroid hormone, or vitamin D. Therefore, the mechanism for the exercise-induced increased bone density in premature infants was unknown. Using the Moyer-Mileur protocol (1995, 2000), Nemet et al. (2002) examined, in a randomized, prospective study, the effect of exercise on bone turnover markers in VLBW preterm infants and found that, compared to control

subjects, exercise led to a greater increase in body weight, to an increase in bone formation marker (bone-specific alkaline phosphatase), and to a significant decrease in bone resorption marker (cross-linked carboxyterminal telopeptide of type I collagen). It is important to note that the postnatal period in premature infants is characterized by increases in bone formation markers (Shiff et al. 2001); however, because changes were greater than in the control preterm infants, the results support the hypothesis that the relatively brief exercise-training intervention in the premature infants stimulated new bone formation independently of the ongoing postnatal increase of these markers.

The exercise training program in the premature infants led to changes in bone turnover markers in the range of 20–40%. This is consistent with previous reports of increased bone formation following 5 weeks of endurance-type exercise training in adolescent males and females (Eliakim et al. 1997). These results may emphasize the important role of exercise training for bone formation during critical periods of rapid bone development.

The same daily exercise protocol was also used to assess the effect of exercise on serum leptin level and on IGF-I, an anabolic hormone that is known to correlate with fetal growth and to increase in response to exercise in children and adults. The brief (4 weeks) passive range of motion daily movements of both the upper and lower extremities resulted in increased weight gain and increases in circulating leptin levels. The changes in leptin correlated with the changes in body weight (Eliakim et al. 2002b). Exercise also led to increased IGF-I circulating levels, which were greater in premature infants with bronchopulmonary dysplasia. It is not clear whether this suggests that daily movement exercise has a stronger effect in the more catabolic premature infants with bronchopulmonary dysplasia, and, therefore, this issue needs to be investigated in a larger sample size. Increases in IGF-I play a major role in exercise-induced muscle hypertrophy, suggesting possibly a greater increase in muscle mass in the preterm infants. Increased IGF-I levels in preterm infants improve brain development and protect from retinopathy of prematurity. Therefore, benefit of exercise-associated increase in IGF-I levels may not be limited only to the bone and muscle tissue.

The exercise intervention studies in premature infants were started mainly at postnatal age, 2–5 weeks after the critical period of the First days of life and when all the preterm infants were stable. Therefore, in a prospective randomized study, we used the same exercise protocol to evaluate the effect of early exercise training (i.e., at the first week of life) on bone strength in VLBW premature infants and found that the bone SOS decreases during the first four postnatal weeks in the control VLBW premature infants, and that the relatively brief, daily, passive range of motion physical activity attenuated the decrease in bone SOS (Litmanovitz et al. 2003). Consistent with previous reports, the results of this study suggested again that exercise has an important role in bone development during the immediate neonatal period and may contribute to the prevention of osteopenia of prematurity. It is still unclear why the same exercise protocol resulted in increased mineralization in the studies by Moyer-Mileur et al. (1995, 2000), but only attenuated the decrease in bone SOS in the study by Litmanovitz et al. (2003). The answer is probably related to the difference between the methods used. As already noted, single-photon absorptiometry and DEXA, as used by Moyer-Mileur et al. (1995, 2000), measure mainly quantitative aspects of bone mass, such as mineral density, whereas QUS, in addition to the quantitative measures (bone mineralization), also assesses qualitative factors that contribute to bone strength, such as bone elasticity, microarchitecture, and fatigue damage. Increase in bone mass is not always accompanied by an increase in bone strength, which is functionally the most important property of the bone. Apparently, the combination of reduced qualitative and quantitative bone properties contributes to the postnatal decrease in tibial SOS and bone strength in VLBW premature infants. Exercise was only able to prevent this decline.

In contrast to exercise interventions that started at a postnatal age of 4–5 weeks (Moyer-Mileur et al. 1995; Nemet et al. 2002), the early exercise intervention was not associated with a greater

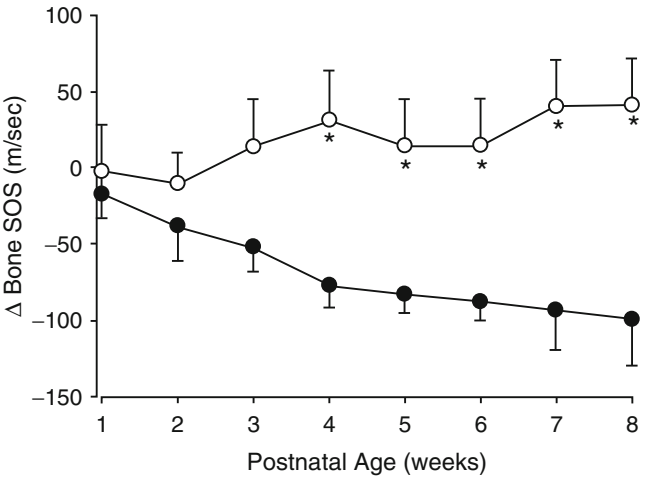

Fig 108.6 The effect of exercise on bone speed of sound (*SOS*) in preterm infants. A significant decrease in bone SOS is shown in the control group (*black circles*) during the first 8 weeks of life, and no change in the exercise preterm group (*white circles*)

increase in weight gain. This observation is in agreement with Moyer-Miller et al. (2000), who found that the increase in weight gain was significant only when the premature infants reached body weight of 1.8–2 kg. This suggests probably that the accelerated weight gain occurs only when exercise training is introduced later in the neonatal course (4–5 weeks vs. 1st week), and that the timing and duration of exercise influence the overall beneficial effect of assisted exercise in preterm infants.

The mechanism for exercise-induced weight gain in premature infants is not clearly understood. It was suggested that at least part of the exercise-induced weight gain is related to increased bone mineralization. This was supported by several studies indicating that leptin is secreted from human osteoblasts and promotes bone mineralization and by the observation that exercise led to increase in circulating leptin in premature infants (Eliakim et al. 2002b). However, considering that beneficial bone effects of exercise were not always accompanied by greater weight gain in preterm infants (Litmanovitz et al. 2003), this potential mechanism cannot fully explain the effect of exercise on body weight. It is possible that other changes in body composition, such as increased lean or fat mass, are responsible for changes in body weight. This needs to be clarified by further research. Whether the degree, frequency, and duration of exercise of 5–10 min/day, 5 days/week, and 4 weeks, respectively, constitute the optimal regimen for bone development in premature infants still needs to be determined. Therefore, recently, we examined the effect of 8 weeks of assisted exercise on bone strength and metabolism in VLBW premature infants (Litmanovitz et al. 2007b) and found that assisted, daily, physical activity prevented the decrease in bone SOS. The decrease in bone SOS in the control subjects was greater during the first 4 weeks of life (Fig.108.6). Therefore, the major protective effect of exercise occurred during this period. Moreover, exercise prevented the decline in bone SOS from the 1st week of life in the VLBW preterm infants. However, the effects of exercise on bone strength during the 2nd month (weeks 4–8) of postnatal life should not be ignored because bone SOS continued to decline in the control group, but remained stable in the exercising preterm infants.

These results suggest that mechanical stimulation is beneficial for bone strength and metabolism in preterm infants, and that exercise has an important role in bone development during the neonatal period. The exact mechanisms that lead to the exercise-induced bone changes in premature infants are yet unknown. The exercise protocol includes passive range of motion exercise with gentle compression at the end of flexion/extension in the exercised joints. This exercise regimen may cause an increase in joint pressure and muscle tension, leading to increased mechanical load on the bone–muscle unit, an increase in lean/muscle mass, and change in bone metabolism and mineralization.

It is also possible that the positive bone effects are not related only to the 5–10 min range of motion exercise, and that the assisted exercise regimen may also lead to increased overall daily movement in preterm infants.

108.7 Applications to Areas of Health and Disease

It is now well established that bone mineralization and strength are significantly lower in preterm infants, even in those reaching term. However, it is not known yet whether this osteopenia of prematurity is a self-resolving condition or a disease with long-term consequences. Reduced bone mineralization was recently demonstrated in prematurely born 7-year-old children (Chan et al. 2008). Even if bone mineralization improves spontaneously, the prolonged period of demineralization in early childhood may lead to overt rickets, bone fractures, and potentially reduce peak bone mass. Thus, the effect of reduced bone mineralization and strength in premature infants, and the possible relation to the development of osteoporosis later in life still needs to be determined.

In addition, we previously demonstrated reduced physical ability in prematurely born 5- to 8-year-old healthy children (Falk et al. 1997). The consequences of reduced physical ability and fitness early in life on the general health of adults who were born prematurely still need to be explored. However, early exercise interventions for preterm infants may increase muscle mass, may lead to earlier maturation of the neuromuscular–skeletal junction, and, if continued, may perhaps improve physical fitness later in life.

Finally, the relationship between the magnitude and rate of change of fat and muscle mass early in life, with conditions, such as obesity, and its accompanying insulin resistance and increased cardiovascular disease risk in adulthood, has gained great interest. The disproportionately higher rate of recovery of fat compared to lean tissue in preterm infants during early postnatal life (i.e., preferential "catch-up fat") may be a central event in the development of obesity and of diseases, such as insulin resistance and metabolic syndrome, seen in this population, particularly in infants who were born SGA.

Summary Points

- DEXA, the gold standard for bone mass measurements, is becoming more widely used in infants, but its availability is limited. An emerging method is QUS measurement of bone SOS, which is a noninvasive, inexpensive, portable method that is free of ionizing radiation, used for the assessment of bone development in premature infants.
- Preterm infants have decreased bone mineralization and decreased bone strength compared to term infants. There is strong positive correlation between bone strength and gestational age. Furthermore, there is a significant decline in bone mineralization and strength in early postnatal life, indicating the importance of intrauterine environment for bone development.
- Enriched PDF at least until the corrected age of 40 weeks were found beneficial for bone development, but there is still no convincing evidence to support beneficial bone effect for their use following this period.
- There is mounting evidence to support the notion that assisted exercise attenuates the natural decrease of bone strength or even increases bone mineralization in premature infants. The optimal exercise regimen for this unique population still needs to be determined.
- Postnatal catch-up of bone strength in premature infants occurs only when the stress and inflammatory state, which accompanies the early postnatal life of preterm infants, is reduced.

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Chapter 109
Anthropometry and Race Performance in Endurance Athletes

Beat Knechtle

Abstract The main endurance disciplines are swimming, cycling and running. In studies of athletes performing in these disciplines, it is mainly the influence of body mass, body height, body mass index, length and girth of extremities, body fat and, in more recent studies, of skin-fold thicknesses, that has been investigated. Body mass seems to correlate with performance in runners and cyclists, but not in swimmers. Body height is associated with performance in female pool swimmers. Body mass index is correlated to performance in marathon and ultra-marathon runners. The length of extremities is a predictor variable in young pool swimmers; the circumference of limbs is related to running performance, depending upon the distance. Body fat is a main predictor variable in runners and swimmers. The thickness of skin-folds is related to running and swimming performance, but not to cycling performance. To summarise, there are different anthropometric variables related to performance in these endurance disciplines. In swimmers, body height is a main predictor variable; in cyclists, body mass is mainly associated with performance and in runners, the variables of body mass, body fat and skin-fold thicknesses are mainly related to performance.

109.1 Introduction

The main disciplines in endurance performance are running, cycling and swimming. In studies of athletes performing these disciplines, it is mainly the influence of body mass, body height, BMI, length and girth of extremities, body fat and, in more recent studies, of skinfold thicknesses, that has been investigated. The aim of this chapter is therefore to report findings of associations between these anthropometric properties and endurance performance.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_109,

109.2 Body Mass

The relationship between body mass and endurance performance has mainly been investigated in runners (see Table 109.3). Marathon performance time was slightly correlated to body mass in male marathoners (Hagan et al. 1981). In female non-elite marathoners, the correlation between body mass and finish time was not significant (Christensen and Ruhling 1983). In shorter distances, such as 3,000-m steeplechase, body mass was related to performance (Kenney and Hodgson 1985). In ultra-endurance runners, body mass showed no association with performance in a 24-h run (Knechtle et al. 2009c) or in a 100-km run (Knechtle et al. 2009g). Apart from runners, body mass also showed a relationship with performance in cyclists (see Table 109.2). Road cyclists with a lower body mass had an advantage in endurance cycling during climbing (Swain 1994). This was confirmed in off-road cyclists (Gregory et al. 2007; Impellizzeri et al. 2005). However, in track cyclists, body mass showed no association with performance (McLean and Parker 1989). In swimmers, body mass showed no association with performance in ultra-endurance swimmers (Knechtle et al. 2008a, 2009d). In triathletes, body mass showed no association with performance (see Table 109.4).

109.3 Body Height

Body height seems to be associated with swimming performance, especially in female swimmers (see Table 109.1), where body height was significantly related to a 100-m freestyle time in girls aged 12–14 years (Geladas et al. 2005). In another study of a 100-yard swim, body height was not related to performance in male swimmers, but was significantly related to each female swimmer's major competitive stroke (Siders et al. 1993). In 125 female breaststroke swimmers, body height was related to performance when only legs were used (Jagomagi and Jurimae 2005). Regarding the length of the swimming distance, body height was related to both short and long distances (from 50 to 800 m) in pool swimmers (Zampagni et al. 2008). However, in ultra-distance swimmers, body height showed no relationship to performance (Knechtle et al. 2008a, 2009d). Open-water ultra-endurance swimming seems to require a different body shape since these swimmers were smaller and lighter compared to pool swimmers (VanHeest et al. 2004). Also in ultra-distance runners, body height was not associated with race time in male 100-km runners (Knechtle et al. 2009g). Furthermore, body height showed no relationship with performance in long-distance triathletes (Knechtle et al. 2009h).

109.4 Body Mass Index

The association between body mass index and endurance performance was mainly investigated in long-distance runners (see Table 109.3). In female marathoners, body mass index was correlated to marathon performance time (Hagan et al. 1987). In ultra-marathoners, body mass index was negatively correlated to running speed in a 161-km trail run (Hoffman 2008). In ultra-endurance runners, however, body mass index showed no association with performance in either a 24-h run (Knechtle et al. 2009c) or a 100-km run (Knechtle et al. 2009g). Body mass index also was not related to performance in swimmers (see Table 109.1) and in long-distance triathletes (Knechtle et al. 2009h).

Table 109.1 Association of anthropometric variables with endurance performance in swimmers

Knechtle et al. (2008a)	12 male ultra-endurance swimmers in a 12-h swim	No correlation between body mass, length of legs and arms, body height, circumferences of extremities, skeletal muscle mass and fat mass to race performance
Knechtle et al. (2009d)	15 male ultra-endurance swimmers in a 26.4-km open-water ultra-endurance swim	The variables body mass, percent body fat, thickness of seven skinfolds, body height, length of arm, length of leg, number of years as swimmer, average weekly training volume in hours and kilometres and average speed in training were correlated to total race time. Speed in swimming during training was the only variable related to total race time ($r = –0.66$, $p = 0.0037$), whereas none of the other investigated variables showed an association
Geladas et al. (2005)	263 competitive swimmers (178 boys and 85 girls) aged 12–14 years	Upper extremity length, horizontal jump and grip strength were detected as significant predictors of 100-m freestyle performance in boys ($r^2 = 0.59$, $p < 0.01$). In girls, body height, upper extremity and hand length, shoulder flexibility and horizontal jump were all significantly related to 100-m freestyle time. Only 17% of the variance in performance was explained by a combination of body height, hand length and horizontal jump in girls
Sekulić et al. (2007)	40 male and 28 female swimmers	In males, body height was a significant predictor variable in 50-m freestyle swimming; in females, body weight was a significant predictor variable in 400-m freestyle swimming
Siders et al (1993)	43 female and 31 male swimmers	Significant partial correlations between swimming performance (100-yard swim of each swimmer's major competitive stroke) and body height ($r = –0.466$, $p < 0.01$), percent body fat ($r = 0.351$, $p < 0.05$) and fat-free weight ($r = –0.332$, $p < 0.05$) among the women, but no significant correlations among the men
Tuuri et al. (2002)	35 women, aged 21–73 years	Abdominal sagittal diameter was related to weekly swimming distance ($r^2 = 0.20$, $p = 0.03$)
Zampagni et al. (2008)	135 elite male and female master swimmers over 50, 100, 200, 400 and 800 m	Age, height and hand grip strength were the best predictors in short-distance events ($r = 0.84$ for 50 m, $r = 0.73$ for 100 m); age and height were predictors in middle- and long-distance events ($r = 0.75$ for 200 m, $r = 0.66$ for 400 m and $r = 0.63$ for 800 m)

109.5 Length and Girth of Extremities

The relationship of circumferences of limbs with performance has also been mainly investigated in runners (see Table 109.3). There seem to be differences between runners up to 5,000 m and ultra-endurance runners. (Tanaka and Matsuura 1982). Circumference of upper arm seemed to be related to performance in ultra-endurance runners (Knechtle et al. 2008b, 2009a). The association between upper arm circumference and performance might be influenced by the length of the race. In a 100-km run, no association has been found (Knechtle et al. 2009g), but it was observed during a multistage run over 333 km (Knechtle et al. 2009a) and one of 1,200 km (Knechtle et al. 2008b). Length of legs, however, showed no association with performance in male 100-km runners (Knechtle et al. 2009g). In contrast to runners, limb circumferences showed no association with performance in cyclists. In track cyclists, no significant correlation between girth of extremities, such as arm, thigh and calf, and endurance performance has been found (McLean and Parker 1989). In swimmers, upper extremity

length is a predictor variable of 100-m freestyle performance in both boys and girls aged 12–14 years (Geladas et al. 2005). The length of legs in swimmers might be influenced by race and gender. There is a difference in leg lengths between Chinese and Estonian girls, the Estonian girls having longer legs (Cicchella et al. 2009).

109.6 Body Fat

The relationship between body fat and endurance performance was mainly investigated in runners (see Table 109.3). Independent of the distances, body fat was related to performance. Body fat percentage was significantly associated with 12-min running performance in male conscripts (Mattila et al. 2007). In female non-elite marathoners, estimated body fat percentage and finish times showed no correlation (Christensen and Ruhling 1983). In another study of female marathoners, body fat was correlated to marathon performance times (Hagan et al. 1987). However, in ultra-endurance running, body fat percentage seems to be of no importance. During a 100-km run, percent body fat was not related to race time (Knechtle et al. 2009g). Also in a 24-h run, body fat showed no association with performance (Knechtle et al. 2009c). Body fat, however, seems to be related to performance in swimmers, especially in female swimmers (Table 109.1). In female adult swimmers, endurance swimming was mildly associated ($r^2 = 0.21$) with body adiposity (Tuuri et al. 2002). This means that female swimmers with a higher training volume showed lower body fat. In another study, percent body fat in competitive swimmers was significantly related to the 100-yard swim of each female swimmer's major competitive stroke, but not that of male swimmers (Siders et al. 1993). We must assume that body fat becomes of importance in very cold water (Keatinge et al. 2001; Knechtle et al. 2009k). In cyclists, body fat was not correlated to performance (see Table 109.2). In triathletes (see Table 109.4), the association between body fat and race performance might be influenced by the length of the competition and the gender. In male ultra-endurance triathletes of distances longer than the Ironman triathlon of 3.8-km swimming, 180-km cycling and 42.2-km running, body fat and race time were not correlated. In male Ironman triathletes, however, body fat percentage was significantly and positively related to race time, but not in females (Knechtle et al. 2009h). Body fat percentage was not only related to total race time in male Ironman athletes, but also to split times. Regarding the relationship to performance in the sub-disciplines in the race, percent body fat was related to swim performance ($r^2 = 0.25$; $p < 0.01$), bike performance ($r^2 = 0.43$; $p < 0.001$) and run performance ($r^2 = 0.27$; $p < 0.01$) (Knechtle et al. 2009i).

109.7 Skinfold Thicknesses

The association between skinfold thicknesses and endurance performance has mainly been investigated in runners (see Table 109.3) where studies of distances from 100 m to ultra-endurance had been performed. In male 10-km runners, the total sum of five skinfold thicknesses was related to performance (Bale et al. 1986). In marathoners, the sum of seven skinfolds was correlated to marathon performance times. There seem to be differences regarding the association of upper and lower body skinfold thicknesses with running performance times. High correlations have been found between the front thigh skinfold and 1,500- and 10,000-m race times, and between medial calf and 1,500- and 10,000-m race times in males. A significant and positive association between calf skinfold thickness and performance has also been found in male mountain ultra-marathoners during a

Table 109.2 Association of anthropometric variables with endurance performance in cyclists

Gregory et al. (2007)	11 male cross-country mountain bike riders in a laboratory-based maximum progressive exercise test and a 15.5 km mountain bike cross-country time trial	Physiological measures relative to total rider mass correlated more strongly to average course speed than did absolute measures
Knechtle et al. (2009e)	In 28 ultra-endurance cyclists at the 'Swiss Cycling Marathon' over 600 km, skinfold thickness at eight sites was measured pre-race. Single skinfold thicknesses, the sum of eight skinfolds and percent body fat were correlated with total race time.	There was no correlation between single skinfold thicknesses, the sum of eight skinfold thicknesses and percent body fat with total race time
Knechtle and Rosemann (2009)	In 36 male recreational mountain bike ultra-endurance cyclists at the 'Swiss Bike Masters' (120 km length and 5,000 m of altitude), the skinfold thicknesses at eight sites were measured. Body mass, percent body fat, skinfold thicknesses and training variables were correlated to race time.	There was no association between the sum of upper body skinfold thickness, the sum of lower body skinfold thickness, the sum of eight skinfold thicknesses and percent body fat with both race time and yearly training volume in cycling. Race time was negatively correlated to yearly cycling volume in road cycling ($r = –0.42$), total yearly volume in both road and mountain bike cycling ($r = –0.30$) and average speed in road cycling during training ($r = –0.35$)
Impellizzeri et al. (2007)	13 competitive off-road male cyclists in an incremental cycling test. Race time and final ranking were determined during a cross-country off-road competition	Race time and physiological parameters scaled to body mass ($r = –0.68$ to $–0.94$, $p < 0.05$) and final ranking and physiological parameters expressed relative to body mass ($r = –0.81$ to $–0.96$, $p < 0.001$) were correlated
McLean, Parker (1989)	35 elite male track cyclists	No significant correlation was seen between any anthropometric parameter (height, bicycle saddle height, thigh girth and body weight) and performance in an individual event.
Prins et al. (2007)	Eight competitive male mountain bikers participated in a cross-country race and subsequently did six performance tests	Outdoor tests correlated better with peak power output relative to body mass (both $r = –0.83$, $p < 0.05$) than with absolute peak power output (outdoor competition: $r = –0.65$; outdoor time trial: $r = –0.66$; non-significant)

seven-day mountain ultra-marathon over 350 km (Knechtle et al. 2009f). The length of a running performance may determine whether skinfold thicknesses are related to performance. In male ultra-endurance runners during a 24-h run, skinfold thicknesses showed no association with performance (Knechtle et al. 2009c). Also during a 100-km run, the sum of skinfolds was not associated with race performance (Knechtle et al. 2009g). The differences between upper and lower body skinfold thicknesses and the association with performance might also be due to gender. For females, high correlations have been observed for marathon race times and both the iliac crest and abdominal skinfold (Arrese and Ostáriz 2006). It is supposed that the skinfold thickness of the lower limb is due to training. Legaz and Eston (2005) found a significant increase in performance and a significant decrease in the sum of skinfolds, namely abdominal, front thigh and medial calf skinfolds, in both male and female top-class runners after 3 years of intense athletic conditioning. In cyclists, no association

Table 109.3 Association of anthropometric variables with endurance performance in runners

Arrese and Ostáriz (2006)	184 top-class runners (130 males and 54 females) over distances from 100 m to the marathon distance	In males, high correlations were found between the front thigh ($r = 0.78$, $p = 0.000$) and medial calf ($r = 0.55$, $p = 0.018$) skinfolds and 1,500-m run time and between the front thigh ($r = 0.59$, $p = 0.014$) and medial calf ($r = 0.57$, $p = 0.017$) skinfolds and 10,000-m run time. In female runners, the front thigh ($r = 0.71$, $p = 0.022$) and medial calf skinfolds ($r = 0.81$, $p = 0.022$) were highly correlated with 400-m run time
Bale et al. (1985)	36 female marathon runners	The number of training sessions per week and the number of years of training were the best predictors of competitive performance at both 10-mile and marathon distances
Bale et al. (1986)	60 male 10-km runners	Total skinfold, the type and frequency of training and the number of years of running were the best predictors of running performance and success at the 10-km distance
Christensen and Ruhling (1983)	23 non-elite women marathoners	The correlation between estimated percentage of both body fat ($r = –0.39$, $p > 0.05$) and body weight ($r = 0.16$, $p > 0.05$) with race time was not significant
Hagan et al. (1981)	50 male marathon runners	Marathon performance time was correlated with body weight ($r = 0.41$) and the sum of seven skinfolds ($r = 0.41$).
Hagan et al. (1987)	35 female marathon runners	BMI ($r = 0.52$), percent body fat ($r = 0.67$) and sum of skinfolds ($r = 0.51$) were correlated to marathon performance times
Hoffman (2008)	270 (216 males and 54 females) finishers of the 2007 Western States Endurance Run over 161 km	Average running speed and BMI were negatively correlated for both men ($r^2 = 0.10$, $p < 0.0001$) and women ($r^2 = 0.10$, $p = 0.02$)
Kenney and Hodgson (1985)	13 runners over 5,000- and 3,000-m steeplechase	Body weight ($r^2 = 0.94$, $p < 0.02$) was related to personal best times for the steeplechasers
Knechtle et al. (2009c)	15 male ultra-runners in a 24-h run	No significant association was found between the achieved distance and the anthropometric parameters body mass, body height, length of limbs, skinfold thicknesses, circumference of extremities, skeletal muscle mass, body fat and body mass index ($p > 0.05$)
Knechtle et al. (2009b)	19 male ultra-runners in a multistage ultra-endurance run over 1,200 km within 17 days (Deutschlandlauf)	A significant association of upper arm circumference with total running time was found ($r^2 = 0.26$, $p < 0.05$)

between skinfold thicknesses and race performance has been found, either in ultra-endurance road cyclists (Knechtle et al. 2009e) or in ultra-endurance mountain bikers (Knechtle and Rosemann 2009) (see Table 109.2). In female elite swimmers, skinfolds were the best predifctor variable of competition performance (Anderson et al. 2008). In triathletes, an association between skinfold thickness and performance has been found. In ultra-endurance triathletes competing in distances longer than the Ironman distance, the sum of eight skinfold thicknesses was related to race performance (Table 109.4). There seems to be a difference between total skinfolds and upper and lower body skinfold thicknesses in the relationship to race performance in long-distance triathletes. With regard to male Ironman triathletes, percent body fat ($r = 0.76$; $p < 0.0001$), the sum of upper body skinfolds ($r = 0.75$; $p < 0.0001$) and the sum of all eight skinfolds ($r = 0.71$; $p < 0.0001$) were related to total race time. Percent body fat ($r = –0.67$; $p < 0.001$), the sum of upper body skinfolds ($r = –0.63$, $p = 0.0004$) and the sum of all eight skinfolds ($r = –0.59$; $p < 0.001$) were also associated with speed in cycling during the race (Knechtle et al. 2009j).

Table 109.4 Association of anthropometric variables with endurance performance in triathletes

Knechtle and Kohler (2007)	Five male ultra-triathletes in a Triple Iron Triathlon over 11.4 km swimming, 540 km cycling and 126.6 km running	Race time was not significantly ($p > 0.05$) influenced by the directly measured variables body height, leg length, body mass, body fat, average skinfold thicknesses or circumferences of thigh, calf or upper arm
Knechtle et al. (2007b)	16 male ultra-triathletes in a Triple Iron Triathlon over 11.4 km swimming, 540 km cycling and 126.6 km running	No significant influence was observed between race time and body height, leg length, body mass, skeletal muscle mass, fat mass, skinfold thicknesses or circumferences of thigh, calf or upper arm
Knechtle et al. (2007a)	Eight male ultra-triathletes in a Deca Iron Triathlon over 3.8 km swimming, 180 km cycling and 42.2 km running per day for 10 consecutive days	Race time was not significantly ($p > 0.05$) influenced by the directly measured variables body height, leg length, body mass, body fat, average skinfold thicknesses or circumferences of thigh, calf or upper arm
Knechtle et al. (2009b)	29 male ultra-triathletes in a Triple Iron Triathlon over 11.4 km swimming, 540 km cycling and 126.6 km running	The sum of eight skinfold thicknesses was associated with total race time ($r^2 = 0.33$, $p < 0.001$)
Knechtle et al. (2009h)	27 male and 16 female Ironman triathletes	For the male athletes, percent body fat was related to final race time ($r^2 = 0.57$, $p < 0.001$) but not for females ($p > 0.05$)
Leake and Carter (1991)	16 trained female triathletes	Regression analysis indicated that training parameters were more important than anthropometric measurements (body height, biacromial and bi-iliac diameters, biepicondylar diameters, skinfold thicknesses and limb girths) in the prediction of performance

Summary Points

- The association between anthropometry and race performance in endurance athletes is mainly dependent upon the kind of exercise and partly upon the gender.
- In swimmers, body height is a main predictor variable for females but not for males.
- In cyclists, body mass is mainly associated with performance where only males had been investigated.
- In runners, body mass, body fat and skinfold thicknesses are mainly related to performance in both males and females.
- In triathletes, body fat and skinfold thicknesses are related to performance in male but not in female athletes.

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Chapter 110
Anthropometry and the Response to Dietary Supplementation in Exercise

Review of the Anthropometric Methods Employed to Evaluate the Effectiveness of Popular Dietary Supplements to Alter Body Composition

Melissa Crowe

Abstract A high proportion of athletes consume dietary supplements in the belief that they will enhance performance or alter body composition. Therefore, research into dietary supplements should accurately evaluate alterations in body composition, specifically muscle and fat mass (FM). A number of factors need to be considered in the selection of anthropometric methodologies to evaluate body composition changes due to dietary supplementation. These factors include measurement details (reliability, validity, accuracy and sensitivity), ethical factors such as invasiveness, statistical effect size and practical considerations such as time, cost and equipment availability. Researchers should first consider the statistical effect size of the supplement under study. Does previous research indicate a marked effect of the supplement on body composition? If so, then a less sensitive methodology can be utilised. Where previous research indicates only a small or negligible effect on body composition, the more sensitive anthropometric methodologies should be employed. The validity and reliability of the anthropometric technique is important. However, there is a lack of research into the reliability and validity of various anthropometric methodologies when assessed in conjunction with dietary supplementation. Examination of recent research into the most popular dietary supplements including creatine monohydrate, β-hydroxy-β-methyl butyrate (HMB), chromium picolinate, Tribulus Terrestris, ephedrine and L-carnitine, reveals utilisation of a wide variety of anthropometric methodologies with no particular methodology associated with detecting significant effects on body composition. Ephedrine, when combined with caffeine, and creatine are amongst the few dietary supplements consistently reported to alter body composition. Changes in hydration status can lead to confounding errors when assessing body composition and researchers should aim to minimise or control alterations in hydration status. Future research is needed in the area of anthropometry and dietary supplementation, particularly investigating the validity and reliability of various anthropometric techniques to detect change in body composition as a result of dietary supplementation. A greater availability of this information would assist researchers to choose appropriate anthropometric methodology to assess the effects of dietary supplements on muscle and FM.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_110,

Abbreviations

ADP	Air displacement plethysmography
%BF	Percentage body fat
BIA	Bioelectrical impedance analysis
BM	Body mass
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
Cr	Chromium
CT	Computed tomography
DXA	Dual energy x-ray absorptiometry
FFM	Fat-free mass
FM	Fat mass
HMB	β-Hydroxy-β-methyl butyrate
LBM	Lean body mass
MRI	Magnetic resonance imaging
NIR	Near-infrared interactance
TBW	Total body water
W:H ratio	Waist to hip ratio

110.1 Introduction

Athletes and the general public consume dietary supplements in the belief they will enhance sports or exercise performance and/or alter body composition. Survey studies of athletes have shown that 94% of swimmers (Baylis et al. 2001) and a similar percentage of Canadian varsity athletes (Kristiansen et al. 2005) consume some form of dietary supplement. Dietary supplements are often heavily marketed on their ability to increase muscle size and strength and/or reduce body fat. It is therefore necessary to accurately assess changes in body composition when evaluating the effectiveness of supplements, specifically fat mass (FM) and fat-free mass (FFM). The methodology employed to assess body composition will affect the ability to detect changes due to dietary supplementation. This chapter will consider a number of factors important in the selection of anthropometric methods to assess body composition during dietary supplementation. Measurement, statistical, ethical and practical factors will be discussed. This will be followed by a review of the different anthropometric methods employed in research investigating dietary supplements, which reportedly alter body composition. The small number of studies which evaluate the reliability of different anthropometric methods for detecting change due to supplementation will also be examined. Although there are a large number of dietary supplements marketed for their ability to increase muscle size or reduce body fat, this chapter will focus on the main supplements utilised by the sporting community and the general public including creatine monohydrate, β-hydroxy-β-methyl butyrate (HMB), chromium picolinate, *Tribulus terrestris*, L-carnitine and ephedrine. These dietary supplements not only are of interest to athletes, but also have medical relevance with the possible treatment of obesity or muscle wasting diseases.

The term ‘anthropometry’ has been used in the general sense throughout this chapter, meaning measurement of the composition and dimensions of the human body rather than specifically referring to the assessment of skinfolds, girths and breadths.

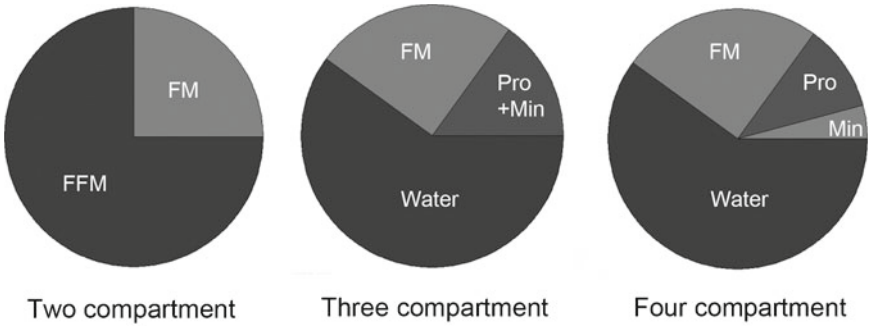

Fig. 110.1 Schematic representation of the two-, three- and four-compartment models of body composition. The two-, three- and four-compartment models of body composition showing the various components in each model. *FM* fat mass, *FFM* fat-free mass, *Pro* protein, *Min* mineral

110.2 Body Composition Compartment Models

In order to appreciate different anthropometric methodologies, it is first necessary to understand the compartment models upon which they are based. In estimating body composition, the body must be divided into its component parts. At a molecular level, there are two-compartment-, three-compartment- and four-compartment models. In the two-compartment model, the body is subdivided into FM and FFM. The three-compartment model further breaks down FFM into water and mineral plus protein. The four-compartment model includes water, mineral, protein and fat (Wang et al. 2005). These models are illustrated in Fig. 110.1. It is generally accepted that methodologies utilising the four-compartment model are more accurate than those based on the three-compartment model, with the two-compartment model methodologies being the least accurate. This is because a greater proportion of the body is accounted for with the four-compartment model. However, this concept has been questioned as greater error can be introduced with the estimation of more parts of the body (Wang et al. 2005). For example, body water may be determined using deuterium dilution, body mineral using dual energy X-ray absorptiometry (DXA), and FFM and FM using hydrodensitometry (underwater weighing). Each of these methods has a certain amount of error associated with it and these errors are additive. If body composition was simply determined using hydrodensitometry (two-compartment model), then only the error associated with this methodology would affect the measurement.

110.3 Factors to Consider When Assessing Alterations in Body Composition Due to Dietary Supplementation

When selecting methodology to evaluate changes in body composition resulting from dietary supplementation, researchers should consider a number of factors (Table 110.1), the most important of which include measurement factors such as accuracy, reliability, validity and sensitivity. Statistically, effect size should also be considered. Once these factors have been taken into account, ethical and practical factors will also influence the choice of methodology.

Measurement factors will influence the ability to detect change in body composition as a result of dietary supplementation. Accuracy, which refers to the closeness of a measurement to the true value (Norton and Olds 1996), is of importance in dietary supplement studies. However, reliability or the

Table 110.1 Factors to consider for selection of anthropometric methodology

Category	Factors
Measurement factors	Reliability
	Validity
	Accuracy
	Sensitivity
Statistical factors	Effect size
Practical factors	Cost
	Accessibility
	Time available
Ethical factors	Invasiveness

This table lists the factors to consider when selecting anthropometric methodology to assess changes in body composition in response to dietary supplementation including measurement, statistical, practical and ethical factors

closeness of repeated measurements (Norton and Olds 1996) is of greater value as the ability to detect change in the measurements is most important. Validity refers to how well the measurement actually measures the characteristic of interest (Norton and Olds 1996). A criterion reference is required to assess the validity of other methods. Hydrodensitometry was traditionally used as the criterion reference by which the validity of other anthropometric methods was compared. However, this is no longer necessarily the case as will be discussed below (see Sect. 110.5). If the error associated with a particular anthropometric methodology is greater than the change in body composition induced by the dietary supplement, then the induced changes will not be detected. Therefore, sensitivity, which is the ability to detect change in a measurement, is also important.

Effect size is relevant to the particular dietary supplement being investigated and will depend on the extent and quality of previous research. If a dietary supplement is expected to have a large effect on body composition, then a less sensitive methodology could be employed. However, if changes in body composition are expected to be small, then a more sensitive methodology with high reliability is required. Furthermore, a larger sample size would enhance the potential of detecting supplement effects, if the expected effect is only small. Meta-analyses are useful in helping to determine the expected effect of a supplement on body composition as the aim of a meta-analysis is to determine the average magnitude of an effect.

When measurement and statistical factors have been considered, researchers are still faced with ethical and practical considerations when choosing methodology to evaluate changes in body composition in response to dietary supplementation (Table 110.1). The principal ethical consideration is the invasiveness of the technique. Does the benefit gained from the study outweigh the risk to the participants? In the case of dietary supplementation studies, rarely does the outcome of the study justify exposing participants to high doses of radiation as would be the case with methodologies such as computed tomography (CT). Therefore, such techniques are rarely utilised in supplement studies. However, such methodologies could be justified when evaluating banned drugs, such as androgenic-anabolic steroids, human growth hormone and erythropoietin, where the side effects can be severe.

Practical considerations include factors such as cost, accessibility to equipment and time constraints. The most sensitive methodologies available to assess body composition are often the most expensive and most difficult to access. For example, modern technologies such as magnetic resonance imaging (MRI) cost in the order of millions of dollars and are usually only available in major hospitals and large private imaging practices. It would be an advantage to utilise MRI, if the dietary

supplement was expected to have only small effects on body composition. However, the cost and availability of such technology make this difficult. Therefore, when we examine the dietary supplement literature, it is unusual to find many studies employing the more sensitive methodologies such as MRI and CT due to the cost in purchasing and difficulty in accessing this type of equipment. By contrast, BIA requires little skill, costs relatively little and is easily accessible and quick to perform. These factors contribute to the increased number of dietary supplement studies utilising BIA. Skinfolds, girths and breadths are also relatively inexpensive and quick to perform by an experienced anthropometrist. However, there is usually greater error associated with these measures as indicated by reliability studies (Kilduff et al. 2007). Thus, practical factors often limit the type of anthropometric methodology selected to assess body composition changes with dietary supplementation.

In conclusion, a number of factors need to be considered when selecting methodology to assess changes in body composition in response to dietary supplementation. The expected magnitude of the supplement's effect on body composition should first be considered. If the dietary supplement has previously been shown to have marked effects on body composition, then a less sensitive methodology is sufficient. However, when the change in body composition is only small, then methodologies such as body mass index (BMI), skinfolds, BIA and DXA are not sufficient and more sensitive methodologies are required (e.g. deuterium dilution, CT or MRI). However, the invasiveness and risk to the participants need also be considered, as the knowledge gained from dietary supplement studies is unlikely to justify the use of high radiation doses such as those delivered with CT. Researchers may desire to use the more accurate methodologies such as MRI but may be limited by practical factors such as cost, time available and accessibility to equipment.

110.4 Past Dietary Supplement Research and Anthropometry

The following sections will examine the anthropometric methodologies employed in past dietary supplementation studies. The supplements reviewed include creatine monohydrate, HMB, chromium picolinate, *Tribulus terrestris*, ephedrine and L-carnitine. These supplements were chosen based on current popularity within the sporting community and with the general population as well as the availability of double-blind, placebo-controlled research. A general discussion of the body composition outcomes will also be provided. However, it is not the aim of this chapter to provide a detailed review of the findings on each supplement and readers are referred to relevant reviews and meta-analyses where possible. There are a number of other supplements available, which supposedly alter body composition, for example, arginine and ginseng. However, a lack of well-controlled research into these supplements with regard to body composition precludes them from this review. In general, by far the most common anthropometric evaluation in all these supplement studies is simple assessment of body weight. Where FFM and FM are determined, there are a wide range of different methodologies employed.

110.4.1 Anthropometric Methodologies Employed in Creatine Monohydrate Studies

Creatine monohydrate and other forms of creatine are by far the most researched dietary supplements on the market. Oral supplementation with creatine increases muscle phosphocreatine concentrations and thereby enables greater generation of adenosine triphosphate (ATP) from adenosine

Table 110.2 Key features of creatine

1.	The most popular dietary supplement for enhancing exercise performance.
2.	Shown to enhance short-term, high-intensity exercise and increase body mass.
3.	Performance is enhanced via greater energy supply in the form of ATP.
4.	ATP is generated from the phosphorylation of ADP by phosphocreatine.
5.	Supplementation is more effective in vegetarians because creatine is naturally found in meat.

This table lists the key features of creatine including the mechanism by which creatine enhances exercise performance and the main effects of creatine

diphosphate (Branch 2003). Theoretically, greater ATP availability facilitates greater short-term, high-intensity activity and therefore greater gains in muscle size and strength with resistance training (Branch 2003). An overview of the key features of creatine can be found in Table 110.2. Examination of the past 10 years of creatine research reveals a large variety of methodologies employed to assess changes in body composition (Table 110.3). Body mass is commonly assessed in most studies using simple weighing scales, with FFM and FM determined primarily by DXA (16 studies), BIA (14 studies), skinfolds and/or girths (12 studies) and hydrodensitometry (8 studies). Ultrasound and near-infrared interactance (NIR) were less commonly used, with air displacement plethysmography (ADP) used in a small number of studies (Table 110.3). For readers not familiar with NIR, a short summary of the key features of this technique can be found in Table 110.4. Skinfolds and/or girths were commonly used in creatine research in conjunction with other methodologies, with only five studies evaluating body composition by these methods alone. A meta-analysis of creatine research has indicated a significant effect of this supplement on body composition (Branch 2003). Furthermore, Kilduff et al. (2007) have shown that five different anthropometric methodologies, including skinfolds, BIA, NIR, ADP and hydrodensitometry, were all able to detect changes in body composition as a result of acute creatine supplementation. Similarly, significant increases in body weight and FFM and significant decreases in FM and %BF were detected by ADP following acute creatine monohydrate ingestion (Vukovich and Peeters 2003). Therefore, it is likely that all the anthropometric methodologies employed in past creatine supplementation studies were able to detect a difference in body composition (specifically FFM) had it occurred. Of 36 studies investigating changes in body composition as a result of creatine supplementation in various populations, only 11 studies reported no change in FFM (Table 110.3). Examination of these 11 studies did not reveal use of any particular anthropometric methodology, with all the methodologies listed above included, except NIR and ultrasound. However, it must be accepted that the dose and duration of creatine supplementation and the populations studied vary widely and that these factors will affect whether or not creatine supplementation increases FFM. Bearing this in mind, there exist many more positive studies showing increased FFM in response to creatine supplementation with various anthropometric methods than those that show no effect, indicating that the type of methodology utilised is unlikely to affect the ability to detect changes in body composition in response to creatine supplementation.

110.4.2 Anthropometric Methodologies Employed in β-Hydroxy-β-Methyl Butyrate (HMB) Studies

β-Hydroxy-β-methyl butyrate (HMB) is another popular dietary supplement. HMB is marketed to improve all types of exercise performance via anticatabolic effects (see Rowlands and Thomson 2009). A summary of the main features of HMB is provided in Table 110.5. The body of scientific research available on HMB is not as great as that available for creatine. A literature search of HMB and body

Table 110.3 Details and outcomes of studies assessing body composition with creatine monohydrate supplementation

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Cornish et al. (2009)	Randomised, double-blind, crossover	9 g/day plus protein and linoleic acid for 5 weeks	69 strength-trained participants (52 male, 17 female) CCP (Creatine, linoleic acid and protein) $n = 22$ CP (Creatine and protein) $n = 25$ P (protein) $n = 22$	BM FM and LBM (ADP) Muscle thickness (ultrasound)	↑ LBM: CCP > CP > P CCP, CP and P all ↑ muscle thickness No effect on %BF or FM
Spillane et al. (2009)	Randomised, double-blind	20 g/day for 5 days + 5 g/day for 42 days	30 non-trained males Creatine monohydrate $n = 10$ Creatine ethyl ester $n = 10$ Placebo $n = 10$	BM %BF, FM and FFM (DXA) TBW and compartment-specific fluid volume (BIA)	No effect of either supplement on body composition variables except FM where the monohydrate group had greater FM than the ethyl ester group
Eliot et al. (2008)	Randomised, double-blind	5 g/day for 14 weeks	42 males (48–72 years) Creatine $n = 10$ Whey protein $n = 11$ Creatine + protein $n = 11$ Placebo $n = 10$	Total and regional measures of body composition (DXA) TBW, ICW and ECW (BIA)	Training effect but no group differences
Gotshalk et al. (2008)	Randomised, double-blind	0.3 g/kg/day for 7 day	27 females (58–71 years) Creatine $n = 15$ Placebo $n = 12$	BM %BF (skinfolds –Jackson & Pollock equation)	Significant ↑ BM and FFM
Chilibeck et al. (2007)	Randomised, double-blind	0.1 g/kg/day for 8 weeks	18 rugby union players Creatine $n = 9$ Placebo/$n = 9$	BM FM and LBM (ADP)	No effect
Cribb et al. (2007a)	Randomised, double-blind	0.1 g/kg/day for 10 weeks	31 resistance-trained males Protein ($n = 10$) Protein/CHO ($n = 11$) Protein/CHO/creatine ($n = 10$)	BM FFM, FM and %BF (DXA)	Greater ↑ LBM in the protein/CHO/creatine group compared to other groups. Greater loss of FM and %BF in the protein/CHO/creatine and protein groups compared to the protein/CHO group.

(continued)

Table 110.3 (continued)

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Cribb et al. (2007b)	Randomised, double blind	0.3 g/kg/day for 1 week + 0.1 g/kg/day for 9 weeks	26 resistance-trained males Creatine/CHO (n= 8) Creatine/protein (n = 6) CHO (n = 7) Protein (n = 5)	BM FFM, FM and %BF (DXA)	No differences in BM, FM or %BF between groups. Greater LBM gain in the creatine/CHO group compared to the CHO group. All groups ↑ LBM over time.
Kilduff et al. (2007)	Reliability study, repeated measures	20 g/day for 7 days	55 male university athletes Reliability study n = 55 Creatine study n = 30	BM FM and FFM (hydrodensitometry, NIR, ADP, skinfolds and BIA)	↑ BM ↑ FFM detected by all five methods
Silva et al. (2007)	Randomised, double-blind	20 g/day for 21 days	16 junior female swimmers Creatine n = 8 Placebo n = 8	BM FM, FFM and TBW (BIA)	No effect
Glaister et al. (2006)	Randomised, double-blind	20 g/day for 5 days	42 physically active men Creatine n = 21 Placebo n = 21	BM %BF (skinfolds – Durnin and Womersley equation)	Statistical significance not reported. Infers ↑ BM and no effect on %BF
Ferguson and Syrotuik (2006)	Randomised, double-blind	0.3 g/kg for 7 days + 0.03 g//kg/day for 9 weeks	26 recreational strength trained females Creatine n = 13 Placebo n = 13	%BF, FM and LBM (DXA)	No effect
Hoffman et al. (2006)	Randomised, double-blind	10.5 g/day for 10 weeks	33 college footballers Creatine n = 11 Placebo n = 11 Creatine + alanine n = 11	BM %BF and LBM (DXA)	No effect on BM or FM Creatine + alanine had significantly greater change in LBM and %BF compared to placebo
Ahmun et al. (2005)	Randomised, double-blind, crossover	20 g/day for 5 days	14 rugby players	BM %BF (from four skinfolds)	No effect
Chilibeck et al. (2004)	Randomised, double-blind, single-side training	0.2 g/kg twice per week after training for 6 weeks	21 weight-trained participants (11 male, 10 female) Creatine n = 11 Placebo n = 10	Muscle thickness (ultrasound) Whole body and regional LBM, FM and bone mass (DXA)	Greater ↑ in muscle thickness on creatine days. Creatine males greater ↑ LBM than placebo males and females (creatine and placebo) No effect on FM or bone mass

Mendes et al. (2004)	Randomised, double-blind	20 g/day for 8 days	18 competitive swimmers (six female, 12 male) Creatine $n = 9$ Placebo $n = 9$	BM LBM, %BF (skinfolds, BIA and DXA) TBW (BIA)	Greater ↑ in BM, LBM and TBW but no change in muscle or bone mass. %BF result not stated
Volek et al. (2004)	Randomised, double-blind	0.3 g/kg/day for 6 weeks Overreaching program (4 weeks then 2 week taper)	17 resistance-trained males Creatine $n = 9$ Placebo $n = 8$	BM TBW (BIA) %BF, LBM and BMC (DXA)	Significantly greater BM and LBM in legs No effect on %BF and BMC
Brose et al. (2003)	Randomised, double-blind	5 g/day for 14 weeks	28 older participants (> 65 year) (15 male, 13 female) Creatine $n = 14$ Placebo $n = 14$	BM %BF and FFM (DXA)	Significant ↑ BM and FFM No effect on %BF
Kutz and Gunter (2003)	Double-blind	30 g/day for 2 weeks + 15 g/day for 2 weeks	17 active males Creatine $n = 9$ Placebo $n = 8$	BM %BF (hydrodensitometry) TBW (BIA)	Greater ↑ BM and TBW No change in %BF
Lehmkuhl et al. (2003)	Randomised, double-blind	0.3 g/kg/day for 7 days + 0.03 g/kg/day for 7 weeks	29 collegiate track and field athletes (17 male, 12 female) Creatine $n = 10$ Creatine + glutamine $n = 10$ Placebo $n = 9$	BM %BF, FM and LBM (hydrodensitometry and skinfolds)	↑ BM greater in creatine groups ↑ LBM greater in creatine groups from skinfolds. No difference between groups from hydrodensitometry No effect on %BF or FM from either method
Van Loon et al. (2003)	Double blind	20 g/day for 5 days + 2 g/day for 37 days	20 non-trained males Creatine $n = 10$ Placebo $n = 10$	BM %BF and FFM (hydrodensitometry)	Greater ↑ BM and trend for ↑ FFM ($p = 0.06$) No effect %BF
Dawson et al. (2002)	Randomised, double blind	20 g/day for 5 days + 5 g/day for 22 days	10 male and 10 female junior swimmers Creatine $n = 10$ Placebo $n = 10$	BM Skinfolds (sum of 6)	No effect
Huso et al. (2002)	Randomised, double-blind, crossover (4 weeks washout)	20 g/day for 4 days + 2 g/day for 17 days	10 recreationally active males	BM FFM and FM (ADP)	Significant ↑ BM with creatine Significant ↑ FFM with creatine and placebo Significant ↓ FM with placebo

(continued)

Table 110.3 (continued)

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Kilduff et al. (2002)	Double-blind	20 g/day for 5 days	32 resistance-trained males Creatine $n = 21$ Placebo $n = 11$	BM %BF, FFM and TBW (BIA)	Significant ↑ BM and FFM No effect on %BF and TBW
Warber et al. (2002)	Randomised, double-blind	24 g/day for 5 days	26 physically active males Creatine $n = 13$ Placebo $n = 13$	BM %BF (DXA)	Significant ↑ BM Greater ↓ %BF
Wilder et al. (2002)	Single-blind	Low dose: 20 g/day for 7 days + 5 g/day for 9 weeks High dose: 12 g/day for 7 days + 3 g/day for 9 weeks	25 male collegiate football players Low-dose creatine $n = 8$ High-dose creatine $n = 8$ Placebo $n = 9$	BM FFM and %BF (hydrodensitometry) Skinfolds (Hagerman, Starr and Murray equation)	No effect
Arciero et al. (2001)	Randomised, double-blind	20 g/day for 5 days + 10 g/day for 23 days	30 non-resistance trained males Creatine alone $n = 10$ Creatine + resistance training $n = 10$ Placebo + resistance training $n = 10$	BM FM, FFM (DXA) TBW (BIA)	Significant ↑ BM and TBW for creatine groups Significant ↑ in FFM with creatine + training and trend for creatine ($p = 0.07$) No effect on FM
Bemben et al. (2001)	Randomised, double-blind	20 g/day for 5 days + 5 g/day up to 9 weeks	25 male collegiate football players Creatine $n = 9$ Placebo $n = 8$ Control $n = 8$ All groups resistance trained	BM FFM and FM (hydrodensitometry) TBW (BIA)	Greater ↑ BM, FFM, TBW and intracellular water No effect on FM
Bennett et al. (2001)	Randomised, double-blind	20 g/day for 6 days + 6 g/day for 4 weeks	16 male soldiers Creatine $n = 8$ Placebo $n = 8$	BM LBM and FM (DXA) TBW (BIA)	Significant ↑ BM No effect on other variables
Burke et al. (2001)	Randomised, double-blind	0.1 g/kg/day for 6 weeks	36 resistance-trained males Whey protein $n = 12$ Whey + Creatine $n = 12$ Placebo $n = 12$	BM FM and LBM (DXA)	Greater ↑ BM for the whey and the whey/creatine groups compared to the placebo group Greater ↑ LBM in the whey/creatine group compared to the whey group, and in the whey group compared to the placebo group No effect on FM

Chrusch et al. (2001)	Randomised, double-blind	0.3 g/kg/day for 5 days + 0.07 g/kg/day up to 12 weeks	30 older men (60–84 year) Creatine $n = 16$ Placebo $n = 14$	BM LBM, FM and %BF (DXA)	Greater ↑ BM and LBM No effect on FM or %BF
Jowko et al. (2001)	Randomised, double-blind	20 g/day for 7 days + 10 g/day for 14 days	40 active males Creatine $n = 11$ HMB $n = 9$ Creatine + HMB $n = 10$ Placebo $n = 10$	LBM, FM and TBW (BIA)	Significant ↑ BM in all groups except placebo, with HMB/Cr significantly greater than HMB or Cr alone Significant ↑ LBM in all groups, with Cr significantly greater than placebo Significant ↑ FM in HMB/Cr compared to other groups Significant ↑ TBW in all groups, with Cr significantly greater than placebo
Syrotuik et al. (2001)	Randomised, double blind	0.3 g/kg/day for 5 days + 0.03 g/kg/day for 5 weeks	22 rowers (12 male, 10 female) Creatine $n = 11$ Placebo $n = 11$	BM Skinfolds (sum of 8) FM and FFM (hydrodensitometry) TBW (BIA)	No effect
Tarnopolsky et al. (2001)	Randomised, double-blind	10 g/day for 8 weeks (dose ingested post-exercise)	19 active males Creatine $n = 11$ Protein $n = 8$	BM %BF and FFM (DXA)	Greater ↑ BM for the creatine group compared to the protein group No effect on %BF or FFM
Volek et al. (2001)	Randomised, double-blind	0.3 g/kg/day for 7 days	20 healthy men Creatine $n = 10$ Placebo $n = 10$ (Exercise in heat)	BM Skinfolds (sum of 7) TBW (BIA)	Significant ↑ BM Significant ↑ TBW but not %TBW %BF and FFM not evaluated post-supplementation
Willoughby and Rosene (2001)	Randomised, double-blind	6 g/day for 12 weeks + resistance training for creatine and placebo groups	22 untrained males Creatine $n = 8$ Placebo $n = 8$ Control $n = 6$	BM %BF, FFM (seven skinfolds)	Greater ↑ BM and FFM for the creatine group compared to the placebo group and for the placebo group compared to control group No difference in %BF

(continued)

Table 110.3 (continued)

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Becque et al. (2000)	Double-blind	20 g/day for 5 days + 2 g/day up to 6 weeks	23 resistance trained males Creatine $n = 10$ Placebo $n = 13$	BM %BF, FM, FFM (hydrodensitometry) Upper arm circumference	Greater ↑ BM, FFM and upper arm circumference No effect on FM or %BF

Research studies from the past 10 years investigating the effects of creatine supplementation on body composition are shown. The dose and duration of supplementation, population studied, anthropometrical methods utilised and main outcomes are detailed. The majority of studies show a significant increase in FFM in response to creatine supplementation

ADP air displacement plethysmography, *BIA* bioelectrical impedance analysis, *BM* body mass, *BMC* bone mineral content, *BMI* body mass index, *CHO* carbohydrate, *CT* computed tomography, *DXA* dual energy X-ray absorptiometry, *ECW* extracellular water, *FM* fat mass, *FFM* fat-free mass, *ICW* intracellular water, *LBM* lean body mass, *NIR* near-infrared interactance, *%BF* percentage body fat, *TBW* total body water

Table 110.4 Key features of near-infrared interactance

1. Field method to assess %BF, which is quick, safe and non-invasive.
2. Assessment of %BF is made using spectrophotometry.
3. Infrared light of various wavelengths is emitted into a body part (usually the biceps brachii) and measurement made of the re-emitted light.
4. The measurement is expressed as an optical density.
5. Optical density is converted into an estimation of %BF via regression equations.

The key features of NIR are indicated in this table explaining the mechanism by which NIR assesses body composition

Table 110.5 Key features of β-hydroxy-β-methyl butyrate (HMB)

1. Metabolite of the amino acid leucine.
2. Claimed to increase strength and FFM and reduce FM.
3. Suggested to act as an anticatabolic agent preventing the breakdown of body protein.
4. Some evidence for increased strength in untrained participants.
5. Little evidence for increased strength in experienced resistance-trained athletes.
6. Little evidence for any effect on body composition.

This table lists the main features of HMB including the proposed mechanism of HMB action and the primary research findings on HMB

composition revealed 14 studies (excluding studies reported in abstract form only). A variety of anthropometric methodologies was used in these studies (Table 110.6), with BIA and DXA the most popular. Skinfolds and/or girths were assessed in 8 of the 14 studies. However, only three studies relied solely on these measures to assess body composition. Hydrodensitometry, CT, ultrasound and ADP were utilised in one study each. In general, the majority of these studies indicated no effect of HMB on FFM. Similar to creatine supplementation studies, there does not appear to be any commonality in the type of anthropometric method used for the few studies that did report significant increases in FFM compared to those that reported no effect of HMB. A meta-analysis conducted by Rowlands and Thomson (2009) on the effects of HMB on strength and body composition indicated a trivial effect of HMB on FFM and FM. Thus, the effects of HMB on body composition are likely to be small or non-existent and studies investigating HMB should utilise the more sensitive anthropometric methodologies such as MRI or a four-compartment model using combined methodologies.

110.4.3 Anthropometric Methodologies Employed in Chromium Picolinate Studies

Chromium has been suggested to increase the efficacy of insulin and may therefore play a role in protein accretion and decreasing fat stores (Vincent 2003). However, the majority of studies investigating the effects of chromium picolinate on body composition in healthy participants have failed to show any effects (Table 110.7). Hydrodensitometry (8 studies) and skinfold assessment (7 studies) were the most commonly utilised methodologies in chromium picolinate supplementation studies where body composition was evaluated (Table 110.7). However, skinfolds were employed in conjunction with other methodologies and were not the main methodology for determining body composition in any of these studies. DXA was employed in three chromium supplementation studies, whilst BIA

Table 110.6 Details and outcomes of studies investigating body composition alterations with β-hydroxy-β-methyl butyrate (HMB) supplementation

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplementation
Thomson et al. (2009)	Randomised, double blind	3 g/day for 9 weeks	22 resistance trained males HMB $n = 13$ Placebo $n = 9$	BM FM, FFM (BIA) Skinfolds (sum of 7)	No effect on BM or FFM Trivial effects on FM
Baier et al. (2009)	Randomised, double blind	HMB/lysine/arginine mix BM <68 kg – 2 g/day HMB BM>68 kg – 3 g/day HMB for 12 months	Elderly participants (≥65 year) (38 males, 39 females) HMB $n = 40$ Placebo $n = 37$	FM, FFM (BIA) FFM (DXA)	Significant ↑ in FFM and body cell mass No effect on FM
Kraemer et al. (2009)	Randomised, double blind	3 g/day HMB + amino acids (Muscle Armor) for 12 weeks with heavy resistance training	17 healthy males HMB/amino acids $n = 8$ Placebo $n = 9$	BM LBM, %BF (DXA) Girths (six sites) Ultrasound (patella tendon)	Greater ↑ in BM and LBM Greater ↓ in %BF Greater ↑ in thigh and chest girths No effect on patella tendon thickness
Lamboley et al. (2007)	Randomised, double blind	3 g/day for 5 weeks	16 active college students (8 male, 8 female) HMB $n = 8$ Placebo $n = 8$	BM LBM, FM (DXA)	No effect
O'Connor and a Crowe (2007)	Partly blinded	3 g/day for 6 weeks	30 elite rugby league players Control $n = 8$ HMB $n = 11$ HMB/Cr $n = 11$	BM Skinfolds, girths and breadths	No effect
Flakoll et al. (2004)	Randomised, double blind	HMB/lysine/arginine mix with 2 g/day HMB for 12 weeks	57 elderly women (62–90 year) HMB $n = 29$ Placebo $n = 28$	Girths (five sites) Study 1 – BIA Study 2 – ADP	Significant ↑ in average limb girth Trend ($p = 0.08$) for ↑ FFM No effect on BM, FM or %BF
Ransone et al. (2003)	Randomised, double blind, crossover (1 week washout)	3 g/day for 4 weeks	35 male collegiate footballers	BM Skinfolds -%BF (Jackson & Pollock equation)	No effect

Jowko et al. 2001	Randomised, double blind	3 g/day for 3 weeks	40 active males Cr $n = 11$ HMB $n = 9$ Cr + HMB $n = 10$ Placebo $n = 10$	LBM, FM and TBW (BIA)	Significant ↑ BM in all groups except placebo, with HMB/Cr significantly greater than HMB or Cr alone Significant ↑ LBM in all groups, with Cr significantly greater than placebo Significant ↑ FM in HMB/Cr compared to other groups Significant ↑ TBW in all groups, with Cr significantly greater than placebo
Slater et al. (2001)	Randomised, double blind	3 g/day for 6 weeks	27 male strength-trained athletes HMB $n = 9$ Time release HMB $n = 9$ Placebo $n = 9$	BM FM, LBM (DXA)	No effect
Vukovich et al. (2001)	Randomised, double blind	3 g/day for 8 weeks	31 elderly participants (15 male, 16 female) (Mean age 70 ± 1 year) HMB $n = 14$ Placebo $n = 17$	BM Skinfolds (eight sites – Jackson & Pollock equation) CT ($n = 20$ subset) DXA ($n = 23$ subset)	Greater %BF loss (by skinfolds and CT) Trend ($p = 0.08$) for ↑ FFM
Gallagher et al. (2000)	Randomised, double-blind	0, 38 or 76 mg/kg/day for 8 weeks	37 untrained college-aged men 38 mg/kg HMB $n = 12$ 76 mg/kg HMB $n = 11$ Placebo $n = 14$	BM Skinfolds (seven sites: Brozek and Jackson & Pollock equations)	38 mg/kg group had greater ↑ FFM compared to 76/mg/kg and placebo No effect on BM or FM
Panton et al. (2000)	Randomised, double-blind	3 g/day for 4 weeks	75 untrained participants (39 male, 36 female) HMB $n = 39$ Placebo $n = 36$	BM Skinfolds (sum of 7; Pollock & Wilmore equation) %BF, FFM (hydrodensitometry)	No effects at $p<0.05$ Trends for ↑ FFM and ↓ %BF ($p = 0.08$)

(continued)

Table 110.6 (continued)

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplementation
Kreider et al. (2000)	Randomised, double blind	3 g/day for 4 wk	28 NCAA division 1 footballers HMB $n = 14$ Placebo $n = 14$	BM TBW (BIA) FFM, FM, %BF (DXA)	No effect
Kreider et al. (1999)	Randomised, double-blind	0, 3 or 6 g/day for 4 weeks	40 male resistance-trained athletes 3 g/day HMB $n = 13$ 6 g/day HMB $n = 12$ Placebo $n = 15$	BM TBW (BIA) FFM, FM and %BF (DXA)	No effect

This table lists the available research on HMB and body composition. The dose and duration of supplementation, population studied, anthropometrical methods utilised and main outcomes are indicated. The majority of studies indicate no effect of HMB on FFM

ADP air displacement plethysmography, *BIA* bioelectrical impedance analysis, *BM* body mass, *BMI* body mass index, *CT* computed tomography, *DXA* dual energy X-ray absorptiometry, *FM* fat mass, *FFM* fat-free mass, *LBM* lean body mass, *%BF* percentage body fat, *TBW* total body water

Table 110.7 Details and outcomes of studies assessing body composition with chromium picolinate supplementation

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Lukaski et al. (2007)	Randomised, double-blind	200 µg/day for 12 weeks	83 females Cr n = 27 Picolinic acid n = 27 Placebo n = 29	BM Skinfolds (sum of 4) FM, fat-free mineral-free mass (DXA)	No effect
Campbell et al. (2002)	Randomised, double-blind	924 µg/day for 12 weeks	17 older females (54–71 year) Cr n = 9 Placebo n = 8	BM Skinfolds (sum of 8) %BF and FFM (hydrodensitometry)	No effect
Livolsi et al. (2001)	Randomised, double-blind	500 µg/day for 6 weeks	15 division one female softball players	BM %BF and LBM (hydrodensitometry)	No effect
Volpe et al. (2001)	Randomised, double-blind	400 µg/day for 12 weeks	Cr n = 8 Placebo n = 7 37 sedentary females Cr n = 20 Placebo n = 17	BM Girths (hip and waist) %BF, FM and LBM (hydrodensitometry)	No effect
Amato et al. (2000)	Randomised, double-blind	1,000 µg/day for 8 weeks	19 older participants (63–77 year) (9 male, 10 female) Cr n = 9 Placebo n = 10	BMI FM and FFM (DXA)	No effect
Crawford et al. (1999)	Randomised, double-blind, crossover	600 µg/day for 2 months	20 females	BM FM and FFM (BIA)	Significant loss of fat and muscle sparing
Campbell et al. (1999)	Randomised, double-blind	924 µg/day for 12 weeks	18 older men (56–69 year) Cr n = 9 Placebo n = 9	BM Skinfolds (sum of 8) Girths (chest and midthigh) TBW (deuterium oxide) Body density (hydrodensitometry) Calculated two- and three-compartment models	No effect

(continued)

Table 110.7 (continued)

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Walker et al. (1998)	Randomised, double-blind	200 μg/day for 14 weeks	20 male wrestlers Cr $n = 7$ Placebo $n = 7$ Control $n = 6$	FM and FFM (hydrodensitometry) Skinfolds (9 sites) Girths (10 sites)	No effect
Grant et al. (1997)	Randomised, double-blind	400 μg/day for 9 weeks	43 healthy, obese young women Cr no ex. Cr + ex. Cr nicotinate + ex. Placebo + ex.	BM %BF, FM and FFM (hydrodensitometry)	No effect except significant BM ↑ in Cr no ex. and significant BM ↓ in Cr nicotinate + ex.
Lukaski et al. (1996)	Randomised, double-blind	3.3–3.5 μg/kg/day for 8 weeks	36 untrained males Cr picolinate $n = 12$ Cr chloride $n = 12$ Placebo $n = 12$	FM and FFM (DXA) Skinfolds (four sites)	No effect
Hallmark et al. (1996)	Randomised, double-blind	200 μg/day for 12 weeks	16 untrained males Cr $n = 8$ Placebo $n = 8$	BM %BF, LBM (hydrodensitometry) Skinfolds (9 sites) Girths (9 sites)	No effect
Clancy et al. (1994)	Randomised, double-blind	200 μg/day for 9 weeks	21 footballers Cr $n = 9$ Placebo $n = 12$	%BF, LBM (hydrodensitometry) Skinfolds (9 sites) Girths (20 sites)	No effect

This table shows research studies, which assessed the effects of chromium picolinate on body composition. The dose and duration of supplementation, population studied, anthropometrical methods utilised and main outcomes are indicated. The majority of studies indicate no effect of chromium on FM or FFM

BIA bioelectrical impedance analysis, *BM* body mass, *BMI* body mass index, *Cr* chromium picolinate, *DXA* dual energy X-ray absorptiometry, *ex.* exercise, *FM* fat mass, *FFM* fat-free mass, *LBM* lean body mass, *%BF* percentage body fat, *TBW* total body water

Table 110.8 Details and outcomes of studies assessing body composition with *Tribulus terrestris* supplementation

Authors	Study design	Dosage/ duration	Participants	Parameters assessed	Effect of supplement
Rogerson et al. (2007)	Randomised, double-blind	450 mg/day for 5 weeks	22 elite male rugby league players *Tribulus* $n = 11$ Placebo $n = 11$	BM FFM (BIA)	No effect
Antonio et al. (2000)	Randomised, double-blind	3.21 mg/kg/day for 8 weeks	15 resistance-trained males *Tribulus* $n = 8$ Placebo $n = 7$	BM %BF (hydrodensitometry) TBW (BIA) Skinfolds (sum of 7)	No effect

This table lists the few research studies available, which evaluate the effects of *Tribulus terrestris* on body composition. The dose and duration of supplementation, population studied, anthropometrical methods utilised and main outcomes are indicated. Both studies indicate no effect of *Tribulus terrestris* on any aspect of body composition
BIA bioelectrical impedance analysis, *BM* body mass, *FFM* fat-free mass, *%BF* percentage body fat, *TBW* total body water

was rarely used (Table 110.7). It would be of interest to assess changes in body composition in response to chromium picolinate supplementation using more sensitive anthropometric methodologies to confirm that this supplement does not affect body composition in healthy participants.

110.4.4 Anthropometric Methodologies Employed in Tribulus Terrestris Studies

Tribulus terrestris is a herbal supplement, which is claimed to increase circulating levels of luteinizing hormone and testosterone and therefore increase muscle mass (Rogerson et al. 2007). Although *Tribulus* has been marketed to athletes for some years, very few scientific studies exist, which investigate the efficacy of this supplement. Two double-blind, placebo-controlled studies that examined body composition showed no effect of *Tribulus* on FFM or %BF in trained individuals (Antonio et al. 2000; Rogerson et al. 2007; Table 110.8). These two studies employed BIA and hydrodensitometry to evaluate body composition (Table 110.8). Future research investigating the effect of *Tribulus* on body composition should employ the more sensitive anthropometric methodologies (e.g., four-compartment model using combined methodologies) with large sample sizes as these initial studies failed to detect any effect using BIA and hydrodensitometry.

110.4.5 Anthropometric Methodologies Employed in Ephedrine/Ephedra Studies

Ephedrine is a sympathomimetic drug which stimulates the release of catecholamines in the body (Bouchard et al. 2002). Ephedrine and its herbal equivalent, ephedra, are claimed to enhance sports performance and to reduce body fat via thermogenesis (see Table 110.9 for the key features of ephedrine). There is a lack of scientific evidence to support the use of ephedrine to enhance sports performance

Table 110.9 Key features of ephedrine

1. A sympathomimetic stimulant drug.
2. Sympathomimetics mimic the effects of sympathetic nervous system stimulation.
3. Sympathomimetics induce the fight-or-flight response and stimulate the central nervous system.
4. Claimed to enhance endurance exercise performance but lacks scientific evidence to support this claim.
5. Claimed to induce fat loss via thermogenesis (increased metabolic rate).
6. Sufficient scientific evidence exists to support the claim of fat loss, but only when supplemented in conjunction with caffeine.
7. Carries considerable health risks, with numerous reports of adverse health effects (including death) resulting from dietary supplementation.

The main features of ephedrine are listed including the mechanism by which it is thought to affect exercise performance and body fat, the main research findings and significant health risks associated with the use of ephedrine

(Bouchard et al. 2002). The majority of body composition studies investigated weight loss in response to ephedrine/ephedra combined with caffeine. Performing research on ephedrine or ephedra is difficult as a large number of adverse health effects, including death, have been reported (Bouchard et al. 2002). Sale of ephedrine-containing products was prohibited by the Food and Drug Administration in USA in 2004 due to the high number of adverse health reports. Hence, research into ephedrine is limited. Research is also hindered by the use of herbal preparations where the constituent ingredients are not independently verified. For example, Coffey et al. (2004) examined the effects of a herbal supplement containing caffeine and ephedrine on body weight and FM in obese individuals. The herbal preparation was evaluated by two independent laboratories and found to contain half the stated concentrations of caffeine and ephedrine. Haller et al. (2004) assayed 35 commercial products containing ephedrine alkaloids and reported that 31% of the products contained greater than 110% and 6% contained less than 90% of the stated concentration of ephedrine. Therefore, one of the limitations of ephedrine research is a lack of independently verified supplement doses, particularly where herbal preparations were investigated.

The few double-blind, placebo-controlled studies of ephedrine where body composition was assessed have, for the most part, employed BIA (Table 110.10). One study utilised DXA (Greenway and Bray 2004) and one ADP (Boozer et al. 2001; Table 110.10). All these studies supplemented ephedrine in combination with caffeine and studied obese individuals. Under these conditions, the selected anthropometric methodologies appear sufficiently sensitive to detect changes in body composition as the majority of the listed studies showed a significant decrease in %BF and/or FM with supplementation (Table 110.10). Two early studies which evaluated ephedrine without caffeine assessed body weight and did not evaluate changes in FM (Pasquali et al. 1985, 1992). Interestingly, ephedrine alone did not affect body weight in these studies. There is a lack of research into the effects of ephedrine alone on body composition, where changes in FM and FFM are ascertained. The majority of studies into ephedrine have used herbal preparations, which combine ephedrine and caffeine in the one powder or pill and therefore did not investigate ephedrine in isolation (Molnár et al. 2000; Boozer et al. 2001, 2002; Coffey et al. 2004; Greenway and Bray 2004). Research into the effects of ephedrine on FM would be enhanced by further research where ephedrine's effects on FM can be differentiated from those of caffeine. Future studies investigating ephedrine in combination with caffeine could effectively employ most of the available anthropometric methodologies. However, investigating ephedrine alone may require the more sensitive techniques given that changes in body mass have not previously been detected (Pasquali et al. 1985, 1992).

Table 110.10 Details and outcomes of studies assessing body composition with ephedrine/ephedra supplementation

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Coffey et al. (2004)	Randomised, double-blind, clinical trial	Herbal formula (ephedrine, caffeine and other ingredients): 60 mg/day ephedrine and 360 mg/day caffeine for 12 weeks	102 overweight/obese patients (14 male, 88 female) Herbal *n* = 52 Placebo *n* = 50	BM Waist girth BMI %BF, FM (BIA)	No effect on %BF or FM Significant ↓ in BM, waist girth and BMI
Greenway and Bray (2004)	Randomised, double blind	Herbal formula: 72 mg/day ephedrine and 210 mg/day caffeine for 12 weeks	40 participants (seven male, 33 female) Herbal *n* = 20 (12 completed) Placebo *n* = 20 (19 completed)	BM %BF, LBM (DXA)	Significant ↓ in BM and %BF No effect on LBM
Hioki et al. (2004)	Randomised, double blind	Herbal formula (bofu-tsusho-san): 24 mg/day ephedrine and 280 mg/day caffeine for 24 weeks	81 obese Japanese women Herbal *n* = 41 Placebo *n* = 40	BM W:H ratio %BF, abdominal visceral fat (BIA)	Significantly greater loss in BM and abdominal fat. No effect on %BF
Boozer et al. (2002)	Randomised, double-blind, clinical trial	Herbal formula: 90 mg/day ephedrine alkaloids and 192 mg/day caffeine for 6 months	Weight-control patients (outpatient clinic) Herbal *n* = 83 (46 completed) Placebo *n* = 84 (41 completed)	BM W:H ratio FM (BIA)	Significantly greater loss of BM and FM No effect on W:H ratio
Boozer et al. (2001)	Randomised, double blind	Herbal formula: 72 mg/day ephedrine and 240 mg/day caffeine for 8 weeks	Overweight men and women Herbal *n* = 24 Placebo *n* = 24	BM W:H ratio %BF (ADP)	Significantly greater loss of BM, %BF and hip and waist girths
Molnár et al. (2000)	Randomised, double blind	Weight-dependent dose: <80 kg – 300/30 mg/day C/E; >80 kg – 600/60 mg/day C/E for 20 weeks	29 obese adolescents (male and female) Ephedrine/caffeine n = 16 Placebo *n* = 13	BM BMI %BF (BIA)	Significant ↓ in BM, BMI and %BF
Breum et al. (1994)	Randomised, double blind. No placebo group	60 mg/day ephedrine and 600 mg/day caffeine or 30 mg/day dexfenfluramine for 15 weeks	Overweight patients Ephedrine/caffeine *n* = 38 Dexfenfluramine *n* = 43	BM	No difference between groups

(continued)

Table 110.10 (continued)

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Astrup et al. (1992)	Randomised, double blind	60 mg/day ephedrine and 600 mg/day caffeine for 8 weeks	14 obese women Ephedrine/caffeine $n = 7$ Placebo $n = 7$	BM FM, FFM (BIA)	No effect on BM loss Greater loss of FM and less loss of FFM

This table lists the research studies, which have evaluated the effects of ephedrine on body composition. The majority of these studies investigated ephedrine supplemented in combination with caffeine. The dose and duration of supplementation, population studied, anthropometrical methods utilised and main outcomes are shown. The majority of studies show significant reduction in FM and/or %BF in response to ephedrine/caffeine

ADP air displacement plethysmography, *BIA* bioelectrical impedance analysis, *BM* body mass, *BMI* body mass index, *C* caffeine, *DXA* dual energy X-ray absorptiometry, *E* ephedrine, *FM* fat mass, *FFM* fat-free mass, *LBM* lean body mass, *%BF* percentage body fat, *W:H ratio* waist-to-hip ratio

110.4.6 Anthropometric Methodologies Employed in L-Carnitine Studies

Carnitine is involved in fatty acid oxidation within muscle and may therefore alter substrate utilisation (see Brass 2000). More recently, L-carnitine-L-tartrate has been suggested to play a role in protein synthesis by stimulating gonadotrophin releasing hormone and preventing the fall in testosterone following intense resistance exercise (Kraemer et al. 2009). The main focus of L-carnitine research has been assessment of the effects on exercise performance. However, a small number of studies have investigated the effects of L-carnitine on body composition, primarily in overweight or obese individuals. The majority of these studies show no effect of carnitine on FM and FFM (Table 110.11), whereas one study reported positive effects of carnitine on FM and muscle mass in elderly participants, with rapid onset of fatigue (Pistone et al. 2003). Three of these four studies employed BIA to assess body composition (Table 110.11). Similar to other dietary supplements where previous research shows little or no effect on body composition, future research should employ the more sensitive anthropometric methodologies. Similar to ephedrine, independent assessment of supplement dose should also be performed as the stated carnitine content of a number of preparations has been found to be inaccurate (Brass 2000).

In conclusion, a wide variety of anthropometric methodologies have been employed in dietary supplement studies, with BIA, DXA and hydrodensitometry most popular. There does not appear to be any trend in the type of methodology used in studies where significant effects on body composition were detected or those where there were no effects. A wider variety of anthropometric methodologies has been used to evaluate changes in body composition in response to creatine monohydrate supplementation compared to the other supplements. However, this most likely reflects the greater number of studies available on creatine compared to the number available on other supplements. Creatine and ephedrine (combined with caffeine) appear to be the only two supplements of those reviewed which have consistent reports of significant effects on body composition. Therefore, future research into these two supplements could employ any of the available anthropometric methodologies. The remaining supplements do not have clear research evidence to support a significant effect on body composition. Therefore, future research into these supplements should employ the more sensitive of the anthropometric methodologies.

110.5 Validity and Reliability of Anthropometric Methods in Dietary Supplement Studies

Only a small number of studies have examined the validity and reliability of various anthropometric methods in relation to detecting change as a result of dietary supplementation (Vukovich and Peeters, 2003; Van Marken Lichtenbelt et al. 2004; Kilduff et al. 2007). The types of supplements investigated in these studies are limited and include creatine monohydrate (Vukovich and Peeters 2003; Kilduff et al. 2007) and androgenic-anabolic steroids (Van Marken Lichtenbelt et al. 2004), the latter of which are classified as drugs rather than dietary supplements. Furthermore, problems arise in selecting a criterion methodology by which the validity of other methods can be assessed. Until recently, hydrodensitometry was considered the gold standard of anthropometric methods. However, with the development of new techniques, particularly in the field of medical imaging, other methods such as DXA (e.g. Fornetti et al. 1999) and four-compartment models using combined methodologies (Van Marken Lichtenbelt et al. 2004) are now used. Interestingly, when the validity of DXA was assessed in comparison to a four-compartment model, the estimations of body fat were higher and

Table 110.11 Details and outcomes of studies assessing body composition with L-carnitine supplementation

Authors	Study design	Dosage/duration	Participants	Parameters assessed	Effect of supplement
Lofgren et al. (2005)	Randomised, double blind	3 g/day for 10 weeks	70 overweight/obese women Carnitine $n = 35$ Placebo $n = 35$	BM BMI, W:H ratio %BF, FM, LBM and trunk fat (DXA)	No effect
Wutzke and Lorenz (2004)	Repeated measures (not randomised)	4.5 g/day L-carnitine-L-tartrate equivalent to 3 g/day L-carnitine for 10 days (after 10 days supplied regular diet)	12 overweight participants (5 male, 7 female)	BM TBW, FM and LBM (BIA)	No effect
Pistone et al. (2003)	Randomised, double blind	4 g/day for 30 days	84 elderly participants with onset of fatigue Carnitine $n = 42$ Placebo $n = 42$	FM, FFM (BIA)	Significant ↑ in muscle mass & ↓ in FM
Villani et al. (2000)	Randomised, double blind	4 g/day for 8 weeks	28 moderately overweight females Carnitine $n = 13$ Placebo $n = 15$	BM Skinfolds (four sites averaged) FM, FFM (BIA)	No effect

This table shows research studies, which assessed the effects of l-carnitine on body composition. The dose and duration of supplementation, population studied, anthropometrical methods utilised and main outcomes are indicated. The majority of studies indicate no effect of l-carnitine on FM or FFM

BIA bioelectrical impedance analysis, *BM* body mass, *BMI* body mass index, *DXA* dual energy X-ray absorptiometry, *FM* fat mass, *FFM* fat-free mass, *LBM* lean body mass, *%BF* percentage body fat, *W:H ratio* waist-to-hip ratio

the error relatively high compared with other methodologies such as hydrodensitometry and deuterium dilution (Van Marken Lichtenbelt et al. 2004). This shift away from hydrodensitometry as the gold standard of anthropometric methodologies generates a need for further research into suitable criterion methods for body composition assessment.

Kilduff et al. (2007) investigated the ability of different anthropometric methodologies to detect changes in body composition as a result of acute creatine monohydrate supplementation. Five two-compartment methodologies were employed including hydrodensitometry, ADP, BIA, NIR and anthropometry (assessment of seven skinfold sites). Initially, the reliability of each method was assessed using 55 volunteers, who were assessed twice, 7 days apart. This was immediately followed by 7 days' creatine monohydrate supplementation by 30 of the original 55 volunteers, using a standard loading dose (20 g per day). Body composition was again assessed at the end of the supplementation period using all five methodologies. Kilduff et al. (2007) reported high reliability of the five methodologies investigated with test–retest correlations ranging from 0.983 to 0.998. Although the 95% limits of agreement were within acceptable ranges for all five methods, the anthropometry method had the widest values (-2.4 to 2.6 kg FFM). The other methods had limits of agreement ranging from -1.4 to 1.7 kg FFM. Interestingly, all five methodologies detected the change in FFM due to creatine supplementation, indicating that any of these methods would be suitable to assess body composition changes with creatine supplementation. Others have also shown that ADP can detect changes in body mass and FFM following acute creatine monohydrate supplementation (Vukovich and Peeters 2003). Creatine is well known to cause a rapid increase in body mass, although the source of this increase in terms of FFM versus water retention is still under discussion (Lopez et al. 2009). Therefore, one would expect a significant effect size for creatine with regard to body composition. Indeed, Branch (2003) performed a meta-analysis examining the effect of creatine on body composition and reported a small but significant effect of creatine on body mass and lean body mass (mean ± SE effect size = 0.17 ± 0.03). The results of Kilduff et al. (2007) support this finding that creatine has significant effects on body composition, with all five methodologies investigated revealing significant increases in FFM. As was discussed above, creatine is one of the few dietary supplements consistently reported to have significant effects on body composition. Therefore, one cannot assume that the five anthropometric methodologies evaluated by Kilduff et al. (2007) would be equally as effective in detecting changes in body composition due to consumption of other dietary supplements such as HMB, chromium, or L-carnitine as past research shows little or no effect of these supplements on body composition.

Van Marken Lichtenbelt et al. (2004) assessed the validity of a number of anthropometric methodologies in comparison to a four-compartment criterion method using bodybuilders. The four-compartment model included a combination of deuterium dilution to assess total body water, DXA to assess total bone mineral content and hydrodensitometry to assess body density. This study also assessed the ability of the different methodologies to detect changes in body composition as a result of 8 weeks' strength training combined with androgenic-anabolic steroid use. Comparison of body composition assessment to the four-compartment criterion method showed that the largest errors were obtained from descriptive methods of body composition assessment including DXA and prediction equations based on BMI, skinfolds and BIA. The authors recommended avoiding these descriptive methodologies to assess changes in body composition in this population. The smallest error was associated with the three-compartment model incorporating total body water (derived via deuterium dilution). Interestingly, when changes in body composition as a result of training and steroid use were evaluated, large biases and large errors were associated with the BMI and BIA methods. The three-compartment model incorporating body water was again the best method when compared to the four-compartment model. However, it should be noted that the average decrease in percentage body fat (%BF) as a result of the training and steroid intervention was only small (1.2%). With such small changes in body

composition, the authors recommended that only the three-compartment water model was sensitive enough to detect changes. These authors also noted the importance of hydration status with the difference between the two- and four-compartment models mainly being attributed to changes in the hydration of the FFM. Given that hydration status can vary widely as a result of exercise and that dietary supplementation most often occurs in conjunction with exercise training, hydration status should be controlled for when assessing body composition changes with dietary supplementation.

Often, dietary supplements are tested on athletes or evaluated in combination with an exercise-training regime. It is therefore of relevance to examine the reliability of literature for anthropometric methods assessed in athletes or other populations undergoing training. Fornetti et al. (1999) examined the validity and reliability of BIA and NIR in comparison to DXA in female collegiate athletes. The study included a good sample size of 132 female athletes. The intraclass correlation coefficients for two trials performed on each participant showed high reliability for both BIA (0.993 and 0.997 for reactance and resistance, respectively) and NIR (0.978 and 0.980 for two optical density measures). Correlations of BIA and NIR with DXA were high and prediction errors were low (approximately 1.8% when values were converted to %BF). Thus, the authors concluded that both BIA and NIR were highly reliable and valid techniques for determining body composition in female athletes. Nelson et al. (1996) also examined female participants but of an older age group (50–70 years) and untrained. The sensitivity of various anthropometric methods to detect changes in soft tissue following 12 months' resistance training was examined. The anthropometric methods investigated included anthropometry (six skinfolds and five girths), BIA, hydrodensitometry, CT, DXA, 24-h total urinary creatinine, total body potassium from potassium-40 counting, total body nitrogen and carbon and tritium dilution. Interestingly, only hydrodensitometry detected the decrease in FM in the strength-trained females ($n = 20$) in comparison to the control group ($n = 19$). DXA, which, as mentioned above, has been utilised as a criterion method in other studies such as Fornetti et al. (1999), failed to detect the change in FM. However, one of the limitations of this study was that participants were required to remain weight stable within 1 kg for the 12-month duration of the training program to comply with a concurrent study. Although the resistance-training program was designed to elicit increases in muscle mass (three sets of eight repeats at 80% 1RM), the constraint on weight gain must be viewed as a limitation in terms of evaluating the ability to detect changes in body composition.

In conclusion, there is a lack of research into the validity and reliability of various anthropometric methods to detect body composition changes in response to either dietary supplementation or exercise training. Studies show that commonly used anthropometric methods have high reliability (Fornetti et al. 1999; Kilduff et al. 2007) and are sufficiently sensitive to detect changes in body composition as a result of creatine monohydrate supplementation (Vukovich and Peeters 2003; Kilduff et al. 2007). However, validity studies are not so positive, with large errors and biases associated with some anthropometric methods when compared to a four-compartment model (Van Marken Lichtenbelt et al. 2004). It is interesting that DXA is sometimes used as the criterion or reference method in validity studies (e.g. Fornetti et al. 1999). However, the results of Van Marken Lichtenbelt et al. (2004) question the validity of DXA. With the development of new imaging technology, the field of anthropometry requires greater numbers of validity studies and a thorough investigation of an appropriate criterion method.

110.6 The Influence of Hydration Status on Body Composition Assessment

It is important to consider the influence of hydration status on body composition as dietary supplements are often evaluated in conjunction with exercise testing and training. Exercise can alter body fluid distribution with plasma movement into interstitial spaces and possible sweat losses. In order to minimise

changes in hydration status, body composition assessment should be performed prior to any exercise testing. Attempts should also be made to standardise fluid intake in the 12–24 h prior to body composition assessment. Minimising changes in body fluid prior to body composition assessment is more important for certain anthropometric methodologies than others. For example, BIA has been reported to underestimate %BF when the participants are dehydrated and to overestimate %BF with rehydration or superhydration (Saunders et al. 1998). Hydration status can also influence measurements from ADP as was shown by Vukovich and Peeters (2003), where ingestion of 2 l of water was registered as an increase in FM rather than FFM values. By contrast, hydrodensitometry (Saunders et al. 1998) and DXA (Lohman et al. 2000) have been reported to be stable with different states of hydration. Thus, researchers should try to minimise changes in hydration status prior to assessing body composition when using methodologies, such as BIA and ADP.

110.7 Applications to Other Areas of Health and Disease

The type of anthropometric methodology selected when investigating the effects of dietary supplements on body composition can affect the ability to detect change. If the supplement is known to have significant effects on body composition, such as creatine monohydrate, then the choice of anthropometric methodology is unlikely to affect the ability to detect change. However, anthropometric methodology should be carefully selected, if past research shows little or no effect of the supplement on body composition. Similarly, in other areas of health and disease, the effect of an intervention on body composition should be evaluated using an appropriate methodology based on the effect size from past research. Where little previous research exists, it is recommended that researchers utilise the more sensitive anthropometric methodologies and larger sample sizes. A further consideration for assessment of body composition is that altered states of hydration can affect body composition estimations. For example, BIA and ADP estimations of %BF and FFM are altered by hydration status, whereas hydrodensitometry and DXA show less variation due to hydration status. Certain medications and disease states, such as cardiovascular disease and chronic obstructive pulmonary disease, also alter hydration status and the methodology used for assessing body composition in these cases should be carefully selected.

Summary Points

- Many dietary supplements reportedly alter body composition.
- Accurate assessment of body composition is necessary to detect changes due to dietary supplementation.
- Selection of anthropometric methodology should consider measurement factors (reliability, validity, accuracy and sensitivity), statistical effect size, ethical factors and practical considerations.
- Practical constraints, such as funding, accessibility and time available may limit selection of the most appropriate anthropometric techniques.
- Many dietary supplements claim to alter body composition; however, only a small number of these supplements have sufficient double-blind, randomised, placebo-controlled research to evaluate their effectiveness.
- Of the six dietary supplements reviewed in this chapter, only creatine monohydrate and ephedrine (in combination with caffeine) show consistent significant effects on body composition.
- The majority of recent studies into the reviewed supplements utilise BIA, DXA or hydrodensitometry to assess body composition, with a smaller number using ADP.

- Skinfolds are still commonly assessed, but are usually performed in conjunction with other anthropometric methods.
- Creatine monohydrate has been investigated with a wide variety of anthropometric methodologies.
- Methodologies including hydrodensitometry, ADP, BIA, NIR and skinfolds have all been shown to detect changes in FFM in response to creatine supplementation.
- Research investigating body composition changes with chromium picolinate, HMB, *Tribulus terrestris* or l-carnitine consistently show little or no effect. Therefore, future research into these supplements should employ the more sensitive anthropometric methodologies, such as those based on three- or four-compartment models.
- Few studies investigate the reliability and validity of anthropometric methods for detecting changes in body composition due to dietary supplementation.
- When supplements are known to have marked effects on body composition, most anthropometric methods are sufficiently sensitive to detect change. However, where effects on body composition are only minor, more sensitive methods are required.
- As hydration status affects assessment of body composition, research investigating change in body composition should try to limit changes in body hydration or control for these changes, particularly with methodologies such as ADP and BIA.

Key Features

Table 110.12 Key facts and features of anthropometry and the response to dietary supplementation in exercise

Validity, reliability, accuracy and sensitivity of anthropometric methodology are important in dietary supplementation studies.
Few studies examine the validity and reliability of various anthropometric methodologies to detect change in body composition as a result of dietary supplementation.
The expected size of the effect of the dietary supplement on body composition will determine the most appropriate anthropometric methodology to be used.
Meta-analyses are good sources of information to determine expected effect sizes.
Supplements with demonstrated significant effects on body composition can be investigated with most anthropometric methodologies, whereas supplements which show small or negligible effects require the more sensitive methodologies.
Practical considerations, such as cost, accessibility and time available, will also influence choice of anthropometric methodology.
A wide variety of anthropometric methodologies have been utilised in recent investigations into the most commonly used dietary supplements including creatine monohydrate, HMB, chromium picolinate, *Tribulus terrestris*, ephedrine and L-carnitine.
The most commonly utilised anthropometric methodologies to assess body composition in dietary supplement studies include BIA, DXA and hydrodensitometry.
Past research shows significant effects of creatine monohydrate and ephedrine (combined with caffeine) on body composition. However, past research into other commonly used supplements has failed to show significant effects on body composition.
Alterations in hydration status, which are often associated with exercise and exercise testing, should be minimised so as not to influence assessment of body composition.

This table summarises the important points to consider when selecting and executing anthropometric assessments of body composition in response to dietary supplementation. A summary of the main anthropometrical findings of research into six of the most popular dietary supplements is also included

BIA bioelectrical impedance analysis, *DXA* dual energy X-ray absorptiometry, *HMB* β-hydroxy-β-methyl butyrate

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Chapter 111
Anthropometry in Premenarcheal Female Esthetic Sports Athletes and Ballerinas

Marjeta Misigoj-Durakovic

Abstract Body size and build influences performance in many sports, especially in those pertaining to the group of female esthetic sports like artistic gymnastics, rhythmic gymnastics and figure skating. These sports pose high specific demands upon the functional, energy, motor and psychological capacities of athletes; but also upon the size, body build and composition of the performers, particularly of elite level females. Similar can be seen in ballet, an artistic theatrical expression of dancing. Contrary to the majority of other sports, morphological predispositions for esthetic sports, rhythmic gymnastics in particular, and ballet are similar: a smaller size and body mass of female performers. Ballet and the group of esthetic sports are specific also because regular serious workouts begin early at the pre-school age and very soon the nature of training programs can be described as of high intensity, high frequency and long duration with the eventual demands of maintaining minimal amounts of subcutaneous body fat. The maintenance of the indispensable anthropometric characteristics and body composition over the years of training and competition frequently determine the kind of diet with a reduced energy intake.

Expectedly, ballerinas and female athletes in esthetic sports mostly belong to the group of late-maturing girls. Namely, body linearity, or slimness, is connected with later maturation. However, there is still an ongoing debate whether a long-lasting, high-volume and intense, early commenced training in gymnastics, along with modified nutrition, which does not follow the energy demands of the training process, may in some girls jeopardize growth and provoke later sexual maturation. In adolescence, female esthetic sports athletes have lower values of body mass index and a body fat percentage with adequate fat-free mass in comparison to non-athletes and female athletes in other sports. Such a body build and composition, typical for the premenarcheal aged girls, particularly artistic gymnasts contributes to the increased strength/weight ratio, stability and a decrease in the moments of inertia (Borms, J and Caine, DJ, In: Sands WA, Caine DJ, Borms J, editors. Scientific aspects of women' gymnastics. Medicine and sport science 45. Borms J, Hebbelinck M, Hills AP, editors. Karger, Basel. p. 110–127, 2003), thus improving the execution of the demanding elements, but also the esthetic impression of performance.

Fat percentage and endomorphy ratings are connected to the performance of esthetic female athletes as well as with the incidence and duration of recovery after injury in ballet dancers. A careful follow-up of the anthropometric characteristics in this group of female athletes and ballerinas,

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_111,

besides any information relevant to the monitoring of training program effects, will give an insight into the dynamics of growth and nutritional state of young athletes.

Abbreviations

ANOVA	Univariate analysis of variance
BMI	Body mass index
% BF	Proportion (percentage) of body fat
CA	Chronological age
M-RG	Menarcheal rhythmic gymnasts
PM-RG	Premenarcheal rhythmic gymnasts
SD	Standard deviation
X ± SD	Arithmetic mean ± standard deviation

111.1 Introduction

Morphological anthropometric measures are well researched in kinesiology and used in sports in the process of selecting male and female athletes for certain sporting branches, and also in the evaluation of training effects. In the selection, the measures of body size, particularly those of the longitudinal skeleton dimensions, are crucial due to their predominant heredity-like nature. In order to control the sports training effects, the measures of body parts' circumferences, body mass and skinfolds are monitored, as are the components of body composition: the proportions of body fat (% BF) and fat-free mass – the measures being sensitive to environmental influence and therefore changeable under the impact of various types, volumes, and intensities of training programs and modifications of the athletes' diet.

111.1.1 The Contribution of Anthropometrics to Performance in Esthetic Sports

Literature describes desirable model characteristics of top athletes in the form of basic anthropometric dimensions, their interrelations (ratios, i.e., indics), body composition components, and somatotypes (mostly using the Heath–Carter somatotyping method).

It has already been well documented that body size and body build contribute significantly to performance in many sports, particularly in esthetic sports and all kinds of dancing. Within the group of the so-called female esthetic sports, the most demanding sports are: artistic gymnastics, rhythmic gymnastics, and figure skating. These are sports that pose high specific demands upon functional and energy capacities and require athletes to have highly developed motor and psychological abilities and specific traits. These disciplines also impose high demands upon the body size, build, and composition of the performers, particularly of elite female athletes. Much the same can be seen in ballet, an artistic theatrical expression of dancing.

Studying the contribution of anthropometrics to a performance score in a sample of top female gymnasts competing at the World Championship in Artistic Gymnastics, Claessens et al. (1999) found that about 32–45% of the variances in the gymnastic performance score were explained with

the anthropometric dimensions and/or derived variables. Moreover, in the investigation of leaping ability, anthropometric dimensions, and body composition in rhythmic gymnasts for talent identification purposes, Di Cagno et al. (2008) found certain anthropometric measures, such as body height, thigh length, and fat-free mass, to be good predictors of a better performance.

Average body height and mass of female athletes in many sports, as in sports games, swimming, or tennis, to mention a few, corresponds to or is often above the median value of the average non-trained peer population of girls. Body mass of female athletes is characterized here with a higher fat-free mass and a lower contribution of fat in comparison to the average non-trained population.

However, in the group of esthetic sports, track disciplines of long-distance running and ballet, but especially in gymnastics, the key advantage is a smaller body size with a considerably reduced portion of fat in body composition and performance-related adequate fat-free mass in female athletes.

111.1.2 Specific Demands of Esthetic Sports and Ballet

Ballet and the group of esthetic sports are specific also because serious workouts begin early at the preschool age and, very soon, the nature of training programs can be described as: high intensity, high frequency, and long duration, with the eventual demands of maintaining minimal amounts of subcutaneous body fat. Dance and esthetic sports include, besides the technical value of performing movements with the body and apparatuses, also an artistic value, that is, the performance of movements should make an enchanting impression on the spectators, in accord with the music. Particularly due to the latter, female performers in esthetic sports strive for slimness and low body mass. This is even truer for ballerinas, for whom the artistic expression and magical impression of illusion and perfection that they make on their audience is everything. Already, at the age of 5 and 7, girls in esthetic sports pay more attention to their own body mass than female athletes in other sports and girls who are not engaged in sports (Davison et al. 2002). This is so because final performance grade in esthetic sports, as well as good performance in ballet, is based upon the judges' subjective evaluation of success in performing the assigned or compulsory elements and upon the esthetic impression, to which body shape contributes as well.

Hence, it is quite clear that the requirements for smaller body size with a low portion of fat and adequate fat-free mass condition the selection of girls for the mentioned sports and ballet, according to morphological criteria. The maintenance of the indispensable anthropometric characteristics and body composition over the years of training and competitions frequently determines the kind of diet with a reduced energy intake, and also with an altered intake of certain nutrients (Ziegler et al. 2002), and sometimes with other weight control measures, as shown in female figure skaters aged 16–22 years by Taylor and Ste-Marie (2001). The consequence is that nutritional habits of female athletes in esthetic sports often do not follow the actual energy demands posed by the high volume and intensity of training programs (Guerra et al. 2001).

Ballerinas and female athletes in esthetic sports mostly belong to the group of late-maturing girls (Vadocz et al. 2002; Thomis et al. 2005). It is expected since body linearity, or slimness, is connected with later maturation. However, there is still an ongoing debate whether or not a long-lasting, high-volume, and intense, early commenced training in gymnastics, along with modified nutrition, which does not follow the energy demands of the training process, may in some girls jeopardize growth and induce later sexual maturation (Theintz et al. 1993; Lindholm et al. 1994; Damsgaard et al. 2000; Caine et al. 2001; Georgopulos et al. 2002; Thomis et al. 2005).

Female artistic gymnastics is a well-investigated sport from the kinesiological, anthropological, nutritional, and health-related aspects (Claessens et al. 1992, 1999; Theintz et al. 1993; Lindholm

et al.1994; Damsgaard et al. 2000; Caine et al. 2001; Georgopulos et al. 2002; Sands et al. 2003; Thomis et al. 2005), where issues related to anthropometry, such as growth and maturation, eating disorders, talent selection, and early started training programs were in focus. In the last decade, the number of studies dealing with these aspects of scientific research in rhythmic gymnastics, figure skating, and ballet has been growing (Lockwood and Gervais 1997; Georgopulos et al. 1999, 2002; Guerra et al. 2001; Taylor et al. 2001; Oleson et al. 2002; Vadocz et al. 2002; Ziegler et al. 2002; Klentrou and Plyley 2003; Misigoj-Durakovic et al. 2005).

Although with regard to dance structures and from the esthetic point of view they show certain similarities, each of the mentioned sporting/artistic disciplines imposes very specific motor and energy supplying requirements upon the performers.

Female artistic gymnastics is a highly demanding sport for young athletes. Training is characterized by high-volume and high-impact loading and requires high self-discipline and motivation to perform endless skill repetitions. Female gymnasts compete in four events: vaults, uneven bars, balance beam, and floor exercise. They perform short routines up to 90 s of duration, depending on the competition event; routines consist of the performance of a large number of skills and movement structures, from vaults to swings, release moves, pirouettes, and dismounts on uneven bars; jumps, leaps, turns, handstands, acrobatic skills, and dance elements on a beam; and series of jumps, leaps, hops, turns, rolls, handstands, somersaults, acrobatic skills, and dance elements harmonized with instrumental music in floor exercise, just to mention some. These events require a highly developed energy supply and motor abilities, particularly strength - with high strength-to-body mass ratio, flexibility, and balance.

The basic motor structures of body movement in rhythmic gymnastics – the youngest sport in this group, are: leaps, pivots, balances, and flexibility/flowing movements. Rhythmic gymnasts also perform a series of supported and unsupported jumps, swings and body rotations, turns and various body shifts. They connect elements between the basic elements performed as the "loads" of various degrees. The specificity of rhythmic gymnastics in the group of esthetic sports is the apparatus manipulation (ribbon, ball, rope, clubs, and hoop). The shape of an apparatus determines the movements to be made with it. In rhythmic gymnastics, the anaerobic energy system fulfills high energy demands (for speed, explosive strength, etc.) in the short period of a minute and a half of one competition routine. With breaks, each competitor has to perform four high-intensity exercises. Due to that, and also because of the training programs system performed at various intensity levels, it is essential for female rhythmic gymnasts to develop optimally both systems of energy supply – aerobic and anaerobic alike.

Similar demands upon morphological and functional (energy supply) characteristics of female dancers are posed by ballet, but with certain specificities, particularly in relation to rotation and leg positions in performing dance movements and with characteristic compulsory figures (such as grand jeté, pirouette, plié, arabesque…).

Figure skating, which uses ballet and other kind of dance movements, has specific demands as it abounds in running starts, powerful take-offs, jumps (mostly with rotation), multi-revolution jumps, fast and multiple rockers and figures, with landings with skates on the ice or landing backward on a single leg on the ice (Lockwood and Gervais 1997). Figure skating develops and demands great aerobic strength.

111.2 Body Size and Proportions

Contrary to the majority of other sports, the morphological predispositions for esthetic sports and ballet are: small size and body mass of female performers. For gymnastics, young girls of a smaller and petite constitution are selected. Before a systematic training has commenced, one looks for a

small body size. One of the selective factors is also the parents' body size. Studying the effect of genetic factors, birth weight, growth during early childhood, sport, training volume, and pubertal status on the stature and body mass index of male and female athletes aged 9–13 years competing in swimming, tennis, handball, and gymnastics, Damsgaard et al. (2000) concluded that prepubertal growth is not adversely affected by competitive sport activity.

In adolescence, not surprisingly, female performers in esthetic sports have significantly lower values of body mass index (BMI) and percentage of body fat in comparison to their peers who are not engaged in sports (Guerra et al. 2001; Klentrou and Plyley 2003; Soric and Misigoj-Durakovic 2008).

111.2.1 Young Female Artistic Gymnasts

Thus, young female gymnasts are smaller and lighter in comparison with the control groups of girls engaged in other sports and with those not engaged in sports at all, with whom they have been compared in many investigations or in relation to reference values in the general peer population (Claessens et al. 1992; Theinz et al. 1993; Malina 1994; Lindholm et al. 1993; Georgulopulos et al. 2002; Erlandson et al. 2008; etc.). Their height and mass are under the 50th percentile (Lindholm et al. 1994; Georgulopulos et al. 2002; Soric and Misigoj-Durakovic 2008). In the study by Claessens et al. (1992), it was shown that elite female gymnasts compared with non-athletes also have narrower shoulders and hips, but they have proportionally broader shoulders relative to their hips. They do not differ from the non-athletes in relative leg length measures. Female gymnasts are also smaller in comparison to female athletes in other esthetic sports, such as rhythmic gymnastics (Georgopoulos et al. 2002; Soric and Misigoj-Durakovic et al. 2008), and in relation to the premenarcheal ballerinas (Soric and Mišigoj-Durakovic 2008) (Fig. 111.1).

Female performers in these sports often have later maturation (Claessens et al. 1992; Theinz et al. 1993; Lindholm et al. 1993; Erlandson et al. 2008; Klentrou and Plyley 2003). In the study by Erlandson et al. (2008), it was shown that elite-level female gymnasts in comparison to other elite female athletes in other sports, such as swimming and tennis, are significantly smaller during adolescence in each chronological age, whereas menarche onsets considerably later. During adolescence, the differences in body proportions, that is, the following ratios: standing height to sitting height measures, leg length to standing height measures, sitting height to leg length measures, between female gymnasts and female swimmers and tennis players do not exist. Significant differences in body height between gymnasts and swimmers and tennis players in adult age have not been found (Erlandson et al. 2008).

In a study of maturity-associated variation in the body size and proportions of elite female gymnasts, it has been shown that the elite premenarcheal gymnasts, the participants of the 24th World Championship in Artistic Gymnastics, Rotterdam, aged 14–17 years, had smaller body dimensions (body height, mass, sitting height, and bi-acromial and bicristal breadths) in all chronological age (CA) groups in relation to postmenarcheal gymnasts, although the significance of the differences among the groups varied (Table 111.1) (Claessens et al. 2006).

According to Lindholm et al. (1993), and later also to Georgopoulos et al. (2002), some female artistic gymnasts do not reach the height in adult age expected on the basis of their parents' height. In the study by Georgopoulos et al. (2002), it was reported that the female artistic gymnasts, in contrast to the female rhythmic gymnasts, followed a growth pattern that was lower than their predicted genetic predisposition. Caine et al. (2001) performed an extensive research of the data on growth and height of female gymnasts published in previous literature and concluded that, in

Fig. 111.1 Young female artistic gymnast. A young female gymnast performing a demanding skill on the balance beam, one of the four competition events in women's artistic gymnastics. The photograph provided by courtesy of the photographer Mr. R. Brandjolica

some gymnasts, attenuated growth during the years of intensive training and competition could be seen, followed during the period of lessened or ceased training (after retirement) by the catch-up growth.

How much smaller body size is desirable? A secular trend has been found in premenarcheal top-level female gymnasts toward ever smaller height and body mass (Borms and Caine 2003). Such a body build, characteristic for the premenarcheal age in girls, contributes to the increased strength/weight ratio, stability, and a decrease in the moments of inertia (Borms and Caine 2003), thus improving the execution of demanding elements, and also the esthetic impression of performance. The average height of female gymnasts at the Tokyo Olympic Games in 1964 was 157 cm (Carter 1984) and, at the 2000 Olympics in Sydney, it was 152 cm (Borms and Caine 2003). The average height of female gymnasts who won medals at the 2008 Olympics in Beijing was about 150 cm. One-third of the medalists were of Asiatic ancestry (based on the data retrieved on June 29, 2009, from the address: http//www.nbcolympics.com/gymnastics/index.htlml).

Table 111.1 Anthropometric characteristics of female gymnasts of contrasting maturity status within chronological age groups (Claessens et al. 2006) (With kind permission from Springer Science + Business Media: Claessens et al. 2006, Table 1, p.186. Copyright July 2009)

	Pre-menarcheal		Post-menarcheal					
	Group 1		Group 2		Group 3			
			Skeletally not mature		Skeletally mature			
Age group	Mean	SD	Mean	SD	Mean	SD	F ratio, group comparisons	Reference means[a]
Body mass (kg)								
14+	40.5	5.2	45.8	5.1	48.8	5.4	8.28*, 3>1	51.2
15+	42.0	5.3	45.4	4.8	47.9	5.9	4.27*, 3>1	53.8
16+	42.7	5.8	50.1	4.2	49.4	4.6	6.11*, 3,2>1	54.6
17+	44.6	4.8	45.4	6.7	50.9	5.3	4.86*, 3>1	56.2
Stature (cm)								
14+	150.6	5.8	152.2	3.4	155.5	5.3	2.13	161.7
15+	152.6	6.3	156.5	5.5	153.2	5.9	1.21	163.0
16+	154.1	6.1	157.9	6.5	157.2	6.1	0.89	163.4
17+	153.8	8.7	156.0	7.9	158.1	4.5	1.28	164.0
Sitting height (cm)								
14+	79.1	3.5	79.3	2.7	83.2	3.1	3.82*, 3>2,1	85.1
15+	79.7	3.8	82.4	2.8	82.7	1.9	3.64*, 3>1,	86.2
16+	80.8	3.2	82.9	2.6	84.4	3.3	3.40*, 3>1,	86.5
17+	80.3	4.7	81.4	5.0	83.9	3.3	3.03	87.1
Estimated leg (subischial) length (cm)								
14+	71.5	3.5	72.9	1.4	72.3	3.4	0.69	76.6
15+	72.9	3.1	74.1	3.7	70.5	4.5	2.30	76.8
16+	72.8	3.8	75.0	4.8	72.8	3.2	0.83	76.9
17+	73.6	3.8	74.6	3.2	74.2	2.4	0.10	76.9
Sitting height/stature ratio (%)								
14+	52.5	1.3	52.1	0.9	53.5	1.2	2.54	52.6
15+	52.2	1.0	52.7	1.3	54.0	1.3	8.36*, 3,2>1	52.8
16+	52.6	1.3	52.5	1.4	53.7	0.7	4.94*, 3>1	52.9
17+	52.2	0.9	52.1	0.9	53.1	1.1	4.85*, 3>1	53.1
Biacromial breadth (cm)								
14+	32.8	1.8	33.0	1.2	33.7	2.0	0.59	34.5
15+	33.5	2.0	34.0	1.9	34.1	1.6	0.45	35.0
16+	33.0	1.9	34.7	1.1	34.4	1.5	3.18*, 2,3>1	35.1
17+	34.1	1.6	32.8	2.2	34.5	1.5	3.38*, 1,3>2	35.2
Bicristal breadth (cm)								
14+	23.1	1.1	24.1	0.9	24.6	1.5	5.71*, 3>1	26.1
15+	23.9	1.6	24.9	1.8	24.9	1.0	1.82	26.6
16+	23.5	1.4	25.0	1.4	25.6	1.2	7.07*, 3,2>1	26.8
17+	23.8	1.3	24.9	1.4	25.4	1.5	2.74	27.1

*$p < 0.05$

[a]Reference data are from a nationally representative sample of Belgian (Flemish) girls (Simons et al. 1990)

Source: Premenarcheal gymnasts were significantly lighter than postmenarcheal skeletally mature gymnasts in all chronological age (CA) groups. They were the shortest within each CA groups but the differences were not significant. They also had the smallest sitting height - the differences were significant at CA 14–16, and the smallest estimated leg length; however, the differences were not significant. Premenarcheal gymnasts had a slightly smaller biacromial and bicristal breadth, but the differences were significant at CA of 14 for biacromial and at CA of 16 for both measures. The ratio of sitting height to standing height was the highest in skeletally mature postmenarcheal gymnasts. The differences between premenarcheal and skeletally mature gymnast were significant at CA 15–17 (Claessens et al. 2006).

111.2.2 Young Female Rhythmic Gymnasts

In addition to the female artistic gymnasts, rhythmic gymnasts have a lower body mass index in relation to the control groups (Guera et al. 2001; Klentrou and Plyley 2003; D'Alessandro et al. 2007; Soric and Misigoj-Durakovic 2008). Among the Spanish female Olympic athletes, the lowest body mass index belonged to the rhythmic gymnasts (Capdevila et al. 2005).

Klentrou and Plyley (2003) observed in the samples of the Canadian and Greek female rhythmic gymnasts that the premenarcheal gymnasts (PM-RG) were significantly shorter and lighter in comparison to the postmenarcheal (M-RG) peer gymnasts, having a lower BMI and proportion of body fat (% BF). The former trained significantly longer per day and more frequently during a week.

Rhythmic gymnasts are taller (above the 50th percentile for their age; Georgopulos et al. 1999, 2001; Misigoj-Durakovic et al. 2005) than their peer female artistic gymnasts, although having a relatively low mass for their age (under the 50th percentile) (Georgopulos et al. 1999, 2001).

In a sample of 255 European rhythmic gymnasts participating in the 13th European Championships in Greece, Georgopulos et al. (1999) established a positive correlation of the height standard deviation (SD) score with the weight SD score (height and weight were, for statistical evaluation purposes, expressed as the SD score of the mean height and weight for age), the number of competitions, and body mass index. The predicted height SD score in adulthood was positively related to the weight SD score and negatively to body fat. The average year of menarche onset was significantly delayed in comparison to their mothers and sisters, and was positively related to the intensity of training and to the difference between the chronological and skeletal age, but negatively to the body fat of rhythmic gymnasts (Georgopulos et al. 1999). In later studies by Georgopulos et al. (2001, 2002), it was found that the delayed skeletal maturation found in female rhythmic gymnasts was compensated for by the accelerated linear growth and it even surpasses the predicted height in adulthood. The deterioration of growth, described in the samples of female artistic gymnasts, was not present in rhythmic gymnasts (Georgopulos et al. 2002) (Fig. 111.2).

111.2.3 Young Female Figure Skaters

The same has been found for female figure skaters. They belong to the group of girls with similar characteristics who have been included into relatively high-volume training process early in their childhood. They are lighter and thinner than female athletes in other sports, also with a pronounced control of their own body mass (Taylor and Ste-Marie 2001), a lower energy intake, and an inadequate intake of particular nutrients (Ziegler et al. 1999, 2002). Later maturation is also characteristic for female figure-skating competitors, particularly the elite ones (Vadocz et al. 2002). The features of their training loads are running starts, powerful take-offs, jumps with rotation, double and triple jumps, as well as landings with skates on the ice, which contributes to expressed density of their bones (Slemenda and Johnston 1993; Oleson et al. 2002). The demands of figure-skating training programs are reflected in the body dimensions of female skaters aged 10–11 years, who are more voluminous in comparison to the other female athletes in esthetic sports and ballerinas (circumferences of the upper and lower extremities). Skaters also have a more robust skeleton of the lower extremities (Tables 111.2 and 111.3) (Misigoj-Durakovic et al. 2005).

Fig. 111.2 Young rhythmic gymnast. A young female rhythmic gymnast performs a demanding skill manipulating two clubs. Rhythmic gymnastics includes, besides the technical value of performing movements with the body and apparatuses, an artistic value, that is, the grade for the enchanting impression of the movements made on the spectators in accord with the music. Photograph provided by courtesy of the photographer Mr. R. Brandjolica

Table 111.2 Physical and training characteristics of menarcheal (M-RG) and premenarcheal (PM-RG) gymnasts (Klentrou and Plyley 2003) (Reproduced from Klentrou and Plyley 2003, Copyright June 2009. With permission from BMJ Publishing group Ltd)

Variable	PM-RG (n = 22)	M-RG (n = 23)
Weight (kg)	39.5 (2.5)**	49.7 (1.7)
Height (cm)	156.1 (2.2)**	167.3 (1.5)
BMI (kg/m^2)	16.3 (0.3)**	18.0 (0.3)
%BF	13.9 (0.4)**	17.5 (0.4)
Training experience (years)	6.8 (1.8)	6.7 (3.4)
Training frequency (days/week)	6.4 (0.8)*	5.0 (0.1)
Training duration (h/day)	5.6 (0.6)*	4.5 (0.3)

Values are means (SEM).
*$p < 0.05$, **$p < 0.01$ compared with M-RG
BMI body mass index; *% BF* percentage body fat

Source: Premenarcheal rhythmic gymnasts (PM-RG) had significantly lower body weight ($p < 0.01$), height ($p < 0.01$), body mass index (BMI) ($p < 0.01$), and body fat percentage (%BF) ($p < 0.01$) than menarcheal rhythmic gymnasts (M-RG). Training session frequency and length were higher in PM-RG ($p < 0.05$). Groups of PM-RG and M-RG were similar in years of training experience (Klentrou and Plyley 2003)

111.2.4 Young Female Ballet Dancers

Ballerinas have similar characteristics of body size as female performers in esthetic sports: they are smaller and lighter during childhood and early adolescence with the catch-up period of growth in later adolescence (Malina 1994). With body build and size, the 10–11-year-old ballerinas are most

Table 111.3 Descriptive statistics and results of ANOVA for the anthropometric variables in young female ballet dancers, rhythmic gymnasts, and figure skaters (Misigoj-Durakovic et al. 2005) (Reproduced from Misigoj-Durakovic et al. 2005, Copyright July 2009. With kind permission of the publisher of the MPPA)

		Rhythmic				
Variables[a]	Total Sample (n = 57)	Ballerinas (n = 21)	Gymnasts (n = 24)	Figure Skaters (n = 12)	F	p Value
Age (years)	10.61 ± 1.45	10.40 ± 1.33	10.54 ± 1.59	10.94 ± 1.62	0.32	0.72
Body height (cm)	146.22 ± 9.77	147.39 ± 7.81	145.05 ± 10.68	145.97 ± 11.46	0.41	0.66
Body mass (kg)	36.02 ± 7.28	36.08 ± 5.00	34.66 ± 7.82	37.67 ± 8.87	0.80	0.45
Leg length (cm)	83.14 ± 5.97	83.74 ± 5.36	82.43 ± 6.23	83.07 ± 6.77	0.37	0.69
Arm length (cm)	63.03 ± 4.57	63.31 ± 4.01	63.09 ± 4.77	62.35 ± 5.55	0.18	0.84
Arm span (cm)	146.17 ± 10.55	145.69 ± 8.33	146.64 ± 11.96	145.58 ± 11.98	0.05	0.96
Bi-acromial span (cm)	32.44 ± 2.11	32.16 ± 1.41	32.61 ± 2.39	32.38 ± 2.57	0.14	0.87
Bicristal span (cm)	22.58 ± 1.95	22.27 ± 1.30	22.67 ± 2.10	22.65 ± 2.63	0.29	0.75
Elbow diameter (cm)	5.60 ± 0.40	5.55 ± 0.29	5.59 ± 0.48	5.66 ± 0.39	0.19	0.83
Knee diameter (cm)	8.21 ± 0.48	8.33 ± 0.36	8.09 ± 0.56	8.20 ± 0.42	1.82	0.17
Ankle diameter (cm)	6.31 ± 0.36	6.35 ± 0.36	6.16 ± 0.36	6.48 ± 0.27	3.99	0.02
Upper arm circumference (in extension) (cm)	20.46 ± 2.23	19.83 ± 1.90	20.03 ± 2.34	22.13 ± 1.64	4.83	0.01
Upper arm circumference (in flexion) (cm)	21.64 ± 2.21	21.08 ± 1.96	21.30 ± 2.35	23.01 ± 1.74	3.16	0.05
Forearm circumference (cm)	19.39 ± 1.68	19.08 ± 1.14	18.90 ± 1.63	20.70 ± 1.83	5.56	0.01
Thigh circumference (cm)	43.66 ± 4.40	43.68 ± 3.68	42.28 ± 4.45	45.81 ± 4.46	2.88	0.06
Calf circumference (cm)	29.25 ± 2.52	29.08 ± 1.70	28.76 ±2.58	30.04 ± 3.01	1.07	0.35
Waist circumference (cm)	60.24 ± 5.74	59.00 ± 5.82	60.36 ± 6.45	60.92 ± 4.01	0.90	0.41
Triceps skinfold (mm)	10.16 ± 3.14	10.27 ± 3.98	8.94 ± 2.45	12.24 ± 1.46	5.13	0.01
Subscapular skinfold (mm)	6.76 ± 3.39	6.48 ± 4.92	6.19 ± 2.24	8.35 ± 1.57	1.77	0.18
Abdominal skinfold (mm)	7.94 ± 5.04	7.15 ± 5.13	7.17 ± 5.49	10.83 ± 3.00	2.65	0.08
Suprailiocristal skinfold (mm)	6.69 ± 4.50	5.49 ± 3.98	5.91 ± 4.79	10.44 ± 2.88	6.35	0.00
Thigh skinfold (mm)	11.89 ± 6.53	11.37 ± 6.22	9.71 ± 6.76	17.29 ± 3.44	6.65	0.00
Calf skinfold (mm)	10.12 ± 3.72	11.01 ± 4.82	8.53 ± 3.14	12.11 ± 1.53	4.82	0.01
Biceps skinfold (mm)	5.47 ± 2.40	5.60 ± 3.74	4.91 ± 1.03	6.39 ± 1.12	1.61	0.21

Chest (axillar) skinfold (mm)	5.23 ± 3.57	5.09 ± 4.75	5.14 ± 2.44	3.37 ± 1.93	0.36	0.70
% body fat	17.47 ± 3.95	15.26 ± 6.39	14.41 ± 3.84	19.32 ± 1.78	5.61	0.01
BMI	16.70 ± 1.93	16.64 ± 2.20	16.25 ± 1.75	17.41 ± 1.41	1.52	0.23

[a]Data expressed as arithmetic mean ± SD.
BMI body mass index

Source: The comparison of anthropometric measures of the samples of young female ballet dancers, rhythmic gymnasts, and figure skaters showed no significant differences in body size (body height and mass, body mass index and skeletal dimensions, with the exception of the ankle diameter). The differences were however significant in four subcutaneous skinfolds (triceps, suprailiocristale, thigh, and calf skinfold) as well in body fat percentage ($p = 01$). Rhythmic gymnasts had the smallest joint dimensions, limb circumferences, and skinfolds of the lower limb, whereas figure skaters were more voluminous, with a more robust skeleton of the lower extremities (Misigoj-Durakovic et al. 2005)

Fig. 111.3 Young female ballet students. Young female ballet students in demi-plié (half-bending of the knee done without lifting the heels from the ground) executed from the fifth position of the feet (the feet are turned out with the heel of one foot placed in front and close to the toe of the other foot). Photograph provided by courtesy of the photographer Mr. R. Brandjolica

similar to their female rhythmic gymnast peers (Table 111.3). They have a relatively low mass for their height, shown by low body mass index values in comparison to their non-trained peers (Soric and Misigoj-Durakovic 2008) (Fig. 111.3).

In a study investigating the anthropometry and body composition of premenarcheal ballerinas and female athletes in esthetic sports, 24 anthropometric measures, body mass index, and the proportion of body fat have been analyzed on a sample of 57 premenarcheal female ballet dancers and esthetic sports athletes including rhythmic gymnasts and female figure skaters, aged 10.61 ± 1.45 years (Misigoj-Durakovic et al. 2005).

The dancers and esthetic athletes had been involved in their respective sports disciplines for an average of 5.5 years. The average height of the ballerinas and athletes was above the 50th percentile and their body mass below the 50th percentile for their age. The girls did not significantly differ in body size measures, such as height and mass, body mass index, and longitudinal skeletal dimensions. Significant differences were, however, found in body composition. Rhythmic gymnasts were the most slender young athletes in this sample, with the smallest lower-limb joint dimensions, limb circumferences, and skinfolds. The female figure skaters were more voluminous, with a more robust skeleton of the lower extremities, which corresponded to the specific requirements and loads of figure skating (Table 111.3) (Misigoj-Durakovic et al. 2005).

Compared to a similar sample of premenarcheal esthetic athletes and ballerinas (mean age 10–11 years), peer artistic gymnasts had the smallest linear and transversal skeletal dimensions as well as skinfold measures (Figs. 111.4–111.6) (Misigoj-Durakovic and Vucetic 2009).

However, the girth of the gymnasts' upper limb was similar or somewhat larger than in rhythmic gymnasts and ballerinas (Fig. 111.7) (Misigoj-Durakovic and Vucetic 2009).

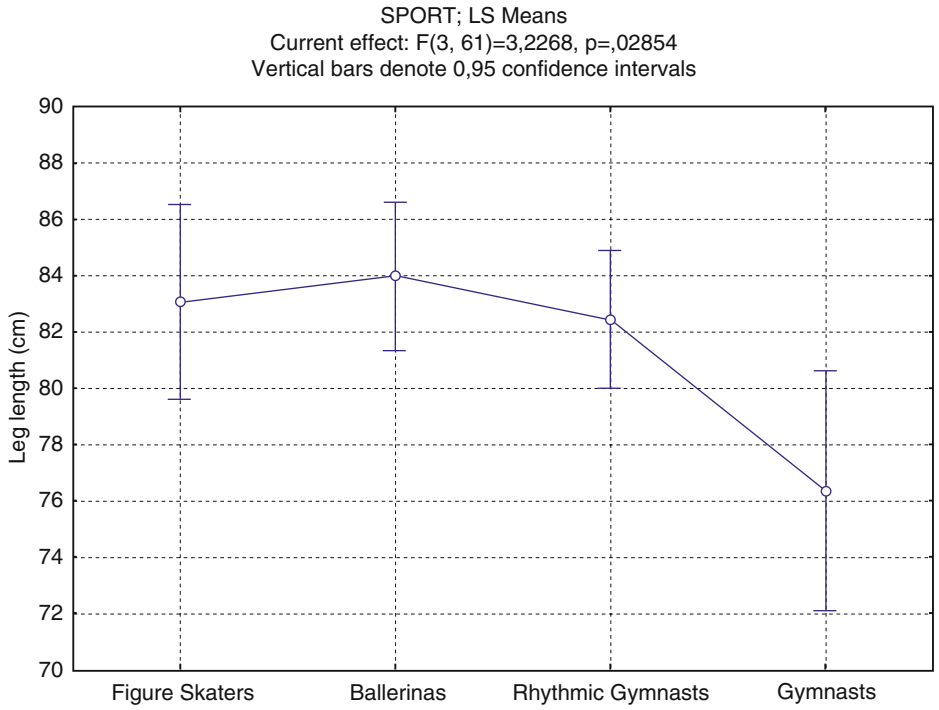

Fig. 111.4 Leg length (*basis – iliocristale*) in young female esthetic sport athletes (figure skaters, rhythmic gymnasts, and gymnasts) and ballerinas (Misigoj-Durakovic and Vucetic 2009). Compared to figure skaters, rhythmic gymnasts, and ballerinas aged 10–11 years, peer artistic gymnasts had the smallest leg length dimension

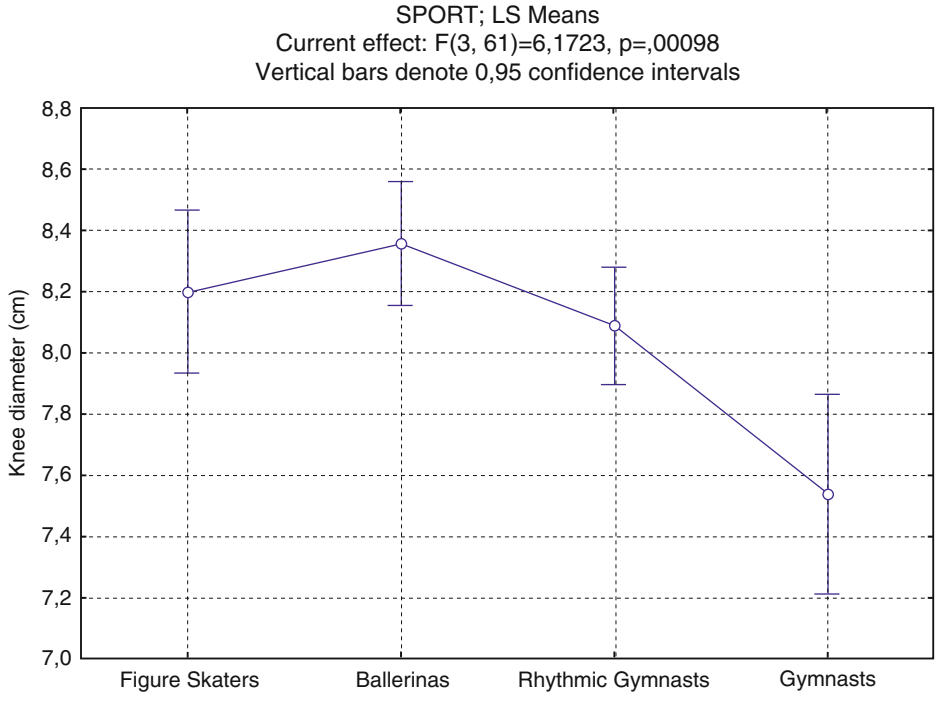

Fig. 111.5 Knee diameter (*femur bicondylar breadth*) in young female esthetic sport athletes (figure skaters, rhythmic gymnasts, and gymnasts) and ballerinas (Misigoj-Durakovic and Vucetic 2009). Compared to figure skaters, rhythmic gymnasts, and ballerinas, aged 10–11 years, peer artistic gymnasts had the smallest knee diameter

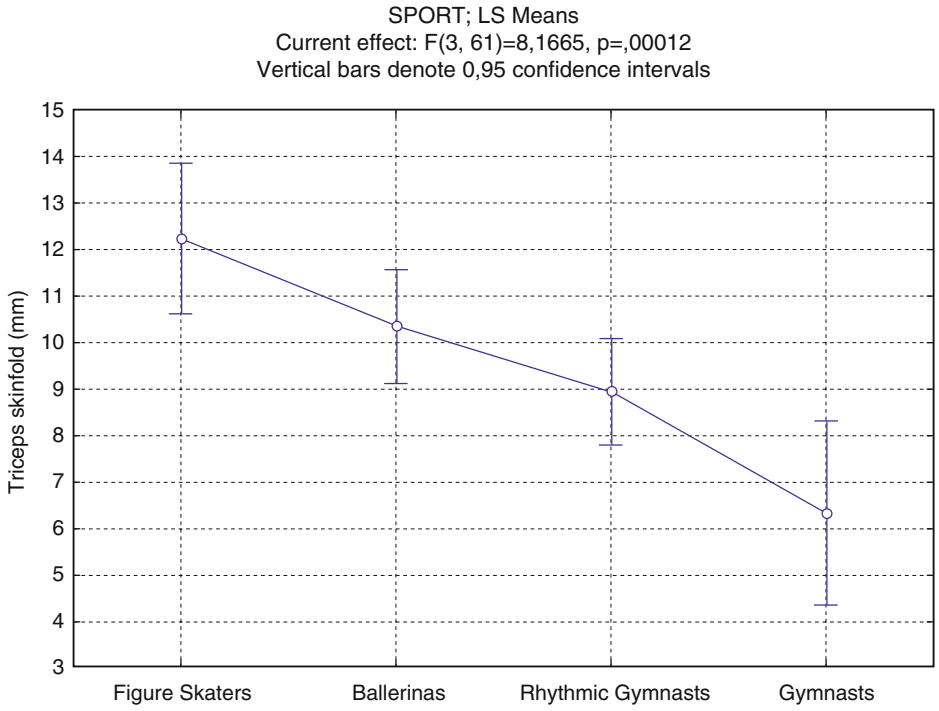

Fig. 111.6 Triceps skinfold in young female esthetic sport athletes (figure skaters, rhythmic gymnasts, and gymnasts) and ballerinas (Misigoj-Durakovic and Vucetic 2009). Compared to figure skaters, rhythmic gymnasts, and ballerinas aged 10–11 years, peer artistic gymnasts had the smallest triceps skinfold

111.3 Body Composition

Ballerinas and female performers of esthetic sports are characterized by slimness, that is, a low portion of body fat with adequate fat-free mass in comparison to non-athletes and female athletes of other disciplines (Guerra et al. 2001; Klentrou and Plyley 2003; Misigoj-Durakovic 2005; D'Alessandro et al. 2007; Soric and Misigoj-Durakovic 2008). The elite-level rhythmic gymnasts are characterized by a larger portion of fat-free mass in comparison to the sub-elite ones (Di Cagno et al. 2008).

Studying dietary intake and body composition of the young female esthetic athletes in a sample of 11-year-old prepubescent girls who compete in two esthetic sports (artistic and rhythmic gymnastics) and ballerinas, no significant difference has been found in the total energy intake between the groups of athletes/dancers and age-matched controls (Soric and Misigoj-Durakovic 2008). Artistic gymnasts reported a higher carbohydrate and a lower fat contribution to the total energy intake as well as a higher intake of carbohydrates relative to body weight than the rhythmic gymnasts, ballet dancers, or controls. The artistic gymnasts also had the lowest body fat percentage among the groups: the application of the Slaughter equation, based on two skinfolds measures, revealed approximately 12.5%. The reported mean daily intakes of most nutrients were higher in all the groups than the current daily recommended intakes. The exceptions were dietary fiber and calcium (Soric and Misigoj-Durakovic 2008). Unhealthy dieting behaviors and dieting itself are more often observed in female athletes aged 14 and onward (Guerra et al. 2001; Taylor and Ste-Marie 2001; Ziegler 2002).

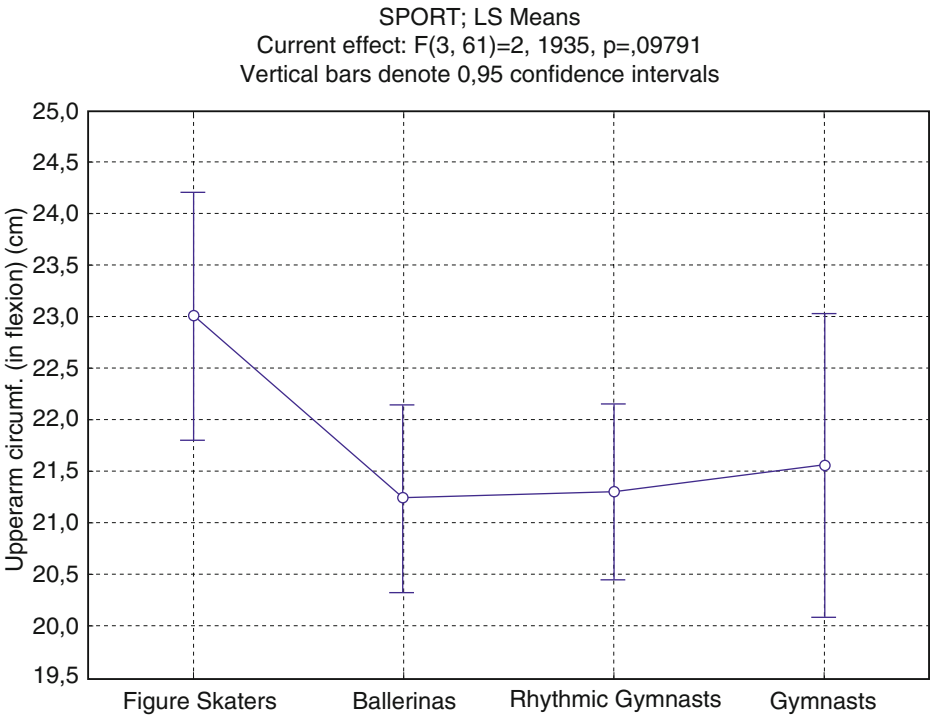

Fig. 111.7 Upper-arm circumference (*flexed and tensed*) in young female esthetic sport athletes (figure skaters, rhythmic gymnasts and gymnasts) and ballerinas (Misigoj-Durakovic and Vucetic 2009). Female artistic gymnasts, aged 10–11 years, had similar or somewhat larger upper arm circumferences (girths) than rhythmic gymnasts and ballerinas of the same mean age. Figure skaters had the largest upper arm girths

Ten- to 11-year-old premenarcheal rhythmic gymnasts and ballerinas, involved in specific training for an average of 5.5 years, have 14.4% and 15.3% of body fat, respectively, and figure skaters have 19.3% (Table 111.3) (Misigoj-Durakovic et al. 2005). The comparison of body fat percentage of young female artistic gymnasts to other female esthetic athletes and ballerinas is shown in Fig. 111.8.

With maturation, the body composition of girls changes, showing the trend of the increased proportion of the fat component. This is documented by the study of Klentrou and Plyley (2003) in 14-year-old elite rhythmic gymnasts: the percentage of body fat is 13.9% and 17.5% in the premenarcheal and the menarcheal gymnasts, respectively, as obtained by the Slaughter equation (Table 111.2).

Following near-infrared body composition analysis, Georgopoulos et al. (2002) reported 13.1% fat in rhythmic female gymnasts in a wide range of biological maturation and of chronological age ranging from 11 to 23 years.

111.4 Somatotype

Body fat percentage and the ratings of endomorphy in the somatotype are connected to the performance of esthetic female athletes (Claessens et al. 1999; Miletic et al. 2004), as well as to the injury incidence and recovery duration in ballet dancers (Twitchett et al. 2008).

In the study investigating the anthropological factors of performance in a sample of 7-year-old rhythmic gymnast beginners, 41% of success in performing basic body elements of rhythmic gymnastics (jumps, rotations, balances, and flexibility elements) was explained by the factors of

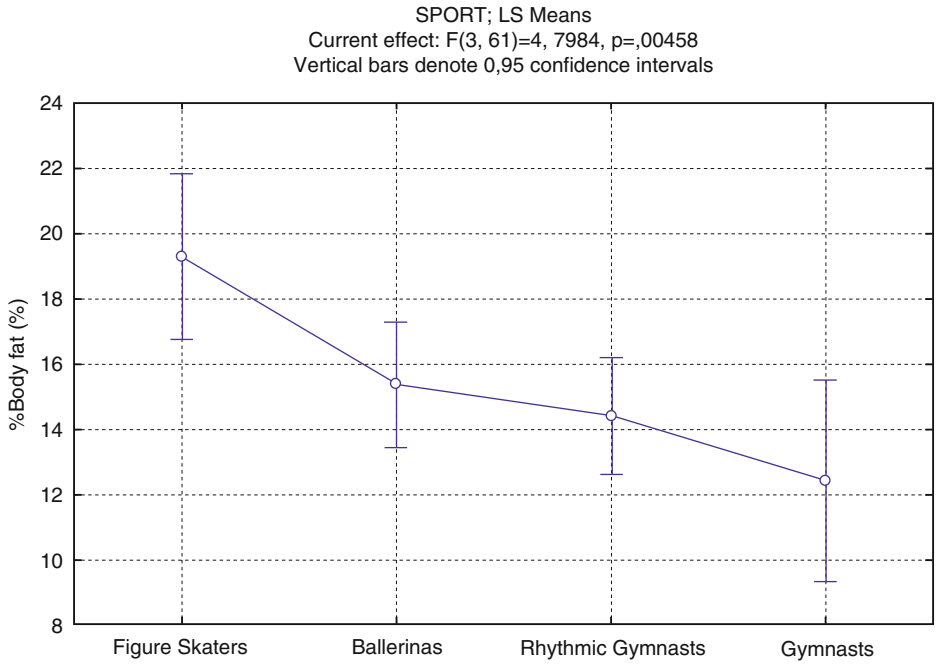

Fig. 111.8 Body fat percentage (% body fat) in young female esthetic sport athletes (figure skaters, rhythmic gymnasts, and gymnasts) and ballerinas (Misigoj-Durakovic and Vucetic 2009). Female artistic gymnasts, aged 10–11 years, have the lowest proportion of body fat among esthetic sport athletes and ballerinas of the same mean age. Figure skaters had the highest body fat proportion (Misigoj-Durakovic and Vucetic 2009)

Table 111.4 Regression analysis of motor and morphological latent space and routines in rhythmic gymnastics (Reproduced from Miletić et al. (2004). Table 4, p. 734 Copyright July 2009. With the kind permission of the publisher of the Coll Antropol)

	Basic body element^{L}	Specific manipulation with apparatus^{S}
Latent dimensions	BETA	BETA
Frequency of movements	0.19	0.44***
Explosive strength	0.25*	0.02
Flexibility	0.26*	0.07
Adipose voluminosity	–0.42***	0.13
Non-adipose voluminosity	–0.06	0.26*
RO	0.64***	0.52**

L movements with large amplitudes; *S* movements with small wrist amplitudes; *BETA* regression coefficient; *RO* multiple correlation

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Source: Multiple correlations between motor and morphological dimensions and the routine movements are significant and high. Flexibility has a significant positive predictive value (Beta coefficient) on the basic body elements (i.e., large amplitude movements) performance, whereas movement frequency, along with the non-adipose voluminosity dimension, significantly predicts proper and coordinated apparatus manipulation. The adipose voluminosity dimension has a significant negative predictive value on the basic large amplitude elements (Miletić et al. 2004).

flexibility, explosive strength, and adipose voluminosity, whereas the movement frequency and non-adipose voluminosity explained 26% of successful performance of RG-specific apparatus handling (club, ribbon, and ball wrist manipulation) (Miletic et al. 2004) (Table 111.4).

Elite female artistic gymnasts are characterized by an ecto-mesomorphic somatotype relatively homogeneously across the ages between 13 and 20 (Claessens et al. (1992). Values of the endomorphic component (showing fatness) are significantly lower than in the reference population and vary

between 1.4 and 1.9 throughout adolescence. Mean mesomorphy (showing muscular and skeletal development) is constant across the age period and varies mainly between 3.6 and 3.8. Mean ectomorphy (showing body linearity) varies between 3.3 and 2.8 (Claessens et al. 1992). Studying the contribution of anthropometric characteristics to performance score in the same sample of elite female artistic gymnasts, Claessens et al. (1999) found that almost one-half of variance (45.7%) in the total competition performance score is explained by the following: endomorphy, chronological age, calf girth, and sitting height. Endomorphy was the most important variable, appearing first (negatively) in the predicted total performance score and in the score in routines with apparatuses (Claessens et al. 1999).

Investigating possible associations between body composition, somatotype components, and self-reported injuries in male and female ballet students, it has been shown that a low percentage of body fat, high ectomorphy ratings, and low mesomorphy ratings in the somatotype of ballet dancers were positively connected to the reduction of injury incidence and duration of recovery (Twitchett et al. 2008).

A follow-up of anthropometric characteristics and the derived components of body composition and somatotypes is of special importance in young ballerinas and performers in esthetic sports due to the crucial selection criterion regarding the size, body build, and composition, further, because of the early commenced training that soon reaches high volume and intensity, and particularly because of the specific demands for maintaining a low body mass with reduced body fat. Therefore, careful control of anthropometric characteristics in this group of female athletes and ballerinas, besides giving information relevant to the monitoring of training program effects, will give an insight into the dynamics of growth and nutritional state of young female athletes. This will enable coaches to notice on time any nutritional deviations and to intervene by ensuring adequate energy intake through food, indispensable for growth and maturation during adolescence, so to prevent any possible behavioral issues, such as eating disorders, or dissatisfaction with one's own body shape, and the introduction of unhealthy body-mass control measures.

111.5 Applications for Other Areas of Health and Disease

More research and longitudinal studies are needed to elucidate the individual effects of and relationships between the process of sport selection, nutrition habits, and early commenced sports training in female esthetic athletes and dancers on their growth and maturation. A proper diet is extremely important in the period of growth, development, and maturation of a child. Long-lasting and intensive training during childhood and adolescence requires adequate energy intake through food for growth, development, and performance. Careful monitoring of anthropometric characteristics, body composition, and adequate nutritional intake is especially important in this group of athletes and dancers for early detection and the prevention of deviation in eating behaviors and body-shape expectations later during adolescence.

Summary Points

- It has already been well documented that certain size and body build contributes to performance in many sports. That is particularly evident in esthetic sports and all kinds of dancing.
- Ballet and esthetic sports such as artistic gymnastics, figure skating, and rhythmic gymnastics pose specific demands upon energy supply and motor and psychological capacities, and also upon

the size, build, and body composition of female competitors, particularly at the elite level, in a sensitive period of growth and development.
- Esthetic sports and dances require early inclusion of girls into specific training programs, which soon become highly intensive, frequent, and of long duration, with demands of maintaining minimal amounts of subcutaneous body fat.
- Contrary to the majority of other sports, morphological predispositions in esthetic sports and ballet are small body size and mass of female performers. For gymnastics, those young female athletes of small and petit constitution are selected.
- Ballerinas and female athletes in esthetic sports mostly belong to the group of late-maturing girls. Body linearity, or slimness, is connected with later maturation, and such a characteristic of body composition is desirable in the process of selection.
- Female athletes in esthetic sports and ballerinas have lower body mass values, body mass index, and the percentage of body fat in comparison to non-athletes and athletes engaged in other sports (except for female long-distance runners).
- The premenarcheal female esthetic athletes have a smaller body size and a lower proportion of body fat in relation to the postmenarcheal ones of the same chronological age.
- Within the group of esthetic female athletes and dancers, female gymnasts have a very low proportion of body fat. Elite female gymnasts are characterized by the ecto-mesomorphic somatotype.
- In some female artistic gymnasts, attenuated growth during the years of intensive training and competition could be seen, followed also in the period of lessened or ceased training (following retirement) by a catch-up growth rate.
- Rhythmic gymnasts have heights above the 50th percentile for their age in comparison to the female artistic gymnasts, although with a relatively low mass for their age (under the 50th percentile) (Georgopulos et al. 1999, 2001).
- Female figure skaters are, in comparison to female athletes in other esthetic sports, more voluminous, having a more robust skeleton of the lower extremities, which reflects figure-skating-specific demands.
- Ballerinas have similar characteristics of body size as female performers in esthetic sports. They have a relatively low mass for their height, shown by low body mass index values in comparison to their non-trained female peers.
- The portion of fat in body composition and the ratings of endomorphy in the somatotype are negatively connected to performance in esthetic female athletes.
- Low body fat percentage, high ectomorphy ratings, and low mesomorphy ratings in the somatotype of ballet dancers are found to be positively connected to the injury incidence and duration of recovery.

Key Facts of Morphology-Related Nutritional Concerns in Female Esthetic Athletes

- Body build and composition, being the morphological predispositions for success in esthetic sports and ballet, are defined as follows: a petite body build and lower body mass values, a lower body mass index, and a low proportion of body fat, that is, low values of endomorphic component with the appropriate fat-free body mass of female athletes.
- Such a build and body composition are characteristic of the premenarcheal age. The maintenance of such morphological characteristics and body composition throughout the years of a sports career frequently lead to a diet with a reduced energy intake.
- The nutritional habits of female athletes in esthetic sports and of ballet dancers often do not follow the actual energy demands imposed by strenuous workouts.

- Although a small body size and later maturation are constitutional predispositions and selective factors for top female gymnastics, there are still debates on the impact of high-volume and intensity training started early in childhood during the premenarcheal age when combined with an inadequate diet (inadequate regarding energy intake and quality) upon growth and maturation.
- Individual effects of selection, nutrition, and sports training have not been distinguished and investigated yet.

Key Facts of Endomorphy Ratings

- Endomorphy expresses relative body fatness.
- It is the first of three somatotype components according to the *Heath–Carter method* based on the Sheldon's somatotype classification.
- According to the *Heath–Carter anthropometric method of somatotyping*, the endomorphy rating is based on the sum of three skinfolds: subscapular, triceps, and supraspinale and is calculated by using *Heath–Carter somatotype rating form* or by using the equation derived from the rating form (Carter and Heath 1990; Carter 2002):

$$\text{ENDOMORPHY}\left(\text{height} - \text{corrected}\right) = -0.7182 + 0.1415(X) - 0.00068(X^2) + 0.0000014(X^3)$$

$$X = \left(\text{sum of skinfolds}\right)\text{multiplied by } 170.18 \,/\, \text{body height}\,\left(\text{cm}\right)$$

Key Facts of the Heath–Carter Anthropometric Somatotyping Method

- The somatotyping method, based on the Sheldon's somatotype classification, is the most commonly used one.
- Somatotype expressed in a three-number rating is the quantification of an individual morphological variation of body shape and composition.
- Somatotype three-number rating represents the quantification of three components always presented in the following order:
  - Endomorphy, the first component, expresses the relative fatness.
  - Mesomorphy, the second component, expresses the relative robustness of the musculoskeletal system.
  - Ectomorphy,the third component, expresses the relative body linearity.
- To calculate the three somatotype components, ten anthropometric measures should be used: body height, body mass, four skinfolds (subscapular, triceps, supraspinale/suprailiac, and medial calf skinfold), two joint diameters (elbow/biepycondylar diameter of the humerus and knee diameter/bicondylar diameter of the femur) and two limb circumferences (upper arm and calf) – all the measures are taken on the right side of the body.
- Anthropometric somatotype components are calculated using somatotype rating forms or equations derived from the rating forms (Carter and Heath 1990; Carter 2002).

Acknowledgment This work was supported by the Research Fund of the Ministry of Science, Education and Sport of the Republic of Croatia, research project ID 034-0342282-2325.

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Chapter 112
Fitness and Anthropometric Testing in Basketball Players

Eric J. Drinkwater

Abstract In intermittent high-intensity team sports such as basketball, there is a clear relationship between a player's body size and fitness and their success in competition. If this relationship is cause-effect is unknown, however. Before cause-effect can be determined there must be several methodological changes made to so-called "field testing" of athletes. Primarily, research implying the importance of body size and fitness to athletes is heavily reliant on individual test results from small (<100) numbers of players being correlated with measures of athlete success. No research has investigated how changes in an athlete's fitness relate to changes in game statistics; if an improvement in a player's size or fitness improves performance. In order to perform large-scale, long-term or meta-analyses research basketball must also agree to a standardised battery of tests with consistent protocols. Basketball research is impeded from progress by most data collection facilities using different variations on tests, thereby meaning test results cannot be compared across facilities. Standardising, for example, which vertical jump protocol is being used would contribute greatly to the academic integrity and use of field-test research. Most basketball research fails to report the reliability of any of its tests and is overly dependent on null-hypothesis significance testing rather than making magnitude-based inferences from effect sizes and confidence limits; while research involving small subject numbers can be useful, testing "statistical significance" is not appropriate and alternative methods of data analysis should be sought. In summary, to improve the quality of research investigating basketball fitness and anthropometry we must collect data over the long term using consistent testing methods and analysing it appropriately. While there are many other components that contribute to a player's success besides fitness, a player's size and fitness afford them the ability to capitalise on opportunities presented to them on the court, in skills development, and in the scouting process.

Abbreviations

∑7 skinfolds	Sum of seven skinfold sites collected from triceps, subscapular, biceps, supraspinale, abdominal, thigh, medial calf
1RM	One-repetition maximum strength test
CMVJ	Countermovement Vertical Jump

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_112,

FIBA	International Basketball Federation
NSSQA	National Sport Science Quality Assurance
NCAA	National Collegiate Athletic Association
NBA	National Basketball Association
SEM	Standard Error of Measurement
SPARQ	Speed, Power, Agility, Reaction, and Quickness
TEM	Typical Error of Measurement
TID	Talent Identification
VO_2 max	Volume of oxygen consumed at maximal work rate

112.1 Introduction

The presupposition that a person's body size, shape and fitness level are related to sporting success has led to decades of research describing and comparing these characteristics in athletes of different sports at different competitive levels. Presumably, the end goal of such research is to develop objective measures that will allow sport scientists and coaches to identify people with the greatest potential for success. Identifying fitness levels of successful athletes would not only help coaches in selecting participants for high-performance programmes, but also assist in setting fitness goals for their current athletes. Considering that each gold medal won by Australian athletes at the 2000 Olympic Games in Sydney cost the Australian Federal Government an estimated AUD37 million or each medal of any colour AUD8 million (Hogan and Norton 2000), the appeal of ways to streamline the system in which sports funding is distributed as well as improve athletic training is clear.

Several recent reviews have summarised testing results of basic anthropometric and fitness tests in basketball (Drinkwater et al. 2008; Ziv and Lidor 2009); hence, these will not be reiterated here. However, as is often the case in the search for simple explanations, cause–effect conclusions are often drawn between fitness and competitive success when relationships between these two variables are identified. Success in sports, such as basketball, is a complex interaction of not just body size and fitness but also of perceptual, motor, cognitive and psychological measures as well as sport-specific skill performance (Trninic et al. 1999; Trninic and Dizdar 2000). To draw useful conclusions from anthropometric and fitness testing, we must instead begin investigating the influence body size and fitness have on game-related statistics in repeated-measures designs using appropriate statistical methods on a standardised battery of highly reliable tests. The purpose of this chapter is not to reiterate already available material describing basketball anthropometric- and fitness-testing techniques (Stapff 2000) and results (Drinkwater et al. 2008; Ziv and Lidor 2009), but more to highlight impediments to advancing the field of knowledge.

The term "fitness" in this particular context is not intended to imply just aerobic fitness, but all of the components of physical fitness necessary for basketball performance. These components of fitness include muscular strength, power, agility, flexibility, local muscular endurance and cardiovascular endurance. While alternative terms such as "performance assessment" could be suggested to indicate that tests must be specific to basketball performance (i.e. have context validity), such a term could also imply the assessment of game-related skills. A test of fitness for athletes should be sufficiently generic that the result is determined primarily by fitness rather than skill but still have sufficient context validity to be a useful determinant of game performance.

112.2 Current Tests in Basketball

Previous reviews (Drinkwater et al. 2008; Ziv and Lidor 2009) have justified the necessity for a standard battery of sport-specific anthropometric and fitness tests. Sport-specific tests are necessary to simulate the demands of the game, whereas a standardised test battery would allow sport scientists and coaches to compare and analyse results across studies. Even slight variations in protocols signify that results across studies cannot be compared. Several sporting bodies have standard batteries of tests, though these batteries have mostly not been adopted by basketball researchers.

112.2.1 National Basketball Association

There is little doubt that the US-based National Basketball Association (NBA) is the premier basketball league in the world and is the league to which elite players aspire to. In the 2006/2007 season, NBA teams paid 510 players $US1.93 billion in salaries, an average of $US3.78 million per player (Drinkwater et al. 2008). To evaluate players competing for NBA contracts each year, the NBA invites prospective players to a draft camp ("the NBA Combine"), which involves a myriad of assessments, including fitness testing. Considering that the goal of most elite players around the world is to secure an NBA contact, it is surprising that more testing systems are not based on the NBA Combine tests. Values for each position on each test averaged across the 2000–2008 NBA Combine are expressed in Table 112.1. The roles of different positions in basketball are outlined in Table 112.2.

112.2.1.1 Local Muscular Strength and Endurance

While strength is the force-generating capacity of a muscle, local muscular endurance is the capacity of a muscle to repeatedly contract. Muscular strength is most commonly measured by a one-repetition maximum (1 RM) test in which single repetitions of a resistance training movement (e.g. bench press and squat) are performed with progressively heavier loads, until the load is too heavy for the athlete to perform even a single movement (repetition). The 1 RM is then expressed in kilograms lifted.

Table 112.1 Results of different fitness tests, broken down by player position, from the 2000 to 2008 National Basketball Association Combine

Fitness component	Test	PG (N = 123)	SG (N = 118)	SF (N = 101)	PF (N = 197)	C (N = 101)
Strength	185-pound bench press (repetitions)	8.0	10.5	11.2	12.8	11.5
Power	No step vertical jump (cm)	74.7	75.2	75.7	72.3	67.7
	Run-up vertical jump (cm)	88.9	88.6	87.6	83.1	77.6
	Maximal touch (cm)	333.7	345.9	351.8	353.4	355.9
Speed	75-ft court sprint (s)	3.20	3.23	3.25	3.32	3.44
Agility	Lane agility (s)	11.16	11.34	11.37	11.73	12.17
Body size	Height (cm)	183.9	192.1	198.4	202.5	208.1
	Body mass (kg)	83.4	91.4	96.8	106.5	113.5
	Wing span (cm)	194.5	203.7	209.4	215.1	220.2

Table 112.2 Different classifications of basketball playing positions and major responsibilities of each (position)

Classification #1	Classification #2	Classification #3	Classification #4	Position's major responsibility
Smalls	Guards	1	Point guard	Ball control; coordinating the offence
		2	Off guard/ shooting guard	Distance shooting
	Forwards	3	Small forward	Mixture of distance and close-range shooting, particularly from awkward positions
Bigs		4	Power forward	aggressive play close in to the basket (e.g., rebounding and close-range shooting)
	Centre	5	Centre	Close-range shooting on offence; coordinating the team's defence

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The NBA Combine therefore does not test muscular strength per se, but a combination of strength and endurance. It assesses only upper body strength – endurance in the form of a bench-press test. While lying horizontally, the goal of the bench-press test is to press a 185-pound (84 kg) barbell vertically off the chest as many times as possible.

112.2.1.2 Anthropometry

Anthropometric tests of the NBA Combine include standing height measured twice, once with shoes and once without, and a test of body mass. They also measure arm span ("wing span"), which assesses the horizontal distance from fingertip to fingertip with the arms fully stretched out.

112.2.1.3 Lower Body Power

To assess lower body power, the NBA Combine uses a no-step countermovement vertical jump as well as a run-up vertical jump. The goal of both of these tests is to jump as high into the air as possible, either from a stationary position or from a run-up approach. Vertical jump tests are usually expressed relative to the athlete's standing height by taking the total height the athlete jumped off the floor and subtracting the height an athlete can reach with his/her hand maximally extended over his/her head while standing with heels on the ground (i.e. "standing reach height"). "Maximal touch" is then expressed as the total height the athlete reached from the floor from a run-up start.

112.2.1.4 Speed

There is a test of straight-line running speed that involves players starting stationary at one end of the court ("baseline") and running 75 ft (22.86 m) to the far free-throw line (Figure 112.1). The "Lane Agility Test" involves the athlete starting from a stationary position on one end of the free-

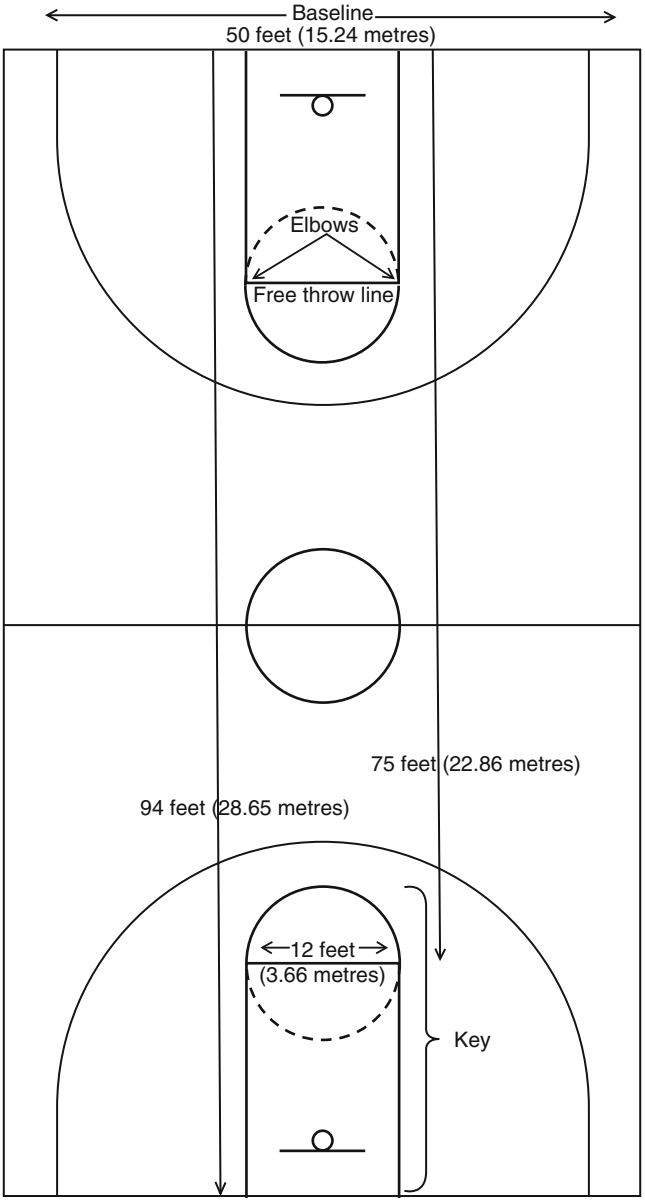

Fig. 112.1 Basic dimensions and terminology of a court for the National Basketball Association

throw line ("elbow") and sprinting towards the baseline, side-shuffling left along the baseline to the opposite intersection of the baseline and key, backwards running ("back peddling") to the opposite elbow and side-shuffling right along the free-throw line to the starting position, thus running a square while never changing facing on the court; the player then repeats this without pausing in the opposite direction to count as one repetition of the test.

112.2.2 Basketball Australia

In Australia, the National Sport Science Quality Assurance (NSSQA) programme has set test standards across a wide variety of sports, including basketball (Stapff 2000). Anthropometric tests include standing height without shoes, nude body mass and a summation of seven skinfold sites taken from the triceps, subscapular, biceps, supraspinale, abdominal, thigh and medial calf as an indirect measure of body fat. Fitness tests include a one-step maximal countermovement jump and a 20-m straight-line sprint from a standing start to assess lower body power, as well as a 20-m multistage shuttle run test to assess aerobic fitness. As a result of standardising a test battery, large-scale, long-term studies have been possible (Drinkwater et al. 2005, 2007).

112.2.3 Speed, Power, Agility, Reaction, and Quickness (SPARQ)

A recent commercial venture from Nike, Inc. (www.sparqtraining.com) has also implemented standard test protocols to assess what they refer to as Speed, Power, Agility, Reaction, and Quickness (SPARQ). The SPARQ test battery was devised to assist strength and conditioning coaches to monitor the training status of junior athletes (of 13–18 years) and also to be practical for self-administration. The battery comprises two tests of lower body power, including a countermovement vertical jump and an approach jump similar to the NBA Combine's maximum vertical jump; two agility drills to assess change-of-direction speed separately in offensive and defensive movement patterns; a medicine-ball chest pass to reveal upper-body power; and a multistage cross-court shuttle with short recovery intervals to reflect game-relevant endurance. For the anthropometric tests, both athlete stature and body mass are also collected. The results of each test are referenced against a geographically diverse normative data set ranking hundreds of teenage basketball players within each gender; a wide range of playing abilities is represented as well. The ranked result of each test is scored and these scores are combined into a single summary statistic, the SPARQ Rating. Although designed to precisely measure components of athletic performance specific to basketball, and to guide training prescription, the SPARQ Rating System has yet to be evaluated or utilised in peer-reviewed research.

112.2.4 Discrepancies in Fitness Tests for Basketball

Despite several sports bodies attempting to standardise testing protocols, consistency between research groups remains an ongoing problem as sport scientists attempt to blend a test's sport specificity (i.e. context validity) with the ability to compare its results over time, across data-collection facilities and between sports. Ziv and Lidor (2009) explicitly state the need for standard fitness-testing protocols in the recommendations. They also illustrate how even slightly different vertical jump protocols can elicit substantially different responses (Epub ahead of print). The advantage of tests, such as a run-up vertical jump or a one-step vertical jump, is their context validity. A standardised no-step vertical jump, while lacking context validity, would allow comparisons of basketball players across studies and between sports as many sports use countermovement vertical jump tests to assess lower body power. As it stands, the vertical jump heights from Drinkwater et al. (2007) cannot be compared to those from Apostolidis et al. (2004) due to the non-standardised jump protocol. Balancing standardisation against sport specificity continues to be debated.

For the purpose of establishing the sport specificity of a test, many "in-house" tests utilise court markings, such as agility tests that take place around the key (Apostolidis et al. 2004). Although convenient and having high context validity, court markings change, depending on the competition level. For example, a court used by high school programmes in USA is 22.56 m long, whereas an NBA court measures 28.65 m. As a result, data from Apostolidis (2004) and from Montgomery et al. (2008) on what is known colloquially as a "suicide run" cannot be compared because they had different running distances of 135.2 and 140 m, respectively. In October 2010, the dimensions of the International Basketball Federation (FIBA) key will change, thus making it impossible to compare previous agility testing results based on the old FIBA key dimensions with new ones. Therefore, caution should be used when designing fitness tests because making them highly sport specific makes their replication difficult over time and between testing facilities.

For historical perspective, though the FIBA acronym originally stood for Fédération Internationale de Basketball Amateurs, the 'Amateur' component was dropped from the official name in 1989 in favour of open competition rather than restricting competition to only amateurs. FIBA retained the 'A' in the acronym and recognised the French-to-English translation to the International Basketball Federation.

112.2.5 Fitness Tests to Consider

112.2.5.1 Aerobic Fitness

While tests of speed and agility are common in most basketball testing batteries, there is commonly debate over the necessity for a test of aerobic capacity. As reviewed by Ziv and Lidor (2009), most time–motion analysis studies highlight the anaerobic demands of basketball. These studies measure heart rate, blood lactate concentration and time spent in high-intensity activities. As test designs become increasingly sport specific by using time–motion analysis research to design test protocols, the role of aerobic endurance in successful performance is often neglected. However, the high frequency of alternating between high- and low-intensity activities and the ability to maintain the so-called "repeat sprint ability" is related to volume of oxygen consumed at maximal work rates ($\dot{V}O_2$ max, the benchmark of a person's maximal aerobic fitness) (Hoffman et al. 1999). It has also been recently shown that there is a relationship between $\dot{V}O_2$ max and proportion of time spent in live play in high-intensity activities, such as running and jumping ($r \approx 0.95$) (Narazaki et al. 2009). Erculj and Supej (2009) further illustrated that basketball-specific fatigue impairs free-throw shooting performance. Finally, that $\dot{V}O_2$ max levels have increased in ball-carrying positions (i.e. guards) since the FIBA rule changes in 2000 that require faster ball movement (Cormery et al. 2008) also seems compelling evidence that aerobic fitness is an important characteristic to assess in basketball testing.

If improving aerobic capacity in a basketball player allows the player to be more resistant to fatigue and able to recover more quickly, the real-world benefits of aerobic fitness seem obvious. As a result of being more aerobically fit, a player may progress their skill development faster because they are able to maintain high-quality practice for longer periods. A fitter player may also get more training or playing time (Hoffman et al. 1996; Hoare 2000) because they recover faster and are ready to be substituted back into the game earlier, thus increasing the quantity of playing and training. A fitter player is also less prone to fatigue-induced decrements in skill performance.

The reason that aerobic fitness is not included in many basketball fitness assessments is that it tends not to be considered sport specific. This is to say that time–motion analysis studies tend to

indicate a discontinuous nature of basketball, but most assessments of aerobic fitness tend to be continuous work protocols. To rectify the nonspecific nature of most tests of aerobic fitness, a discontinuous court running test has been developed, referred to as a Yo-Yo Intermittent Recovery test (Castagna et al. 2008). Whereas in tests, such as a 20-m multistage shuttle run test (Stapff 2000), participants run continuously in time with a series of audio tones, the Yo-Yo Intermittent Recovery test allows participants a 5-m recovery area at the end of each return trip of the court to walk and come to a complete stop before resuming the test (Krustrup et al. 2003). Despite the high context validity to high-intensity intermittent team sports, the Yo-Yo Intermittent Recovery test is not widely utilised, with only 30 articles in the National Library of Medicine listing as using it between 2001 and 2009.

112.2.5.2 Balance

Tests of balance are rarely included in published basketball fitness test batteries, probably due to the specificity in the types of balance (e.g. static vs. dynamic and stable vs. unstable surfaces). As a result, a widely accepted test of balance specific to basketball does not, as of yet, exist. However, a test referred to as the Star Excursion Balance Test has been demonstrated to reliably predict lower limb injury in both male and female high-school basketball players (Plisky et al. 2006). Although Emery and colleagues (2007) did not utilise the Star Excursion Balance Test, they did demonstrate the potential for focussed balance training to reduce the likelihood of injury.

112.2.5.3 Strength

Another component of fitness commonly omitted from basketball test batteries is strength. Whereas long-term monitoring of strength is standard practice in organised strength and conditioning programmes, strength testing results are rarely published as a routine subject descriptor. Although it is relatively easy to find normal values for anthropometric and fitness testing data on junior athletes from a wide variety of countries, ages and levels (Tables 112.1 and 112.3–112.5), finding strength testing results on basketball players from outside the US collegiate-based National Collegiate Athletic Association (NCAA) system is rare. This is unfortunate considering the value that strength can have on athletic performance (Liow and Hopkins 2003) and in the resistance to overuse injury (Gaida et al. 2004). When strength training is concurrently integrated with the routine court training, conventional beliefs regarding the detrimental impact of high-force, low-velocity training due to velocity specificity may not apply, particularly when it relates to acceleration (Liow and Hopkins 2003).

The only organisation that widely uses strength-testing data is the NBA Combine, though they only test upper-body strength – endurance. The usefulness of the 84-kg bench press used by the NBA is widely questioned due to its low context validity. For example, Kevin Durant scored zero on the bench-press test at the 2007 NBA Combine, yet was the second player drafted into the NBA; he continues to be one of the top players in the game today, albeit in a position generally not requiring physical strength.

Features of current tests in basketball:

1. Although several basketball organisations have standardised batteries of fitness and anthropometric tests, none are widely accepted outside their respective organisations.
2. Components of fitness include strength, power, aerobic endurance and body composition.

Table 112.3 A comparison of Australian junior National- versus State-level males and females on a standard battery of anthropometric and fitness tests ($n = 2000$) (Drinkwater et al. 2007)

	Height		Weight		Sum of seven skinfolds		One step vertical jump		20-m Sprint		Aerobic 20-m shuttle run	
	Mean	Variance ratio	Mean	Variance ratio	Mean	Variance ratio	Mean	Variance ratio	Mean	Variance ratio	Mean	Variance ratio
Men: National versus State	7.0 cm (3.6%)	0.95	6.7 kg (8.0%)	0.93	No difference	0.93	2.9 cm (4.6%)	1.14	–0.07 s (–2.3%)	0.83	0.7 levels (7.0%)	0.84
Women: National versus State	3.6 cm (2.0%)	1.18	4.0 kg (5.7%)	1.00	–7.5 mm (–7.8%)	0.86	No Difference	0.93	–0.04 s (–1.2%)	0.99	0.4 levels (3.7%)	0.92

"Mean" represents the difference between National- and State-level players. Note that in the categories of Sum of Seven Skinfolds and 20-m Sprint, lower scores represent a more favourable result. A "Variance ratio" of less than 1.00 indicates that variability in test results across National players were less than for State

Table 112.4 Summary of studies specifically investigating anthropometric- and/or fitness field test data in female basketball players, organised chronologically. Data expressed as means

First author (year)	Sample studied	Player position	Height (cm)	Mass (kg)	20-m sprint (s)	Σ 7 skinfolds (mm)[a]	Shuttle run (level)	CMVJ[b] (cm)
Drinkwater (2007)	Female, Australian State	Unspecified	174.3	65.6	3.42	103.4	9.3	45.6
	Female, Australian National		177.9	69.6	3.38	95.9	10	45.7
Carter (2005)	Female, International	Guards	171.9	66.1				
		Forwards	181.3	73.3				
		Centres	189.8	82.6				
Woolstenhulme (2004)	NCAA females	Unspecified	180	74				49.5
Hoare (2000)	Female, Australian State (under 16 years)	Point guard	166.2	57.8	3.4	83.5	9.65	46.5
		Off guard	169.4	61.6	3.46	93.3	9.83	44.9
		Small forward	173.5	64.1	3.56	88.8	9.58	42.4
		Power forward	177.4	69.4	3.53	108.7	8.59	43
		Centre	181.6	70.5	3.53	96.6	8.63	46.6
Stapff (2000)	Female, Australian State (14–17 years)	Unspecified	178.4	69.2	3.4	91.7	10.5	46.5
Lamonte (1999)	NCAA females	Guards	169.6	62.2				49.4
		Forwards	179.6	73.6				49.4
		Centres	188.1	80				43.5
Bale (1991)	Female, English National (under 17 years)	Guards	162.2	57.9				47.6
		Forwards	172.6	63.9				47.2
		Centres	180	71.2				47.6

This table contains a summary of anthropometric and fitness testing results of females from a range of player ages, levels and locations

NCAA National Collegiate Athletic Association; Shuttle run A progressive test of cardiovascular endurance involving repeatedly running a 20-m distance at fixed time intervals to voluntary exhaustion

[a]∑7 skinfolds triceps, subscapular, biceps, supraspinale, abdominal, thigh and medial calf

[b]*CMVJ* Countermovement Vertical Jump

Table 112.5 Summary of studies specifically investigating anthropometric and/or field-test fitness data in male basketball players, organised chronologically

First author (year)	Year	Sample studied	Player position	Height (cm)	Mass (kg)	20-m sprint (s)	Σ 7 skinfolds (mm)[a]	Shuttle run (level)	CMVJ[b] (cm)
Drinkwater (2007)		Male, Australian State		187.8	77.3	3.15	68.4	11.2	59.1
		Male, Australian National		194.9	84	3.08	67.5	11.6	62
Sallet (2005)		Male, French tier I and II	Guards	185.7	82				
			Forwards	195.8	89.4				
			Centres	203.9	103.9				
Apoltolidis (2004)		Male, Greek juniors		199.5	95.5				40.1
Hoare (2000)		Male, Australian State (under 16 years)	Point Guard	177.9	68.1	3.12	57.5	11.78	63.6
			Off Guard	180.5	71.3	3.15	51.6	11.62	63
			Small Forward	186.1	76.4	3.21	66.3	11.36	59
			Power Forward	191.3	83.8	3.24	69	11.21	58.5
			Centre	194.6	84.5	3.21	70	10.75	57.9
Staff (2000)		Male, Australian State (14–17 years)		198.4	94.4	3.04	72	12	65.5
Trninic (1999)		Male International, Olympic	Guards	192	88.7				
			Forwards	200.5	99.4				
			Centres	209.9	110.8				
Latin (1994)		NCAA Males	Unspecified	195.3	91.3				71.4

This table contains a summary of anthropometric and fitness testing results of males from a range of player ages, levels and locations. Data expressed as means

NCAA National Collegiate Athletic Association; Shuttle Run – A progressive test of cardiovascular endurance involving repeatedly running a 20-m distance at fixed time intervals to voluntary exhaustion

[a]□7 skinfolds triceps, subscapular, biceps, supraspinale, abdominal, thigh and medial calf

[b]*CMVJ* Countermovement Vertical Jump

3. Typically, fitness test batteries include height, body mass, straight-line sprint, jump height and agility.
4. The wide variation of "in-house" test methods and court markings from different leagues limits the ability of researchers to compare data.
5. Aerobic fitness is important even in sprint-based sports, as it may improve recovery time between sprint efforts, reduce fatigue-induced decrements in performance and contribute to skill development by increasing the quality and quantity of practice.

112.3 Anthropometric and Fitness Testing For Basketball Talent Identification

The premise for using fitness and anthropometric tests for talent identification (TID) is not unfounded. Evidence exists to illustrate that anthropometric and fitness characteristics can help distinguish between different competitive levels in a wide range of sports including basketball (Hoare 2000; Drinkwater et al. 2007). Anthropometric and fitness test scores have also been linked with measures of success in individual basketball players (Hoare 2000; Drinkwater et al. 2007), their playing time (Hoffman et al. 1996) and skill performance (Apostolidis et al. 2004) as well as the success of the team (Carter et al. 2005). Hoare (2000) accounted for approximately 40% of performance of a player's playing time during a game using the player's anthropometric and fitness characteristics. Hoffman (1996) further calculated that up to 84% of the variance in the playing time that a player was given by the coach was determined by fitness test scores. Additionally, in a sample of over 2,000 male and female Australian junior basketball players, Drinkwater et al. (2007) demonstrated that national-level players scored higher with a greater consistency on a standardised battery of tests over the span of 7 years than their state-level counterparts (Table 112.3). Hence, if players improve their fitness alone, is that enough to improve their chance of being selected to the next level? The answer to this question may be positive.

Tests of fitness that have context validity can be used to assess a player's readiness to train and compete. Therefore, a bigger, stronger, fitter player may have greater opportunities presented to them, as coaches are more likely to perceive such a player positively (Hoffman et al. 1996). Examples may include a coach spending more time with an unskilled but very tall player to develop his/her basketball skills for the exact reason that the player is tall. A fitter player can train longer before fatigue-induced decrements in skill performance occur, thus allowing for even greater skill development. Faster players have a clear advantage in launching attacks quickly or retreating into defensive positions, thus allowing them the opportunity to execute their offensive and defensive skills. Although it is likely that players will always be selected by scouts based on their ability to play, a player must be fit enough to capitalise on opportunities that fitness affords. Whereas the direct influence of fitness and anthropometry on game-related statistics has not been empirically demonstrated, favourable fitness and anthropometry set the stage for successful performance.

112.3.1 Differences in Anthropometric Test Scores by Player Position

Players on a basketball team are designated to their playing position based heavily on their anthropometry and fitness. While it is widely accepted that basketball players in high-performance programmes are taller than those in the general population (Drinkwater et al. 2008) and often self-select to play basketball for this reason (Delorme and Raspaud 2009), there are substantial differences in

body size amongst players on a basketball team (Table 112.2). Considering that a regulation basketball hoop is 10 ft (3.05 m) from the ground, taller players are at an advantage when shooting on the goal or retrieving missed shots (Trninic et al. 1999). Therefore, a team with tall players close to the basket is at an advantage because shooting on goal and the retrieval of missed shots are the two most dominant game statistics that determine game outcome (Sampaio et al. in press). This strategy became particularly clear between 1980 and 1990 when the number of players in the NBA over 7 ft (213 cm) tall rose from 3.5% to 11% (Norton and Olds 2001).

Empirical research often struggles to demonstrate differences in playing positions that basketball coaches intuitively know, such as the difference between guards and centres on 20-m sprint speed (Hoare 2000) or agility (Latin et al. 1994). Data collectors often find it difficult to classify players by three- and five-position systems (Table 112.2) because many players cross in and out of, for example, the "guard" and "forward" positions (#2 as an "off guard" and #3 as the "small forward"). Such a player would therefore designate him/herself as a 2–3 (i.e. playing either the "shooting guard" or "small forward" position). Another player may be a 4–5 (i.e., playing either the "power forward" or "centre" positions), changing position depending on what is needed in the game at the time. Additionally, by subdividing teams into small subgroups, there is a dramatic decrease in statistical power; thus, a lack of statistical differences between groups more likely represents type II errors rather than a true finding. Therefore, perhaps a broader system of grouping players into "smalls" (comprising position #1–3) and "bigs" (comprising positions #4 and #5) may be useful.

112.3.2 Fitness Tests for Goal Setting

Summary tables of anthropometric and fitness-test values (Tables 112.4 and 112.5) are often viewed by coaches with the intent of establishing reference values for setting the fitness goals of players; if players can see the test scores of athletes in the next level of competition, they can set goals for themselves. However, many studies post overall averages for test scores, but do not distinguish between playing positions (Drinkwater et al. 2007) due to difficulty in classifying players. As a result, a player reaching the mean value on a test may actually be underperforming for his or her position. For example, according to Drinkwater et al. (2007), a state-level guard sprinting 20 m in 3.15 s is an "average" score across all positions, but would likely be sprinting quite slowly relative to other guards because one of the key roles of a guard is movement speed.

Typically, basketball coaches will divide an annual plan into three phases: the off-season in which they focus on developing players' aerobic and anaerobic conditioning, the pre-season in which they focus on the development of players' anaerobic and technical abilities and the in-season in which they focus on maintaining their players' fitness levels and keep training focussed on technical and tactical skills. Drinkwater et al. (2005) studied changes in fitness and anthropometric tests of high-level junior basketball players between phases (i.e., off-season, pre-season and in-season), and even across years in the programme. Whereas mean changes within groups were mostly trivial to small in size, individual responses typically exceeded small effect sizes. These results indicate that whereas the fitness levels of groups of players may be difficult to detect as a whole, individual players can make considerable personal improvements.

Features of anthropometric and fitness testing for basketball talent identification:

1. The direct influence of anthropometric and fitness testing on game-related statistics is unclear.
2. Favourable anthropometric and fitness tests probably allow a player to make the most of opportunities presented to him/her. This may be in favourable rankings of team selectors, higher quality and quantity of practice, or being in place during a game.

3. Anthropometric and fitness characteristics play a determining role in a player's playing position on a team.
4. Widely available anthropometric and fitness test scores on standardised tests allow coaches and players to more effectively goal set.

112.4 Problems with Using Anthropometric and Fitness Testing for Talent Identification

112.4.1 Exceptions

Critics of using anthropometric and fitness tests as a TID tool usually point to the medley of perceptual, motor, cognitive and psychological measures as well as sport-specific skills that are necessary for basketball performance (Trninic et al. 1999; Trninic and Dizdar 2000). Accounting for sporting success is not as easy as measuring a player's body size as there are many other components necessary for basketball success. For example, Spud Webb played 814 games over 12 seasons in the NBA with a height of only 167 cm and body mass of 60 kg. Whereas any TID tool will inevitably have exceptions, taller and stronger players will always have an advantage if they are sufficiently skilled, and, therefore, will be more valued in professional leagues. According to 1993 values, an NBA player was paid an additional $US43,000 over his playing career for every 1.0 cm of height or 1.3 kg of body mass (Norton and Olds, 2001). While, clearly, body size is highly valued in professional basketball, it should be noted that Norton and Olds (2001) did not conclude a cause–effect relationship between body size and remuneration.

112.4.2 Correlation Is Not Cause–Effect

Studies that postulate a relationship between body size or fitness and sporting success usually do so based on correlation-style analysis (e.g. Pearson, linear and multiple regressions). For example, this is how both Hoare (2000) and Hoffman et al. (1996) drew conclusions about the relationship between a player's fitness to playing time. Apostolidis and colleagues (2004) further showed that fitness, particularly peak power, correlates well with a variety of basketball-specific skills. However, correlations describe relationships but not cause–effect. There is clearly more to fitness testing than collecting data from an athlete once. Perhaps the greater value of anthropometric and fitness testing lies in repeat testing of the same player over time (Drinkwater et al. 2005). From this, sport scientists could investigate the interactions between body size, physical fitness and position-specific skill performance (Angyan et al. 2003).

112.4.3 Adolescence

The purpose of TID programmes is the identification potential for sporting success early in an athlete's career, preferably while still a child or adolescent. Predicting adult fitness from testing results of children and adolescents is difficult, however. Whereas the relationship between childhood and

adult fitness may be moderate for selected fitness parameters (e.g. grip strength), Trudeau and colleagues (Trudeau et al. 2003) did not find any that seem sufficiently stable to reliably predict adult sporting success. Considering that the onset of puberty occurs at different times and progresses at different rates, there seems only limited chance of using fitness-test results to predict adult fitness with sufficient precision to choose high-performance teams. However, as previously discussed, a player's size and fitness afford him/her the ability to capitalise on opportunities presented on the court, in skill development and in the scouting process.

To highlight how even the difference of a few months in maturation can make, there is a known "seasonal effect" by which coaches tend to choose teams consisting of children born early in the selection year (Brewer et al. 1995). This was likely due to their more advanced growth at that time. Since these children were played more and received more coaching, they tended to advance more quickly. Delorme and Raspaud (2009) found an over-representation of players born in the first half of the year of all registered basketball players, regardless of competitive level, and conclude that being taller is a major factor in children choosing to play basketball.

Features of using anthropometric and fitness testing for talent identification:

1. The field of talent identification in sport is heavily dominated by correlation-style data analysis.
2. Correlation statistics are used to describe relationships but are not inferential. Whereas original scholars of correlation research are often careful to not make inferences about their data, secondary sources of the original data often do make such inferences.
3. Talent identification is often about targeting children and adolescents for future sporting success, though there are few characteristics sufficiently stable through to adulthood to make such predictions.

112.5 Statistical Analysis and Test Reliability

112.5.1 Reliability

Reliability refers to the repeatability of a test in returning a consistent result when no intervention is made (i.e. test–retest). For example, the 20-m sprint test is unlikely to return the exactly the same result when performed twice, even when repetitions are separated only by several minutes of quiet rest. Sources of unreliability can come from test setup (e.g. measuring an exact 20-m distance), the test operator (e.g. stopwatch timing the 20-m sprint) or variation from the athlete (e.g. motivation to perform the test and hydration status).

In an age in which the near-universal approach to research is to accept or reject a null hypothesis based on an observed p-value, many exercise and sport science researchers give little thought to the reliability of their measures. However, if we know that the reliability of the 20-m sprint test is 1.3% and we show in an experiment that there was a change of 1%, we cannot be confident that the change was not due to unreliability of the test, regardless of the *p*-value. Whereas researchers can do their best to control as many sources of error as possible in a field test, to control all would be impossible. Therefore, reporting test reliability is vital to the process of interpreting test results in human performance research. Although a correlation coefficient of greater than 0.90 is considered by many researchers as "acceptable" reliability, there can never be quantitative descriptors for an acceptable level of reliability; it will always depend on the magnitude of observed changes or differences. Unreliability of 1.3% may be acceptable, if 10% changes are expected, but would be unacceptable, if 0.5% changes were expected.

For those researchers who do consider reliability, it is often assessed by testing for a statistically significant difference between the two repeat trials, by analysing variance (e.g. *t*-test). High variability in the differences between means would be described as "non-significant," though differences between trials fluctuating wildly would clearly indicate poor reliability. Furthermore, statistical significance is not a relevant question in reliability because the purpose of reliability is not to test *if* there is a difference between the two trials, but to describe *how much* difference there is there between two trials.

To consider reliability, other researchers will assess the statistical significance of the correlation between trials. However, since correlation coefficients only describe the reproducibility of the order of the data, two measures could be vastly different, but still correlate quite well, if the difference is consistent. For example, if the retest is consistently 300% higher than the original test, there would be an excellent correlation due to the consistency of the result, though, once again, the ability to compare the test and the retest is clearly poor. Therefore, neither correlation coefficients nor analysing variance between repeat trials sufficiently assesses reliability.

Both the standard error of measurement (SEM) and the typical error of measure (TEM) describe how much difference exists between the two measures in a useful metric (Newtons, centimetres, etc.). Whereas SEM is generally more conventional, TEM describes the true within-athlete variation. Reliability can be expressed as a percent of the mean total (i.e. coefficient of variation) (Drinkwater et al. 2007). By expressing reliability in a useful metric, an author can discuss the magnitude of the observed change relative to the magnitude of the error rather than in inferring qualitative terms of "good" or "poor" reliability, based on a statistically significant correlation coefficient and a statistically non-significant mean difference.

$$\text{SEM} = \text{SD}\sqrt{1-r}$$

$$\text{TEM} = \frac{\Delta\text{SD}}{\sqrt{k}}$$

SEM = standard error of the measurement, TEM = typical error of the measurement, SD = standard deviation of the trials, ΔSD = the standard deviation of the difference scores between trials, r = the correlation coefficient between trials and k = the number of trials.

112.5.2 Magnitude-Based Inferences

Considering that sport research often is conducted on individual teams, participant numbers, and, therefore, statistical power, are often low. As a result, the determination of statistically non-significant results may be more often the result of type II error rather than a difference actually not existing. Furthermore, when a statistically non-significant result is found, it is often misinterpreted to mean that no difference exists. Statistical non-significance simply implies that the result cannot be inferred to be greater than zero with 95% confidence; researchers should not misinterpret such a result to mean that no difference exists.

Human performance research should be about describing the magnitude and meaningfulness of differences between groups. Thus, null-hypothesis significance tests relying on a *p*-value of less than 0.05 are inappropriate for many studies in human performance research. By using statistical procedures, such as Cohen's d and confidence limits, researchers will be able to make "magnitude-based inferences" (Batterham and Hopkins 2006, p. 53) about their data, describing the likelihood that observed results may be meaningful in an applied setting. Simply because a result is statistically significant does not mean the result is meaningful with respect to performance. Rather than trying to

describe results with a simple dichotomous "yes" or "no" answer as in the null-hypothesis significance test, researchers can quantify the likelihood that an effect could have a meaningful influence on performance (Liow and Hopkins 2003).

Features of statistical analysis and test reliability:

1. Reliability relates to the stability of repeated test results.
2. Few exercise and sport scientists report reliability of their tests, despite reliability being a critical value in the interpretation of research results.
3. Reliability should not be established by correlation coefficients between repeat tests and null-hypothesis significance testing mean differences.
4. Reliability should be quantified by typical or standard error of the mean.
5. A statistically non-significant result does not mean no difference existed; a statistically significant result does not mean the difference is practically useful.
6. Human performance cannot be assessed by null-hypothesis significance testing. Magnitude-based inferences would allow researchers to quantify likelihood that an effect could have a meaningful influence on performance.

112.6 Allometric Scaling of Testing

As previously discussed, the anthropometric makeup of a player can play a determining factor for their role on a basketball team. However, the anthropometric makeup of a player can also give mechanical advantages as well. For example, it is well known that larger individuals tend to be stronger and, thus, they tend to score higher on tests of strength. However, it would also be expected that, when heavier players are working against their own bodyweight, such as in a chin-ups test, they would be at a disadvantage. VO_2 max is routinely expressed in oxygen consumption per kilogram of body weight. Aside from centres contesting for position under the basket, few events in basketball are heavily determined by force output; but, since considering centres contesting under the basket is a typical strategy on most plays, having greater body mass, and thus greater strength, is clearly an advantage for centres.

However, when making comparisons across positions, the CV between junior Australian players' height is approximately 4.5% and that between weight is approximately 13% (Drinkwater et al. 2007), thus representing a substantial range of heights and weights on a team. A coach may want to make relative comparisons when evaluating results from strength testing. Most allometric scaling for strength tests work on an exponent of 0.67. This is to say, normalised strength value (S_n) is equal to the result of the strength test (S) divided by body mass (m) to the 0.67 exponent (b):

$$S_n = \frac{S}{m^b}$$

This indicates that simply dividing the result of the strength test by body mass of the subject is not a sufficient correction for the relationship between strength and body mass (i.e. participants with greater mass tend to exert greater force); strength test results actually increase at a lower rate than body mass.

Most of the fitness-dependent components of basketball are dependent on muscular power (e.g., sprinting down court and jumping for rebounds). When evaluating tests of power, such as jumping and sprinting, there does not seem to be any way to correct for body size (i.e., $b = 0$). Unlike in tests where the body mass is entirely supported, participants with low body mass are at a clearer advantage

(b = -0.33); there are no events in basketball such as this. A similar relationship exists when considering height where taller people tend to be stronger (b = 1), less able to support body mass (b = –1.5) and height is unrelated to tests of speed (b = 0) (Markovic and Jaric 2004). It, therefore, can be concluded that mass is never a disadvantage in basketball, particularly when we specify to lean mass. This may seem like a non-intuitive conclusion as most coaches will rarely have seen a centre run faster than a guard. However, considering that the guard as well as forwards are running designated positions, it seems logical that players selected to the "small" positions have other mechanical advantages, such as fibre typing and muscle architecture, and spend more time training for speed running. Players selected to "big" positions are more commonly selected to play those positions for their size and strength and spend relatively less time training for speed and endurance (Latin et al. 1994).

112.7 Conclusion

It is unclear if an improvement in fitness or body size necessarily directly *causes* an increase in playing ability; however, a player's size and fitness likely affords him/her the ability to capitalise on opportunities presented, be that in direct competition with another player or in talent scouting. One of the major impediments to large-scale, long-term fitness and anthropometric research in basketball is the lack of standardised test protocols, due largely to disagreement among sport scientists and coaches about balancing the sport specificity of a test with its reliability. As sport researchers, we also struggle with low or incorrect reporting of test reliability and have an over-reliance on null-hypothesis significance testing rather than making magnitude-based inferences. Rather than analysing data collected repeatedly on an individual over the long term, most TID research draw their conclusions from correlation-based data analysis methods by comparing one-off test results with level of success. Most sample sizes probably lack statistical power to accurately detect statistically significant differences; hence, larger-scale research is required. To conduct large-scale, long-term research, however, we, as sport scientists investigating basketball, should endeavour to agree on a battery of tests with known validity and reliability and express our results using magnitude-based inferences.

112.8 Applications to Other Areas of Health and Disease

Health practitioners and researchers must be wary of conclusions of cause–effect relationships when they are drawn from correlation-based research; though two measures may covary, they may not be linked by a cause–effect relationship. Often, direct cause–effect relationships are not made by the original researchers but are implied in secondary sources.

As a scientific field, it is important for sports science to strive for a general consensus on the tests that will be used. Even slight variations in testing methods or in how they are executed can inhibit the growth of knowledge by making literature reviews difficult and meta-analyses impossible. Many scientists develop "in-house" tests for their specificity, but results from these test protocols lack the ability to be shared with colleagues or included in meta-analysis. This is not to say that researchers should not strive to develop more specific test protocols, but the tests' validity and reliability should be widely disseminated.

Reporting test–retest reliability of protocols should be a key statistical feature of all sport science research. Measurement error is not limited to only the measurement instruments, but is an inherent part of human performance research. Reliability should be reported as typical or standard error of

measurement rather than correlation coefficients and p-values so as to establish the true within-subject variability. Reliability expressed in absolute units of the test or as a coefficient of variation is necessary to assess if observed changes exceed the measurement error. This is true regardless of the presence of statistically significant differences.

There is a growing body of support for the notion that the near-universal approach of null-hypothesis significance testing is not appropriate in human performance research and that the meaning of the p-value is widely misunderstood. Researchers should investigate the use of magnitude-based inferences by expressing data as confidence limits and effect sizes.

Summary Points

- Exercise and sport scientists need to be cautious about drawing cause–effect relations from correlation-based research.
- Body size and fitness will always play a role in basketball, though the influence of each will be determined by the player's dominant role on the team. Data collection and analysis should include the player's position on the team.
- To advance the investigation of the influence of anthropometry and fitness on basketball performance, testing the same player over time and relating results to game-related statistics time would be very useful.
- Basketball as a community should develop a standardised battery of sport-specific tests that do not rely on court markings, so that results can be compared, tabulated, meta-analysed and culminated into large-scale, long-term studies.
- The standardised battery of tests should include tests of strength, balance and aerobic fitness in addition to the current tests of height, body mass, speed, agility and jumping.
- Although aerobic fitness is important in basketball, an intermittent test of fitness, such as the Yo-Yo Intermittent Recovery test, is required for a higher degree of sport specificity.
- Research should always report test reliability as standard error of the measurement or typical error of the measurement.
- Current basketball research relies mostly on null-hypothesis significance testing, though it should make magnitude-based inferences from effect sizes and confidence limits to indicate the likelihood of an effect being meaningful to performance.
- To compare the testing scores of players on a team, allometric scaling may be applied to strength and body-supporting exercises due to the respective advantage and disadvantage of larger players. Allometric scaling of propulsive activities is not indicated.
- Although a player's body size and fitness have not been shown to have a cause–effect relationship, a player's size and fitness afford them the ability to capitalise on opportunities presented to them on the court, in skill development and in the scouting process.

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Chapter 113
Anthropometric Digit Ratio 2D:4D and Athletic Performance

Johannes Hönekopp

Abstract 2D:4D (the length of the second finger divided by the length of the fourth finger) appears to be a marker of prenatal testosterone levels, with lower 2D:4D indicating higher prenatal testosterone. 2D:4D has become a prominent tool for studying potential effects of prenatal testosterone on human development and behavior. Athletic performance is positively affected by circulating testosterone levels; similarly, prenatal testosterone may have a positive effect on athletic performance. In order to investigate this possibility, I here review studies on the relationship between 2D:4D and athletic performance. In line with expectations, most studies found a negative relationship between 2D:4D and various measures of athletic performance in either sex. There is some evidence that 2D:4D shows stronger relationships with measures of endurance than with measures of strength. This suggests that prenatal testosterone promotes some components of physical fitness more than others.

113.1 Introduction

In most species, the sexes differ in how much time and energy they invest in offspring. Necessarily, the sex that invests more (usually females) is more limited in the maximum lifetime number of offspring than the sex that invests less (usually males). This difference in parental investment and maximum reproductive success means that males and females optimize their evolutionary success with different strategies. In many species, males are evolutionary most successful by mating often and with many females in order to sire many offspring. Females, by contrast, do not need to mate often in order to achieve their maximum number of offspring. With offspring quantity being strongly limited, females usually optimize their evolutionary success by optimizing offspring quality, partly by choosing high-quality mates. As a consequence of this sex difference in optimal mating strategy, male reproductive success is limited by access to mates in many species. Therefore, males compete for access to females by fighting other males (intra-sexual selection) or by advertising their high

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_113,

quality to potential mates by means of sexual displays, such as colourful plumage, impressive vocalization, and dances, which is known as inter-sexual selection. (For a very readable introduction to sexual selection, see Miller 2000).

Women invest, on average, more in their progeny than men. Consequently, we would expect to see adaptations for intra-sexual competition in men. Intra-sexual selection often leads to males' being bigger and stronger than females, a pattern also observed in humans (Gaulin and Boster 1992; Pheasant 1983). Indeed, given the ubiquity of male–male fighting throughout human prehistory (Keeley 1996), their fighting ability should have importantly contributed to our male ancestors' evolutionary success. Successful participation in sports often requires abilities, such as strength, endurance, aggressiveness, and dexterity, which would appear to prepare males for intra-sexual selection. Thus, intra-sexual selection in males may largely explain why men outperform women in virtually all sports. Physical features involved in sexual selection are often under the control of testosterone. Further, this also appears likely for characteristics that support successful athletic performance in humans because sex differences in performance usually emerge or greatly increase with puberty (Thomas and French 1985); the effects of doping with androgenic steroids to boost athletic performance point to a similar direction (Hartgens and Kuipers 2004).

Somewhat simplified, two actions of testosterone can be differentiated: circulating testosterone levels in adults have 'activational' effects, that is, the effects are relatively short-lived and wax and wane with testosterone levels. By contrast, testosterone during early development induces permanent, 'organizational' changes, which take place prenatally from gestational months three to six in humans (Cohen-Bendahan et al. 2005). Measurements of foetal testosterone levels are not readily available and longitudinal studies are laborious, which makes studying effects of prenatal testosterone in humans challenging. However, digit ratio 2D:4D (i.e., the length of the index finger divided by the length of the ring finger) appears to be a marker of prenatal testosterone levels in humans, with lower (and thus more male-like) values indicating higher levels of prenatal testosterone (see the chapters of Manning and Voracek in this volume). As 2D:4D can be easily measured, it has become increasingly popular as a (putative) tool for studying effects of prenatal androgenisation in humans (Voracek and Loibl 2009).

The emergence of sex differences in athletic performance during puberty and improved athletic performance after androgenic steroid doping indicate that the activational effects of testosterone have a beneficial effect on athletic performance. It appears plausible that the same might be true for the effects of prenatal testosterone. For this reason, a number of studies have looked at the relationship between 2D:4D and various indicators of athletic performance. To review these studies is the aim of the present chapter.

113.2 Some Methodological Considerations

113.2.1 Measurement of Athletic performance

Whereas the measurement of 2D:4D is relatively straightforward, studies have related digit ratios to aspects of athletic performance in very different ways. First, different sports have been considered, among them running, skiing, and fencing (see below); also, variables that do not pertain to a specific sport discipline have been used (e.g., hand-grip strength). Second, whereas some studies correlated the outcome of a specific athletic activity (e.g., running time) with 2D:4D, other studies have compared the digit ratios of athletes with those of nonathletes (see below).

These differences across studies can be expected to affect results in three important ways. First, physical fitness is multifaceted (Bouchard et al. 1994) and various sports differ in their requirements regarding athletes (a long-distance runner certainly needs other qualities than a weight lifter). Differences in the strength of the relationship between 2D:4D and athletic performance across various measures may therefore provide some insight into which facets of physical fitness (e.g., muscle strength and endurance, cardiorespiratory fitness, flexibility, and glucose tolerance; cf. Bouchard et al. 1994) may be (especially) susceptible to prenatal testosterone effects. Second, the strength of any relationship between two variables partly depends on the quality of the measurements and, ceteris paribus, more reliable measures will give rise to stronger relationships; however, it appears next to impossible to compare the reliabilities of the various measures that have been used in the domain reviewed here, and this aspect will therefore be ignored in this chapter. Third, the strength of the relationship between two variables (as measured by a correlation) will diminish when the variance in the variables is restricted. To take an arbitrary example, the correlation between brain size and IQ can be expected to be higher in a community sample than in a student sample, because IQ should show less variability in the latter than in the former.

The studies reviewed here differ greatly with regard to variance in performance. Some draw on samples that are relatively heterogeneous with respect to athletic performance; for example, Hönekopp et al. (2006) looked at the relationship between pupils' 2D:4D and their physical education marks. This sample can be expected to comprise talented as well as hardly talented individuals, and, accordingly, performance variability in such a sample is high. Other studies look at relatively homogeneous samples. Take Voracek et al. (2006) as an example, who studied elite fencers' national rank; necessarily, the variability in fencing performance in this sample will be relatively low because only people above a high performance threshold entered the study. Homogeneous samples, such as the latter, should tend to underestimate the relationship between 2D:4D and athletic performance in the population due to the range restriction in that sample. This is not true for heterogeneous samples, such as the pupils sample. Table 113.1 lists the studies that looked into the relationship between 2D:4D and athletic performance and it indicates, for each sample, whether or not a substantial restriction in the performance range is present; although necessarily rough, such a classification can shed additional light on the findings.

113.2.2 Effect Sizes

A recent meta-analysis into 2D:4D and athletic performance suggests that no hand's 2D:4D is a systematically better predictor of athletic performance than the other hand's 2D:4D (Hönekopp and Schuster, 2010). This chapter therefore does not differentiate between right-hand and left-hand 2D:4D here. Instead, results (which are largely based on Hönekopp and Schuster, 2010) were averaged across both hands, where separate results for each hand were reported in the original studies.

For each sample, the strength of the relationship between 2D:4D and the variable of interest is given as a Pearson correlation (r). This measure, immediately plausible for studies correlating 2D:4D with some athletic outcome (e.g., running time), may appear awkward for studies comparing the 2D:4D values of athletes and controls. In the latter case, measures of effect size that express the raw difference between groups in units of standard deviations (e.g., Cohen's d) are typically used. However, Cohen's d and r can be readily transformed into each other. Further, the meaningfulness of r for comparing differences between two groups is illustrated by the fact that the 'correct' r can be obtained directly from raw scores by correlating the dependent variable (e.g., 2D:4D) with two arbitrary numbers that code for group membership (e.g., 'athletes' and 'nonathletes').

In this review, *p*-values are not the point of focus because statistical significance is largely a function of statistical power (i.e., sample size) and focussing on significance instead of effect size (or some other descriptor of the effect at hand) may be detrimental for scientific progress (e.g., Cohen 1994).

113.3 The Relationship Between 2D:4D and Athletic Performance

Table 113.1 gives an overview over the relevant studies and their results. For ease of communication, all samples are numbered consecutively (left-most column). The reference for each sample can be found by matching the entries in the second column with the respective numbers in the reference list. Of the 28 samples listed in Table 113.1, 11 are female samples with an overall *N* of 1,406, 16 are male samples with an overall *N* of 2,292, and, finally, one mixed-sex sample comprises 144 participants.

All measurements of athletic performance in the original studies were coded such that higher scores denote better athletic performance. Consequently, we should expect negative correlations between 2D:4D and athletic performance. (This is because 2D:4D appears to be negatively related to prenatal testosterone [see above], and any relationship between prenatal testosterone and athletic performance should be positive.) Studies are listed according to effect size, that is, the correlation of athletic performance with 2D:4D. Multiple relationships between 2D:4D and measures of athletic performance were averaged into a single effect size for each sample.

When studying the results (Table 113.1), two key features are striking. First, all but one sample (#28) find a negative relationship between 2D:4D and athletic performance, which suggests that associations between athletic performance and 2D:4D are robust. Second, the strength of the relationship between 2D:4D and various measures of athletic performance differs greatly, from about zero to $r = –58$ (#1). Large differences in effect size are also found between studies with large samples (e.g., compare #6, #7, and #8 with #21, #22, and #28), which indicates that these differences reflect 'real' differences and do not simply emerge from random sampling error, a view that is confirmed by a more technical analysis in a recent meta-analysis (Hönekopp and Schuster, 2010).

As the results are so heterogeneous, can we then identify factors that account for the large differences in effect sizes across studies? One potential factor might be sex. This, however, does not appear to play an important role. First, the unweighted average correlation between 2D:4D and athletic performance is $r = .23$ for the female samples and $r = .31$ for the male samples, which is not a dramatic difference when we consider the heterogeneity of effect sizes within each sex. Second, and more importantly, comparable female and male samples tend to yield quite similar results whenever the same measure of athletic performance is used. Thus, correlations between pupils' physical education marks and 2D:4D are $r = –.17$ for girls (#19) and $r = –.16$ for boys (#20); correlations between a gym-based fitness test and 2D:4D are $r = –.24$ for females (#16) and $r = –.17$ for males (#18); the relationship between 2D:4D and opting-in versus not opting-in for physical education in school is $r = –.31$ for girls (#13) and $r = –.24$ for boys (#15); the correlation between 2D:4D and rank in fencing is $r = –.13$ for females (weighted average across #23 and #26) and $r = –.08$ for males (#27); finally, the relationship between 2D:4D and hand-grip strength is $r = .08$ in females (#28) and $r = –.24$ in males (weighted average across #12 and #17). Only the latter domain represents a sizable difference between the sexes regarding the predictive power of 2D:4D. Future studies will have to show if this particular difference represents more than chance.

Table 113.1 Overview of studies on 2D:4D and athletic performance

#	Reference	Conceptualization of athletic performance and sample	Age	Sex	*N*	*r* with 2D:4D	Range restriction
1	Latourelle (2008)	Athletes versus student controls		F	74	–0.58	No
2	Manning et al. (2003)	Reserve versus first team squad; professional soccer players		M	33	–0.53	Yes
3	Manning et al. (2003)	Times for six-mile race; participants in cross-country race	21	M	47	–0.52	Yes
4	Manning et al. (2007)	Mean rank across three races; participants in cross-country race	28	M	43	–0.51	Yes
5	Manning et al. (2007)	One-mile race; athletic club members	34	F	40	–0.41	Yes
6	Manning et al. (2003)	Self- and other-rated playing ability; soccer amateurs	19	M	108	–0.41	Yes
7	Manning (2002a)	Soccer professionals versus controls		M	839	–0.40	No
8	Manning (2002b)	Ski-race participants versus matched controls	21	M/F	144	–0.36	No
9	Manning (2002a)	Highest participation level for favourite sport; university sample	22	M	128	–0.35	No
10	Tester and Campbell (2007)	Highest participation level for favourite sport; sport team members	20	M	73	–0.34	Yes
11	Tester and Campbell (2007)	Highest participation level for favourite sport; sport team members	20	F	82	–0.33	Yes
12	Fink et al. (2006)	Hand-grip strength; students	23	M	52	–0.32	No
13	Tlauka et al. (2008)	Pupils who did/did not opt-in for physical education at school	17	F	52	–0.31	No
14	Manning et al. (2003)	Personal best time for 800 m; participants in cross-country race	23	M	97	–0.26	Yes
15	Tlauka et al. (2008)	Pupils who did/did not opt-in for physical education at school	17	M	26	–0.24	No
16	Hönekopp et al. (2006)	Fitness test (gym-based); students	20	F	77	–0.24	No
17	Fink et al. (2006)	Hand-grip strength; students	26	M	88	–0.18	No
18	Hönekopp et al. (2006)	Fitness test (gym-based); mixed student/community sample	22	M	102	–0.17	No
19	Hönekopp et al. (2006)	Mark for physical education; pupils	17	F	174	–0.17	No
20	Hönekopp et al. (2006)	Mark for physical education; pupils	17	M	114	–0.16	No
21	Manning and Hill (2009)	Sprint time 50 m; children in talent identification program	13	M	241	–0.15	Yes
22	Manning (2002a)	Had/had not represented their country; soccer players		M	264	–0.15	Yes
23	Bescos et al. (2009)	Ranking; elite fencers	25	F	87	–0.14	Yes
24	Pokrywka et al. (2005)	Elite athletes versus medical students		F	97	–0.12	No
25	Paul et al. (2006)	Highest participation level for various sports	54	F	607	–0.11	No
26	Voracek et al. (2006)	National rank; elite fencers	23	F	17	–0.10	Yes
27	Voracek et al. (2006)	National rank; elite fencers	23	M	37	–0.08	Yes
28	van Anders (2007)	Hand-grip strength; university sample	24	F	99	0.08	No

The strength of the relationship between 2D:4D (the length of the second finger divided by the length of the fourth finger) and athletic performance is indicated as a correlation in the column '*r* with 2D:4D'. Negative relationships are expected (i.e., low, 'masculine' 2D:4D tends to coincide with good performance).

As sex can hardly explain the substantial differences in effect sizes between studies, can we identify any other characteristic as relevant? Looking at correlations between 2D:4D and running time, Hönekopp and Schuster (2010) found a significant relationship between running distance and effect sizes, indicating that the predictive power of 2D:4D significantly increases with running distance. This suggests that 2D:4D tracks an endurance component especially well. Further support for this idea comes from the fact that the four soccer samples (#2, #6, #7, and #22) tended to find strong relationships with 2D:4D, with weighted average $r = –.35$, and endurance appears to play an important role in soccer performance (Helgerud et al. 2001). In the group of the 23 non-soccer samples, only five showed larger effect sizes, three of which resulted from middle- and long-distance running. By contrast, those measures of athletic performance for which an endurance component does not appear particularly important (e.g., hand-grip strength, sprint speed, and fencing performance) tended to produce small effect sizes (unweighted average across seven samples: $r = –.13$). The very substantial relationships between 2D:4D and performance in soccer, and middle- and long-distance running ($r \approx .40$) are the more remarkable as most of these samples show a range restriction, which works against finding large effects (see Sect. 113.2.1).

113.4 Conclusions

Reporting bias (especially omission of non-significant results in the published literature) is a threat to the validity of any review or meta-analysis (for a brilliant account, see Palmer 2000). For the relationship between 2D:4D and athletic performance, a meta-analysis which included most of the studies reviewed here found no evidence for a substantial effect of publication bias (Hönekopp and Schuster, 2010). Moreover, 2D:4D research is a field in which non-significant and contradictory findings appear to be readily published (e.g., Puts et al. 2008; Putz et al. 2004). Therefore, optimism regarding the veracity of the data presented here appears justifiable.

The great heterogeneity of samples and, especially, methods (i.e., conceptualization of athletic performance) makes generalizations across studies difficult. Nonetheless, some conclusions appear warranted. First, negative relationships between 2D:4D and athletic performance are reliably found across domains. This suggests that prenatal testosterone either has a positive influence on some aspect of physical fitness that is relevant for athletic performance across a wide range of sports or positively affects various facets of physical fitness. Second, the present data suggest that prenatal testosterone affects athletic performance about equally strongly in both sexes. Future studies will have to show if strength is an exception, which is hinted at by results on hand-grip strength. Third, a comparison of effect sizes across domains suggests that prenatal testosterone has an especially strong effect on endurance, but probably a small effect (if any) on strength. This is remarkable because effects of doping with androgenic steroids appear to be particularly strong for muscle mass and strength (Hartgens and Kuipers 2004). This contrast then suggests that prenatal testosterone and adults' circulating testosterone affect various components of physical fitness in different ways. The results so far obtained for 2D:4D and endurance running suggest large effects (although it should be remarked that all relevant studies stem from the same group, and independent replication appears desirable). The effects are so large, in fact, that 2D:4D might prove a viable tool for early talent identification.

The next step for elucidating the relationship between 2D:4D and athletic performance should be to determine which components of physical fitness and, more specifically, which physiological aspects and/or morphological body characteristics are linked with 2D:4D and explain the relationship(s) between 2D:4D and athletic performance.

113.5 Applications to Other Areas of Health and Disease

The current review suggests a reliable link between 2D:4D and athletic performance, and the relationship with endurance appears to be particularly strong. Also, there is very good evidence for a negative relationship between cardiovascular fitness and mortality. In a large (N > 13,000) prospective study with an eight-year follow-up, participants with initially low fitness, as measured by a treadmill test, showed an increase in age-adjusted mortality of about 40% (Blair et al. 1989). Could 2D:4D then serve as an indicator of general health, life expectancy, or the like? Not much research has been undertaken regarding a link between 2D:4D and cardiovascular health; however, there is some evidence for a link. Testosterone may have a protective effect against myocardial infarction and, in affected males, a negative relationship between 2D:4D and age at infarction was found; thus, men with lower, more male-like 2D:4D had their infarction relatively late in life (Manning and Bundred 2001). More indirect evidence comes from a study that found a positive link between 2D:4D and neck circumference, a risk factor for coronary heart disease (Fink et al. 2006). Although there is therefore some evidence for beneficial effects of prenatal testosterone on cardiovascular health, it cannot be assumed that prenatal testosterone has a general protective effect on health because low 2D:4D has been repeatedly linked to autism and ADHD (e.g., de Bruin et al. 2006; Manning et al. 2001; Stevenson et al. 2007).

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Chapter 114
Anthropometric Variables and Its Usage to Characterise Elite Youth Athletes

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Abstract Talent identification programs usually monitor several parameters, once of which is kinanthropometry. There are a variety of anthropometric techniques that are used in talent identification. With respect to youth sport performance, the focus of this chapter was upon the use of techniques to assist with talent identification and performance within the adolescent (from 8–18 years for girls and 10–22 years for boys) phase of growth as competitive sport is not a regular occurrence in children <8 years old. Using evidence from a variety of studies, information has been provided about how sports have used kinanthropometry for talent identification purposes taking into consideration physical growth and maturation, absolute size and proportionality, somatotyping and body composition. The sports covered include individual sports (cycling, figure skating, gymnastics, rock climbing, track and field), field sports (cricket, hockey, soccer), contact team sports (American football, Australian rules football, rugby), court sports (badminton, basketball, handball, netball, tennis, volleyball), weight classified sports (judo, taekwondo, sumo wrestling, weightlifting) and water sports (rowing, sprint kayaking, swimming). Athletes are characterised by a combination of body composition/body size traits which are believed to influence the chance of success in any given sport therefore it is suggested that the measurement of kinanthropometry is a crucial tool in the search for information to assist coaches and athletes in the quest for success at the highest level in sport.

Abbreviations

ADP	Air displacement plethysmography
ARF	Australian Rules Football
BIA	Bioelectrical impedance analysis
BMI	Body mass index
% BF	Percentage body fat
% MM	Percentage muscle mass
C_s	Swimming economy

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_114,

DXA Dual-energy X-ray absorptiometry
FFM Fat free mass
H-C Heath-Carter method
SK Skinfold

114.1 Introduction

Ackland (2006) has written extensively about the talent identification process and has identified the following elements for successful programmes: (1) understanding the important aspects for success in competition, (2) recording a set of data on an athlete, (3) gathering a set of normative or comparative data, (4) using these data to construct a profile of an athlete and (5) interpreting the profile to guide the selection process or provide the basis for an ongoing training program.

Talent identification programs usually monitor several parameters, once of which is kinanthropometry. This is the study of human size, shape and form and how those characteristics relate to human movement and sporting performance (Eston and Reilly 2009). Ackland (2006) believes that the elements outlined above have not always been used in the most effective manner, with some talent identification programs running a large battery of tests without the importance of the selected parameters being taken into consideration. It is thought that, in certain situations, it may be better to measure fewer, but more discriminatory, variables. This is an approach which should be considered in the measure of anthropometrical measures, given the depth and breadth of techniques available. The aim of this chapter is to cover some of the kinanthropometry techniques that are used in the talent identification with some evidence of how they have been used in a variety of sports. For the purposes of its relation to youth sport and performance, the focus will be upon the techniques used within the adolescent (from 8 to 18 years for girls and 10 to 22 years for boys) phase of growth as competitive sport is not a regular occurrence in children <8 years old (Barker et al. 2009) (Table 114.1).

Table 114.1 Key features of Kinanthropometry

1. Kinanthropometry is the study of human size, shape, proportion, composition and maturation to assist in the evaluation of growth and of the effects of exercise, performance and nutrition.
2. Kinanthropometry utilises a combination of anatomy and movement from which data are collated and body composition predictions applied to the measurement and description of the human physique.
3. Growth is a reference to the increase in size of the body as a whole or the size attained by the specific parts of the body.
4. Maturation is the process of achieving a fully mature biological state.
5. There is a possibility that training for sport can accelerate growth and maturation; however, there are also concerns about the possible negative effects of rigorous training on growth and maturation, particularly in females compared to males.
6. Size and proportionality can play a fundamental role in selection, particularly when considering height and weight.
7. Talent ID generally monitors morphological and skeletal maturation status in young athletes; however, there are a number of growth spurts and plateaus which can affect both selection and performance.
8. The shape and proportions of an athlete are an important feature in talent identification; therefore, to increase the chance of success in sport, children should be directed towards sports for which they are physically suited. This is referred to as "morphological optimisation."

114.2 Physical Growth and Maturation

Growth is a reference to the increase in size of the body as a whole or the size attained by the specific parts of the body. The growth of the whole body is usually measured by assessment of changes in stature or by assessment of the specific parts of the body using appropriate anthropometric techniques (Beunen 2009). Maturation is the process of achieving a fully mature biological state. The predominant types of maturation that are monitored during talent identification are morphological and skeletal. The rate of development can differ significantly between individuals; however, selection bias of early maturers is a common occurrence in selection for sport based upon chronological age (Helsen et al. 2005). Rowley (1987) believed that, to be successful in sport at an international level, intensive training must begin before puberty. What must be considered, however, is the average age of elite competition. For example, gymnasts normally peak in their performance around 16 years of age compared to weightlifters who tend to peak around 30 years of age. This will affect the intensity and volume of training from a young age and can affect selection. It is believed that training for sport is important to support normal growth and maturation, although it has also been suggested that training for sport can accelerate growth and maturation (Malina et al. 2004). Moreover, there is concern about the possible negative effects of rigorous training on growth and maturation, particularly in females compared to males.

114.3 Size and Proportionality

With respect to success in specific sports, proportionality can play a fundamental role in selection. Height and body mass are two of the main discriminatory factors in selection for sport and subsequent success for both individual and team sports (see Tables 114.2–114.4). When considering height, there are two factors to consider. The first is success at sport during childhood, whereby, in the majority of sports, taller athletes are generally the more successful, although there are exceptions to this, such as in gymnastics, where a shorter stature is regularly a discriminatory factor (Malina et al. 2004). The second factor is prediction of adult height for talent identification. During adolescence, which is the growth phase we are concentrating on for this chapter, growth is fairly unstable. There are a number of growth spurts and plateaus which can affect both selection and performance. To attempt to overcome these, predictions of adult height have been developed and used through the years (Lowery 1978; Sherar et al. 2005).

Table 114.2 Key features of Somatotyping

1.	Somatotyping is a method whereby the body is described in terms of a number of traits that have a relation to body shape and composition.
2.	It is a classification of three empirically determined and visually rated extremes of body build.
3.	A somatotype of an athlete consists of a three-numeral rating, which describes the current morphological representation of an individual.
4.	The three numerals represent the three components of the physique, endomorphy, mesomorphy and ectomorphy.
5.	Endomorphy is a general indicator of an individual's adiposity level or "roundness."
6.	Mesomorphy refers to the level of muscularity of an individual.
7.	Ectomorphy is considered to be an indicator of linearity of an individual.
8.	The higher the rating of each component, the more prevalent it is in an individual.
9.	The results of somatotyping can be plotted on a somatochart, which allows the comparison between individuals and/or sports.

Table 114.3 Somatotype scores for a variety of sports in youths

Sport/position	*n*	Level	Age (y)	Endomorphy	Mesomorphy	Ectomorphy	Method	Reference
Individual sports								
Men								
Figure skating	12	Sub-elite	18.2 ± 3.6	1.7 ± 0.3	5.0 ± 0.9	2.9 ± 0.6	H-C	Ross et al. (1977)
Track and field: Hammer throwers	5	Elite	19.0 ± 1.7	3.1 ± 0.4	6.0 ± 1.0	1.2 ± 0.8	H-C	Kidd and Winter (1983)
Women								
Figure skating	18	Sub-elite	15.7 ± 1.6	2.6 ± 0.7	3.8 ± 0.6	3.0 ± 0.9	H-C	Ross et al. (1977)
	46	Elite	17.7 ± 2.2	3.3 ± 0.1	3.8 ± 0.1	2.7 ± 0.1	H-C	Monsma and Malina (2005)
Track and field: Long-distance runners	28	Elite	13.4 ± 1.7	2.1 ± 0.7	1.4 ± 0.8	4.5 ± 1.1	H-C	Wilmore et al. (1977)
Field team sports								
Men								
Soccer	16	Elite	16.4	2.1 ± 0.5	4.0 ± 0.9	2.9 ± 0.9	H-C	Reilly et al. (2000)
Forwards	56	Sub-elite	17.6 ± 2.6	2.2 ± 0.5	4.5 ± 1.0	2.9 ± 1.0	H-C	Gil et al. (2007)
Midfielders	79	Sub-elite	17.2 ± 2.4	2.6 ± 1.0	4.4 ± 1.0	2.8 ± 0.9	H-C	
Defenders	77	Sub-elite	17.3 ± 2.7	2.5 ± 0.8	4.4 ± 1.0	2.8 ± 1.1	H-C	
Goalkeepers	29	Sub-elite	17.6 ± 2.4	2.7 ± 0.7	4.4 ± 0.9	2.8 ± 0.8	H-C	
Contact team sports								
Men								
Rugby	45	Sub-elite	10	2.6 ± 1.3	4.5 ± 1.0	3.6 ± 1.4	H-C	Pienaar et al. (1998)
Court sports								
Men								
Badminton	6	Elite	17.5 ± 0.5	2.0 ± 0.9	5.2 ± 1.0	3.8 ± 1.3	H-C	Amusa et al. (2001)
Netball	17	Elite	19	4.1 ± 0.7	3.7 ± 0.4	3.4 ± 0.9	H-C	Bale and Hunt (1986)
	68	Elite	14.8 ± 0.4	4.2 ± 1.0	3.4 ± 1.1	2.5 ± 0.9	H-C	Hopper (1997)
Tennis	170	Sub-elite	10–11	2.4 ± 1.1	4.3 ± 0.8	3.4 ± 1.1	H-C	Elliot et al. (1989)
	208	Sub-elite	12–13	2.4 ± 1.1	4.1 ± 1.0	3.8 ± 1.3	H-C	
	116	Sub-elite	14–15	2.1 ± 1.0	3.8 ± 1.0	4.2 ± 1.1	H-C	
	22	Sub-elite	16–17	2.2 ± 0.9	4.1 ± 0.6	3.9 ± 1.1	H-C	
	17	Elite	11	2.2 ± 0.8	4.1 ± 0.7	3.9 ± 1.0	H-C	Elliot et al. (1990)
	57	Elite	16.2 ± 0.4	2.4 ± 0.7	5.2 ± 0.8	2.9 ± 0.7	H-C	Sánchez-Muñoz et al. (2007)
	17	Sub-elite	12.6 ± 0.9	2.2 ± 0.8	4.1 ± 0.7	3.9 ± 1.0	H-C	Juzwiak et al. (2008)

Volleyball								
Setters		Elite	17.0 ± 0.5	2.6 ± 0.9	1.9 ± 1.1	5.3 ± 1.2	H-C	Duncan et al. (2006)
Hitters		Elite	17.0 ± 0.5	2.4 ± 0.5	2.6 ± 0.6	4.6 ± 0.8	H-C	
Centres		Elite	17.0 ± 0.5	2.2 ± 0.8	3.9 ± 0.4	3.6 ± 0.7	H-C	
Opposites		Elite	17.0 ± 0.5	2.3 ± 0.8	2.5 ± 1.0	5.1 ± 1.1	H-C	
	19	Sub-elite	15.5 ± 1.0	2.3 ± 0.8	2.5 ± 1.0	5.1 ± 1.1	H-C	Gabbett et al. (2007)
Women								
Badminton	8	Elite	17.2 ± 1.1	4.2 ± 1.6	4.9 ± 0.6	2.9 ± 1.6	H-C	Amusa et al. (2001)
Tennis	103	Sub-elite	10–11	3.2 ± 1.2	3.9 ± 0.8	3.3 ± 1.0	H-C	Elliot et al. (1989)
	140	Sub-elite	12–13	3.4 ± 1.4	3.6 ± 0.9	3.6 ± 1.2	H-C	
	89	Sub-elite	14–15	4.0 ± 1.5	3.3 ± 1.1	3.4 ± 1.3	H-C	
	18	Sub-elite	16–17	4.2 ± 1.1	3.4 ± 1.0	3.1 ± 1.2	H-C	
	13	Elite	11	3.4 ± 1.3	3.7 ± 0.9	3.7 ± 1.4	H-C	Elliot et al. (1990)
	16	Elite	13	2.9 ± 0.8	2.9 ± 1.0	4.3 ± 1.0	H-C	
	15	Elite	15	3.9 ± 1.0	3.2 ± 1.0	3.4 ± 1.2	H-C	
	66	Elite	15.9 ± 0.6	3.8 ± 0.9	4.6 ± 1.0	2.4 ± 1.0	H-C	Sánchez-Muñoz et al. (2007)
	27	Sub-elite	16.4 ± 1.1	2.2 ± 0.8	4.1 ± 0.7	3.9 ± 1.0	H-C	Juzwiak et al. (2008)
Weight-classified sports								
Men								
Weightlifters								
Weight class: 52 kg	5	Elite	15–16.9	2.0 ± 0.5	5.1 ± 0.6	3.1 ± 0.5	H-C	Orvanova (1990)
	5	Elite	17–18.9	2.0 ± 0.2	5.2 ± 0.3	3.2 ± 0.7	H-C	
Weight class: 56 kg	5	Elite	15–16.9	2.6 ± 0.3	5.5 ± 0.8	2.7 ± 0.7	H-C	
	3	Elite	17–18.9	2.3 ± 0.1	5.2 ± 1.1	3.6 ± 0.8	H-C	
Weight class: 60 kg	9	Elite	15–16.9	2.5 ± 0.7	5.4 ± 1.0	2.9 ± 1.2	H-C	
	4	Elite	17–18.9	2.6 ± 0.6	6.1 ± 0.3	2.0 ± 0.6	H-C	
Weight class: 67.5 kg	7	Elite	15–16.9	3.1 ± 1.0	5.7 ± 0.7	2.5 ± 0.8	H-C	
	12	Elite	17–18.9	3.1 ± 1.0	5.9 ± 0.9	1.9 ± 0.8	H-C	
Weight class: 75 kg	11	Elite	15–16.9	2.6 ± 0.6	6.5 ± 0.8	2.0 ± 0.7	H-C	
	14	Elite	17–18.9	3.1 ± 0.7	6.2 ± 1.2	1.8 ± 0.9	H-C	
Weight class: 82.5 kg	3	Elite	15–16.9	4.7 ± 1.6	7.0 ± 0.4	0.8 ± 0.3	H-C	
	7	Elite	17–18.9	3.0 ± 0.5	6.2 ± 1.2	1.6 ± 0.7	H-C	
Weight class: 90 kg	2	Elite	15–16.9	5.9 ± 0.4	6.6 ± 1.5	0.5 ± 0.4	H-C	
	8	Elite	17–18.9	4.0 ± 1.3	7.3 ± 0.7	1.0 ± 0.5	H-C	
Weight class: 100 kg	10	Elite	17–18.9	2.8 ± 0.6	7.9 ± 0.9	0.8 ± 0.4	H-C	
Weight class: 110 kg	7	Elite	17–18.9	5.8 ± 1.1	7.9 ± 0.4	0.2 ± 0.0	H-C	
Weight class: >110 kg	3	Elite	17–18.9	8.7 ± 0.2	9.7 ± 0.3	0.0 ± 0.0	H-C	

Table 114.4 Key features of body composition

1. Body composition is defined as the division of the relative percentages of body weight into several compartments, according to definable tissues.
2. Usually, body composition is expressed as a two-compartment model in which the body is divided into fat and fat-free compartments. A four-compartment model divides the body into a fat portion, and further subdivides the fat-free portion into bone, muscle and the remainder (organs, nerves, blood, vessels and fluids).
3. Body composition measurements are applied regularly in a variety of fields including medicine, anthropology, ergonomics, human growth and sport performance.
4. Body composition techniques on athletes have been largely directed towards estimating the amount of fat in the body.
5. Assessment of body composition and the resulting computation of relative fatness contribute significant information to determine an athlete's training and nutritional programmes. Body composition estimates provide important information about an athlete's physical profile and affect the athletes' training.
6. Estimates of the body composition can only be made at present by indirect laboratory and field techniques due to the only direct method of quantifying the different compartments or tissues being cadaver dissection.
7. Traditional laboratory procedures for the estimation of body fat, such as hydrostatic weighing and total body water, are comparatively cumbersome, expensive and not always readily available, whereas more expedient methods, such as anthropometry, suffer from concerns about validity and accuracy. The technique used most often for assessing body fat in athletes has been skinfolds, although recent technological advances offer a variety of new methods for body composition assessment.

Of considerable interest is the gender differences that exist that may influence performance. Peak height velocity (PHV) is the maximum rate of growth occurring during the adolescent growth spurt (Baxter-Jones and Sherar 2007). Girls usually begin their growth spurt between 8 and 10 years, which is two years before boys usually begin their growth spurt (at 10–12 years). This may present a transitory advantage until boys begin to progress through their PHV phase by which point they have already had two years additional pre-PHV growth than girls. The time frame for PHV is also longer in boys, with the resultant height advantage in boys compared to girls measuring approximately 13 cm. Growth in the lower extremities is evident in the early phase of the growth spurt for both boys and girls; however, gender differences exist in regional muscle mass development (Malina et al. 2004). Still, there may be as much as five years' difference in the occurrence of PHV between genders; therefore, the chronological age can differ significantly compared to biological age. This is important since, during adolescence, selection for sports is likely to be influenced significantly by biological age as evidenced by the early maturers having an advantage (Helsen et al. 2005).

The shape and proportions of an athlete is an important feature in talent identification since it has been suggested that children should be directed towards sports for which they are physically suited (Bloomfield 1992). This process of "morphological optimisation" (Norton et al. 1996) is particularly useful for sports where height and body mass are important performance predictors.

114.4 Somatotyping

Somatotyping is a method whereby the body is described in terms of a number of traits that have a relation to body shape and composition. Sheldon et al. (1940) introduced the method from studies of Kretschmer's (1921) classification of three empirically determined and visually rated extremes of body build and Viola's (1933) ratio of trunk and limb measures. Heath and Carter (1967) developed this further with the Heath–Carter somatotype method, which is now the most universally applied of the available methods and is the method we have focussed on in this chapter. A somatotype of an athlete consists of a three-numeral rating, always recorded in the same order, which describes the current morphological representation. The three numbers, expressed as 2-5-1, for example, describe the value of each component – endomorphy, mesomorphy and ectomorphy – of the physique.

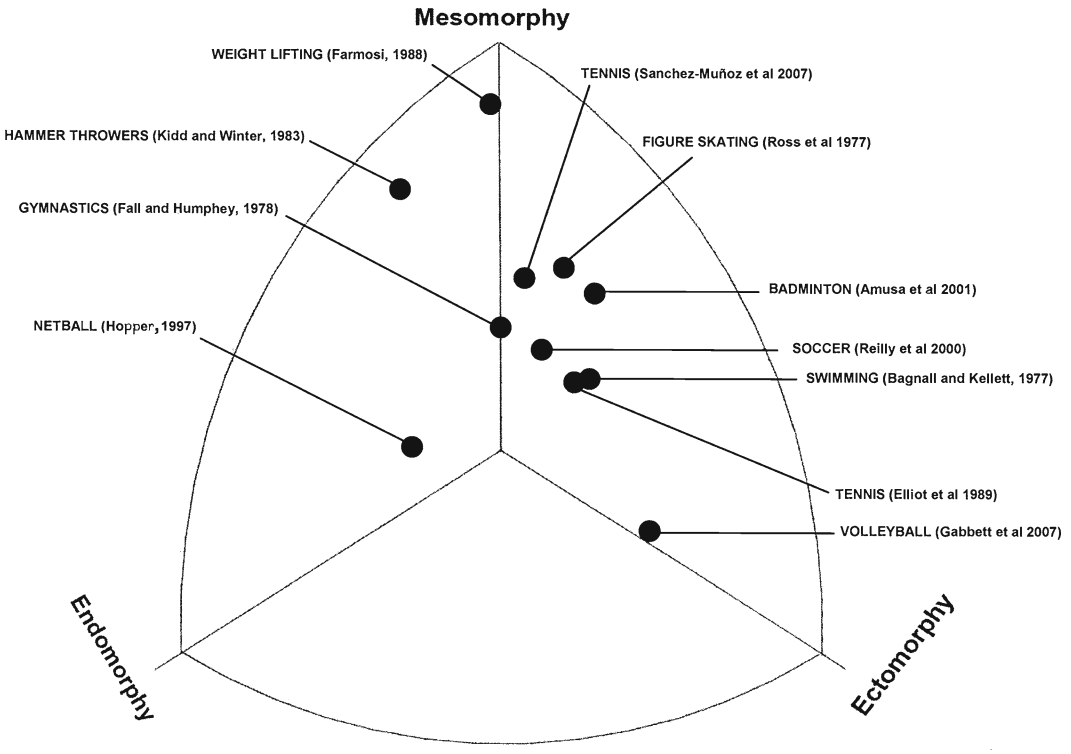

Fig. 114.1 Somatotype distribution of mean somatotypes for various youth male sports

The higher the rating of each component, the more prevalent it is in an individual. The results of somatotyping can be plotted on a somatochart, which also allows the comparison between individuals or sports (see Table 114.1 and Figs. 114.1 and 114.2).

114.4.1 Components

The first component, endomorphy, describes the relative amount of adiposity of an individual's body. It does not take into consideration the distribution. Endomorphy also provides descriptors of physical aspects, such as roundness, relative volume and the distal tapering of the limbs. Mesomorphy is the second component and describes the level of muscularity of an individual. It also refers to the descriptors of physical aspects, such as robustness, the relative volume of the trunk and other muscle mass within an individual. The measures of endomorphy and mesomorphy are considered to be an anatomical model of body composition. Ectomorphy is the third component and is a description of the linearity of the body. It also describes physical aspects of slenderness in the absence of muscle or fat mass. The category that an individual will be placed in is dependent upon the dominant component, with an indication of their secondary component. For example, a rating of 3-5-1 would suggest that an individual is an endomorphic mesomorph as they have a high mesomorphic value (5) as the primary trait and a relatively high (3) value on the endomorphic scale. If an individual has equal values in two of their ratings, they are considered to be a balanced body type as dictated by the dominant components. For example, a 1-5-1 would be considered to be a balanced mesomorph as the values for endomorphy and ectomorphy are equally low compared to the high value for mesomorphy.

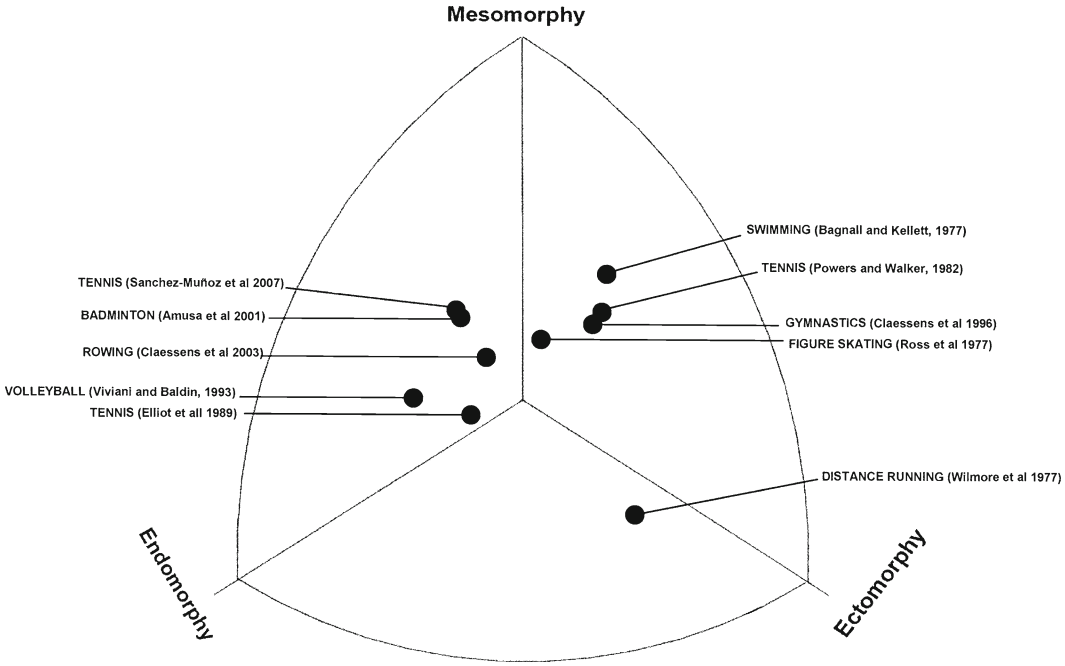

Fig. 114.2 Somatotype distribution of mean somatotypes for various youth female sports

A somatotype is an indication of the physique as a whole. It allows the assessment of the body as a whole, taking into consideration levels of adiposity, muscularity and linearity. Its application in sport and performance has been significant with the ability to compare body types across a huge range of sports and at all levels of competition. With respect to youth sport, somatotyping allows the monitoring of training, growth and maturation over time. Additionally, there is evidence to suggest that the physique characteristics of young athletes in a variety of sports are consistent with those of adult athletes in the respective sports (Heath and Carter 1990), which is potentially a useful tool in talent identification.

114.5 Body Composition

Techniques for the measurement of body composition give a more accurate indicator of what makes up an individual's shape, thereby allowing further selection criteria to be identified. There are a number of techniques available for the measurement of body composition, which range from simple to in-depth. One of the simplest estimates of body composition is body mass index (BMI); however, there are issues surrounding its accuracy, particularly in adolescent boys where the increase in body mass between 11 and 16 years may be more to do with an increase in muscle mass than adipose tissue, therefore giving an incorrect estimate of relative obesity. If BMI is used, then, an attempt to classify young people against age- and gender-specific cutoff points should be made (Cole et al. 2000). The usefulness of BMI is greater in sports that do not rely on high power/weight ratios, such as field and court sports, as opposed to sports, such as gymnastics or cycling, where body composition can have a large impact upon a height/weight ratio value (see Tables 114.1–114.3).

In addition to BMI, there are a number of techniques available to assess body composition, such as skinfolds, bioelectrical impedance analysis (BIA), hydrodensitometry, air displacement plethysmography (ADP) and dual-energy X-ray absorptiometry (DXA). Some of these techniques, such as

hydrodenistometry or DXA, require a high level of technical expertise and expensive equipment and can be quite timely to administer. One of the most used methods for the estimation of percentage body fat is skinfolds and body density. What must be taken into consideration is the effect of growth on the concepts associated with estimation of body density (Armstrong and Welsman 1997), since the water content of a child's fat-free mass and the increases seen in bone density during adolescence will affect those assumptions. Where an estimation of percentage body fat is attempted, child-specific equations should be used (Lohman 1992). To attempt to overcome this, some sports have opted to use the sum of skinfolds as an indicator of adiposity, which can also be used longitudinally. In sports, where rapid movements as well as movement of the body mass must occur, or in weight-classified sports, minimal body fat and a lean body shape is a distinct advantage (Tittel 1978). Such sports could include track and jumping sports, or combat sports. Talent identification in these types of sports should consider using a more in-depth estimation of body composition, such as skinfolds.

When considering team sports, positional differences should be accounted for, as different roles within a squad will have different energy requirements. For example, a midfielder in soccer will require a lower body fat than the goalkeeper due to the movement patterns of that position. Whilst body composition is an important element of the talent identification process, it is only one of the many factors that will contribute to success. Athletes can still perform at the highest level in the absence of the most favourable body composition, due to their excellence in other areas, such as physiology, tactics, technique and psychological approaches.

The factors outlined earlier have potential to affect performance prediction, the extent of which will depend upon a number of factors, such as the requirements and level of the sport, the application and the correct selection of techniques upon performance and their role in performance prediction. The use of the techniques in specific sports is outlined below and in Tables 114.5–114.7, with an attempt to compare the data to reference where possible. An effort to only use data from high-level youth sport had been made.

Table 114.5 Anthropometric measures of individual, field team and contact team sports in youths

Sport/Position	*n*	Level	Age (y)	Height (cm)	Body mass (kg)	BMI (kg/cm^2)	Reference
Individual Sports							
Men							
Artistic Gymnastics	65	Elite	16.0±0.7	168.1±7.6	60.3±8.0	–	Faria & Faria, 1989
	10	Elite	16.9±0.6	165.4±7.3	62.1±7.8	–	
	10	Elite	15.3±0.7	168.6±7.1	58.2±7.8	–	
Cycling (Road)	15	Elite	15.0±1.7	179.2±1.1	69.0±8.4	–	Faria et al 1989
Figure Skating	12	Sub-elite	18.2±3.6	164.4±7.3	56.5±8.2	–	Ross et al 1977
Rock climbing	52	Elite	13.5±3.0	162.2±15.6	51.5±13.6	19.1±2.2	Watts et al 2003
Track & Field							
Runners	13	Sub-elite	11.7±1.1	147.0±6.8	36.6±4.1	–	Unnithan et al 1995
Runners	11	Sub-elite	16.6±0.7	169.5±7.7	53.8±8.1	18.6±1.5	Larsen et al 2004
Runners	11	Sub-elite	16.6±0.8	170.4±7.9	53.3±5.3	18.4±1.6	
Runners: Sprint/ Hurdles	14	Sub-elite	19.8±1.3	179.1±6.6	72.8±4.8	–	Hollings & Robson, 1991
Runners: Middle/ Long distance	10	Sub-elite	19.6±1.3	178.1±2.8	66.8±4.2	–	
Jumpers: long, triple, high, pole vault	7	Sub-elite	19.3±0.9	181.6±8.1	75.5±6.3	–	
Throwers: discus, shot, put, javelin	7	Sub-elite	19.9±1.7	184.6±5.3	105.2±11.6	–	

(continued)

Table 114.5 (continued)

Sport/Position	*n*	Level	Age (y)	Height (cm)	Body mass (kg)	BMI (kg/cm^2)	Reference
Women							
Artistic Gymnastics	46	Elite	9.7±2.4	135.2±12.7	29.4±8.3	–	Claessens & Lefevre, 1998
	14	Sub-elite	11.6±1.3	143.0±10.0	35.6±8.0	17.1±2.0	Courteix et al 1999
Figure Skating	18	Sub-elite	15.7±1.6	156.8±5.0	48.6±6.0	–	Ross et al 1977
Rhythmic Gymnastics	8	Elite	14.7±2.2	165.0±3.0	47.9±3.4	17.3±1.4	Di Cagno et al 2008
	15	Elite	13.4±1.6	151.1±9.5	35.6±5.5		Douda et al 2008
Rock climbing	38	Elite	13.5±3.0	151.3±11.9	40.6±9.6	17.5±2.1	Watts et al 2003
Field Team Sports							
Men							
Cricket	48	Sub-elite	14.8±1.3	175.7±9.8	65.8±12.9	–	Pyne et al 2006
Field Hockey	21	Elite	13.2±1.3	169.0±1.0	55.1±8.7	–	Elferink-Gemser et al 2004
	17	Elite	13.2±1.3	165.0±1.0	54.9±8.1	–	
	21	Elite	13.9±1.4	169.0±1.0	55.1±8.7	–	Elferink-Gemser et al 2004
	15	Elite	16.0±1.0	176.0±8.0	64.4±8.0	–	Elferink-Gemser et al 2007
	15	Elite	15.7±1.0	166.0±5.0	57.1±6.4	–	
Soccer	16	Elite	16.4	171.0±5.0	63.1±1.1	–	Reilly et al 2000
Forwards	56	Sub-elite	17.6±2.6	174.8±6.8	68.4±9.1	22.2±2.2	Gil et al 2007
Midfielders	79	Sub-elite	17.2±2.4	174.6±7.6	68.5±9.7	22.4±2.2	
Defenders	77	Sub-elite	17.3±2.7	175.5±7.6	68.9±9.1	22.3±2.2	
Goalkeepers	29	Sub-elite	17.6±2.4	179.5±5.9	74.0±7.9	22.9±1.7	
	16	Elite	13.4±0.4	165.2±10.5	52.5±9.9	–	Le Gall et al 2010
	56	Elite	13.6±0.4	165.0±8.8	53.8±9.5	–	
	16	Elite	14.4±0.4	171.5±9.4	59.3±10.3	–	
	54	Elite	14.5±0.4	170.8±8.0	60.3±9.2	–	
	16	Elite	15.4±0.4	176.1±7.5	65.3±8.8	–	
	57	Elite	15.4±0.4	175.3±8.2	66.0±8.2	–	
Women							
Field Hockey	17	Elite	13.9±1.3	165.0±1.0	54.9±8.1	–	Elferink-Gemser et al 2004
Contact Team Sports							
Men							
American Football							
All	18	Sub-elite	16.2±0.8	180.6±2.3	89.1±13.4	–	Williford et al 1994
Backs	8	Sub-elite	16.1±0.6	180.1±5.3	80.5±7.6	–	
Linemen	10	Sub-elite	16.3±0.8	180.9±2.5	96.0±4.6	–	
All	65	Sub-elite	18.4±1.2	189.0±7.0	107.0±22.0	29.8±4.7	Kaiser et al 2008
Offensive line	12	Sub-elite	18.4±1.2	196.9±3.8	137.0±9.8	35.3±2.8	
Tight end	3	Sub-elite	18.4±1.2	194.7±5.3	112.0±2.5	29.6±1.6	
Defensive line	10	Sub-elite	18.4±1.2	193.7±3.3	127.0±12.6	33.9±4.0	
Quarterback	4	Sub-elite	18.4±1.2	188.6±2.4	92.0±4.0	25.9±1.3	
Linebacker	9	Sub-elite	18.4±1.2	188.4±3.7	104.0±6.3	29.4±6.1	
Kicker	2	Sub-elite	18.4±1.2	188.0±7.2	88.0±14.1	24.7±2.3	
Wide receiver	6	Sub-elite	18.4±1.2	186.3±3.7	88.0±8.4	25.4±2.3	
Defensive back	13	Sub-elite	18.4±1.2	181.5±2.9	84.0±6.6	25.6±1.7	
Running back	6	Sub-elite	18.4±1.2	180.8±3.3	99.0±16.6	30.4±4.1	
Australian Rules Football	29	Elite	15.9±0.8	180.2±7.2	74.6±8.3	–	Keogh, 1999
Rugby	45	Sub-elite	10	146.6±5.8	36.4±5.6	–	Pienaar et al 1998
All	28	Elite	16.0±0.2	178.0±5.9	77.5±10.0	–	Gabbett et al 2009
Hip-up forwards	28	Elite	15.9±0.4	180.9±6.7	87.0±11.1	–	
Adjustables	28	Elite	16.0±0.2	175.5±4.9	73.0±6.2	–	
Outside backs	28	Elite	16.0±0.2	178.8±5.5	74.9±7.6	–	

Table 114.6 Anthropometric measures of court and weight-classified sports in youths

Sport/position	*n*	Level	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/cm^2)	Reference
Court sports							
Men							
Badminton	6	Elite	17.5 ± 0.5	171.0 ± 4.7	54.8 ± 3.0	18.7 ± 0.8	Amusa et al. (2001)
Basketball							
Point guard	28	Elite	15.4	177.9 ± 5.3	68.1 ± 0.6	–	Hoare (2000)
Off/shooting guard	25	Elite	15.4	180.5 ± 4.6	71.3 ± 8.6	–	
Small/shooting guard	31	Elite	15.4	186.1 ± 5.7	76.4 ± 8.3	–	
Power/forward	25	Elite	15.4	191.3 ± 3.7	83.8 ± 10.1	–	
Centre	16	Elite	15.4	194.6 ± 4.4	84.5 ± 9.2	–	
Handball	34	Elite	13.1 ± 0.5	157.0 ± 9.0	45.1 ± 8.3	–	Mohamed et al. (2009)
	47	Elite	15.0 ± 0.6	174.0 ± 8.0	61.3 ± 9.4	–	
	18	Elite	15.0 ± 0.6	179.0 ± 4.0	67.1 ± 6.4	–	
Netball	17	Elite	19	172.9 ± 4.8	65.5 ± 3.9	–	Bale and Hunt (1986)
	68	Elite	14.8 ± 0.4	169.1 ± 6.1	59.0 ± 6.2	–	Hopper (1997)
Tennis	170	Sub-elite	10–11	142.0 ± 6.2	35.0 ± 6.2	–	Elliot et al. (1989)
	208	Sub-elite	12–13	151.1 ± 7.4	40.4 ± 7.0	–	
	116	Sub-elite	14–15	163.4 ± 9.4	49.3 ± 8.8	–	
	22	Sub-elite	16–17	172.6 ± 6.5	59.5 ± 8.2	–	
	17	Elite	11	142.40 ± 5.7	33.5 ± 4.0	–	Elliot et al. (1990)
	27	Elite	13	153.4 ± 7.7	41.1 ± 6.3	–	
	13	Elite	15	169.6 ± 8.3	54.0 ± 8.8	–	
	57	Elite	16.2 ± 0.4	176.8 ± 6.4	69.9 ± 6.8	22.3 ± 1.4	Sánchez-Muñoz et al. (2007)
	17	Sub-elite	12.6 ± 0.9	159.0 ± 10.0	49.2 ± 7.0	19.4 ± 1.6	Juzwiak et al. (2008)
	27	Sub-elite	16.4 ± 1.1	177.0 ± 10.0	67.0 ± 9.5	21.5 ± 2.2	
Volleyball							
Setters		Elite	17.0 ± 0.5	191.0 ± 5.0	71.2 ± 9.3	–	Duncan et al. (2006)
Hitters		Elite	17.0 ± 0.5	193.0 ± 4.5	77.9 ± 8.4	–	
Centres		Elite	17.0 ± 0.5	187.0 ± 3.6	77.6 ± 5.9	–	
Opposites		Elite	17.0 ± 0.5	190.0 ± 5.9	71.3 ± 9.2	–	
	19	Sub-elite	15.5 ± 1.0	184.0 ± 8.0	71.1 ± 9.6	–	Gabbett et al. (2007)
Women							
Badminton	8	Elite	17.2 ± 1.1	159.5 ± 5.6	51.2 ± 6.1	20.2 ± 2.7	Amusa et al. (2001)
Basketball							
Point guard	32	Elite	15.2	166.2 ± 5.2	57.8 ± 6.6	–	Hoare (2000)
Off/shooting guard	30	Elite	15.2	169.4 ± 3.4	61.6 ± 6.0	–	
Small/shooting guard	17	Elite	15.2	173.5 ± 5.3	64.1 ± 6.7	–	

(continued)

Table 114.6 (continued)

Sport/position	*n*	Level	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/cm^2)	Reference
Power/ forward	25	Elite	15.2	177.4 ± 3.6	69.4 ± 7.3	–	
Centre	19	Elite	15.2	181.6 ± 3.8	70.5 ± 6.9	–	
Tennis	103	Sub-elite	10–11	141.5 ± 6.2	34.9 ± 6.1	–	Elliot et al. (1989)
	140	Sub-elite	12–13	153.4 ± 8.4	43.3 ± 8.2	–	
	89	Sub-elite	14–15	162.8 ± 7.5	52.5 ± 7.2	–	
	18	Sub-elite	16–17	165.1 ± 5.2	56.2 ± 8.1	–	
	13	Elite	11	145.1 ± 5.8	36.4 ± 5.3	–	Elliot et al. (1990)
	16	Elite	13	159.0 ± 7.9	44.9 ± 6.6	–	
	15	Elite	15	164.5 ± 7.5	54.2 ± 6.8	–	
	66	Elite	15.9 ± 0.6	165.4 ± 6.3	59.9 ± 6.2	21.9 ± 1.7	Sánchez-Muñoz et al. (2007)
Volleyball	29	Sub-elite	14.3 ± 1.3	169.0 ± 8.0	59.6 ± 8.2	20.9 ± 2.5	Melrose et al. (2007)
	14	Sub-elite	13.1 ± 0.6	167.0 ± 9.0	56.1 ± 8.5	20.1 ± 2.6	
	15	Sub-elite	15.5 ± 0.6	170.0 ± 7.0	62.8 ± 6.6	21.6 ± 2.1	
Weight-classified sports							
Men							
Judo	17	Elite	14.7 ± 0.9	165.6 ± 10.4	55.5 ± 13.4	–	Little (1991)
	9	Elite	17.3 ± 0.8	175.3 ± 8.8	67.2 ± 7.2	–	
Weightlifting							
Weight class: 52 kg	5	Elite	15–16.9	160.1 ± 1.8	50.7 ± 1.2	–	Orvanova (1990)
	5	Elite	17–18.9	161.3 ± 3.8	51.6 ± 0.3	–	
Weight class: 56 kg	5	Elite	15–16.9	163.4 ± 3.5	55.8 ± 0.4	–	
	3	Elite	17–18.9	167.9 ± 3.8	55.7 ± 0.3	–	
Weight class: 60 kg	9	Elite	15–16.9	166.3 ± 6.0	58.4 ± 1.1	–	
	4	Elite	17–18.9	163.7 ± 2.8	60.3 ± 1.8	–	
Weight class: 67.5 kg	7	Elite	15–16.9	170.1 ± 3.6	64.5 ± 1.3	–	
	12	Elite	17–18.9	168.5 ± 4.6	66.4 ± 1.3	–	
Weight class: 75 kg	11	Elite	15–16.9	174.4 ± 4.7	73.2 ± 2.4	–	
	14	Elite	17–18.9	173.9 ± 5.3	74.2 ± 1.7	–	
Weight class: 82.5 kg	3	Elite	15–16.9	171.7 ± 3.3	80.5 ± 1.6	–	
	7	Elite	17–18.9	177.0 ± 3.7	79.7 ± 2.7	–	
Weight class: 90 kg	2	Elite	15–16.9	173.9 ± 3.2	88.0 ± 1.1	–	
	8	Elite	17–18.9	177.6 ± 4.6	87.0 ± 3.6	–	
Weight class: 100 kg	10	Elite	17–18.9	180.6 ± 4.4	97.1 ± 2.2	–	
Weight class: 110 kg	7	Elite	17–18.9	182.1 ± 2.5	105.4 ± 4.1	–	
Weight class: >110 kg	3	Elite	17–18.9	181.2 ± 2.7	126.3 ± 5.1	–	
	25	Elite	17.4 ± 1.4	170.0 ± 2.8	67.6 ± 11.8	–	Conroy et al. (1993)
	20	Elite	14.8 ± 2.3	165.5 ± 11.7	67.3 ± 10.4	24.1 ± 3.2	Fry et al. (2006)
Women							
Judo	9	Elite	15.5 ± 0.7	163.0 ± 4.7	58.1 ± 10.0	–	Little (1991)

Table 114.7 Anthropometric measures of water sports in youths

Sport/position	n	Level	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/cm^2)	Reference
Water sports							
Men							
Rowing	383	Elite	17.8 ± 0.7	187.4 ± 5.8	82.2 ± 7.4	–	Bourgois et al. (2000)
	48	Sub-elite	12.9 ± 0.6	164.7 ± 8.0	57.0 ± 10.7	–	Mikulic and Ruzic (2008)
Sprint Kayak	15	Elite	13–14	184.0 ± 4.0	86.8 ± 5.2	–	Aitken and Jenkins (1998)
Swimming							
Freestyle: short distance	31		12–13	169.4 ± 8.0	58.2 ± 5.6	–	Avlonitou (1994)
Backstrokers	30		12–13	169.4 ± 8.6	56.7 ± 8.8	–	
Breaststrokers	27		12–13	163.2 ± 7.2	49.7 ± 7.5	–	
Fliers	12		12–13	161.4 ± 9.6	57.6 ± 8.8	–	
Freestyle: long distance	12		12–13	160.0 ± 6.9	47.0 ± 6.0	–	
Freestyle: 100 m	178	Sub-elite	12.8 ± 0.1	165.5 ± 0.7	54.1 ± 0.7	–	Geladas et al. (2005)
	15	Sub-elite	11.9 ± 0.3	154.9 ± 7.5	42.5 ± 7.0	17.5 ± 1.9	Jürimäe et al. (2007)
	15	Sub-elite	14.3 ± 1.4	172.9 ± 7.9	61.3 ± 10.6	20.3 ± 2.1	
Women							
Rowing	220	Elite	17.5 ± 0.8	174.5 ± 6.2	69.5 ± 6.2	–	Bourgois et al. (2000)
Sweep rowers	108	Elite	17.5 ± 0.8	176.3 ± 5.4	71.6 ± 5.6	–	
Scullers	111	Elite	17.5 ± 0.8	173.5 ± 6.5	67.4 ± 6.1	–	
Sprint Kayak	10	Elite	13–14	171.0 ± 3.0	67.5 ± 3.5	–	Aitken and Jenkins (1998)
Swimming							
Freestyle: Short distance	29		12–13	167.2 ± 7.2	57.9 ± 6.3	–	Avlonitou (1994)
Backstrokers	28		12–13	164.4 ± 7.6	53.2 ± 6.2	–	
Backstrokers	29		12–13	162.7 ± 5.8	52.7 ± 6.4	–	
Fliers	19		12–13	155.4 ± 2.6	50.6 ± 5.4	–	
Freestyle: Long distance	14		12–13	159.5 ± 5.2	49.5 ± 7.9	–	
Freestyle: 100 m	85	Sub-elite	12.7 ± 0.1	161.2 ± 0.6	48.3 ± 0.6	–	Geladas et al. (2005)

114.6 Individual Sports

114.6.1 Cycling

Track cyclists are known to be more powerful than road cyclists, especially those involved in the shorter distances, although there are similarities across both groups. Road versus track cycling should also be taken into consideration. Faria et al. (1989) indicated that youth cyclists were notably taller, heavier and leaner than non-athletes and when compared to junior swimmers and runners, and they were found to be similar to endurance athletes. Measures of body composition revealed a high

correlation between estimated percentage fat, triceps skinfold and suprailium skinfold, which suggests that these are the most appropriate skinfold measurements for this homogeneous population.

114.6.2 Figure Skating

The importance of morphological characteristics for most optimal performance in aesthetic sports has been noted. Monsma and Malina (2005) demonstrated that elite skaters had shorter leg lengths than pre-elite skaters; however, this may be due to maturation levels, as pre-elites are generally younger and in an earlier phase of their adolescent growth spurts. Additionally, lower-level test stream skaters had greater skinfold values than both pre-elite and elite skaters, suggesting an effect of level on kinanthropometry. Ross et al. (1977) demonstrated that, compared to Mexican Olympic athletes, Canadian Olympic skaters (senior and junior men and ladies) were ectomorphic/mesomorphic on the scales and that they closely resembled gymnasts in size, being relatively small, lean and only slightly less muscular.

114.6.3 Gymnastics

Success in gymnastics relies on attaining the highest score during competition. It is claimed that anthropometrics are the greatest predictor of performance in rhythmic gymnastics (Douda et al. 2008), accounting for 41% of the success in performances of basic body elements of difficulty, whereas non-adipose voluminosity accounts for 26% of rhythmic-gymnastics-specific manipulations with the apparatus (Miletic et al. 2004). Rhythmic gymnastics relies in part upon the ability to leap and hop. It was found that height accounted for 16% of variance in hopping height. Elite rhythmic gymnasts were taller and had significantly longer thigh lengths and higher values of FFM than sub-elites (Di Cagno et al. 2008), therefore supporting the use of these parameters to select gymnasts in the early stages of development.

When attempting to predict the best independent predictors of annual changes in bone mineral density (BMD) for total body, lumbar, spine, trochanter and femoral neck sites of highly trained gymnasts, Courteix et al. (1999) found that variations in lean mass, bone age and fat mass were the greatest independent predictors. With respect to male gymnasts, it was found that top male class II gymnasts were significantly leaner than class I and lower class II gymnasts. Additionally, class II gymnasts, when compared to other classes, were characterised as shorter in stature, were leaner and possessed more muscle mass (Faria and Faria 1989). The length of the arms with respect to trunk length and percentage body fat are key factors due to their potential impact on achieving skill at the highest level and should therefore be included in the talent identification process of high-level gymnasts.

114.6.4 Rock Climbing

The popularity of climbing continues to grow, with normative data on adult climbers beginning to emerge regularly. In evaluations of young competitive rock climbers, significant differences in height, mass, ratio of arm span to height, biiliocristal/bi-acromial ratio, sum of skinfolds and estimated percentage fat were found compared to age-matched controls. Watts et al. (2003) suggested that young competitive climbers have general characteristics similar to adult climbers, although young climbers

appearing to be more linear with narrow shoulders relative to hips. Continued monitoring of youth climbers is useful to form normative databases both for selection for elite levels and for comparison to adult climbers.

114.6.5 Track and Field

There is a plethora of data relating to kinanthropometry of runners of differing distances and a variety of ages. The data of Graves et al. (1987) showed that elite female runners had smaller girths than gymnasts, body builders and normative references. Male Kenyan runners had measures of BMI, height and mass that were smaller than age-matched Scandinavian athletes. This suggests that there may be an affect of race on performance (Larsen et al. 2004). Hollings and Robson (1991) indicated that, in a cohort of field and track athletes including throwers, sprinters, middle-distance runners and jumpers, throwers were a distinct group as far as body build was concerned. They were taller, heavier and had higher levels of subcutaneous fat than the other groups. Throwers had a low ponderal index with their limbs appearing as a series of relatively short levers, which would assist them in performance. Middle-distance runners were lighter than the other groups, whereas the sprinters and jumpers were similar to each other, suggesting that anthropometric variables can differentiate between groups of events in track and field athletes and should be considered for talent selection.

114.7 Field Team Sports

114.7.1 Cricket

Cricket is a sport which requires all players to field and bat and is supported by a set of skills that defines a player's role which will contribute to the success of the team. One of the aspects of crickets that can affect the potential for success is peak bowling speed (Stuelcken et al. 2007). A study of the anthropometric and strength correlates in junior cricketers revealed multiple predictors of success in achieving peak bowling speed, which included height, body mass and estimated percentage muscle mass. From these measures, it was found that body mass and estimation of percentage muscle mass were considered to be the most useful anthropometric predictors of peak velocity in junior bowlers (Pyne et al. 2006); therefore, they should be used as part of a battery of tests for talent detection in youth players.

114.7.2 Hockey

Field hockey requires intermittent running, accelerations and decelerations, requiring a high level of effort. Differences in anthropometric measures have been reported in players of differing levels (Ready and Van der Merwe 1986). A study of female players demonstrated that higher-level regional players had significantly lower skinfold thickness values and estimated percentage fat than the lower-level club players, suggesting that talent identification programmes should potentially use these anthropometric measures as part of the selection process (Keogh et al. 2003). A study of elite and sub-elite male and female junior players over three seasons demonstrated that elite male and female

players increased in height and mass. Males also reduced estimated percentage body fat over time. Elite players appear to score better than their sub-elite counterparts in a number of characteristics and it is suggested that players should be tracked into adulthood (Elferink-Gemser et al. 2004).

114.7.3 Soccer

Soccer is intermittent in nature and is multifactorial in terms of the elements required for success. A talent identification study by Reilly et al. (2000) demonstrated that elite-level junior players had significantly lower endomorphy scores than lower-level players. Additionally, elite-level players were leaner than lower-level players when considering both sum of skinfolds and estimated percentage fat. The sum of skinfolds also more clearly distinguished between the groups than did estimated percentage fat. With respect to positions, Gil et al. (2007) demonstrated that forwards were the leanest players, presenting the highest level of muscle. By contrast, the goalkeepers were found to be the tallest and heaviest players, with the largest skinfold values and the highest percentage fat values. For midfielders, height was one of the anthropometric discriminants of selection. Le Gall et al. (2010) demonstrated that graduate players from an elite youth academy were taller and heavier than amateurs. The findings of these studies suggest that anthropometric measures should be taken into consideration when attempting to detect talented for soccer.

114.8 Contact Team Sports

114.8.1 American Football

American football players are thought to have a morphological profile similar to rugby players due to the similarities in playing profiles involving discontinuous bouts of intensive exercise with high levels of tackling. Research indicated that BMI values of collegiate players were classified as overweight or obese; however, average body fat percentage estimations placed them into the acceptable age- and gender-referenced normal ranges (Kaiser et al. 2008). With respect to positional differences, morphology of the players in the study was consistent with the positional specialisation requirements. For example, positions specialised for the line-off scrimmage blocking and tackling were taller and heavier than players at other positions. The positions specialised for sprinting and dynamic agility demonstrated lower height, weight, body fat percentages and BMI compared to the overall group (Kaiser et al. 2008). It was also suggested that, as the level of competition increases, so do weight, height and fat-free mass (FFM) (Williford et al. 1994), highlighting the importance of monitoring body composition at all levels of development.

114.8.2 Australian Rules Football (ARF)

Like other contact field sports, ARF requires players to cover the majority of distances during a game at submaximal speeds, with shorter bursts of speed interspersed with longer periods of recovery. One of the main anthropometrical attributes for success is considered to be height, especially for key positions, such as forwards. A study to predict selection in an elite youth ARF team found that height and mass were anthropometric measures that could be used in a discriminant analysis to predict selection,

with height considered to be one of the two most important discriminators for selection in elite under-18 ARF players. Additionally, selected players were shown to be significantly taller and heavier than non-selected players (Keogh 1999). Selected junior players appear to be relatively similar to senior players in terms of height (Douge 1988), but not in terms of body mass, although anthropometric measurements, such as girths and body mass, increase significantly as teenage males mature (Housh et al. 1997), signifying that under-18 ARF players are still maturing physically, which is required if players are to compete at the senior level. Anthropometric measures should be monitored at junior through to senior levels to maximise the chance of selection of optimal body types for ARF.

114.8.3 Rugby

Rugby league is a collision sport that is intermittent in nature. The positions can be broadly classified into forwards or backs. Forwards are involved in significantly more collisions and tackles than backs and have a higher activity ratio of high:low intensity. Forwards also cover a larger distance than backs during a match. Studies of senior rugby league players have shown significant differences between positions in measures of height, body mass and skinfold thickness (O'Connor 1996). Research on junior elite rugby league players indicates that forwards are taller, heavier and have greater skinfold thicknesses than backs. When discriminating between starters and non-starters, elite starters were taller and heavier than non-starters, whereas sub-elite starters were taller than sub-elite non-starters (Gabbett et al. 2009). In a study attempting to identify and develop rugby talent, calf and upper-arm girths as well as humerus and femur diameters showed practical significance (Pienaar et al. 1998). The findings of the studies earlier indicate that physical characteristics of junior rugby players should be taken into account in talent identification models and should therefore be a consideration when setting realistic junior performance standards.

114.9 Court Sports

114.9.1 Badminton

Badminton is considered to be an agility sport, which requires movements to be executed by the upper extremities, although performance is multifactorial. A study by Amusa et al. (2001) showed that height, weight and arm span are the most important indicators for performance in junior national players. Somatotype measures indicated that, in male players, mesomorphic ectomorph was the predominant measure, whilst endomorphic mesomorph was the main measure for females. It was also suggested that, to allow free movement around the court, lower weight athletes with low BMI values would have an advantage.

114.9.2 Basketball

Basketball is an agility-based, intermittent sport that partially relies on jumping ability. Morphological proportions to support those activities is key; therefore; height is one of the key determinants of success, so are long limb lengths for defending, passing and shooting. In junior elite players, arm span was considered to be a predictor of overall success. When positions are considered, the best male

point guards were taller than the rest, though the best power forwards were significantly taller and had a longer arm span than the rest. The best small forward players were also taller than the rest of the players in that position (Hoare 2000). In female players, positional differences existed between centres and point guards demonstrating lower levels of FFM and smaller arm span values. In best versus rest tests, the best females had proportionally longer legs than the rest of the cohort. Since significant differences exist in certain anthropometric measures in young players, monitoring anthropometric attributes appears to be a successful tool for predicting success alongside other factors related to basketball performance (Hoare 2000).

114.9.3 Handball

Handball is a dynamic sport characterised by speed, agility, reaction speed, explosive power, endurance, strength and coordination. In handball, absolute size of the body is an important factor in handball for both youth and adults. It is also suggested that the size of the hand is an important factor when selection criteria for players are set. This is due to hand size and finger length being useful for throwing accuracy. In a study of male youth players for talent detection purposes, significant differences were seen between the elite and non-elite players for body mass, arm length, relative arm length, arm span and both upper limb muscle circumferences (stretched and flexed). For the long-term development of talented players, a careful follow-up of the maturation process, including growth of the most important body segments, is considered necessary. In a discriminant analysis, height was considered an important determinant for performance and corresponds well with characteristics suggested as essential in youth and adult handball (Mohamed et al. 2009).

114.9.4 Netball

Netball is a court sport that is intermittent in nature with agility and jumping two of the key skills for success. Bale and Hunt (1986) demonstrated that elite players were heavier, significantly taller and had significantly smaller femur bone widths than players classified as good. Elite players showed total skinfold and estimated fat levels which suggested a larger muscle mass but lower levels of adiposity in relation to their height. Somatotype analysis showed most players were of the mesomorphic endomorph type or balanced mesomorphs (Hopper 1997). With respect to positions, centres were significantly shorter, lighter and had less fat than attackers and defenders. Attackers and defenders were the tallest and heaviest of the players, whereas central players were more mesomorphic than the attackers and defenders who tended to show more ectomorphic traits. There are several parameters that should be monitored to assess ability, of which body composition is one.

114.9.5 Tennis

Tennis is characterised by explosive activities interspersed with intermittent bouts over a long period of time. A high lean body mass/height ratio is thought to be an advantage. A study of adolescent

junior players found the BMI and estimated percentage fat of players to be in the recommended range for young athletes (Juzwiak 2008), whereas, in a study by Elliot et al. (1990), it was indicated that, in male players, estimated percentage fat was lower in high-level players across age groups. The cohort of players were also shown to be more linear, expressing high ectomorphy levels, which is line agreement with the findings of Copley (1980), who suggested that ectomesomorphy is a required characteristic for successful tennis performance at the professional level.

For females, body composition was considered an important indicator of tennis performance from 11 to 15 years. Higher level players were leaner than the controls in both endomorphy levels and sum of skinfolds. Copley (1980) also showed that professional female players were more endomesomorphic than amateur players, although height and mass were not thought to discriminate between higher level and control subjects. A study by Sanchez-Muñoz et al. (2007) demonstrated that significant differences were observed in height and humeral and femoral breadths when comparing the first 12 and the lower ranked female players. The first 12 players were significantly taller than the lower ranked players, providing evidence for the use of talent identification in junior tennis.

114.9.6 Volleyball

Volleyball is an intermittent sport that requires players to participate in frequent short bouts of high-intensity exercise, followed by periods of low-intensity activity. Thissen-Milder and Mayhew (1991) demonstrated that height and weight were two of the anthropometric characteristics measured in high-school players that could discriminate amongst starters and non-starters. Data from Melrose (2007) suggested that lean body mass and shoulder, hip and thigh girths are the key anthropometric physical determinants of performance in adolescent female volleyball players. In measures of junior national and state players, significant differences were detected between levels for height, standing-reach height and skinfold thickness. Male players were found to be taller, heavier and leaner and with greater standing-reach height than female players. A study of somatotypes in elite players showed positional differences, with setters tending to be endomorphic ectomorphs, hitters and opposites tending to be balanced ectomorphs, and centres tending to be ectomorphic mesomorphs (Duncan et al. 2006). The analysis of performance standards for junior volleyball highlights the importance of some characteristics as the level of playing increases.

114.10 Weight-Classified Sports

114.10.1 Judo

Successful participation in Judo is thought to depend upon appropriate levels of technical skill, supported by a number of physical characteristics. In a study of junior males and female judokas, Little (1991) demonstrated that the estimated percentage body fat for junior males and females was less than the normative reference value. Given that the nature of Judo is to continuously grip your opponent whilst actively trying to remove them from a balanced stable position, it would seem that biological maturity would have an impact on performance and chance of success and performance differences, especially in junior males of the same chronological age, but contrasting maturity status,

the difference of which is most apparent between the ages of 13 and 16 (Malina et al. 2004). This indicates the importance of monitoring maturity in junior judokas.

114.10.2 Sumo Wrestling

Sumo wrestlers are well known for their very large bodies, which has often raised questions about their health status. The anthropometric dimensions of sumo wrestlers, such as stature, body weight, length and circumference of the limbs and trunk have been reported previously. A study of wrestlers in the higher leagues demonstrated larger bodies than those who belong to the lower leagues (Nishizawa et al. 1976; Hattori et al. 1999). In college-level sumo wrestlers, BMI and estimated percentage fat was very high compared to non-athletes and all were characterised as obese, although further measures of body composition also demonstrated that the wrestlers had excessive fat-free mass values. To monitor the health status as well as the talent detection element, accurate methods should be used to estimate body composition in junior sumo wrestlers.

114.10.3 Taekwondo

Taekwondo is a weight-classified combat sport using a variety of kicking and punching movements. Fleming and Costarelli (2007) showed that following an analysis of skinfold measurements, a cohort of international standard athletes were very lean, with low levels of fat mass and high levels of muscle mass. Measures of BMI were high, which may be due to their lean body mass/height ratio as opposed to their level of obesity. Evidence from other combat sports suggests that athletes regularly compete at 5–10% below their natural body weight (Filaire et al. 2001), highlighting the importance of body composition.

114.10.4 Weightlifters

Somatotyping by Orvanova (1990) indicated that the athletes at the higher levels showed greater levels of mesomorphy and lower levels of endomorphy. Depending upon their pubertal growth spurt, young lifters have varying levels of mesomorphy and ectomorphy. When separated into weight groups, the lighter athletes showed higher levels of mesomorphy, whereas the heavier athletes demonstrated higher levels of endomorphic mesomorphy. Ectomorphy decreases, whereas mesomorphy and endomorphy were shown to increase with weight class. Comparison of age groups revealed that the younger lifters in each weight class had higher endomorphy and lower mesomorphy levels than the adult lifters. Ectomorphy was found to be higher in the youngest lifters, but only below the weight class of 82.5 kg. All age and weight classes of weightlifters demonstrated greater mesomorphy and lower ectomorphy than non-athletes and the differences tended to increase with weight class. Measures of bone mineral density revealed that it is found to be much higher in junior weightlifters due to the influence of the chronic overloads experienced with training for that sport (Conroy et al. 1993). When attempting to predict performance, Fry et al. (2006) showed that body mass and relative fat are two of the five screening tools that should be utilised for detection in junior weightlifters.

114.11 Water Sports

114.11.1 Rowing

Extensively studied, anthropometric data from both males and females have emphasised the importance of body mass (Secher and Vaage 1983) and body size (Rodriguez et al. 1986) in rowing. In a cohort of youth rowers, from a selection of anthropometric measures, thigh girth and lean body mass, when entered into a regression table, were significant predictors of 1-km rowing performance (Mikulic and Ruzic 2008). Bourgois et al. (2000) also showed that male junior rowers had increased bicep, thigh and calf girths compared to reference data, whereas female junior rowers had increased biceps thigh, and calf compared to references and non-finalists. Of the rowers who reached the finals, all had larger measures in the biceps and thigh than the non-finalists. Therefore, anthropometric measures should be considered for performance prediction measures in rowing events for both males and females, as clear differences between athletes and reference data exist.

114.11.2 Sprint Kayak

Sprint kayaking requires the athlete to propel themselves predominantly using the upper body. Aitken and Jenkins (1998) showed differences in body mass, biceps girth, upper arm length, forearm length, thigh length, lower leg length and biliocristal breadth between elite kayakers and controls. The elite female paddlers had greater mass and bicep girths than the female controls. With respect to key determinants of performance in male paddlers, those who had greater bi-acromial breadth and extremity lengths demonstrated greater improvements following training. Additionally, the morphological proportions of kayakers who performed at Olympic level revealed that elite paddlers had distinct characteristics compared to the general population, which included a greater than average thigh length, shoulder and chest breadths along with proportionally large upper body girths (arm and chest girth) and proportionally narrow hips in males and lean physiques as demonstrated by low skinfold scores (Ackland et al. 2003). The data from previous studies clearly indicate that anthropometric measures can be useful in the selection of individuals for high-level performance and should therefore be considered in athlete monitoring protocols.

114.11.3 Swimming

Training for high-level swimming begins at an early age. Due to the large number of swimming events, research has attempted to classify the variety of characteristics which help to distinguish which event an individual should select and train for. Analysis of youth data for the prediction of 100-m freestyle performance suggested that upper extremity length was a significant predictor of 100-m freestyle performance, whereas body height, upper extremity and hand length were all significantly related to 100-m freestyle time (Geladas et al. 2005). In a variety of swimming events, Avlonitou (1994) showed that sprint and back swimmers were the tallest and heaviest among the events for both sexes. This group also had the highest values for upper and lower limbs and hand and foot lengths. The long-distance group was the shortest and lightest group for males and the lightest group for

females. The female fly group had the lowest values for height, upper and lower limb lengths as well as hip width. Significant correlations were obtained between performance and somatometric variables. For swimmers participating in different events, variation in body size and form is already present at an early age. Analyses of swimming performance including body composition measures found significant relationships between the energy cost of swimming (C_s) and body mass, FFM and body mass in prepubertal and pubertal swimmers, suggesting that body composition parameters have a significant impact on C_s (Jürimäe et al. 2007). It was also shown that, of the anthropometric measures, arm span was the best predictor of swimming performance. Swimming is clearly influence by anthropometrics; therefore, every effort should be made to clarify which anthropometric measures distinguish between events, thus allowing a talent identification option available for all events.

114.12 Practical Application to Sport and Performance

The data from these studies suggest that participants are characterised by a combination of body composition/body size traits which are believed to influence the chance of success in any given sport. It is also clear that success in sport is multifactorial and that the value of anthropometric measures in assisting with talent identification or predicting success is varied between and within sports. It is, however, clear that the measurement of kinanthropometry is a crucial tool in the search for information to assist coaches and athletes in the quest for success at the highest level in sport.

Summary Points

- Talent identification programmes usually monitor several parameters, once of which is kinanthropometry.
- For talent identification purposes, measurements of kinanthropometry take into consideration physical growth and maturation, absolute size and proportionality, somatotyping and body composition as measured by a variety of methods.
- Athletes are characterised by a combination of body composition/body size traits which are believed to influence the chance of success in any given sport.
- It is thought that, in certain situations, it may be better to measure fewer but more discriminatory variables for potential athlete selection purposes.
- Success in sport is multifactorial; therefore, the value of anthropometric measures in assisting with talent identification or predicting success is varied between and within sports.

Acknowledgements The authors would like to take this opportunity to thank their respective Universities, Liverpool John Moores University and University of Granada, for the continued support during the writing of this chapter.

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Chapter 115
Anthropometry in Athletes with Spinal Cord Injury

Mina C. Mojtahedi and Ellen M. Evans

Abstract Whole body fat and lean soft tissue appear to be reduced in athletes with spinal cord injury (SCI) compared to sedentary able-bodied (AB), however this does not reflect distribution of lean soft tissue and fat mass throughout the body. Research findings using dual energy X-ray absorptiometry (DXA) assessing regional body composition indicate that as a result of upper-body exercise, athletes with SCI have increased arm and trunk lean soft tissue compared to sedentary AB, and decreased arm FM compared to sedentary SCI. Due to muscle atrophy following SCI, lower-body lean mass is reduced compared to sedentary AB, as found in sedentary individuals with SCI. Although DXA is currently the most feasible method for accuracy and for measuring regional body composition, it is not a practical tool for practitioners working with athletes. Therefore field methods such as skinfold measurements and bioelectrical impedance analysis (BIA) have been evaluated for use in athletes with SCI. Unfortunately, these field methods and prediction equations for estimating relative body fat do not appear to be accurate or reliable for use in athletes with SCI. Currently, limited body fat prediction equations for skinfold and BIA measurements have been developed specifically for athletes with SCI. Generally, limited research data is available on body composition assessment in athletes with SCI, and many of the studies are limited in sample size, varying methodology and inclusion criteria. Further research utilizing multicenter studies are likely needed to contribute to the literature and to create better prediction equations for the SCI athlete population.

Abbreviations

%BF	Body fat percentage
AB	Able-bodied
BIA	Bioelectrical impedance analysis
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
DXA	Dual energy X-ray absorptiometry
FM	Fat mass
HDL	High density lipoprotein

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_115,

IMAT	Intermuscular adipose tissue
LST	Lean soft tissue
MRI	Magnetic resonance imaging
SCI	Spinal cord injury
SEE	Standard error of the estimate
TE	Total error
TOBEC	Total body electrical conductivity

115.1 Introduction

Spinal cord injury (SCI) causes motor and sensory loss at and below the level of lesion. The resulting complete or incomplete paralysis of the affected limbs leads to alterations in body composition and bone which include reductions in regional lean soft tissue (LST) and bone mineral of affected limbs, and an increase in whole body and regional fat mass (FM) (Jones et al. 1998; Spungen et al. 2000; Maggioni et al. 2003). Effects of exercise on body composition are well documented (Williams et al. 2005) in able-bodied (AB) populations and are opposite to changes following SCI, that is, increased LST and bone mineral, and decreased FM.

This chapter focuses on anthropometry using the three-compartment model with regard to athletes with SCI: fat, water (lean), and mineral (bone). The term 'athlete' is defined as an individual who participates in elite and recreational sports, and has trained at a duration, volume, and intensity above the standard physical activity recommendations for the general population (Pollock et al. 1998).

115.2 Soft-Tissue Composition

115.2.1 Multicompartment Models

115.2.1.1 Dual Energy X-Ray Absorptiometry

A limited number of studies have been conducted in athletes with SCI, but generally these studies show that paraplegic athletes with SCI have less FM and more LST than sedentary SCI (Olle et al. 1993), but less FM and less LST compared with sedentary AB controls (Mojtahedi et al. 2008a, b, 2009; Sutton et al. 2009). A study with DXA (Mojtahedi et al. 2008a, b) reports that, in absolute values (kg), athletes with thoracic and lumbar SCI had 20% less whole-body LST and 25% less whole-body FM than sedentary AB.

However, several studies have shown that whole body values do not reflect distribution of LST and FM throughout the body in individuals with SCI (Spungen et al. 2000, 2003; Maggioni et al. 2003). Therefore, it is important to assess regional body composition, particularly in athletes with SCI, who are using only their upper body to generate muscle force and, thus, whose upper body primarily is impacted by physical activity. Mojtahedi et al. (2008a, b) have shown that arm LST is 24% more and arm FM is 23% less in athletes with SCI than in sedentary AB. This same study (Mojtahedi et al. 2008a) also showed that leg LST is about 50% less in athletes with SCI than in sedentary AB. Therefore, upper-body responses to physical activity are as would be expected when comparing SCI athletes with sedentary individuals, but lower-body muscle remains atrophied due to severed muscle innervation and disuse following SCI.

Table 115.1 Key facts of spinal cord injury (SCI)

1. Major causes of SCI include motor vehicle accidents, falls, sports, and violence.
2. An SCI results in paralysis of innervated muscles. A complete SCI results in total loss of sensation and function, whereas an incomplete SCI results in only partial loss.
3. The neurological level of injury determines the proportion of affected limbs. Cervical lesions result in complete and incomplete quadriplegia (also tetraplegia), affecting all four limbs and trunk. Thoracic and lumbar lesions result in complete and incomplete paraplegia, affecting the legs and part or all of the trunk.
4. Loss of innervation to muscles leads to muscle wasting of affected limbs, and is often accompanied by fat accumulation.

This table lists some key facts about spinal cord injury including basic terminology. *SCI* = spinal cord injury

No studies are currently available using DXA methodology to compare body composition of athletes with SCI to sedentary individuals with SCI. However, compiling findings from multiple studies show, surprisingly, that athletes have similar levels of arm LST, but, as expected, significantly less arm FM than sedentary SCI. Arm LST values of 7.3–8.3 kg have been reported in sedentary individuals with SCI (Spungen et al. 2000, 2003) and 7.6 kg in athletes with SCI (Mojtahedi et al. 2008a). Arm fat mass values were 3.2 kg (Spungen et al. 2003), which is almost twice the amount of 1.7 kg found in SCI athletes (Mojtahedi et al. 2008a).

Importantly, when body size differs between populations, absolute soft-tissue mass also differs. As shown in Table 115.2 (Mojtahedi et al. 2008a), although relative size (i.e., BMI) was not different, athletes with SCI differed in height and weight from sedentary AB. Therefore, comparisons of body composition compartments (i.e., fat mass) must be assessed in relative terms. Table 115.2 and Fig. 115.1 show that whole body and regional fat percentages did not differ and LST percentages did differ between athletes with SCI and sedentary AB (Mojtahedi et al. 2008a). Compiling data available from multiple studies indicates that relative body fatness in sedentary individuals with SCI ranges from 27 to 31% (Jones et al. 1998, 2003, 2004; Maggioni et al. 2003), which is somewhat greater than the 25% in athletes with SCI (Mojtahedi et al. 2008a). Many of these studies are, however, confounded by differences in gender, age range, spinal cord injury levels, and use of different DXA machines. Nevertheless, in summary, relative values indicate that:

- As a result of upper-body exercise, athletes with SCI have increased arm and trunk LST compared to sedentary AB, and decreased arm FM compared to sedentary SCI.
- As with sedentary individuals with SCI, lower-body lean mass is reduced in SCI athletes due to muscle atrophy.

115.2.1.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has gained increased use over recent years in the area of body composition assessment, as it provides access to measuring specific adipose tissue depots, such as subcutaneous and intermuscular adipose tissue (IMAT, defined as adipose tissue located beneath the fascia lata and between muscle groups.) (Shen et al. 2003), which have been found to be associated with metabolic disorders (Goodpaster et al. 2003, 2005). This is relevant to individuals with SCI, as muscle disuse is known to increase IMAT and decrease muscle in AB individuals (Manini et al. 2007). Moreover, absolute and relative thigh IMAT areas are increased in the SCI population, both athletic (Mojtahedi et al. 2008a, b) and sedentary (Elder et al. 2004; Gorgey and Dudley 2007). Sedentary SCI appear to have more thigh IMAT than athletes with SCI (Fig. 115.2A and 2B). However, as the level of muscle disuse is similar in both groups, the mechanism for this apparent difference is as yet unclear.

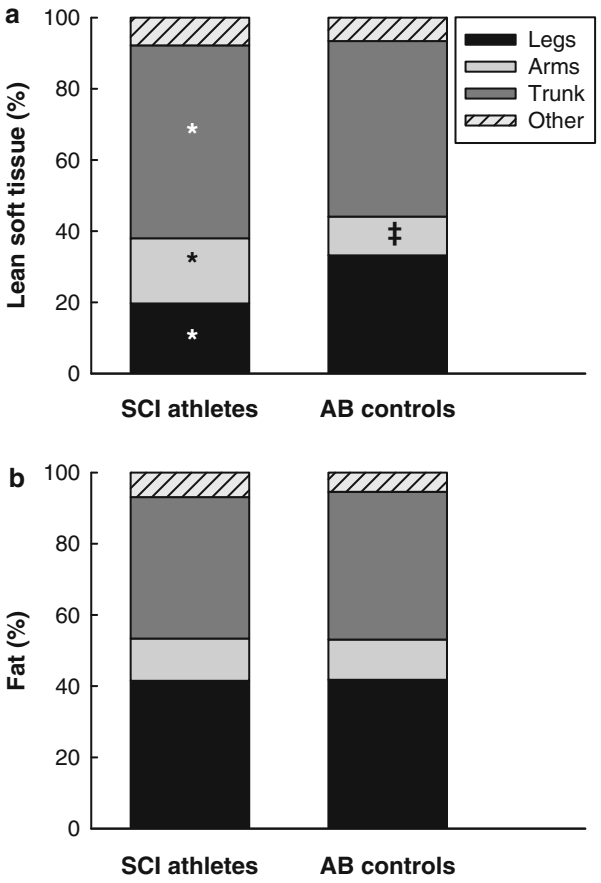

Fig. 115.1 Regional distribution of relative lean soft tissue (**a**) and fat (**b**). Whole body and regional lean soft-tissue percentages differ and fat percentages do not differ between athletes with SCI and sedentary AB. *SCI* = individuals with spinal cord injury, *AB* = able-bodied individuals. * Indicates significant group differences in the distribution of lean soft tissue ($p < 0.05$). ‡ Indicates within-group interaction ($p < 0.05$) between gender and the regional distribution of lean soft tissue in the arms (Reprinted with permission from Mojtahedi et al. 2008a)

115.2.2 Field Methods and Prediction Equations

115.2.2.1 Skinfold Prediction Equations

Body fat percentage (%BF) prediction equations combine a variety of skinfold sites often with other variables, such as age, weight, circumference, and measurements, to predict a gold-standard measurement of body composition. Equations are often developed for specific populations. Currently, no body fat prediction equation for skinfold measurements has been developed specifically for athletes with SCI. Nevertheless, a number of equations have been evaluated for acceptability for the SCI population.

Table 115.3 shows selected equations from three cross-validation analyses in athletes with SCI, comparing the accuracy of skinfold body fat measurements to hydrodensitometry and DXA. Equations that are used often in general populations and have been derived from AB populations include Durnin and Womersley (1974), Jackson and Pollock for men (Jackson and Pollack 1978) and women (Jackson et al. 1980), Sloan for men (Sloan. 1967), Sloan and Weir for men and women (Sloan et al. 1970), Katch and McArdle (Katch et al. 1973, 1975), and Wilmore and Behnke for men (Wilmore et al. 1969)

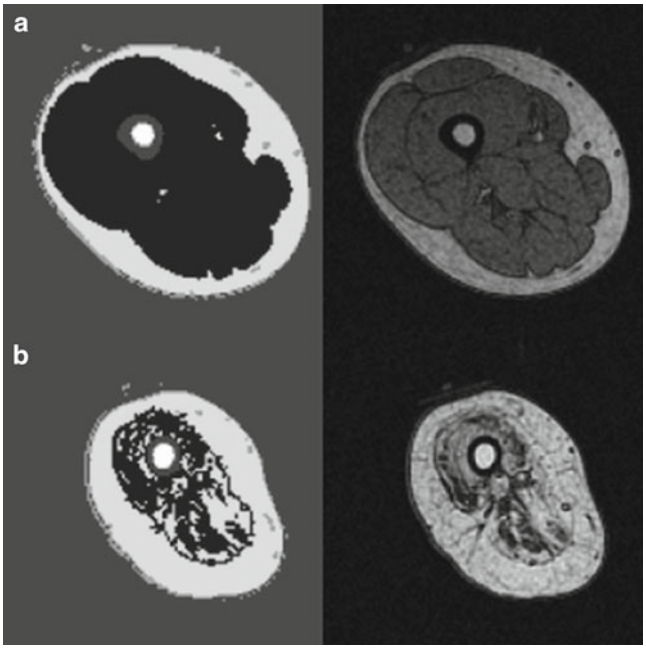

Fig. 115.2 Magnetic resonance cross-sectional analyzed and unanalyzed images of the right mid-thigh of a male sedentary able-bodied participant and a male athlete with spinal cord injury (SCI). Magnetic resonance cross-sectional analyzed and unanalyzed images of the right mid-thigh of a male sedentary able-bodied participant, (**a**: displayed in the upper half) and a male athlete with spinal cord injury (**b**: displayed in the lower half). In the analyzed images on the left, muscle is displayed in black and fat in white. Intermuscular fat (IMAT) is defined as adipose tissue located beneath the fascia lata and between muscles, and is displayed in white in the analyzed images (Reprinted with permission from Mojtahedi et al. 2008a)

and women (Wilmore et al. 1970). Many of these equations have been shown to be largely inadequate for use in athletes with SCI. Key features of other equations derived from AB populations but which have been evaluated and shown to better predict %BF in athletes with SCI include:

- Lean et al. (1996):
  - Derived from a Caucasian, broadly representative population;
  - Includes triceps skinfold, waist circumference, and age;
  - ~1–2%BF difference between skinfold prediction and DXA measurement; and
  - Directional bias compared with DXA %BF: predicted skinfold %BF decreases as measured DXA %BF increases.
- Evans et al. (2005):
  - Derived from athletic population;
  - Three-site equation includes abdomen, thigh and triceps skinfolds, gender, and race;
  - ~5–7%BF difference between skinfold prediction and DXA measurement; and
  - No directional bias compared with DXA %BF.

Although limited data exist, it appears that %BF estimations from many skinfold prediction equations correlate well with hydrodensitometry and DXA in athletes with SCI (Bulbulian et al. 1987; Olle et al. 1993; Mojtahedi et al. 2009); however, most prediction equations systematically underpredict %BF. Some of the first studies to assess %BF of athletes with SCI showed 7–12 lower %BF predictions from skinfold measurements compared with total body potassium (Lussier et al. 1983) and 1–8 lower %BF when compared with hydrodensitometry (Bulbulian et al. 1987). More recent

Table 115.2 Body composition by dual energy x-ray absorptiometry (DXA) (Reprinted with permission from Mojtahedi et al. 2008a; 2009)

Variable	SCI athletes (n = 14)	AB controls (n = 17)
Age (years)	22.5 ± 3.7	22.5 ± 3.8
Weight (kg)	57.6 ± 11.0	70.5 ± 12.5*
Height (cm)	161.6 ± 11.1	172.1 ± 11.4*
BMI (kg/m^2)	22.2 ± 3.6	24.3 ± 2.7
Body fat (%)[a]	25.1 ± 7.0	26.5 ± 7.2
Fat mass (kg)	14.3 ± 4.0	19.1 ± 5.0*
Trunk fat mass (kg)	5.7 ± 1.6	7.9 ± 2.1*
Leg fat mass (kg)	6.1 ± 2.1	8.1 ± 2.9*
Arm fat mass (kg)	1.7 ± 0.5	2.2 ± 0.6*
Lean soft tissue (kg)	41.7 ± 10.0	51.9 ± 12.8*
Trunk lean soft tissue (kg)	22.5 ± 5.2	25.5 ± 6.0*
Leg lean soft tissue (kg)	8.4 ± 3.3	17.2 ± 4.4*
Arm lean soft tissue (kg)	7.6 ± 2.1	5.8 ± 2.2*
Trunk fat mass (%)†[b]	39.7 ± 3.1	41.5 ± 5.6
Leg fat mass (%)[b]	41.5 ± 5.4	41.8 ± 6.7
Arm fat mass (%)[b]	11.9 ± 1.5	11.3 ± 1.2
Trunk lean soft tissue (%)[c]	54.2 ± 2.6	49.3 ± 1.5*
Leg lean soft tissue (%)[c]	19.7 ± 4.3	33.2 ± 1.3*
Arm lean soft tissue (%)[c]	18.3 ± 2.4	10.9 ± 1.5*

Absolute and relative values for whole body and regional fat and lean soft tissue show that while absolute fat differs between athletes with SCI and sedentary AB, fat percentages do not differ, due to difference in body size between groups. Absolute and lean soft-tissue percentages differ between athletes with SCI and sedentary AB. Results are mean ± SD

SCI = individuals with spinal cord injury. *AB* = able-bodied individuals

[a]Denotes percentage of body weight

[b]Denotes percentage of total fat stored in this region

[c]Denotes percentage of total lean soft tissue stored in this region

* Indicates significant difference between SCI and AB, $p \leq 0.05$

† Indicates $p = 0.012$ for gender by group interaction (SCI and AB females had similar values, whereas AB males had higher values than SCI males)

studies with somewhat larger sample sizes comparing skinfolds to DXA have shown similar results with under-prediction ranging from 1–4%BF (Sutton et al. 2009) to 2–12%BF (Mojtahedi et al. 2009), depending on the prediction equation used. Furthermore, Lohman's (1992) classification for prediction error based on the standard error of the estimate (SEE) and accuracy based on total error (TE) suggests that none of the equations (where data are available from cross-validation) are a good fit for predicting %BF in athletes with SCI.

Factors that may impact prediction error and accuracy are likely related to altered fat-free tissue distribution following SCI. First, as noted earlier, individuals with SCI have much more FM in their lower body than an age- and gender-matched AB individual. Equations that are based on an AB population will assume a regional LST distribution found in AB individuals, and may not be applicable to individuals with SCI. Therefore, the skinfold sites included in a prediction equation are of importance in gaining a representative sample of fat distribution throughout the body. However, a thick layer of subcutaneous fat can often be difficult to measure with skinfold calipers, especially if this is accompanied by little muscle mass, for example, due to atrophy found in individuals with SCI. Second, individuals with SCI often experience edema in the lower limbs, further compounding accurate skinfold measurements. Edema may also impact predicted %BF estimates by altering weight, and by changing the relationship between skinfold thickness and subcutaneous fat.

115.2.2.2 Bioelectrical Impedance Analysis Prediction Equations

To date, only one study has cross-validated BIA %BF prediction in athletes with SCI (Mojtahedi et al. 2009). Table 115.4 shows the prediction equation from this cross-validation analysis. Equations used in this analysis included a generalized one from Stolarczyk et al. (1997), Kocina and Heyward (1997) developed for the SCI population, Houtkooper et al. (1989) for female athletes, and Oppliger et al. (1991) for male athletes. It should be noted that the equation for individuals with SCI was derived from sedentary SCI, and that the equations derived from athletes were sports specific and did not match the sports of the population against which it was cross-validated.

Findings from Mojtahedi et al. (2009) indicate that BIA results in greater variation between and within individuals, but that mean predicted %BF tends to be closer to DXA body fat measurements than %BF predicted from skinfold measurements. In contrast to skinfold predicted %BF, BIA did not correlate well with measured DXA %BF in this population despite differences between BIA and DXA %BF ranging only 0.5–4%, which was much less than found with skinfold predictions. However, this equation was found to have increased measurement error with greater predicted BIA %BF. Moreover, SEE and TE classifications (Lohman 1992) indicated that none of the BIA prediction equations, including the SCI-specific one, were a good fit for this population (Table 115.4).

Several factors that impact the reliability of BIA measurements can create potential limitations for its use in athletes with SCI, and may explain the wide variation in measurements. First, hydration status plays an important role in BIA measurements in any population, and even more so in athletes, whose training can result in varied levels of hydration depending on the time since workouts and rehydration. Second, fluid retention is often experienced by individuals with SCI, as mentioned earlier, further compounding BIA measurements, as the electrical current passes through extracellular water. The hydration status of athletes can be standardized to some extent when taking BIA measurements; however, edema found in individuals with SCI is more difficult to control and measure. Lastly, %BF estimates from prediction equations, such as the typically used Siri equation (Siri 1956), assume a certain body density, which may not apply to athletes with SCI. Athletes have a higher water fraction in fat-free mass, resulting in lower fat-free mass density (Modlesky et al. 1996), and individuals with SCI are likely to have lower fat-free mass density because of bone mineral loss following SCI (Kocina 1997). Both these factors may lead to greater predicted %BF estimates.

115.3 Applications to Other Areas of Health and Disease

The prevalence of adiposity and risk for metabolic disease has been shown to be greater in SCI than in the AB populations, with impaired glucose tolerance and insulin resistance occurring at a younger age in those with SCI than in AB individuals (Bauman et al. 1999; Karlsson 1999; Bauman and Spungen 2001). The favorable effects of exercise on body composition and disease risk is well established in AB populations, but has received limited investigation in individuals with SCI.

Studies show that functional electrical stimulation of lower-limb muscles in individuals with incomplete paraplegia can increase LST of these limbs, and can have a favorable impact on metabolic disease risk (Mahoney et al. 2005). However, this kind of treatment is not feasible and accessible for all individuals with SCI, unlike physical activity. Unfortunately, some studies indicate that exercise is not associated with favorable changes in glucose regulation or insulin sensitivity (Midha et al. 1999; Manns et al. 2005), and therefore may not decrease disease risk at the same level found in AB individuals.

One explanation for this could be that favorable changes from physical activity in upper-body composition and metabolism may not be enough to counter effects from altered lower-body

Table 115.3 Selected body fat prediction equations for skinfold measurements used in athletes with spinal cord injury (SCI) (Reprinted with permission from Bulbulian et al. 1987; Mojtahedi et al. 2009; Sutton et al. 2009)

	Cross-validation analysis													
Equation from original study	Sport	Gender	Injury levels	*N*	Age (years)	BMI	Reference method	%BF from reference method	%BF from SKF	Difference from reference method (%BF)	Correlation with reference	SEE	TE	Source
Jackson and Pollock (1978)	Variety	M	T1-L2	23	27.5 ± 5.9	22.3	Hydro-densitometry	22.3 ± 8.8	NA	−3.8*	0.85	0.0108	0.0149	Bulbulian et al. (1987)
Jackson et al. (1980)[a]	Basketball, racing	F	T5-L5	8	22.0 ± 2.7	20.8 ± 2.6	DXA	31.9 ± 3.8	24.0 ± 9.0	−7.9*	0.73†	2.81	11.66	Mojtahedi et al. (2009)
Jackson et al. (1980)[b]	Basketball, racing	F	T5-L5	8	22.0 ± 2.7	20.8 ± 2.6	DXA	31.9 ± 3.8	29.1 ± 11.1	−2.8	0.64	3.18	12.12	Mojtahedi et al. (2009)
Jackson et al. (1980)[c]	Basketball, racing	F	T5-L5	8	22.0 ± 2.7	20.8 ± 2.6	DXA	31.9 ± 3.8	24.5 ± 9.8	−7.4*	0.64	3.17	10.40	Mojtahedi et al. (2009)
Jackson et al. (1980)[a]	Basketball, racing	M	T5-L5	8	21.9 ± 4.2	22.5 ± 2.1	DXA	20.6 ± 8.4	8.8 ± 10.5	−11.8*	0.93†	3.30	14.37	Mojtahedi et al. (2009)
Jackson et al. (1980)[b]	Basketball, racing	M	T5-L5	8	21.9 ± 4.2	22.5 ± 2.1	DXA	20.6 ± 8.4	9.7 ± 11.9	−10.9*	0.92†	3.63	15.17	Mojtahedi et al. (2009)
Jackson et al. (1980)[c]	Basketball, racing	M	T5-L5	8	21.9 ± 4.2	22.5 ± 2.1	DXA	20.6 ± 8.4	8.3 ± 8.7	−12.3*	0.84†	4.86	13.96	Mojtahedi et al. (2009)
Jackson et al. (1980)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	+1.2 ± 4.1	NA	NA	NA	Sutton et al. (2009)
Durnin and Womersley (1974)	Variety	M	T1-L2	23	27.5 ± 5.9	22.3	Hydro-densitometry	22.3 ± 8.8	NA	−3.6*	0.75	0.0136	0.0163	Bulbulian et al. (1987)
Durnin and Womersley (1974)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	+ 2.8 ± 4.0*	NA	NA	NA	Sutton et al. (2009)
Sloan (1967)	Variety	M	T1-L2	23	27.5 ± 5.9	22.3	Hydro-densitometry	22.3 ± 8.8	NA	−4.0*	0.76	0.0134	0.0164	Bulbulian et al. (1987)
Sloan and Weir (1970)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	−3.5 ± 5.4*	NA	NA	NA	Sutton et al. (2009)
Wilmore and Behnke (1969)	Variety	M	T1-L2	23	27.5 ± 5.9	22.3	Hydro-densitometry	22.3 ± 8.8	NA	−3.0*	0.82	0.0117	0.0134	Bulbulian et al. (1987)
Wilmore and Behnke (1970)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	−1.7 ± 3.7	NA	NA	NA	Sutton et al. (2009)

Katch and McArdle (1973)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	−3.3 ± 4.5*	NA	NA	NA	Sutton et al. (2009)
Katch and McArdle (1975)	Variety	M	T1-L2	23	27.5 ± 5.9	22.3	Hydro-densitometry	22.3 ± 8.8	NA	−1.8*	0.88	0.0097	0.0107	Bulbulian et al. (1987)
Lohman (1981)	Variety	M	T1-L2	23	27.5 ± 5.9	22.3	Hydro-densitometry	22.3 ± 8.8	NA	−4.8*	0.80	0.0123	0.0168	Withers et al. (1987)
Withers et al. (1987) (modified)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	+4.4 ± 3.6*	NA	NA	NA	Sutton et al. (2009)
Lean et al. (1996)	Basketball, tennis	F	Varied‡	19	26.0 ± 8.1	24.5	DXA	33.0 ± 6.3	NA	−1.2 ± 3.1	NA	NA	NA	Sutton et al. (2009)
Evans et al. (2005)[d]	Basketball, racing	F	T5-L5	8	22.0 ± 2.7	20.8 ± 2.6	DXA	31.9 ± 3.8	23.7 ± 3.8	−8.1*	0.71†	2.89	9.93	Mojtahedi et al. (2009)
Evans et al. (2005)[e]	Basketball, racing	F	T5-L5	8	22.0 ± 2.7	20.8 ± 2.6	DXA	31.9 ± 3.8	26.3 ± 5.4	−5.6*	0.81†	2.41	7.35	Mojtahedi et al. (2009)
Evans et al. (2005)[d]	Basketball, racing	M	T5-L5	8	21.9 ± 4.2	22.5 ± 2.1	DXA	20.6 ± 8.4	12.3 ± 5.5	−8.3*	0.95†	2.95	10.45	Mojtahedi et al. (2009)
Evans et al. (2005)[e]	Basketball, racing	M	T5-L5	8	21.9 ± 4.2	22.5 ± 2.1	DXA	20.6 ± 8.4	13.7 ± 7.1	−6.9*	0.97†	2.34	8.41	Mojtahedi et al. (2009)

The accuracy and reliability of prediction equations can evaluated in several ways, including difference in mean %BF from reference method, correlation with reference method, TE, and SEE. Studies evaluating the accuracy of prediction equations for athletes with SCI vary as regards the sample population, methodology, and evaluation criteria. However, in general, prediction equations using skinfold measurements do not appear to accurately estimate %BF. Results are mean ± SD

BMI = body mass index. *%BF* = body fat percentage. *SKF* = skinfold. *SEE* = standard error of the estimate. *TE* = total error. *NA* = not available. *DXA* = dual energy X-ray absorptiometry

[a] Denotes Jackson et al. (1980) prediction equation using seven skinfold sites

[b] Denotes Jackson et al. (1980) prediction equation using three upper-body skinfold sites

[c] Denotes Jackson et al. (1980) prediction equation using two upper-body and one lower-body skinfold site

[d] Denotes Evans et al (2005) prediction equation using seven skinfold sites

[e] Denotes Evans et al (2005) prediction equation using three skinfold sites

* Indicates significant difference from reference method, $p < 0.05$

† Indicates significant correlation of %BF from skinfold prediction equation with reference method, $p < 0.05$

‡ Sutton et al. included all physical disabilities ranging from chronic arthritis to complete SCI

Table 115.4 Selected body fat prediction equations for BIA measurements used in athletes with spinal cord injury (SCI) (Reprinted with permission from Mojtahedi et al. 2009)

		Women ($n = 8$)					Men ($n = 8$)				
		%Fat (mean ± SD)	SEE	TE	Correlation coefficient	*P*-value	%Fat (mean ± SD)	SEE	TE	Correlation coefficient	*P*-value*
DXA		31.9 ± 3.8					20.6 ± 8.4				
BIA											
	BIA_{GEN}	31.4 ± 5.6	3.39	5.06	0.568	0.141	24.1 ± 6.0	7.53	8.68	0.550	0.158
	BIA_{SCI}	28.0 ± 7.1	3.60	8.12	0.484	0.224	20.9 ± 8.3	6.21	6.69	0.725	0.042
	BIA_{ATH}	35.6 ± 9.0	3.46	9.31	0.542	0.165	13.6 ± 3.0	6.24	10.74	0.722	0.043

As with evaluating skinfold prediction equations, many criteria have been used to assess the accuracy and reliability of BIA %BF estimates, but most equations do not appear to be a good fit for use in athletes with SCI

SD = standard deviation. *SEE* = standard error of the estimate. *TE* = total error. BIA_{GEN} = Stolarczyk generalized equation. BIA_{SCI} = Kocina and Heyward SCI-specific equation. BIA_{ATH} = Houtkooper (female) and Oppliger (male) athlete-specific equations

* Indicates significance of the correlation coefficient, $p < 0.05$

composition following SCI (decreased LST and increased FM) of individuals with thoracic and lumbar SCI, in terms of metabolic profile (Mojtahedi et al. 2008b). Increased IMAT, trunk fat, and whole body fat have been associated with insulin sensitivity in athletes with SCI, and therefore may contribute to health risks despite decreased upper-body fat (Mojtahedi et al. 2008b). However, at the same time, metabolic factors that can lead to disease and are known to be impacted by physical activity, that is, glucose and insulin responses to an oral glucose tolerance test as well has HDL cholesterol, were found to be better in athletes with SCI compared to sedentary AB, although this was not a statistically significant finding (Mojtahedi et al. 2008b). The non-significant finding could have been partly due to the small sample size, and provides a foundation for future, larger studies that should include a sedentary SCI comparison group.

115.4 Practical Methods and Techniques/Guidelines

115.4.1 What Is the Most Accurate and Practical Method of Assessing Body Composition of Athletes with SCI?

Anthropometry is standard for evaluating the effectiveness of training programs for athletes. Although whole-body soft-tissue composition can play a role in sports performance, as shown from data presented in this chapter, whole-body measurements of LST and FM do not represent regional distribution in athletes with SCI. As upper-body physical activity for individuals with SCI will naturally only impact upper-body body composition, it is useful to be able to assess regional changes resulting from a training program. However, this means access to use of equipment that is expensive, such as the DXA, and is not practical for use in the field. Field methods, such as skinfolds and BIA, are typically used by practitioners working with athletes. However, unfortunately, they do not appear to be accurate or reliable for use in athletes with SCI either.

The relatively small literature regarding body composition in the SCI athletic population is further confounded by: (a) small sample sizes, (b) inclusion of all types of physical disabilities in addition to SCI, (c) combining quadriplegic and paraplegic athletes in their analyses, and, (d) either do not include a sedentary comparison group or include a sedentary AB control group rather than a sedentary SCI group. Also, comparisons of studies are difficult because the body composition assessment methods used vary from field methods, such as skinfolds and BIA, to clinical methods, such as total body electrical conductivity (TOBEC), DXA, and MRI. It is likely that multicenter studies are needed to enable the use of larger sample sizes and standard methodology to create better prediction equations for the SCI athlete population.

115.4.2 What Is the Level of Physical Activity Needed to Result in Body Composition Changes in Individuals with SCI?

Exercise intervention studies have had equivocal results; nevertheless, most have found no association between physical activity and changes in body composition (Midha et al. 1999; Duran et al. 2001; Bizzarini et al. 2005). However, the duration and exercise intensity of these interventions vary

with a range of 6–10 weeks at 55–90% of maximum heart rate. These may not be sufficient to invoke changes in body composition or changes that are detectable by the sensitivity of methods used in these studies in the absence of a concurrent dietary intervention. Main factors that appear to be associated with change in body composition of athletes with SCI are training load and age (Inukai et al. 2006). Therefore, this chapter primarily presents studies where data were obtained from athletes of a variety of sports, competing at national and international levels, and whose training regimens involved high-intensity activity over several years. Thus, these data are not necessarily generalizable to individuals who perform habitual physical activity at a low or moderate intensity. Longitudinal exercise interventions that include different levels of intensity are needed to determine physical activity recommendations for SCI populations with respect to invoking favorable changes in body composition and health status.

Summary Points

- As with sedentary individuals with SCI, lower-body lean mass is reduced in SCI athletes due to muscle atrophy.
- Although %BF predicted from skinfold measurements are correlated with DXA %BF measurements in athletes with SCI, skinfold prediction equations underestimate measured %BF.
- %BF predicted from BIA results in wide variation and does not correlate well with DXA %BF measurements.
- Underlying body-density assumptions are likely to impact the inaccuracy of %BF prediction equations in athletes with SCI.
- It appears that long-term high-intensity physical activity is required to invoke body composition changes, and for these changes to contribute to health benefits.
- The current body of literature on anthropometry in athletes with SCI is limited, and further studies that include large sample sizes and standardized methodology are needed.

Key Features

Table 115.5 Key points of body composition assessment in athletes with spinal cord injury (SCI)

As a result of upper-body exercise, athletes with SCI have increased arm and trunk lean soft tissue compared to sedentary able-bodied individuals, and decreased arm fat mass compared to sedentary SCI.
Field body composition methods, such as skinfolds and bioelectrical impedance analysis, typically used by practitioners working with athletes, do not appear to be accurate or reliable for use in athletes with SCI.
Factors that impact prediction error and accuracy when using field body composition assessment methods in athletes with SCI include altered lean soft-tissue and fat-mass distribution depending on SCI level, difficulty of obtaining precise skinfold measurements at certain sites, fluid retention and hydration status, and inaccuracy of body density assumptions used in prediction equations.

This table lists key points of body composition in athletes with spinal cord injury discussed in this chapter.
SCI = spinal cord injury

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Chapter 116
Anthropometry in 55–75-Year Olds in Response to Exercise

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Abstract As the population ages, physical activity in older adults is increasingly important for the maintenance of health and independence to prevent further burden on the health care system and to preserve quality of life. As people age, they tend to do less activity at a lower intensity. This leads to decreased energy expenditure and ultimately body composition changes that have adverse effects. Increased fat mass is related to development of diabetes and other cardiovascular diseases. Decreased muscle mass leads to frailty, falls and loss of independence. Decreased bone mineral density often results in osteoporosis, which increases the risk of fracture and subsequent morbidity and mortality. While physical activity and exercise cannot necessarily reverse the aging process, these changes can be significantly attenuated if sufficient activity is performed. Aerobic exercise has positive effects on the cardiovascular system and may reduce fat mass. Unfortunately, it may result in reduced muscle mass and it does not have positive effects on bone mineral density unless it is weight bearing exercise of sufficient intensity. Progressive resistance training effectively maintains muscle mass and bone mineral density and may reduce fat mass, depending on the protocol. Resistance exercise improves glycaemic control in diabetics and it is the best type of exercise to reduce the risk of falling. One of the most effective ways to trigger a behaviour change in older adults is for the advice to come from a physician. Indeed, physician prescribed exercise has been shown to positively affect anthropometric indices, fitness and cardiovascular risk factors in older adults.

Abbreviations

ACSM	American College of Sports Medicine
BMD	Bone mineral density
BMI	Body mass index
CT	Computed tomography
CVD	Cardiovascular disease
DaTA	Diabetes and technology for increased activity
DXA	Dual energy x-ray absorptiometry
HbA1c	Glycated haemoglobin
HRR	Heart rate reserve

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_116,

MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
PRT	Progressive resistance training
SNAC	Staged Nutrition and Activity Counseling
SO	Sarcopenic obesity
STEP™	Step Test Exercise Prescription
VO_2	Oxygen uptake
VO_2max	Maximal oxygen uptake
VO_2peak	Peak oxygen uptake

116.1 Introduction

Exercise and sport activities play an important role in older adults to maintain health and independence. Unfortunately, many people become more sedentary over time, exacerbating the effects of aging. As the population ages, the burden on the healthcare system will increase; hence, preventative interventions should be a priority. The following chapter will briefly review the normal aging process and associated diseases, then discuss how exercise attenuates these changes and improves health outcomes. Finally, practical applications will be discussed regarding how exercise programming can be best delivered in this population of adults aged 55–75 years.

116.2 Age-Associated Changes in Body Composition

Aging is accompanied by a number of anthropometric changes including decreased height and increased body weight. There is also often a decrease in upper-arm- and thigh circumferences associated with decreased muscle mass and an increase in waist circumference associated with abdominal obesity. Changes in body composition associated with aging generally include increased fat mass and decreased muscle mass and bone mineral density (BMD). These changes result partly from the natural slowing of metabolism with age and partly from decreased quantity and intensity of physical activity, which commonly occurs as people age. Changes in body composition may be difficult to assess because they often occur with no change in body weight, which is the most popular means by which people monitor themselves at home. Although a young adult and an older adult may have similar body weight and body mass index (BMI), the actual mass and quality of their muscle are not equal, nor is their adipose distribution (St-Onge 2005). This highlights the fact that specific tools and protocols are necessary to measure body composition in older adults. Dual energy x-ray absorptiometry (DXA) is useful to assess the three main compartments: fat mass, muscle mass, and BMD. The sub-compartments measured by computed tomography (CT) or magnetic resonance imaging (MRI) show more important differences than measures of the major compartments, but these are less often completed due to cost, equipment, and skill necessary to attain and analyze these measures. A study using DXA and MRI measures noted that, over a two-year follow-up period in 65-year-old women, skeletal and leg muscle mass and BMD decreased and visceral and intramuscular adipose tissue increased despite no change in either body weight or BMI (St-Onge 2005). Magnetic resonance spectroscopy (MRS) can be used to determine the location of fat within muscles and organs. Cross-sectional studies with MRS have found increased intramyocellular (inside the muscle cell) and liver fat content in older compared to young adults (St-Onge 2005). For more examples of body composition changes with aging, refer to the review by St-Onge (2005).

Numerous physiological changes occur with aging that lead to increased risk of cardiovascular diseases (CVD) and mortality. These include decreased cardiorespiratory fitness, decreased insulin sensitivity, and increased vascular stiffness. Whereas a discussion of these factors is beyond the scope of this chapter, it is important to keep them in mind, since exercise positively affects these and other factors important to quality of life and longevity in older adults.

116.2.1 Fat Mass

Aging is often accompanied by increased whole-body adiposity. Adults generally gain weight from young adulthood up until approximately 65–75 years of age. Thereafter, there is a steady decline in body weight associated with frailty and mortality. Increased fat mass is the primary cause of increased body weight. There tends to be a greater increase in central adiposity, increasing the risk of CVD including diabetes, hypertension, myocardial infarction, and stroke. A recent longitudinal study showed that, over an average 9.4-year follow-up period, women gained body weight and fat mass, whereas men did not change body weight, but fat mass measured by hydrodensitometry was significantly increased (Hughes et al. 2004). In this same study, there was an increase in waist circumference in women, but not in men. Interestingly, despite an increase in overall and central adiposity, there was a decrease in fat estimated by skinfold thicknesses (Hughes et al. 2004). Therefore, using skinfold thicknesses to estimate fat mass over a long-term follow-up period is inappropriate in older adults due to the redistribution of fat to central visceral locations.

116.2.2 Muscle Mass

The age-related loss of muscle mass, termed sarcopenia, results from a decreased number and size of muscle fibres. Quadriceps muscle mass can be decreased by 30% or more. Type II, or fast-twitch, fibres are affected most by this condition. Since these fibres are necessary for power and higher-intensity movements, loss results in decreased strength and power and may result in loss of independence when maximal strength drops below that needed for activities of daily living. In older adults, it has been shown that thigh circumference in women and arm circumference in men are significantly decreased over an average of 9.4 years (Hughes et al. 2004). These circumferences are associated with muscle mass and, in women, the decrease occurred despite the fact that self-reported physical activity levels were maintained. In men, there was a significant decrease in physical activity over the 10-year follow-up period, which may explain in part the loss of muscle mass.

Sarcopenic obesity is a relatively new category of obesity for the elderly. As the name suggests, this condition is a combination of decreased muscle mass and increased fat mass and it is thought that the adverse effects are potentiated by the presence of both. Currently, there is no specific definition for the disease. Some researchers classify sarcopenic obesity as a person with a fat mass in the upper two quintiles and a muscle mass in the lower three quintiles according to age and sex. Others use a DXA-derived appendicular skeletal muscle mass per height squared less than two standard deviations below the mean of a sex-specific group and body fat percentage greater than 27% in men and 38% in women (Zamboni et al. 2008). Although little research has examined sarcopenic obesity in detail, older adults with this condition may be more likely to have physical disabilities than those with only obesity or sarcopenia; however, findings are equivocal. More research is needed to study this newly recognized phenomenon to conclude whether or not it is harmful to the elderly population.

116.2.3 Bone Mineral Density

Loss of BMD occurs with normal aging in both men and women. Increased stress on the bone, which can occur with increased body weight or weight-bearing activity, is needed to increase or maintain BMD. Since abdominal obesity appears to protect bone, weight loss in the absence of exercise may have detrimental effects on BMD. Osteopenia is a preclinical decrease in BMD that often leads to osteoporosis. This condition is most common in postmenopausal women and increases the risk of fracture and disability. It is also important to note that once osteoporosis is diagnosed, special precautions must be undertaken during exercise. For example, forward flexion should be limited to prevent spontaneous fracture of the spine.

Although aging is associated with body composition changes, regular physical activity, and exercise can help to counter or attenuate these changes, reducing the risk of dependence, morbidity, and mortality. The following section will describe how different types of exercise alter anthropometric indices and health status in older adults.

116.3 Anthropometric changes in response to exercise

116.3.1 Active Living

Active living involves finding ways to incorporate physical activity into daily living. This includes lifestyle modifications such as walking instead of driving to the mailbox or taking the stairs instead of the elevator. Assessment of leisure-time physical activity is one way to capture the amount of activity completed over a range of intensities from sedentary (low physical activity) behaviors, such as reading and watching television, to vigorous activities, such as competitive sports and hard physical training. A study by Byberg and associates (2009) showed that all-cause mortality rate was significantly less in the high physical activity group than in either the low or moderate physical activity group. This study shows that although moderate activity, such as pleasure walking and cycling, offered benefits compared to sedentary behaviours, greater benefits resulted from higher activity levels. Additionally, active living may have positive effects on energy expenditure and mobility, but it does not attain the intensity necessary to elicit changes in BMD or muscle mass. Therefore, it is better for an older adult to be moderately active than sedentary, but maximal benefits are attained from higher intensities of physical activity.

116.3.2 Aerobic Exercise

Aerobic exercise is repetitive movement that increases heart rate and oxygen uptake (VO_2). Walking is most commonly performed in older adults because it is relatively low impact, inexpensive, and can be done almost anywhere. Other types of aerobic exercise are cycling, swimming, and aerobic dance. The American College of Sports Medicine (ACSM) 2009 guidelines recommend that older adults exercise at least three days per week at a minimum intensity of 60% of maximum oxygen uptake (VO_2max). Exercise can be completed in short bouts of 10 min as long as 30–60 min/day are completed for moderate or 20–30 min/day for vigorous intensity aerobic exercise (Chodzko-Zajko et al. 2009). Key facts about VO_2 are explained in Table 116.1.

Table 116.1 Key facts about oxygen uptake (VO_2)

VO_2…
• Is the amount of oxygen used by the muscle.
• May be expressed in absolute (L/min) or relative (ml/kg/min) units.
VO_2max
• Is the maximum amount of oxygen that can be used by the muscle.
• Is an index of aerobic fitness.
• Is linearly related to heart rate.
• Is estimated by measuring gas exchange at the mouth.
• Testing involves exercising to fatigue (usually on a treadmill or cycle ergometer).
• May be estimated with submaximal tests (i.e., exercising to a submaximal heart rate and estimating VO_2max based on its relationship with heart rate).
• Generally decreases with age, disease, and sedentary lifestyle.
VO_2peak
• Is the term used to describe the maximum amount of oxygen used by the muscle when there is doubt that a true maximum was reached during an exercise test.
• Is often used in populations of older adults or people with diseases.

This table highlights the importance of measuring maximal oxygen consumption, including its general meaning and relevance. *VO_2max*: maximal oxygen uptake; *VO_2peak*: peak oxygen uptake

Aerobic exercise is beneficial to older adults because it increases cardiorespiratory fitness and mobility and may decrease fat mass. However, a recent study (Nicklas et al. 2009) showed that calorie reduction decreased body weight and fat mass equally in all groups whether calorie reduction was through diet alone, diet plus moderate exercise, or diet plus vigorous exercise. There were also similar reductions in metabolic risk factors including cholesterol profiles, fasting glucose, and insulin (Nicklas et al. 2009), suggesting that changes in body composition and risk were due to weight loss, not exercise. This study also reported similar decreases in lean mass in all three groups, supporting previous findings that aerobic exercise is not a sufficient stimulus to maintain muscle mass (Nicklas et al. 2009).

116.3.3 Resistance Exercise

Resistance or strength exercise involves using muscular effort against an opposing force. The most common resistance exercise is weight lifting, but exercises can also be done using resistive tubing or body weight. The 2009 ACSM guidelines recommend that resistance exercises be performed at least two days per week. Eight to ten repetitions should be completed for eight to ten exercises to target upper and lower body (Chodzko-Zajko et al. 2009).

Strength training is especially important in older adults, as it is essential for the maintenance of muscle mass and BMD. Progressive resistance training (PRT) is a type of training where the load is constantly increased as strength is gained so that the intensity of the exercise is maintained. A 16-week PRT program was delivered to young and old men and women to assess the effectiveness of performing strength training three times per week for 16 weeks to counter sarcopenia (Kosek et al. 2006). This trial found that whereas there was no training effect for body composition improvements, strength was improved in all four groups. There were also changes in muscle composition that differed for older and young adults. There was an increase in type I muscle fibres in the young, but not older adults, whereas type IIa fibres hypertrophied in both young and old, though to a greater extent in young adults (Kosek et al. 2006). Additionally, there were no significant increases in fibre cross-sectional area in older women, though it tended to increase for type IIa fibres (Kosek et al. 2006).

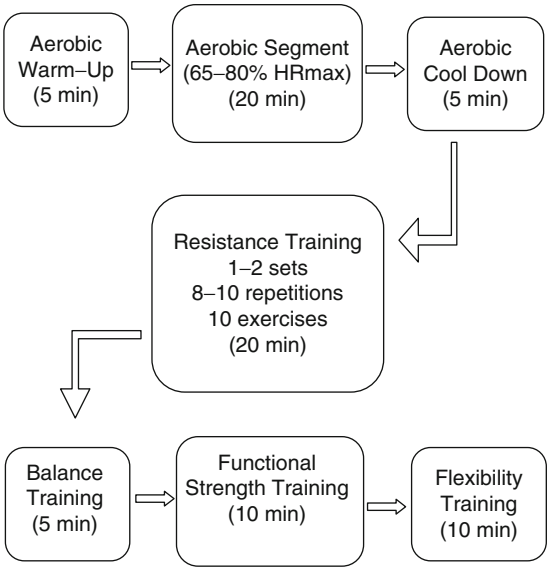

Fig. 116.1 Flowchart of the composition of a 75-min exercise class for older adults at the Canadian Centre for Activity and Aging. (Adapted from Tudor-Locke et al. 1997.) This figure shows the composition of a typical class delivered by the Canadian Centre for Activity and Aging in London, Ontario, Canada. Modifications are made for special populations. HR_{max}: Maximum predicted heart rate

This may be clinically significant, as sarcopenia affects primarily type II muscle fibres. Therefore, though overall muscle mass was not changed with 16 weeks of PRT, the cellular changes suggest that a longer training stimulus may increase muscle mass. This also highlights the generally accepted notion that improved strength in the first few weeks of PRT is primarily due to neural adaptations including improved motoneuron recruitment and decreased contraction of opposing muscle groups. Longer training programmes may be necessary to elicit changes in muscle mass in older adults.

116.3.4 Combined

Combined exercise is likely most beneficial to older adults to get optimal benefits for fat-mass reduction and muscle-mass- and BMD increases. The Canadian Centre for Activity and Aging incorporates this standard in its model for delivering community-based exercise programmes for older adults. Composition of a usual class is shown in Fig. 116.1, though this format is modified for special populations (Tudor-Locke et al. 1997).

A combined programme was recently used to examine the effects of exercise on body composition and BMD. The programme consisted of stretching exercises followed by two sets of 10–15 repetitions of seven resistance exercises for the upper and lower body and 45 min of aerobic exercise at 60–90% of peak oxygen uptake (VO_2peak) (Stewart et al. 2005). After six months of training, both men and women had significantly increased VO_2peak, strength, and total and percent lean mass assessed with DXA. There were also significant decreases in body weight, BMI, total and percent body fat, and visceral and subcutaneous body fat (Stewart et al. 2005). There were no changes in BMD in men and slight decreases in total and greater trochanter BMD in women. However, Pearson correlations showed that, in women, increases in femoral neck BMD were related to increased

Table 116.2 Exercise guidelines for older adults

Type	Frequency	Intensity	Duration
Aerobic	≥3×/week	≥60% VO_2max (moderate to vigorous)	Moderate intensity: 30–60 min/day. Vigorous intensity: 20–30 min/day.
Resistance	≥2×/week	Moderate to vigorous	Eight to ten exercises for the whole body. Eight to ten repetitions.

This table summarizes guidelines for aerobic and resistance training that should be followed by older adults. VO_2max: Maximal oxygen uptake

VO_2peak, decreased BMI and decreased body weight (Stewart et al. 2005). Therefore, although there was an overall decrease in BMD in women, those who had the greatest increases in VO_2peak (which usually occur at higher exercise intensities) actually increased BMD. Likewise, for men, increases in BMD were associated with increases in lean mass and lower body strength (Stewart et al. 2005). It appears that exercise intensity is important to elicit changes in BMD, whether it is high-intensity aerobic training (likely weight bearing) in women or high-intensity resistance training in men.

116.4 Summary of Exercise Training Protocols

Table 116.2 is a summary of current exercise recommendations for older adults.

116.5 Special Concerns for Older Adults

116.5.1 Dependence

Dependence not only imposes a significant burden upon the healthcare system, it, more importantly, decreases quality of life. As mentioned above, aging is associated with a decrease in muscle mass and cardiorespiratory fitness. Once, one or both of these variables reaches a threshold, activities of daily living can no longer be carried out. Multivariate modeling has shown that cardiorespiratory fitness is the most important determinant of independence in the elderly (Paterson et al. 2004), highlighting the importance of physical activity in older adults. In this study, body composition was not a significant determinant of independence, but BMI was the only index of body composition included. The limitations of BMI have been previously discussed. Another study found that although lean mass was not associated with future functional limitation, the ratio of lean mass to fat mass was (Haight et al. 2005). For women, the benefits of an increased lean mass-to-fat mass ratio were not as great in the absence of physical activity.

116.5.2 Falls

There are a number of changes that occur in older adults that increase the chance of falling (Table 116.3). Most important for this textbook is the decrease in muscle mass associated with aging. Interestingly, a study that examined the effects of three different training programmes (resistance, agility, and

Table 116.3 Changes with age that increase the risk of falling in older adults

Falling risk in older adults
Decreased muscle mass
Decreased balance
Slowed reaction time
Decreased vision
Joint disorders of the knee and hip
Gait and posture disturbances
Cognitive impairment
Orthostatic hypotension

This table lists some of the factors that are associated with falls in older adults

stretching) found that all three reduced the risk of falling (Liu-Ambrose et al. 2004). Stretching was the least effective, but still reduced the risk of falls by 20%. Agility training reduced the risk of falling by 48%, but resistance training was most effective, reducing the risk of falling by 57%. Considering that resistance training may also have had secondary effects, such as increased BMD, this training could significantly reduce the risk of fracture and dependence in this population. Since hip fracture is one of the leading causes of hospitalization and subsequent death in older adults, a resistance training programme is beneficial to aging populations.

116.5.3 Diabetes

Aerobic exercise is generally accepted as a safe and effective lifestyle intervention to complement medical control of blood sugar and insulin levels. The 2008 Canadian Diabetes Association Guidelines recommends that diabetics perform a minimum of 150 min of moderate to vigorous aerobic exercise each week spread over at least 3 days (Bhattacharyya et al. 2008). Exercise should be spread out over the week, as physical activity's effect on insulin and blood glucose lasts for longer than 24, but less than 48 h. One of the issues with this recommendation is that it is difficult to get sedentary people to adhere to a moderate to vigorous intensity exercise programme. A study (Hansen et al. 2009) found that when exercise expenditure was matched, there was a greater decrease in trunk fat mass in the moderate- to high-intensity group than in the low- to moderate-intensity group despite no significant differences in body weight, BMI, leg fat mass or trunk or leg lean mass. Although the moderate- to high-intensity group had greater anthropometric improvements during this 6-month intervention, this did not translate into greater glycaemic control. At 6 months, glycated haemoglobin (HbA1c), which gives an index of glycaemic control over the past three months, was improved equally in the low- to moderate- and moderate- to high-intensity groups (Hansen et al. 2009). Other measures of insulin sensitivity and glycaemic control showed similar results. Therefore, the intensity of the exercise may not be of utmost importance when prescribing exercise for diabetics. Although more long-term research with larger sample sizes is needed, at the current time, it is likely more important to get the diabetic patient to initiate and adhere to an exercise programme, irrespective of intensity. However, cardiovascular complications are one of the major concerns for diabetics and body composition modification may offer greater cardiovascular protection in this population.

Dunstan and colleagues (2002) showed that adding PRT to a weight-loss regimen for diabetic patients was beneficial. Whereas weight-loss groups with or without PRT both attained decreases in body weight, waist circumference, and fat mass measured by DXA, there was a significant group

Table 116.4 Cardiovascular risk factors

Modifiable	Non-modifiable
Obesity	Family History
High blood pressure	Sex
High cholesterol	Age
Smoking	
Psychological stress or depression	
Physical inactivity	
Diet low in fruits and vegetables	

This table lists factors that increase the risk of cardiovascular disease

time interaction showing that the PRT group increased lean body mass, while the group without PRT actually decreased lean body mass over the 6-month intervention. Additionally, HbA1c decreased from 8.1% to 6.9% over 6 months in the PRT group, whereas there was no change in the weight-loss-only group (Dunstan et al. 2002). This is clinically significant because the goal for diabetics is to reach an HbA1c level below 7.0%, which was accomplished in the PRT group. Additionally, each 1% improvement in HbA1c results in a 15–20% decrease in cardiovascular risk in diabetics. Further lowering cardiovascular risk, the 6-month PRT plus weight loss intervention also resulted in an average decrease of systolic and diastolic blood pressure by 6.7 and 4.4 mmHg, respectively (Dunstan et al. 2002). Systolic blood pressure was 145 mmHg at baseline; hence, whereas the diabetic target of 135 mmHg was not reached during this intervention, cardiovascular risk was decreased and a longer trial may have resulted in attainment of target blood pressure.

116.5.4 Cardiovascular Disease

CVD is the leading cause of mortality in North America. Although there is a genetic component often associated with early-onset CVD, later in life, CVD is often related to poor lifestyle habits including inactivity. Modifiable and non-modifiable cardiovascular risk factors are shown in Table 116.4. Essential hypertension is one of the leading risk factors of CVD and is highly prevalent worldwide, especially in developed and developing countries. Numerous studies have shown that aerobic exercise reduces blood pressure and limited studies have shown blood-pressure reductions following resistance exercise. A recent study examined the effects of exercise intensity on blood pressure in adult men and women aged 55 years and older (Cornelissen et al. 2009). This study found that, whereas both low-intensity (33% heart rate reserve (HRR)) and high-intensity (66% HRR) aerobic exercise lowered systolic blood pressure to a similar degree, only the high-intensity exercise improved body composition as evidenced by reduced body weight, BMI, body fat, and waist circumference (Cornelissen et al. 2009). Exercise sessions were held three times per week and consisted of treadmill walking or jogging, stationary cycling, stepping, or a combination of these exercises. Similar to the improvements in glycaemic control in the above-mentioned type 2 diabetic trial, improvements in blood pressure were independent of improvements in anthropometric indices. Long-term studies would be interesting to assess whether the reduction in body weight with high-intensity exercise provides additional cardiovascular protection.

Petrella and colleagues (2005) proved that commencing a supervised exercise programme later in life (average age 68 ± 5 years) provided beneficial effects on cardiovascular risk factors. Although many risk factors were not actually improved over an eight-to-ten-year follow-up period, the exercise

group had less of an increase in systolic blood pressure, total cholesterol, and low-density lipoprotein cholesterol compared to the sedentary group. The exercise group showed a slight increase in high-density lipoprotein cholesterol as opposed to a significant decrease in the sedentary group and a decrease in triglycerides as opposed to an increase in sedentary. Waist circumference was only increased by 2 cm in the exercise group, as opposed to 10 cm in the sedentary group. Additionally, the exercise group maintained their maximal activity level (expressed in metabolic equivalents: METs), whereas the sedentary group experienced a 13.79% decrease over 10 years. Interestingly, a recent study (Byberg et al. 2009) found that men, who increased their activity level between the ages of 50 and 60 years, had no difference in all-cause mortality compared to the sedentary group in the first five years, but, following ten years of increased activity, their mortality rate declined to the same as that of men who had been doing high physical activity previous to the beginning of the study. Collectively, this shows that beginning a relatively intense exercise programme later in life (50 years of age and beyond) effectively decreases the risk of CVD and all-cause mortality, but that more than five years of exercise is needed to achieve these long-term benefits.

116.6 Clinical Applications: Exercise Prescription

As discussed through this chapter, exercise is beneficial for older adults and considerable adaptations can occur, even if an exercise program is not taken on until later in life. One of the major issues, however, is how to get an older adult to commence one. One of the most effective ways to trigger a behaviour change in this population is for the recommendation to come from the family physician. Unfortunately, during physician visits, little time is devoted to physical activity counselling, which may be a result of lack of time, training, knowledge, or instruments and materials. The Step Test Exercise Prescription (STEP™) project was carried out to test the effectiveness of a short, simple test to predict VO_2max and prescribe physical activity to older adults (Petrella et al. 2003). The protocol for the STEP™ test is shown in Fig. 116.2 and key facts are explained in Table 116.5. Following the test, a few minutes were devoted to discussing physical activity goals and barriers and an individualized exercise prescription was written out. In healthy older adults, this prescription alone resulted in increased VO_2max compared to a group that did not receive a prescription at 6 or 12 months (Fig. 116.3). The STEP™ group also showed increased exercise self-efficacy and decreased systolic blood pressure and BMI compared to the control group.

As discussed in detail previously (Section 8 of this textbook), the metabolic syndrome is a clustering of risk factors that puts an individual at an increased risk of CVD. The Staged Nutrition and Activity Counselling (SNAC) study examined the effects of exercise prescription using the STEP™ protocol and physician recommendation to follow the Mediterranean diet in participants with and without the metabolic syndrome (Aizawa et al. 2009). Results showed increased VO_2 max in groups with and without the metabolic syndrome. The group with the metabolic syndrome showed improvement of risk factors at 24 weeks, as shown in Table 116.6. Changes were accompanied by decreased arterial stiffness, further improving cardiovascular health.

In a high-risk population, such as with metabolic syndrome, it may be worthwhile to monitor its risk factors more closely. The Diabetes and Technology for Increased Activity (DaTA) pilot study, utilized the STEP™ test and exercise prescription along with remote monitoring of risk factors to examine the effectiveness of increased activity to reduce the impact of metabolic syndrome. Participants received a Bluetooth™-enabled glucometer and blood-pressure monitor, a pedometer and a heart-rate monitor (Fig. 116.4). A BlackBerry® cellular telephone with HealthAnywhere® software

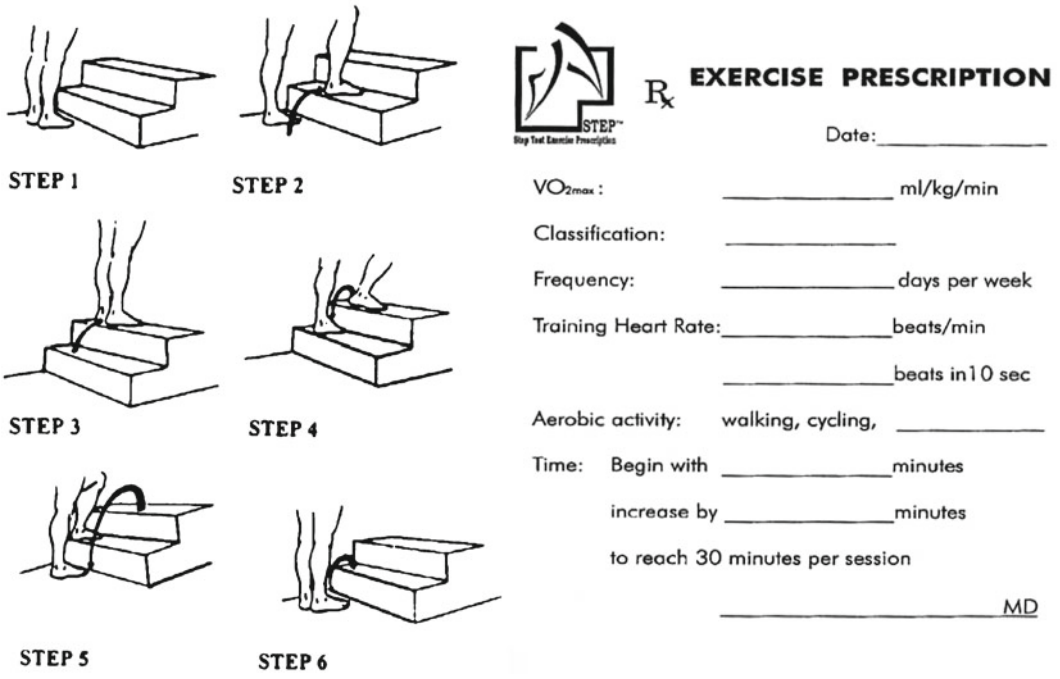

Fig. 116.2 STEP™ Test protocol. Patient steps up and down the stairs 20 times. Heart rate is assessed before and after the test. VO_2max is predicted using a validated equation that incorporates body weight, age, sex, time to completion of test, and heart rate at the end of the test. This figure shows how the STEP™ test is done. On the left, it shows one cycle of the test. The exercise prescription on the right would be filled out by the healthcare professional and given to the patient. VO_{2max}: maximal oxygen uptake

Table 116.5 Summary of key facts about the STEP™ test

STEP™ test
Protocol:
• The healthcare professional administering the test measures resting heart rate and blood pressure.
• The test is described and completed as shown in Fig. 116.4.
• At the end of the test, heart rate and blood pressure are measured.
• The following equation is used to calculate predicted VO_2max:
1. (1511/time) × weight/heart rate = _____
2. ([answer from step 1.] × 0.124) – (age × 0.032) – (sex × 0.633) + 3.9 = _____
3. ([answer from step 2.] × 1000)/weight = VO_2max
◦ where, 'time' is the time to complete the STEP™ test in seconds, 'weight' is body weight in kg, 'heart rate' is the heart rate at the end of the STEP™ test in beats per minute, age is in years, 'sex' is 1 for males and 2 for females, and VO_2max is expressed in ml/kg/min.
Significance:
• This test is a practical tool for exercise assessment in a clinical setting. Exercise stress testing is difficult for the patient, requires specialized staff, is time consuming, and is costly to the healthcare system. The STEP™ test is relatively short and simple to conduct.
• Tools and guidelines are provided to healthcare professionals for exercise testing and prescription. The intention is to increase the amount of time spent discussing physical activity habits and to provide safe and effective exercise advice to patients.

This table summarizes some key points about the STEP™ test and exercise prescription including how it is completed and why it is important. VO_2max: Maximal oxygen uptake

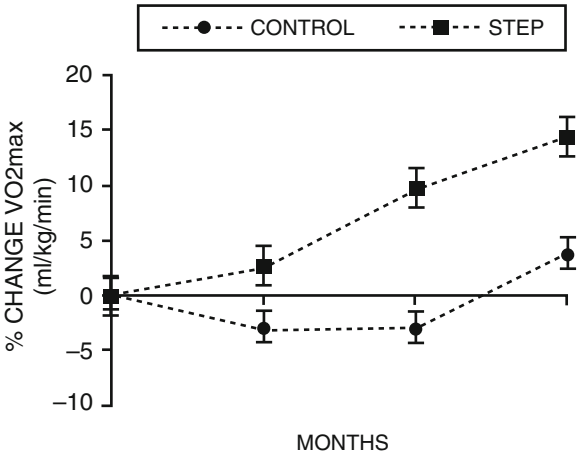

Fig. 116.3 Percent change in VO_2max at baseline, 3, 6, and 9 months following STEP™ assessment and exercise prescription or control. Reprinted with permission from Elsevier (Petrella et al. 2003). This figure shows the changes in VO_2max that occurred over a nine-month follow-up period when older adults either (a) were assessed using the STEP™ test and exercise prescription or (b) received usual care from their family physician. The STEP group had greater improvements in cardiorespiratory fitness than the control group. *VO_2max*: maximal oxygen uptake

Table 116.6 Summary of the changes in metabolic syndrome risk factors following a 24-week intervention in the SNAC study (Adapted from Aizawa et al. 2009)

Changes in metabolic syndrome risk factors
Decreased weight
Decreased BMI
Decreased waist circumference
Decreased systolic and diastolic blood pressure
Decreased fasting glucose
Decreased total and low-density lipoprotein cholesterol

This table shows what metabolic syndrome risk factors changed following a 24-week nutrition and physical activity intervention

acted as an interface for data to be transmitted from the devices to a secure database that was monitored by investigators. Over the two-month intervention period, physical activity increased as evidenced by an increase in predicted VO_2max from the STEP™ test and an overall increase in steps per day recorded by the pedometer (Russell-Minda et al. 2009). These were accompanied by decreased diastolic blood pressure, BMI, waist circumference and cholesterol. The pilot study was done to prove the feasibility of using the technology and showed that overall compliance was high (an average of 96.81 ± 3.98% of all measures was transmitted from the participants) and that it was not a great burden to the participants (Stuckey et al. 2009). Remote monitoring of diabetic patients using cellular telephone technology has been shown to be particularly effective in older adults (Kwon et al. 2004). A similar type of monitoring may be effective to promote increased levels of physical activity and to monitor anthropometric and cardiovascular risks in older adults. A larger study to assess clinical outcomes associated with using technology to remotely monitor high-risk adults is currently underway.

In summary, the STEP™ test is an effective tool for physicians to use to promote physical activity in older adults. People who were given a written physical activity prescription showed increased fitness, modified anthropometric measures, and decreased cardiovascular risk (Table 116.5). Physical

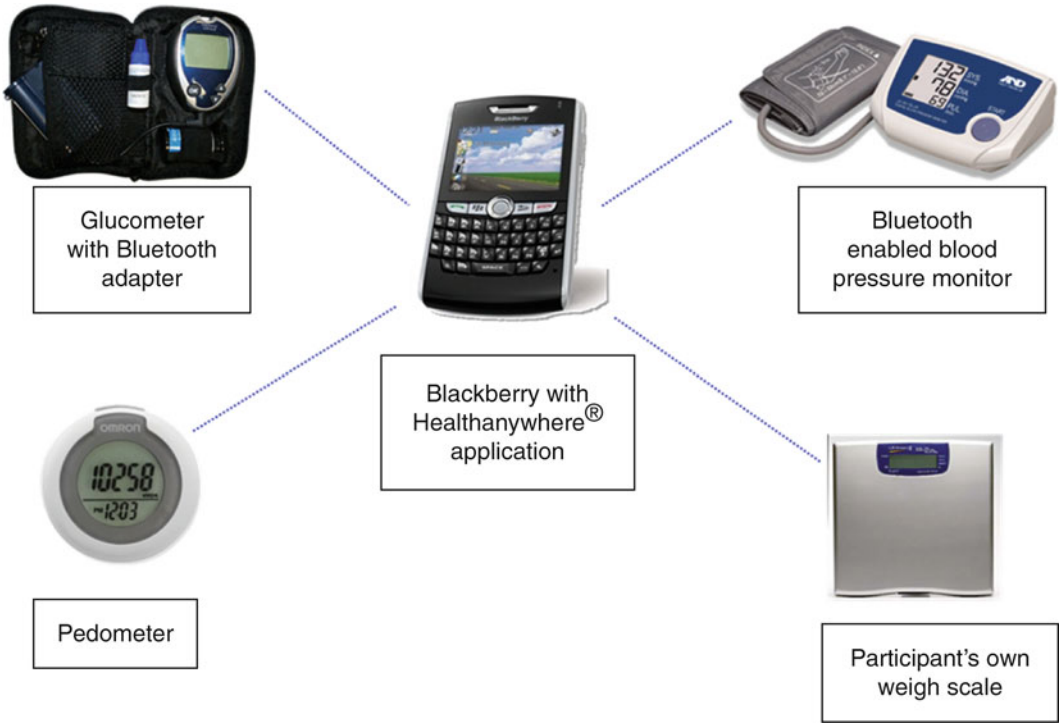

Fig. 116.4 Devices provided to participants of the DaTA pilot study. This figure shows the devices used for home monitoring of cardiovascular risk factors in the DaTA pilot study. Bluetooth-enabled glucometer and blood-pressure monitor were used for twice daily blood glucose and thrice weekly blood pressure evaluation, respectively. Pedometer was used to monitor daily activity with step count and the weigh scale was used to monitor weight weekly. All measurements were entered into the Blackberry and automatically sent to a secure database to be monitored by researchers

activity and exercise in older adults is a key component for maintaining health and fitness, and, ultimately, for retaining independence for as long as possible. Table 116.8 reviews key points to note about exercise in older adults.

Summary Points

- Aging is associated with a decline in muscle mass and bone mineral density and an increase in fat mass.
- Aerobic exercise training of sufficient intensity results in improved cardiorespiratory fitness and may reduce body weight, but only if negative calorie balance is reached.
- Resistance-exercise training following recommendations increases strength and may have positive effects on muscle mass, bone mineral density, and fat mass.
- Physical activity is important in older adults to prevent falls and maintain independence.
- Exercise helps to manage glycaemic control in diabetic patients and blood pressure in hypertensive patients.
- The STEP™ test is an effective means of assessing fitness in a clinic setting. Exercise prescription leads to positive changes in cardiorespiratory fitness, anthropometric indices, and cardiovascular risk.

Key Features

Table 116.7 Summary of changes in anthropometry, fitness, and cardiovascular risk after receiving an exercise prescription from a clinical setting

Modifications elicited by exercise prescription via the STEP™ test
Anthropometry
Decreased waist circumference
Decreased BMI
Decreased weight
Fitness
Increased VO_2max
Increased steps per day
Cardiovascular risk
Decreased systolic and diastolic blood pressure
Decreased cholesterol
Decreased arterial stiffness

This table summarizes the findings from different studies in which the STEP™ test was performed in a clinical setting and exercise prescription was given by clinic staff

Table 116.8 Summary of key facts about exercise in older adults

Key facts: Exercise in older adults
• Higher intensity exercise results in greater body composition modifications, though low intensity exercise is sufficient to improve glycaemic control and blood pressure.
• Higher exercise intensities elicit greater improvements in cardiorespiratory fitness, which are positively associated with longevity and independence.
• Exercise programmes adopted later in life are beneficial in reducing the chance of dependence and reducing the risk of morbidity and mortality.
• Written exercise prescriptions from a family physician or affiliated exercise specialist are effective means for triggering behaviour change and subsequent commencement of an exercise programme.

This table summarizes some key points that are important to keep in mind when prescribing exercise to older adults

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Chapter 117
Anthropometry and Exercise in Obesity

Fusun ARDIC

Abstract This chapter aims to review the effects of exercise on body measurements in overweight and obese people. Firstly, obesity is described in detail with regard to frequently associated medical problems and weight-related health risk. The necessity of the inclusion of an exercise training program in obesity management is underlined, and exercise training and exercise prescription for obese patients described. An overview of the anthropometric measurements used in assessing body fat distribution and monitoring the changes in body composition over an exercise training program in obese people is presented. The most commonly used body measurement methods in obesity outcome studies include simple anthropometric measurements and body composition measurement techniques. The outcome of body composition alterations with exercise is summarized as a slight decrease in total body weight, prevention of decrease in fat-free mass and relative increase in visceral fat-mass loss. The magnitude of these changes varies directly with the intensity, duration, and type of the exercise, e.g., aerobic versus strength training. The implementation of resistance exercise improves body composition by increasing fat-free mass. Dissimilar results of exercises on genders should be taken into consideration in obese men and women. Studies with a longer follow-up duration would provide further information regarding the effects of regular exercise in overweight or obese people.

Abbreviations

WHO	The World Health Organization
BMI	Body mass index
WC	Waist circumference
CVD	Cardiovascular disease
HRmax	Maximum heart rate
HRR	Heart rate reserve
METs	Metabolic equivalents
RPE	Rating of perceived exertion
VO_2max	Maximum oxygen consumption

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_117,

BIA	Bioelectrical impedance analysis
CT	Computerized tomography
MRI	Magnetic resonance imaging
DXA	Dual-energy X-ray absorptiometry
AE	Aerobic exercise
RE	Resistance exercise
AR	Combined aerobic resistance training
WHR	Waist-to-hip ratio
FM	Fat mass
FFM	Fat free mass
CR	Calorie restriction
LBM	Lean body mass
PF	Percent body fat

117.1 Introduction

This chapter aims to review the effects of exercise on body measurements in overweight and obese people. The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that may impair health. Body mass index (BMI), which is calculated by dividing the weight by the square of the height (kg/m^2), is commonly used in classifying obesity in adults. A BMI of 25–29.9 and ≥30 defines overweight and obesity respectively (WHO 2006). Because obesity is associated with an increased risk of multiple health problems including hypertension, type 2 diabetes, dyslipidemia, degenerative joint disease, and some malignancies, it still remains as an important public health issue. Anthropometric measurements allow cross-sectional analysis of the relationship between obesity and the risk of chronic diseases.

The central reason in the development of obesity is an excess of energy intake relative to energy expenditure. This occurs due to the storage of energy excess as adipose tissue. The inclusion of an exercise training program is a useful strategy for reducing obesity. Exercise prescriptions include specific recommendations for the type, intensity, frequency, and duration of any physical activity with specific objectives like weight loss, increase of fitness.

Distribution of fat mass is as important as the amount of fat. As abdominal obesity is more related with the severity of chronic diseases, monitoring changes in abdominal adiposity are becoming important in obesity treatment. Anthropometric measurements are used in assessing body fat distribution and in tracking changes in body composition over exercise training programs in obese people.

117.2 Applications to Disease

117.2.1 Weight-Related Health Risk

As sedentary lifestyle and obesity are important lifestyles related to public health problems throughout the world resulting with serious medical conditions, excess body fat must be taken seriously. Abdominal excess fat (abdominal adiposity) is more correlated with obesity associated complications than excess total body fat. Moreover, waist circumference (WC) has been included among the diagnostic criteria for the metabolic syndrome consisting of diabetes mellitus, insulin resistance, and

Table 117.1 Classification of overweight and obesity by BMI, waist circumference and associated disease risk

	Disease risk[a] relative to normal weight and waist circumference		
	BMI (kg/m^2)	Men ≤ 102 cm (≤40 in.) Women ≤ 88 cm (≤35 in.)	> 102 cm (> 40 in.) > 88 cm (> 35 in.)
Underweight	<18.5	–	–
Normal weight[b]	18.5–24.9	–	–
Overweight	25–29.9	Increased	High
Obesity (class 1)	30–34.9	High	Very high
Obesity (class 2)	35–39.9	Very high	Very high
Extreme obesity (Class 3)	≥40	Extremely high	Extremely high

Bethesda (2000).

[a]Disease risk for type 2 diabetes, hypertension, and CVD

[b]Increased waist circumference can also be a marker for increased risk even in persons of normal weight

hypertriglyceridemia (Alberti et al. 2005). Insulin resistance is associated with increased visceral fat mass and with alterations in fat deposition within the skeletal muscle (Fenkçi et al. 2006). The National Heart Lung and Blood Institute Expert Panel used an evidence-based methodology in developing key recommendations for assessing and treating overweight and obese patients. The recommended classification for overweight and obesity by the Expert Panel is shown in Table 117.1 (Bethesda 2000). This classification includes WC values besides BMI in assessing the risk of type 2 diabetes, hypertension, and cardiovascular disease (CVD). According to the guidelines, assessment of overweight involves the evaluation of three key measures – body mass index (BMI), waist circumference, and a patient's risk factors for diseases and conditions associated with obesity. WC measurement is particularly useful in patients who are categorized as normal or overweight. Men who have waist circumferences greater than 40 in. (102 cm), and women who have waist circumferences greater than 35 in. (88 cm), are at a higher risk of diabetes, hypertension, and cardiovascular disease because of excess abdominal fat.

Physical inactivity and excess body mass are independent risk factors for CVD. The prevalence of coronary artery disease and high blood pressure exhibits a significant linear relationship with BMI for both genders and all ages. The presence of overweight or obesity is moderately associated with high blood cholesterol which is observed in both sexes without an increase with BMI classes. The relationship with increased triglyceride, low HDL cholesterol, and altered composition of lipoprotein particles are stronger than a high cholesterol level. Increased body weight is also associated with an increased risk of certain forms of cancer, including colon cancer, endometrial cancer, and postmenopausal breast cancer (Hansen et al. 2007). Monitoring the alteration in body fat is important in understanding the impact of different types of weight loss interventions on health benefits and risks.

117.2.2 Exercise Prescription

Weight reduction is an important first step in controlling health risk factors. There is sufficient evidence supporting the role of exercise training in promoting weight loss (Shaw et al. 2006). Studies about the metabolic effects of exercise have yielded contradictory results. Differences in intensity, type (aerobic or resistance), and duration of exercise protocols employed might be responsible for the discrepancies among these studies. The degree of glucose intolerance and distribution of body fat of enrolled subjects may suggest other explanations for conflicting results. In some studies, calorie-restricted diets were given to subjects concomitant with an exercise regimen. Differences in these dietary programs may affect the outcomes of exercise protocols.

117.2.3 Exercise Training

Intervention programs aimed at reducing body weight should include an exercise component. The exercise not only improved the measures of obesity and the metabolic risk factors but also improved the physical fitness in terms of endurance, strength, and flexibility of performance.

117.2.4 Definition of Terms

Physical activity is a broad term that encompasses all forms of muscle movement. These movements range from various sports to lifestyle activities. Furthermore, *exercise* can be defined as a physical activity with planned, structured and repetitive movement of the body designed to enhance physical fitness. The FITT principle of exercise prescription features an individually tailored exercise program including how many sessions a week one should exercise (*F*requency), how intense (*I*ntensity) and how long (*T*ime) the workout should be and what modality should be used (*T*ype of exercise).

117.2.5 Exercise Types

1. *Aerobic (Cardiovascular Endurance) Exercise (AE)*:
Cardiovascular endurance represents the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity. Aerobic exercise is defined as any activity using large muscle groups which can be maintained continuously and rhythmically (walking, running, stair climbing, swimming, cycling, rowing, dancing, etc.). It is a type of exercise that overloads the heart and lungs causing them to work harder and offers the greatest improvement with maximum oxygen consumption (VO_2max) (Table 117.2). Various methods such as the percent age-predicted maximum heart rate (HRmax) (220 – Age), heart rate reserve (HRR) which takes into account the resting heart rate, metabolic equivalents (METs), rating of perceived exertion (RPE), or VO_2 max can be used for prescribing the intensity of exercise. The duration of the exercise should be increased with adaptation unless evidence of undue fatigue or injury occurs (Thompson et al. 2009).

2. *Resistance Exercise (RE)*:
Muscular strength is the ability of muscles to exert force. Resistance exercise (strength training) refers to any type of training using a resistance against the force of muscular contraction. The recommendations proposed by the ACSM for resistance training exercise are summarized in Table 117.3 (Thompson et al. 2009). A stretching exercise program is also recommended to be included to an exercise training program (Thompson et al. 2009).

117.2.6 Exercise Prescription for Obese Patients

The effectiveness of exercise was investigated in several designs as a weight loss intervention in people with overweight or obesity in the literature (Shaw et al. 2006). These are – comparison of exercise with no treatment, comparison of exercise with a diet, comparison of exercise in combination with

Table 117.2 Key features of Aerobic Exercise (AE)

1. Aerobic exercise is physical exercise that intends to improve the oxygen system. Aerobic means "with oxygen" and refers to the use of oxygen in the body's metabolic or energy-generating process.
2. Aerobic activity makes the heart beat faster and breathe harder than usual. Aerobic activity strengthens the heart and improves lung function.
3. Aerobic capacity is defined as the ability of the body to transport and use oxygen and is dependent on the effective integration of both the cardiac and the pulmonary systems. The terms aerobic capacity, cardio respiratory (CR) fitness, maximum oxygen consumption (VO_2max) and cardiovascular fitness are used synonymously. These terms refer to the maximal capacity to produce energy aerobically and are usually expressed in METs or ml O_2/kg/min. One MET (metabolic equivalent unit) is equal to approximately 3.5 ml O_2/kg/min.
4. Aerobic activities that involve large muscle groups over prolonged periods of time offer the greatest improvement in VO_2 max. Examples of aerobic activities include walking, running, swimming, and bicycling, etc.
5. Exercise recommendations to improve CR fitness include four components; Frequency (how many sessions a week one should exercise), Intensity (how intense), Time (how long) and Type of exercise (modality which should be used) also known FITT principles.

This table lists the key facts of aerobic exercise including definition, basic concept and FITT principles of aerobic exercise

Table 117.3 Key features of Resistance Exercise (RE)

1. Resistance exercises (strength training) improve the strength, power and endurance of muscles.
2. Free weights, machines with stacked weights or hydraulic resistance and elastic bands can be used for resistance.
3. A minimum of 8–10 exercises for training the major muscle groups with 8–12 repetitions per set for at least 2 days per week should be performed.

This table lists the key facts of resistance exercise including definition, intensity, frequency and duration of resistance exercise

diet to diet alone, and comparison of high with low intensity exercise. Exercise stimuli including *exercise intensity* was moderate to vigorous, *frequency* was 3–5 days a week for most trials, *duration* ranged from 20 to 60 min. Muscle strength training has been used either alone or in combination with aerobic exercise. The types of exercise include aerobic exercise as a walking/jogging/cycling/stair stepping/treadmill exercise/ball games/calisthenics or resistance exercise as a weights training/circuit training or combined aerobic and resistance exercise (Shaw et al. 2006).

Table 117.4 lists exercise recommendations for overweight and obese individuals from selected leading health organizations. The American College of Sports Medicine recommends minimal FITT framework for overweight and obese individuals (Thompson et al. 2009). These parameters are also consistent with the current guidelines such as The Institute of Medicine (IOM) (IOM 2002), The International Association for the Study of Obesity (IASO) (Saris et al. 2003) and The U.S. Department of Health and Human Services (DHHS) guidelines (DHHS 2008).

117.3 Practical Methods and Techniques

117.3.1 Assessment of Obesity Using Body Measurements

In clinical obesity treatment programs, it is important to obtain detailed body measurements, especially in evaluation of the alterations. These are used as outcome measures for effectiveness of interventions in obesity.

Table 117.4 Exercise recommendations for overweight and obese individuals from leading health organizations

Organization: The American College of Sports and Medicine (Thompson et al. 2009).
Recommendation: Minimal FITT framework is recommended.
Frequency: ≥ 5 session times a week
Intensity: Moderate (i.e., 40–60% VO_2R or HRR) to vigorous (50–75% VO_2R or HRR) intensity
Time: Starting with a total 150 min and progressively increasing up to 300 min of moderate intensity physical activity per week; 150 min of vigorous physical activity or alternatively accumulating intermittent exercise of at least 10 min in duration
Type of exercise: Primary mode should be aerobic exercise and resistance training exercise should be incorporated
Organization: The Institute of Medicine (IOM) (IOM 2002).
Recommendation: 60 min of activity per day, but the main purpose of these guidelines was to prevent weight gain.
Organization: The U.S. Department of Health and Human Services (DHHS) (DHHS 2008).
Recommendation: 150 min of moderate activity or 75 min of vigorous activity per week in bouts of 10 min emphasizing that activity for weight loss or maintenance the weight more activity may be required than the base amount needed to produce other health benefits
Organization: The International Association for the Study of Obesity (IASO) (Saris et al. 2003).
Recommendation: 45–60 min of moderate intensity activity each day to prevent excess weight gain.

This table summarizes the exercise recommendations for overweight and obesity from leading Health Organizations including The American College of Sports and Medicine, The Institute of Medicine, The U.S. Department of Health and Human Services, The International Association for the Study of Obesity

Table 117.5 Methods of body measurements commonly used in obesity outcome studies

Anthropometric measurements
• Weight
• Body mass index (BMI)
• Measurement of Circumference
– Waist circumference
– Hip circumference
– Waist-to-hip ratio (WHR)
• Skinfold thickness
Techniques for measuring body composition
• Bioelectrical impedance analysis(BIA)
• Dual-energy absorptiometry (DXA)
• Imaging techniques
– CT
– MRI

This table summarizes commonly used anthropometric measurements and techniques for measuring body composition in obesity outcome studies highlighted in this chapter

Anthropometric measurements include height, weight, skinfold thickness and waist circumference measurements. Monitoring of body composition is applicable in obese people by using various methods and equipments. Many methods have been used to estimate body composition and fat distribution but less is known about their suitability to assess the differential changes in body composition following endurance and strength training. Simple anthropometric measurements such as body mass index (BMI), skinfold thicknesses, and waist circumference are used as indirect and crude estimates of adiposity and abdominal obesity. Bioelectrical impedance analysis (BIA) is an inexpensive method to analyze total and regional body composition. However, BIA is not considered to be as accurate as underwater weighing, computerized tomography (CT), magnetic resonance imaging (MRI), or dual-energy X-ray absorptiometry (DXA) (Sillinpaa et al. 2008). Commonly used body measurements in obesity outcome studies are shown in Table 117.5.

117.4 Effects of Exercise Training on Anthropometric Measurements and Body Composition in Obesity

117.4.1 Weight – BMI

Measurements of height and weight provide vital information for evaluating obesity. Weight is measured with a standard scale. Height is assessed with a wall-mounted stadiometer. BMI is calculated as weight (kg) divided by squared meters of height.

A large amount of research on people who are overweight or obese has been undertaken to assess the effects of exercise on weight loss. While most trials reported weight change as kilograms lost, some trials reported weight change as change in BMI alone (Shaw et al. 2006). In the literature, the degree of weight loss varies from one study to another and the magnitude of weight loss after exercise was less than expected. Although a variety of exercise prescriptions for weight control exist, the literature reveals that the effects of exercise on body weight is rather small, but significant. In a meta-analysis of 28 exercise and weight loss studies, it was concluded that weight lost in exercise programs without caloric restriction is small and usually ranges from 2 to 7 kg (Garrow and Summerbell 1995).

Miller et al. state that while the average weight loss as a result of 16 weeks of combined endurance exercise and caloric restriction averages ~11 kg, only aerobic exercises provide a lesser extent (on average ~3 kg of bodyweight loss). This meta-analytical review reported that exercise causes decrease in body weight at a rate of about 0.2–1 kg/week and people do not lose weight as much as expected from the prescribed exercise. More information on long-term effects of exercise in weight control is needed (Miller et al. 1997). In a recent meta-analysis of 18 randomized trials, it was found that interventions including a combined diet + exercise program produced greater long-term weight loss than interventions that only included a diet program (Wu et al. 2009).

Many studies investigated the effects of exercise types (aerobic and/or resistance) on weight loss; while in some studies it was demonstrated that both exercises were ineffective (Wadden et al. 1997; Lambers et al. 2008) in the others, aerobic exercise (Ross et al. 2000; Mayo et al. 2003; Sasai et al. 2009) or both were found to be effective (Park et al. 2003; Ghroubi et al. 2009). These differences may depend on methodology and variety of patient groups in the studies. Some studies implicated patients with chronic diseases (Lambers et al. 2008), some applied different caloric restrictions (Ghroubi et al. 2009) and some without dietary restriction exercise training (Mayo et al. 2003, Sasai et al. 2009). The study suggesting that the type of exercise does not have a differential effect on weight regain and long-term weight loss was conducted by randomizing obese participants to one of four groups: (1) diet alone, (2) diet plus aerobic training, (3) diet plus strength training, and (4) diet with aerobic and strength training combined. After 48 weeks of treatment, there were no differences between any of the groups on measures of weight and body composition (Wadden et al. 1997).

In two studies conducted in our clinic, no diet restriction and physical activity training were applied during the training program. The first study was a randomized, prospective, controlled trial investigating the effects of aerobic and resistance exercises in obese women who were not under an energy restricted diet (Sarsan et al. 2006). At the end of the 12th week, the average weight of the AE and RE group decreased from 87.52 ± 11.68 to 84.00 ± 12.02 kg and from 83.77 ± 9.49 to 80.95 ± 9.52 kg, respectively. In the control group, no weight change was detected (86.82 ± 11.27 vs. 86.40 ± 11.46 (86.82 ± 11.27 vs. 86.40 ± 11.46 kg). While a significant weight loss compared to baseline was observed in both exercise groups, there was no significant difference compared to the control group in terms of actual weight loss (Sarsan et al. 2006). In a recent randomized study conducted in our clinic, we demonstrated that both combined aerobic resistance training and aerobic training programs were effective in weight loss and gender was not found as a factor on weight loss (Sanal et al. 2009). However, the shortcoming of this study was that it did not have a control group.

Table 117.6 Summary of body weight changes of the intervention groups in overweight or obese people from a meta-analysis (Adapted from Shaw et al. (2006). Copyright Cochrane Collaboration, reproduced with permission)

Intervention	Body weight	BMI
Exercise versus no treatment	Exercise increased weight loss compared with no treatment.	Exercise reduced BMI more than no treatment.
	Exercisers lost 0.5–4.0 kg.	Exercisers lost between 0.3 and 0.7 kg/m^2.
	No treatment changed weight from −0.1 kg loss to 0.7 kg gain.	No treatment changed BMI from 0.3 to 0.4 kg/m^2 gain.
High versus low intensity exercise	Increasing the intensity increased the weight loss if participants were not on a diet.	Insufficient data for analysis.
	High intensity exercisers lost 1.5 kg more than low intensity exercisers.	
	Range of weight change for high intensity exercisers was from 1.3 to 8.9 kg loss.	
	Range for low intensity exercisers was from 6.3 kg loss to 0.1 kg gain.	
High versus low intensity exercise with dietary change	Increasing the intensity did not increase the weight loss if they were on a diet.	Insufficient data for analysis.
	Range of weight change was 6.4–19.6 kg loss across groups.	
Exercise versus diet	Diet resulted in greater weight losses compared with exercise.	Diet resulted in greater BMI reductions than exercise.
	Dieters lost 2.8–13.6 kg of weight.	Diet resulted in a loss of 0.3–3.3 kg/m^2.
	Exercisers lost 0.5–4.0 kg of weight.	Exercise resulted in a loss of 0.3–0.8 kg/m^2.
Exercise and diet versus diet alone	Diet + exercise resulted in greater weight loss than diet alone.	Diet + exercise resulted in greater reductions in BMI than diet alone.
	Dieters + exercisers lost 1.1 kg more than dieters.	Dieters + exercisers lost 0.4 kg/m^2 more than dieters.
	Range of weight change for dieters + exercisers was from 3.4 to 17.7 kg loss.	Range of BMI change for dieters + exercisers was from 0.6 to 4.0 kg/m^2 loss.
	Range for dieters was 2.3–16.7 kg loss.	Range for dieters was 0.3–4.0 kg/m^2 loss.

kg kilograms, *BMI* body mass index, *WHR* waist–hip ratio
This table summarized results of a meta-analysis of 43 randomized controlled clinical trials consisting of 3,476 participants assessed exercise in achieving weight loss in overweight or obese individuals

A meta-analysis of 43 randomized controlled clinical trials consisting of 3,476 participants assessed exercise in achieving weight loss in overweight or obese individuals. Summary of body weight changes of the intervention groups are shown in Table 117.6 (Shaw et al. 2006).

117.4.2 Circumference and Skinfold Measurement

The need for having a simple, inexpensive, noninvasive and universally applicable technique of measuring changes in body and truncal fat during weight loss is important in weight loss programs. Waist circumference is the most practical tool a clinician can use to evaluate a patient's abdominal fat before and during the weight loss treatment.

Waist and hip circumference are taken at the smallest girth of the waist and widest girth of the hip. Waist-to-hip ratio (WHR) is preferred to an anthropometric method which was developed in epidemiologic studies as an indicator of fat mass distribution. Simple anthropometric measurements such as WC, WHR, and skinfold thickness provide a useful estimation of the proportion of abdominal or upper-body fat but they do not distinguish between accumulations of deep abdominal (visceral) fat and subcutaneous abdominal fat. These are used as indirect and crude estimates of adiposity and abdominal obesity.

There is insufficient evidence that exercise-induced weight loss is associated with reductions in abdominal fat. Limited evidence from non-randomized or controlled studies suggest that a modest reduction in waist circumference is observed in response to exercise-induced weight loss (*Ross and Jansessen* 1999). The authors stated that better-quality studies that investigated the impact of exercise on the components of abdominal fat were needed before any conclusions could be made. It was noted that the combination of endurance and strength exercises produced a more notable improvement in weight loss and waistline (Ghroubi et al. 2009). There is an agreement that changes in WHR, WC, weight, and BMI are not always evident in estimating visceral and total abdominal fat mass, however imaging techniques have to be used (Kay and Fiatarone 2006). Indeed, we have shown that after a 12 week training program, while the aerobic and combined exercises declined the fat mass of trunk measured with DXA, a statistically significant change in WHR was not observed (Sanal E et al. 2009).

Skinfold measurement is frequently used for estimating body fat dispersion and abdominal measurements are especially consequential for abdominal obesity. Skinfold technique can be preferred in epidemiologic studies with many subjects. Sillanpaa et al. compared the usefulness of different methods for the analysis of body composition to detect training-induced adaptations. They indicate that simple anthropometric measurements such as waist circumference and skinfold thickness seem to accurately assess changes in body fat percentage during exercise training as correlated with DXA (Sillanpaa et al. 2008). Mayo et al. conducted a study to investigate whether abdominal fat is reduced in response to substantial weight loss induced by exercise in young obese men. Thirty obese men in the army were evaluated before and after a 4-month training program comprising large muscle group activities at 40–60% maximum heart rate. Thirty obese male subjects without training were evaluated as control subjects. Fat free mass (FFM), fat mass and body fat percentages were determined from skinfold measurements. Substantial weight loss induced by exercise was found to be associated with maintenance of lean tissue, unlike diet-induced weight loss of the same magnitude (Mayo et al. 2003).

In our study, after a 12-week training program, both aerobic and combined exercises were found to be effective on decreasing WC and lowering all skinfold measurements, but no differences were observed between the two training groups (Sanal et al. 2009).

117.4.3 Fat Mass (FM) and Fat-Free Mass (FFM) Measurements

Weight reduction is the common goal in the treatment of obesity. An optimal weight reduction program should selectively deplete body fat while maintaining lean tissue. Fat-free mass is composed of muscle, bone, organs, and water, whereas fat is the underlying adipose tissue. Higher proportions of fat-free mass indicate an increase in muscle and thus enhanced physical workload capacity.

Several investigators have reviewed the effects of exercise on the reduction in total fat mass and/or visceral fat mass. A meta-analysis of 46 studies has evaluated the effects of endurance exercise

Table 117.7 Randomized controlled trials: (a) changes in abdominal imaging measures in the absence of changes in body mass and (b) a reduction in body mass and changes in imaging measures of abdominal fat (Taken from Kay and Fiatarone Singh (2006) by permission from John Wiley)

References	Group	Mass kg Δ (%Δ)	CT cm^2 Δ (%Δ)	MRI cm^2 kg^{-1} Δ (%Δ)	DXA kg Δ (%Δ)
(a) Boudou et al. (2003)	A + I	−1.9 (2.2)		−69.05 cm^2 (44)***	
	C	−1.65 (1.8)		−6.5 (4.1)	
Castaneda et al. (2002)	PRT	+0.2 (0.3)			−0.9 (4.8)**
	C	+0.8 (1.0)			+0.8 (4.4)
Mourier et al. (1997)	A + I	−1.5 (1.8)		−75.7 cm^2 (48)*	
	C	−0.2 (0.2)		−4.5 (3.2)	
Ross et al. (2000)	ANL	−0.5 (0.5)		−32 cm^2 (16.8)*	
	C	+0.1 (0.1)		0 (0)	
Ross et al. (2004)	ENL	−0.5 (0.6)		-0.4 (18.2)*	
	C	+0.5 (0.6)		-0.1 kg (4.3)	
(b) Irwin et al. (2003)	Ex	−1.3 (2.0)**	−8.5 (5.8)*		
	C	+0.1 (0.1)	0.1 (0.07)		
Pritchard et al. (1997)	Ex	(−3.0)*			(−12.9)***
	C	(+1.03)			(−0.6)
Ross et al. (2000)	AWL	−7.5 (7.4)*		−52 (28)*	
	C	+0.1 (0.1)		0 (0)	
Ross et al. (2004)	EWL	−5.9 (6.8)*		−0.7 (30.4)*	
	C	+0.5 (0.6)		−0.1 kg (4.3)	

This table shows randomized controlled studies which assessed the effect of exercise alone on body composition in overweight/obese subjects. There is limited evidence that exercise can lead to a loss of visceral and total abdominal fat without a change in body mass by using new technologies that can quantify fat stores. Studies providing outcome measures of trunk fat mass or area, visceral fat mass, area or volume that were measured via ultrasound, DXA, CT or MRI were considered.

Pre- vs. post-Δ significantly different from control group $*P \leq 0.05$; $**P \leq 0.01$; $*** P \leq 0.001$.

Ex exercise; *A* aerobic exercise; *AWL* aerobic with weight loss; *I* interval training; *PRT* progressive resistance training; *ANL* aerobic with no weight loss; *C* controls; *CT* computed tomography; *DXA* dual-energy X-ray absorptiometry; *EWL* exercise with weight loss; *ENL* exercise with no weight loss; *MRI* magnetic resonance imaging

training on FFM preservation during diet-induced weight loss. The percentage of weight lost as fat-free mass for diet-plus-exercise subjects was approximately half of that for dietary restriction subjects of the same sex (Ballor and Poehlman 1994). In another review was published in 2006, using new technologies that can quantify fat stores, researchers concluded that there was limited evidence that exercise could lead to a loss of visceral and total abdominal fat without a change in weight or waist circumference (Table 117.7). However, the authors also pointed out that none of the studies they reviewed met the criteria of a "gold standard" randomized clinical trial and stressed that such trials needed to be conducted (Kay and Fiatarone 2006). In a recent review, it seems that the addition of physical exercise to a diet is important to prevent a decrease in fat-free mass, increase relative visceral fat-mass loss, improve dietary compliance and eventually maintain long-term weight control (Hansen et al. 2007).

Exercise type: Results vary regarding the effects of AE and RE on the protection of the FFM. Some studies have demonstrated that both AE and RE have no effect on FFM, (Wadden et al. 1997) but other studies have indicated that additional RE is more helpful in protecting FFM than only AE is (Ghroubi et al. 2009). Although all these studies suggest positive effects of exercise on different systems, the evidence is not conclusive.

Exercise intensity: A review researching dose–response effect suggested that aerobic exercise as a weight loss intervention had a dose-response relationship for significant visceral fat reduction; at least 10 METs_h/w was required in obese subjects, excluding groups with metabolic-related disorders (Ohkawara et al. 2007). In contrast to this finding, Nicklas et al. showed no influence of training intensity on selective loss of abdominal adipose tissue. 112 overweight and obese postmenopausal women were assigned to one of three 20-week interventions of equal energy deficit: calorie restriction (CR), CR plus moderate-intensity aerobic exercise or CR plus vigorous-intensity exercise (45–50% vs. 70–75% of heart rate reserve). They concluded that lean mass was preserved with a similar amount of total weight loss, but there was not a preferential loss of abdominal fat when either moderate- or vigorous-intensity aerobic exercise was performed during caloric restriction (Nicklas et al. 2009).

117.5 Determination of Effects of Exercise Training Program on Body Composition

Accurate measurements of body composition using reference standards are impracticable such as a 4-compartment model and underwater weighing, expensive such as magnetic resonance imaging (MRI) or involve a small dose of radiation such as dual energy X-ray absorptiometry (DXA) and computerized tomography (CT) (Garaulet et al. 2006). The techniques used during the assessment of the effects of exercise training program on body composition profile were as follows:

117.5.1 Hydrostatic Weighing

Hydrostatic weighing is a method of determining body composition using the Archimedes' principle of displacement. Hydrostatic weighing had been considered as the gold standard for body composition assessment, however, new and more practical and sophisticated techniques took the place of this method. Furthermore, this displacement method could not analyze the regional body fat distribution. Some studies were conducted to determine the effectiveness of exercises by this method. It was reported by applying underwater weighing that in obese subjects, the inclusion of resistance exercise to the diet prevented loss of FFM compared to aerobic training and diet, or diet only groups (Geliebter et al. 1997). Nevertheless, in a study with opposite results, Donnelly et al. investigated the effects of very-low-calorie diet and physical-training regimens (diet only, diet plus endurance exercise, diet plus weight training, or diet plus endurance exercise and weight training) on body composition in obese females. Hydrostatic weighing at residual volume was used to determine body fat percentage. They showed that preservation of FFM after RE was not found to be successful in obese people. This can be explained by a greater loss in FFM as a result of very low-calorie diet (Donnelly et al. 1991).

117.5.2 Bioelectrical Impedance Analysis

BIA is a body composition assessment technique used in tracking changes in body composition over exercise training program in obese people in a variety of settings (e.g., hospital based fitness facilities, wellness fairs, and health clubs). FM and FFM of the patients were measured by BIA after 10 h of fasting.

This technique is very portable, easy to use and reduces the overall time of assessing relative body fat in the general public. Although BIA has emerged as a popular method of assessing changes in body composition, its accuracy to identify these changes in overweight patients and during weight loss is not certain. In the most recent research, Aslam et al. reported that BIA underestimated total body fat changes in males and overestimated total body fat changes in females compared to DXA. They suggested that BMI, body weight, and WC provided a simple and more accurate estimate to that of BIA which estimated relative changes in total and truncal fat during moderate weight loss in adults (Aslam et al. 2009).

There are a small number of studies about the efficacy of pure exercise. We conducted a longitudinal, controlled clinical study with the endocrinology department to compare the effects of RE and AE on BMI, weight, FM, in obese women who cannot adhere to energy-restricted diets (Fenkci et al. 2006). A total of 60 obese women were randomly divided into three groups: control group with no exercise, AE group, and RE group. The AE group performed both walking and leg cycle exercises with increasing duration and frequency. The RE group performed progressive weight-resistance exercises for the upper and lower body. Before and after a 12-week period, all subjects were evaluated by anthropometric measurements. Percentages of total body FM and FFM were measured by BIA. In this study, significantly decreased BMI, waist, and weight measurements were observed in both study groups but reduced FM was seen only in the AE group. Lambers et al. conducted a double-blind, randomized controlled trial to investigate the effect of exercise in 42 obese patients with type 2 diabetes. No significant difference among the three groups (combined exercise, aerobic exercise or no training) was detected in anthropometric variables (weight, waist, and BMI) and fat mass assessed by BIA (Lambers et al. 2008). Ghroubi and colleagues suggested that the combination of dietary measures with exercise training including resistance exercise may contribute to improvements in body composition in the management of obesity. Eight-three obese patients were randomized into three groups: (1) control group (no diet-no exercise), (2) low calorie diet (25–30% decrease in calorie intake relative to previous levels) plus aerobic treadmill training, (3) diet plus aerobic exercise and segmental strength training of the arm, leg, and abdominal wall muscles. The aerobic treadmill training involved 45–60-min exercise sessions three times a week for a 2-month period and the intensity was set to 60% of the HRmax. The strength training was performed at 60% of the maximal voluntary force for each muscle group, with three sets of 20 repetitions. BIA analysis was applied to assess body fat mass and lean mass. They did not note any variations in lean mass in the patients having performed aerobic training; in contrast, patients having performed additional strength exercises displayed an increase in lean mass and a greater decrease in fatty mass (Ghroubi et al. 2009).

117.5.3 Imaging Techniques

Both whole body and regional measurements of fat distribution are required for the determination of whether abdominal fat is preferentially reduced in response to exercise. CT and MRI allow changes in intra-abdominal fat (visceral and/or subcutaneous) to be monitored. MRI provides results similar to CT without exposure to ionizing radiation. It demonstrates good reproducibility for total and visceral adipose tissue volumes. CT and MRI are both more accurate but impractical for routine clinical practice being expensive and time consuming. Additional limitations that include lack of portability and scanner size that may be too small for some obese individuals are shared by MRI and CT (Aslam et al. 2009).

Park et al. showed by CT that combined training (aerobic training plus resistance training) decreased abdominal subcutaneous fat and visceral fat more than aerobic training only (Park et al. 2003). Thirty middle-aged obese women were separated into a control group, aerobic training group

and a combined training group. The aerobic training was performed 60 min a day for 6 days a week at 60–70% of HRmax for a period of 1–24 weeks. The combined training group was composed by aerobic training plus resistance training which was performed 60 min a day at 60–70% of one-repetition maximum test for a period of 1–24 weeks. The levels for abdominal fat volume were measured by determining the subcutaneous fat volume and visceral fat volume by CT. They observed that subcutaneous fat and visceral fat decreased by combined training rather than by aerobic training alone. Also, the lean body mass (LBM) significantly increased only in the combined training group (Park et al. 2003).

A previous study using MRI reported that the combination of diet and exercise resulted in a greater reduction of adipose tissue and preservation of lean tissue and skeletal muscle compared with only diet in women. This report provides the evidence that lean tissues are preserved and adiposity is substantially reduced in response to weight loss induced by the combination of RE and moderate energy restriction (Ross et al. 1995). Another study applying MRI showed greater preservation of skeletal muscle and decrease of subcutaneous adipose tissue in the abdominal region, when compared with the gluteal/femoral region, following diet combined with either aerobic or resistance exercise in males (Ross et al. 1996). Ross et al. by MRI, have shown that 12 weeks of daily aerobic exercise without weight loss is associated with significant reductions in both abdominal and visceral fat (Ross et al. 2000).

In a recent study, the effect of aerobic exercise training in 19 sedentary obese men and women using MRI was assessed. It was shown that 4 weeks of aerobic cycling exercise did not alter body weight but significantly reduced hepatic lipids and visceral adipose tissue volume by 12% (Johnson et al. 2009).

117.5.4 Dual Energy X-Ray Absorptiometry

DXA, which is mainly known as the gold standard for assessment of bone mineral density, can also be used to assess fat mass and fat-free mass volume. DXA provides precise estimates of total and regional fat and skeletal muscle mass. It is an objective and reliable technique for measuring body composition and its changes. Simple anthropometric measurements seemed to be useful in the cross-sectional analyses but only DXA was able to detect the group differences in training-induced changes in lean body mass (Sillanpaa et al. 2008). Andersen et al. reported, by DXA, that the percentage of weight loss from FFM was significantly less in the diet plus AE group compared to the diet plus lifestyle group in obese women at the end of 16 weeks (Andersen et al. 1999).

Sasai et al found that participants classified as HIF obesity (high intra-abdominal fat >200 cm^2) exhibited greater reductions in intra-abdominal and total fat in response to regular aerobic exercise than those classified as MIF obesity (Moderate intra-abdominal fat <200 cm^2). Whole-body fat mass (FM), FFM, intra-abdominal fat and subcutaneous fat areas were measured by DXA before and after the 12-week aerobic exercise program (Sasai et al. 2009).

In a recent study conducted in our clinic, the effects of a 12-week combined aerobic resistance training (AR) versus aerobic training alone (AE) on changes in FM, FFM, and percent body fat (PF) in 65 untrained obese males and females were examined (Sanal et al. 2009). Before and after the 12-weeks of training body composition was obtained by DXA. We confirmed that while AR and AE exercises were effective on decreasing FM and PF of the whole body, only AR exercises were found to be effective on increasing FFM of the whole body (Table 117.8). In addition, when evaluating the regional body composition changes, we found that AR exercises were more effective on increasing FFM and decreasing PF of all regional measurements, decreasing FM of trunk and legs than AE exercises. As a conclusion, our findings indicate that AR exercises lead to more gains on regional and the whole body FFM than AE exercises.

Table 117.8 Changes in body composition at baseline and 12-week for aerobic (AE) and combined aerobic resistance (AR) training groups

	Group AE		Group AR		
	n = 33		*n* = 32		
Whole body composition	Baseline (mean ± SD)	12 week (mean ± SD)	Baseline (mean ± SD)	12 week (mean ± SD)	
FM (kg)	30.2 ± 9.4	28.0 ± 8.0*	33.9 ± 8.7	28.5 ± 6.9*	
Change %		(6.70 ± 6.1)		(14.1 ± 14.4)	#
FFM (kg)	51.4 ± 10.3	51.3 ± 9.7	50.7 ± 11.6	53.8 ± 11.2*	
Change %		(0.01 ± 6.0)		(−7.3 ± 13.5)	#
PF	35.8 ± 8.8	34.1 ± 7.8*	39.0 ± 8.6	33.8 ± 7.0*	
Change %		(4.0 ± 5.6)		(11.8 ± 13.9)	#

FM fat mass; *FFM* fat-free mass; *PF* percentage of fat

*$p < 0.001$, significant difference between baseline and 12-week, #$p < 0.01$, significance between group-change

Evaluating the whole body composition, findings indicate that only AR exercises increased whole body FFM and declining FM and PF were more significant for AR group than AE group. DXA measurements revealed that AR exercises were superior on increasing whole body FFM, and reducing whole body of PF and FM than AE. (Sanal et al. 2009) Unpublished data

117.6 Gender: Sex Differences in Fat Loss

In the literature, a few studies compared the effect of exercise training on body composition in both genders. Ballor and Keesey observed in their meta-analysis that men showed a larger bodyweight loss as a result of dietary restriction and exercise training, when compared with women (Ballor and Keesey 1991). In contrast, Andersson et al. showed that the bodyweight and fat-mass loss was comparable between obese men and women as a result of a 3-month combined intervention program. However, when we looked at the data in more detail, it revealed that the baseline fat mass was greater in the female participants. After correction for differences in baseline fat mass, the men had actually lost a higher amount of fat (Andersson et al. 1991). In HERIGATE Family Study, the effect of a 20-week aerobic training program on body composition was assessed in 557 individuals (258 men, 299 women) by hydrostatic weighing and CT. They reported that aerobic endurance exercises provided small but significant increase in the FFM of the whole body, a decrease in FM and PF in both men and women, but men lost a greater amount of abdominal visceral fat in comparison to women (Wilmore and et al. 1999).

Geer and Shen reviewed gender differences in body composition. They concluded that men and women differed in regard to body composition. For a given BMI, men had higher lean mass and more visceral and hepatic adipose tissue, whereas women had elevated general adiposity, SAT in particular (Geer and Shen 2009). Recently Kuk and Ross investigated how body fat was distributed in obese men and women and how it changed after some sort of weight loss program (Kuk and Ross 2009). The participants were 153 men (81) and women (72) with a starting BMI of over 27. Besides anthropomorphic measurements such as weight, waist, and hip circumference, body fat distribution was assessed by whole-body MRI scans initially and after 12–16 weeks. In this study, three weight loss methods were used: calorie restriction, exercise or both (calorie restriction & exercise). On comparison of men and women after the weight loss intervention it was found that there was no difference in total fat loss. Both men and women had lost about 6 kg (14 lb) of fat as was found by the MRI. The main finding of the study is that there are sex differences in visceral fat and lower body fat loss. While men lose more visceral fat, women lose lower body, total subcutaneous fat as a percent of weight loss. It seems impossible to distinguish the cause between whether it is the sex difference or starting fat distribution. The findings of this study suggest that there are sex differences in the

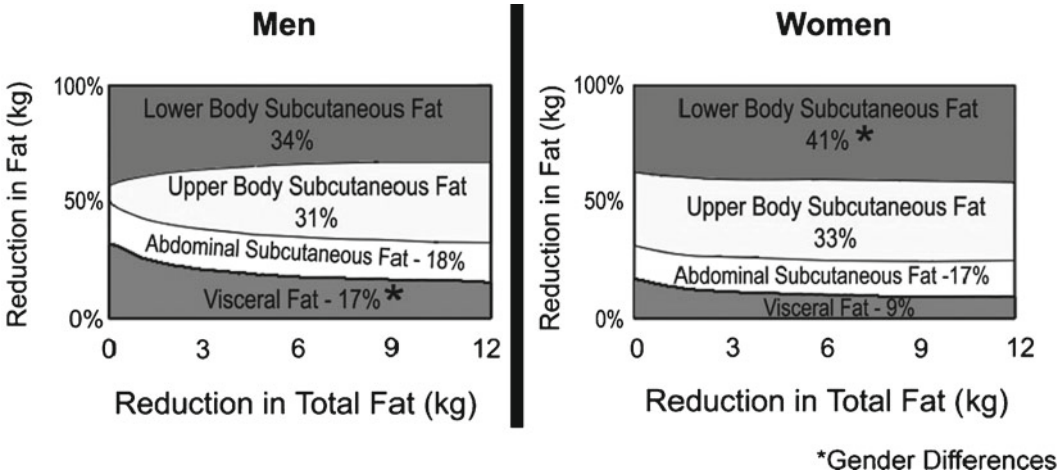

Fig. 117.1 Contribution of visceral and regional subcutaneous fat loss in relation to total fat loss. The main finding of the study is evidence of sex differences in visceral fat and lower body fat loss. Men lose more visceral fat and women lose lower body weight (and total subcutaneous) as percent of weight loss. Taken from Kuk, Ross. (2009) by permission from Macmillan Publishers Ltd: *International Journal of Obesity*

regional adipose tissue loss, not in total adipose tissue loss observed for a given reduction in body weight or WC. The relationship between total and regional adipose tissue loss is shown in Fig. 117.1. The limitation of this study is the variety of diet and/or exercise interventions which induce a wide range of weight losses. It is unclear whether diet and/or exercise interventions are effective in the pattern of fat loss, or whether the sex difference is a factor for the results observed in this study. However, in our study we have investigated the effects of 12-week combined aerobic resistance training versus aerobic training alone in both genders of non-dieting, overweight and obese individuals.

- AR; ↓ trunk and whole body mass ♀>♂
  AR exercises were more effective on lowering mass of trunk and whole body in women in comparison with men.
- ♂; AR> AE arm, trunk and whole body FFM ↑
  In regards of evaluating the effectiveness of the type of exercises in men, AR exercises were more effective on increasing the FFM of arms, trunk and whole body than AE exercises.
- ♀; AR> AE FM and mass of legs ↓

In assessing the effectiveness of the type of exercises in women, AR exercise was observed to be superior on FM and mass of legs compared to AE exercise. When women were usually considered as gynecoid type body shape, more fat mass in legs, this result showed the importance of AR exercises (Sanal et al. 2009). We can conclude that, as there was no calorie restriction and not too much weight loss in our study group, an increase in FFM instead of a decrease was observed. RE exercises have a favorable impact on body composition by preventing the loss of FFM.

Summary Points

- Anthropometric measurements are used as outcome measures for the effectiveness of interventions in obesity. It is important to obtain the detailed body measurements, especially in evaluation of the alterations.

- Most commonly used body measurement methods in obesity outcome studies include simple anthropometric measurements such as weight, BMI, WC, hip circumference, WHR and skin-fold thickness and body composition measurement techniques such as BIA, CT, MRI, or DXA.
- Exercise is an effective weight loss intervention, particularly when combined with dietary interventions.
- With respect to body composition alterations with exercise, slight decreases in total body weights were observed.
- The magnitude of body composition changes vary with the intensity, duration and the type of the exercise program.
- Including resistance exercises increases FFM.
- Dissimilar results of exercises on genders must be taken into consideration prescribing exercises in overweight and obese men and women.
- Studies with a longer duration of follow-up would provide further information regarding the long-term effects of regular exercise in people who are overweight or obese.

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Chapter 118
Anthropometry and Exercise in Down Syndrome

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Abstract In recent years, there has been a growing concern as to the importance of exercise in the holistic management of individuals with Down syndrome (DS). In fact, several studies have reported that regular exercise may improve the health of these individuals, since it may help reduce obesity, insulin resistance and oxidative damage, among other problems. Similarly, exercise may improve the quality of life of individuals with DS by promoting their functional independence as well as their social integration in the workplace, since most of their jobs are based on physical tasks. In addition, an increasing number of sport events are being organised all over the world for individuals with DS by national federations and international institutions, such as the Special Olympics and International Paralympics Committee. In this regard, improving the physical performance of high performance athletes with mental retardation also requires specialised attention from a multidisciplinary team.

Fortunately, anthropometric assessment, including body composition and somatotype analysis, may help these professionals not only achieve all these goals, but also achieve them safely. It should also be noted that this assessment is inexpensive, easy to perform and non-invasive. However, anthropometric assessment is not widely used by professionals in their daily practice to date, which may be explained, at least in part, by the dearth of available information in the literature.

Consequently, this chapter has been written to provide an update on this topic for healthcare providers and sport-related professionals who work with individuals with DS.

Abbreviations

BMC	Bone mineral content
BMD	Bone Mineral density
DS	Down syndrome
DXA	Dual X-ray densitometry
H/A	Height for age
volBMD	Volumetric Bone Mineral Density
W/A	Weight for age

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_118,

Table 118.1 Key facts on exercise and down syndrome

1. Several studies have reported that low to moderately intense aerobic exercise may improve the health status, quality of life and social integration of individuals with Down syndrome.
2. The HRmax = 194.5 – (0.56 × age) equation should be used to determine intensity, since it takes chronotropic incompetence into account.
3. Since hypotonia is very common in Down syndrome, resistance training may improve quality of life and social integration in job settings.
4. Training programmes originally designed for the general population should not be copied or applied, since they are difficult to follow for participants who are predisposed to sport-related injuries.

118.1 Anthropometry and Exercise in Down Syndrome: An Update

It is widely accepted that obesity is a serious problem that is overwhelmingly prevalent in the general population. However, the magnitude of this problem is even worse in individuals with mental retardation in general and Down syndrome in particular. Although individuals with Down syndrome are born with a genetic predisposition for becoming overweight, obesity is actually nurtured throughout childhood and adolescence when they develop food and lifestyle choices (Grammatikopoulou et al. 2008; Hawn et al. 2009) (Table 118.1).

Regular exercise may improve the quality of life and health for a variety of population profiles. However, there is a lack of information on the effectiveness of exercise in individuals with Down syndrome. Fortunately, recent studies have reported that regular exercise may help this population, which may be explained, at least in part, by the reduction in their fat mass percentage.

Similarly, there is an increasing interest in improving the high performance of athletes with mental retardation. In this respect, it is generally accepted that athletes with intellectual disabilities have less muscle strength compared with their athletic peers without mental retardation (Van de Vliet et al. 2006). Accordingly, assessing the muscle mass of these individuals would be of interest, especially if we accept the premise that muscle strength may play an important role in ensuring their quality of life and job-related social integration.

With the increasing life expectancy of individuals with DS, concerns have been raised about bone mass in terms of reducing the risk of osteoporosis and falls that may ultimately impair their health (Hale et al. 2007; Guijarro et al. 2008).

Consequently, in order to be safe and effective, intervention programmes based on physical activity to reduce fat mass or improve fat-free mass should be adequately designed and supervised during their application by a multidisciplinary team. In this regard, anthropometric assessment may play an important role in achieving these goals. However, the lack of information on the reliability of anthropometric measurements in subjects with mental retardation means that the use of anthropometric assessment at institutions and schools for individuals with intellectual disabilities is rare.

118.2 Fat Mass and Exercise in Individuals with Down Syndrome

Current findings suggest that more attention needs to be paid to the rising fat mass percentages seen in individuals with Down syndrome in order to minimise negative, long-term health consequences (Sohler et al. 2009) (Table 118.2).

Anthropometric measurements are widely used as a reliable way to quantify body composition and estimate the risks of being overweight in healthy subjects and patients. However, information on

Table 118.2 Key facts on exercise and fat mass in individuals with Down syndrome

1. The prevalence of obesity in Down syndrome is higher than in the general population, even at early life stages.
2. Fortunately, regular, low to moderately intense exercise reduces fat mass.
3. Test-retest reliability and feasibility for several anthropometric variables are acceptable for subjects with mental retardation. Furthermore, most of these variables are strongly correlated to the serum lipid profile.
4. Potentially confounding factors include misunderstanding, motivational problems and agitation.

the reliability of anthropometric measurements in subjects with severe intellectual and sensory disabilities is lacking. Accordingly, their use at institutions and schools for individuals with intellectual disabilities is limited (Ohwada and Nakayama 2004). Fortunately, test-retest reliability and feasibility for several anthropometric variables (body weight; body height; body mass index; waist circumference; fat skinfolds) are acceptable in subjects with severe intellectual and sensory disabilities, according to Waninge et al. (2009). Furthermore, anthropometric measurements are a universally applicable, inexpensive, non-invasive and painless technique.

On the other hand, potentially confusing factors include motivational problems, agitation and misunderstanding, e.g., some of these subjects do not understand why they are being pinched during fat skinfold measurements and may become agitated. Conversely, researchers have more time to read measurement values when subjects are relaxed, thus ensuring more accurate measurements (Waninge et al. 2009).

Percentile distributions of anthropometric indexes such as weight for age (W/A) and height for age (H/A) specific to children and adolescents with Down syndrome have been reported by several authors in different countries, which reflects the lower pace of growth and restricted height observed in this group. The distribution compiled in the United States (Myrelid et al. 2002) is one of the most often cited in the literature covering the 2- to 18-year-old age group. However, there is no consensus on the reference distributions and classification criteria to be used in assessing the nutritional status of children and adolescents with Down syndrome. Fortunately, assessment using the Spanish distribution (Pastor et al. 1998) makes it possible to implement interventions for reducing the body fat of those categorised above P95 for W/A. In any case, the need to use distributions produced specifically for individuals with Down syndrome is based on the recognition of their different rates of growth and development (Lopes et al. 2008).

Our research group reported that adolescents with Down syndrome were able to reduce their fat mass percentage significantly when they completed a 12-week aerobic training programme on a treadmill. This programme consisted in 3 sessions/week and included a 15-min warm-up followed by a 20- to 35-min main section (that was increased by 5 min every 3 weeks) at a work intensity of 60–75% of the peak heart rate according to the HRmax = 194.5 – (0.56 age) formula that takes their chronotropic incompetence into account (Fernhall et al. 2009) and a 10-min cooling-down period (Ordonez et al. 2006). In a similar study, Mendonca and Pereira (2009) concluded that young adults with Down syndrome decreased their fat mass from 27.3 ± 11.2 to 23.5 ± 11.1% ($p < 0.01$) and increased their absolute fat-free mass from 48.4 ± 8.6 to 50.8 ± 9.3 kg ($p < 0.01$) after a 28-week training programme. In this respect, the most striking feature was that our protocol lasted only 12 weeks, which may facilitate its follow-up by participants.

Also of interest is the role of anthropometric variables as potential biomarkers of clinical parameters in order to facilitate the medical follow-up of participants in training programmes. In this respect, anthropometric measurements such as waist circumference, waist or hip ratio and body mass index have been strongly correlated to serum lipid profiles in adolescents with Down syndrome (Ordonez et al. 2005). Furthermore, a weak correlation to antioxidant enzyme activities was also

Table 118.3 Influence of a 12-week aerobic training program in anthropometrical parameters in young adolescents with DS. Control group included 7 age, sex, and body mass index matched adolescents with trisomy 21

	Down syndrome (n = 19)	Controls (n = 7)	P value
Age	16.1 (1.7)	16.4 (1.6)	ns
Height (cm)	155.2 (5.7)	155.3 (5.6)	ns
Weight (kg)	76.8 (4.5)	73.9 ()	<0.05
Body mass index (kg/m^2)	31.7 (2.9)	30.7 (2.5)	<0.05
Fat mass (kg)	28.7 (2.4)	26.3 (2.6)	<0.05
Fat free mass (kg)	47.3 (3.5)	47.6 (3.3)	<0.05
Waist circumference (cm)	103.4 (5.9)	100.2 (5.2)	<0.05
Hip circumference	107.5 (7.1)	105.6 ()	<0.05
Waist to hip ratio	0.96 (0.03)	0.94 (0.02)	<0.05

Results are expressed as mean (sd). Significance was ascertained at p value <0.05. ns (no significant)

shown (Ordonez et al. 2007). Accordingly, anthropometric assessment may be considered easier to carry out, more economical and faster when compared with biochemical assessment.

It is widely known that individuals with Down syndrome exhibit lower peak aerobic capacities and maximal heart rates when compared with healthy peers, which may be explained, at least in part, by a different catecholamine response to exercise (Fernhall et al. 2009). Accordingly, intervention programmes based on regular exercise should be designed by taking Down syndrome individuals' chronotropic incompetence into account to prevent sessions that are moderately intense for the general population from becoming exhausting for participants with Down syndrome and leading to undesired results.

It should also be emphasised that no sport-related injuries were reported during the whole experience, which may indicate not only the effectiveness, but also the safety of our 12-week programme, which is based on low to moderately intense aerobic exercise for individuals with Down syndrome. This is of particular interest, since injuries and discomfort may lead participants to interrupt their programmes (Table 118.3).

Finally, since children and adolescents with Down syndrome tend to obesity, increasing participation in exercise programmes may be appropriate for preventing obesity and promoting lifelong health (Whitt-Glover et al. 2006).

118.3 Fat Free Mass and Exercise in Individuals with Down Syndrome

118.3.1 Muscle Mass

It is generally accepted that individuals with Down syndrome suffer from hypotonia, which may have a negative impact not only on their health status but also on their quality of life and work-related aspects.

Along these lines, Mercer and Lewis (2001) reported that children with DS had significantly lower mean peak torque values for hip abduction and knee extension than age- and gender-matched peers without mental retardation. Similarly, Carmeli et al. (2002) reported that the situation of individuals with Down syndrome was even worse when compared with other individuals with mental retardation (Table 118.4).

Table 118.4 Key facts on oxidative stress and body composition in individuals with Down syndrome

1. Individuals with DS have been described as having higher oxidative damage than their healthy siblings do.
2. Oxidative damage has been proposed as a pathogenic mechanism of early aging, neurodegeneration, carcinogenic events and immunological disorders in individuals with DS.
3. Oxidative damage has been associated with obesity in both the general population and individuals with DS and regular exercise may reduce oxidative damage by boosting the antioxidant system.
4. Since antioxidant enzyme activities and products derived from the oxidation of lipids and proteins have been correlated to body fat distribution indices, the latter can be used as potential biomarkers in an easier and non-invasive manner

Hand-held dynamometry can be used to obtain reliable measurements of isometric muscle strength in children with Down syndrome. Furthermore, regression analyses indicated that weight, body mass index, height, activity level and gender were significant predictors of peak torque production in the sample (Mercer and Lewis 2001).

Progressive resistance training is a safe and feasible fitness option that can improve muscle performance and physical functioning in adults with Down syndrome. One progressive resistance training programme consisted in six exercises using weight machines carried out twice a week for 10 weeks. Participants completed two to three sets of 10 to 12 repetitions of each exercise until they were fatigued. It should also be emphasised that no major adverse events were noted during the intervention (Shields et al. 2008).

118.3.2 Bone Mass

With the increasing life expectancy of individuals with Down syndrome, concerns have been raised about bone mass, since it may reduce the risk of osteoporosis and falls (Hale et al. 2007), above all, if we take into account that individuals with Down syndrome have lower lumbar spine bone mineral density not only in comparison with healthy controls (Baptista et al. 2005), but also in comparison with intellectually average, age, sex and race-matched subjects (Angelopoulou et al. 2000).

In fact, individuals with trisomy 21 present a number of features (muscle hypotonia, sedentarism, poor calcium and vitamin D intake, hypogonadism, growth retardation and thyroid dysfunction) that may contribute to substantial impairments in skeletal maturation and bone-mass accrual, which predisposes these patients to fragility fractures (Hawli et al. 2009). In this regard, independent body composition variables selected by stepwise regression indicated that muscle mass was the main variance predictor of upper and lower limb-adjusted bone mineral content (BMC), lumbar spine-adjusted BMC and volumetric bone mineral density (volBMD) in young males and females (ages 14–40) with Down syndrome (Baptista et al. 2005). Fat mass was also the main predictor of composite indices of femoral neck strength (conversely, no body composition predictor for femoral neck adjusted BMC or volBMD was found) (Table 118.5).

In a recent study, Guijarro et al. (2008) reported that young adults with DS had a reduced area bone mineral density (aBMD) in all regions (spine, hip and total body) measured by dual X-ray densitometry (DXA). In this respect, it is widely accepted that area BMD as measured by DXA is influenced not only by the "true density" of bone tissue, but also by bone size. Therefore, given a series of bone samples with the same BMD but different sizes, smaller bones tend to have lower area BMD values than larger bones. This confusing effect of body-size differences has prompted authors to analyse not only the usual area BMD, but also the volBMD estimated from the DXA output after modelling bones as cylinders (Guijarro et al. 2008) (Table 118.6).

Table 118.5 Resting, submaximal, and peak physiological responses at pre- and post-training periods in young adults with down syndrome (Mendonca and Pereira 2009)

Variable	Pre-training	Post-training
Rest		
VO_2 (ml/kg/min)	3.1 (0.8)	3.3 (1.0)
HR (bpm)	69.5 (12.5)	68.8 (13.1)
Submaximal		
VO_2 (ml/kg/min)	9.1 (2.6)	10.3 (3.9)
HR (bpm)	90.7 (14.8)	90.5 (12.9)
RER	0.91 (0.11)	0.83 (0.05) *
Ventilation (l/min)	17.1 (4.2)	18.7 (4.7)
Maximal		
VO_2 (ml/kg/min)	20.9 (4.7)	26.7 (7.6) *
HR (bpm)	145.6 (19.5)	151.0 (21.9)
RER	1.19 (0.09)	1.16 (0.10)
Ventilation (l/min)	49.9 (13.8)	60.4 (20.1) *
Time to exhaustion (min)	44.0 (9.0)	39.0 (9.5) *

Values are expressed as mean (sd). VO_2 Oxygen uptake. *HR* Heart rate, *RER* Respiratory exchange ratio

* Significance level at p value <0.05

Table 118.6 Key facts on resistance training and muscle mass in individuals with Down syndrome

1. Individuals with DS are described as having lower muscle strength when compared not only with healthy controls but also with individuals with other intellectual disability.
2. Hypotonia may impair daily activities of individuals with DS as well as their workplace activities.
3. Progressive resistance training improves upper- and lower-limb muscle mass and strength.
4. Participants should be supervised during training sessions to prevent withdrawals and injuries.

Similarly, Baptista et al. (2005) concluded that Down syndrome was shown to be a risk factor for low volumetric bone mineral density (volBMD) in the lumbar spine. Furthermore, some studies (Sornay-Rendu et al. 2007) have shown that volBMD is more closely associated with fractures than area BMD is. In any case, although lean mass is the body component that shows a stronger correlation with area BMD, fat mass was also correlated with volBMD (Guijarro et al. 2008).

It should be also pointed out that skeletal resistance depends not only on bone mineral density and quality, but also on bone size (larger bones resist higher loads). The reduced stature in Down syndrome is mainly the result of the disproportionate shortening of the legs. Thus, the reduced skeletal size of individuals with Down syndrome may be associated with a reduced absolute resistance. Furthermore, the largely reduced femoral neck, particularly the narrowest femoral neck, might be associated with diminished bone strength relative to the loads that the femoral neck must bear.

Further studies on this topic are needed to identify the true dimension of this problem and the efficacy of the various preventive or curative procedures put forward (Zylstra et al. 2008). However, an active lifestyle and increased physical activity should be instituted to maintain and/or improve bone mineral density and prevent the development of osteoporosis in young adults with Down syndrome (Angelopoulou et al. 2000) (Table 118.7).

Table 118.7 Bone mineral density in young adults with Down syndrome and healthy matched controls (Guijarro et al. 2008)

	Down syndrome (n = 39)	Controls (n = 78)	P value
Age	26 (7)	27 (7)	Ns
Fat mass (kg)	15.4 (6.8)	16.1 (6.3)	Ns
Lean mass (kg)	37.7 (6.4)	45.0 (9.3)	Ns
Calcium intake (mg/day)	754 (209)	728 (275)	Ns
Spine BMD (g/cm^2)	0.919 (0.100)	1.056 (0.108)	<0.001
Spine Area (cm^2)	43.65 (4.93)	50.13 (5.72)	<0.001
Spin volBMD (g/cm^2)	0.140 (0.017)	0.149 (0.017)	0.007
Femoral neck BMD (cm^2)	0.815 (0.111)	0.908 (0.134)	<0.001
Femoral neck area (cm^2)	4.65 (0.55)	5.37 (0.69)	<0.001
Femoral neck volBMD (g/cm^2)	0.327 (0.055)	0.315 (0.069)	Ns
Total Hip BMD (g/cm^2)	0.872 (0.108)	1.023 (0.133)	<0.001
Total Hip area (cm^2)	32.85 (4.72)	38.00 (6.79)	<0.001
Total Body BMD (g/cm^2)	0.929 (0.067)	1.051 (0.097)	<0.001
Total Body area (cm^2)	1445 (140)	1870 (214)	<0.001

Results are expressed as mean (sd)
BMD Bone Mineral Density; *volBMD* volumetric BMD; *ns* not significant

118.4 Somatotype and Sport in Individuals with Down Syndrome

Several studies have concluded that not only body composition, but also somatotype may be predictors of high performance in healthy athletes. Somatotypes may also play an important role in determining their sport modality and even their different playing positions in each sport (Carter et al. 2005). In this regard, future research that seeks to explain the sources of variation in high performance should consider including somatotype as an independent variable.

In recent years, an increasing number of athletes with Down syndrome have taken part in Special Olympics events all over the world (Tassone and Duey-Holtz 2008). Since they also may be considered high performance athletes, they need to be assessed by multidisciplinary teams, just as non-disabled athletes are. Anthropometric assessment may play an important role within this context. However, there is no information in the literature regarding the endomorphic, mesomorphic or ectomorphic components of athletes with Down syndrome. In fact, there is only one study, by Bronks and Parker (1985), on adults with Down syndrome, which concluded that all subjects had high endomorphic components. Accordingly, further studies on this topic are also needed, since an accurate assessment of somatotypes may provide valuable insight into the ideal conditions for the optimal physiologic function of athletes with Down syndrome.

Furthermore, the association between somatotype and the prevalence of several chronic diseases in the general population recently reported by Koleva et al. (2002) suggests the importance of somatotype assessment for both athletes and non-athletes with Down syndrome. Conversely, Malousaris et al. (2008) concluded that somatotype does not influence the incidence of sport-related injuries.

118.5 Applications to Other Areas of Health and Disease

Anthropometric assessment may play an important role for healthcare providers and sport-related professionals who work with individuals with DS. In this line it may be of interest not only in Sports Medicine but also in several medical specialties such as: Family Medicine, Paediatrics, Cardiology, Endocrinology, Internal Medicine, Trauma, Preventive Medicine, among others.

Summary Points

- Obesity, hypotonia and osteoporosis are very common in individuals with Down syndrome and may play a role in undermining their health status and quality of life.
- Fortunately, intervention programmes designed by multidisciplinary teams and based on regular exercise specifically for this group may help solve these problems.
- Similarly, there is a growing interest in boosting the physical performance of individuals with Down syndrome, given the many national and international sport events for individuals with DS.
- An anthropometric assessment that includes body composition and somatotype analysis may help healthcare providers and sport-related professionals not only to achieve all these goals, but also to achieve them safely.
- Furthermore, long-term follow-up studies on this topic are sorely needed to confirm these findings, which may ultimately increase their use in daily practice.

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Part XVIII
Anthropometry in Metabolic Disease and Obesity

Chapter 119
Value of Waist Circumference in Metabolic Diseases

V. Saroja Voruganti and Anthony G. Comuzzie

Abstract Obesity is a global health problem affecting adults, adolescents, and children alike. It has reached epidemic proportions in the United States with approximately 34% of adults classified as clinically obese and additional 34% overweight. Abdominal obesity, characterized by excess visceral fat, is associated with an increased risk for several metabolic diseases including type 2 diabetes, cardiovascular disease, and metabolic syndrome. Imaging modalities are the best measures for abdominal obesity, but are not always feasible in clinical settings. Waist circumference is an anthropometric measurement that is easy, cost effective, informative, and well suited for assessment in nearly all clinical settings. It is strongly correlated with, and used as a surrogate marker for, abdominal fat mass and has been associated with all-cause mortality. Increased waist circumference is closely associated with alterations in carbohydrate and lipid metabolism as well as inflammation and atherosclerosis. Other metabolic diseases such as asthma, sleep apnea, and certain types of cancer have also been associated with an increase in waist circumference. In addition, a larger waistline is generally associated with an overall decrease in cardio-respiratory and general physical fitness and health-related quality of life. In conclusion, waist circumference is an easily obtainable measure that can be used to quickly assess an individual's susceptibility to cardiometabolic disease risk.

Abbreviations

ApoB	Apolipoprotein B
BMI	Body mass index
CRP	C-reactive protein
CVD	Cardiovascular disease
GLUT4	Glucose transporter 4
HDL	High-density lipoprotein
ICAM 1	Intercellular adhesion molecule 1
IDF	International Diabetes Federation
IL6	Interleukin 6
IRS-2	Insulin receptor substrate-2

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_119,

LDL	Low-density lipoprotein
NHLBI	National Heart, Lung and Blood Institute
PAI-1	Plasminogen activator inhibitor 1
T2DM	Type 2 diabetes mellitus
TNF α	Tumor necrosis factor alpha
VLDL	Very low-density lipoprotein
WHR	Waist to hip ratio

Key Features

Table 119.1 Key messages

- Waist circumference is a major risk factor for metabolic disorders
- Carbohydrate as well as lipid metabolism pathways are adversely affected by increase in waist circumference
- Measurement of waist circumference as part of routine health check will provide a clinical marker for metabolic diseases

119.1 Introduction

Obesity is a global health problem affecting adults, adolescents, and children alike (Vega 2002). It has reached epidemic proportions in the United States with approximately 34% of adults classified as clinically obese and additional 34% overweight (Flegal et al., 2010). Obesity is a clearly recognized risk factor for metabolic diseases such as type 2 diabetes mellitus and cardiovascular disease (CVD) (Klein 2001). Central or abdominal adiposity is more closely associated with cardiometabolic risk than gluteofemoral obesity and is generally thought to worsen the metabolic disorders that are associated with overall obesity (Poirier and Despres 2003). Women are more likely to have gluteofemoral obesity as compared to men. However, with weight gain, women too tend to accumulate more abdominal fat (Pi-Sunyer 2002). Several studies have shown that excess abdominal fat is an independent predictor of metabolic diseases (Poirier and Despres 2003; Klein et al. 2007; Despres and Lemieux 2006).

Overweight and obesity are usually characterized by body mass index (BMI). However, BMI, which is calculated as weight in kilograms divided by height in meters squared (kg/m^2), does not take into account the regional variation in adiposity. Hence, there is a need for a measure of body fat that is easy to obtain and is a strong indicator of regional, particularly abdominal, adiposity. Traditionally, the waist to hip ratio (WHR) was considered to be a good measure of central obesity. Although WHR has been considered as a measure of abdominal adiposity, waist circumference and hip circumference capture two different aspects of body composition. The WHR provides information on the relative accumulation of abdominal fat and includes the combined effects of adiposity, skeletal muscle, and body frame (Seidell et al. 2001). The WHR remains unchanged if both waist and hip circumferences increase in the same proportion, resulting in misleading results. Waist circumference, on the other hand, provides an estimate of the absolute amount of abdominal adipose tissue (Despres and Lemieux 2006). Abdominal fat is best measured by imaging modalities such as magnetic resonance imaging or computerized tomography. However, Sabir et al. found that visceral fat accumulation as measured by ultrasound correlates significantly with waist circumference. Therefore, waist circumference provides a reasonably accurate estimate of abdominal obesity that can be computed in clinical settings.

Waist circumference alone has been found to be an informative measure of central obesity and has been associated with all-cause mortality. The National Heart, Lung and Blood Institute (NHLBI) has recommended that waist circumference be included as a part of any initial assessment in weight loss therapy, and is now widely recognized as an indicator of metabolic abnormalities (Klein et al. 2007). In this chapter, we describe the utility of waist circumference as a measure of abdominal obesity in the evaluation of an individual's cardiometabolic risk.

119.2 Abdominal Obesity and Waist Circumference

Abdominal obesity, characterized by the accumulation of excess visceral fat, is associated with an increased risk for several diseases including cardiovascular disease (CVD) (Table 119.2). Individuals with abdominal obesity show greater metabolic complications than those with peripheral obesity (Despres and Lemieux 2006). Abdominal obesity is associated with an increased supply of plasma free fatty acids that are directly drained into the portal vein (Bosello and Zamboni 2000). Fat in this area has a high turnover rate and is metabolically active. These fatty acids cause insulin resistance, especially in skeletal muscle and liver by interfering with the activities of insulin receptor substrate-2 (IRS-2) associated phosphatidyl inositol 3 (PI 3) kinase and the glucose transporter, GLUT 4 (Schinner et al. 2005). Visceral obesity is associated with impaired levels of triglycerides, increased very low-density lipoproteins (VLDLs) and lower HDL cholesterol. Higher levels of VLDL diminish HDL cholesterol because of an exchange of core lipids, which is mediated by cholesterol ester transfer protein (Ginsberg 2003). High triglycerides and low HDL cholesterol levels are associated with a greater risk of atherosclerosis (Ginsberg 2003). Figure 119.1 depicts a simplified presentation of how abdominal fat is an integral risk factor for metabolic disorders.

An increase in waist circumference is also associated with a hypertrophic form of obesity. Hypertrophic obesity is characterized by an increase in fat cell (adipocyte) size, which is associated with several metabolic alterations (Aronne 2002). Adipocyte hypertrophy leads to increased lipolysis, activation of proinflammatory cytokines and chemokines, reduced adiponectin release and insulin resistance (Gustafson et al. 2009). Visceral adipocytes, in particular, are known to be hyperlipolytic,

Table 119.2 Metabolic disorders associated with abdominal obesity

Disorders associated with abdominal obesity (Increased waist circumference)
• Impaired glucose tolerance
• Insulin resistance
• Hypertriglyceridemia
• Dyslipidemia
• Endothelial dysfunction
• Inflammation
• Hypertension
• Microalbuminuria
• Atherosclerosis
• Fatty liver disease
• Asthma
• Sleep apnea
• Several types of cancer
• Osteoarthritis

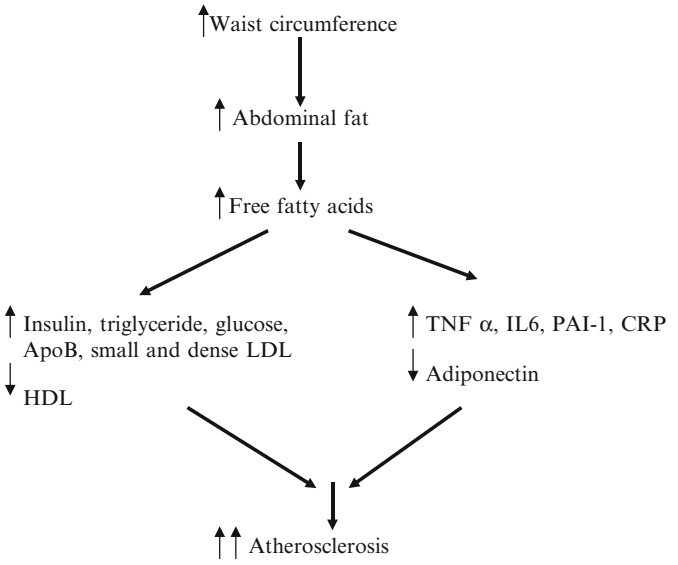

Fig. 119.1 Simplified presentation depicting how high abdominal fat affects cardiometabolic profile (Adapted from Poirier and Depres 2003)

highly sensitive to catecholamines and poorly sensitive to insulin. Enzyme lipoprotein lipase (LPL) plays an important role in lipolysis and subsequent release of fatty acids. Both lipolysis and adipose LPL activity were found to be elevated with increased waist circumference in normal to obese men (Biovin et al. 2007). Increased flux of fatty acids through the portal vein is known to overwhelm the liver leading to hypertriglyceridemia, hyperinsulinemia, and glucose intolerance (Mathieu et al. 2009). Given these implications of increased waist circumference, a consensus statement issued by the Association of Weight Management and Obesity Prevention, NAASO, The Obesity Society, the American Society for Nutrition and the American Diabetes Association in 2007 describes the usefulness of waist circumference in evaluating patients at risk for cardiometabolic complications (Klein et al. 2007). Individuals with similar BMI but different waistlines show distinct differences in their risk for cardiometabolic disease. The risk for a metabolic disease is increased with a larger waist circumference even in individuals with normal weight and BMI (Despres and Lemieux 2006). Waist circumference provides useful information along with BMI in the management of metabolic disorders and weight loss therapy (Fig 119.2).

119.3 Waist Circumference in Metabolic Diseases

119.3.1 Carbohydrate Metabolism

Cells metabolize nutrients (carbohydrates, proteins, lipids) supplied through our diets to provide energy. Alterations in these metabolic pathways or processes increase the risk for diseases such as diabetes, metabolic syndrome, cardiovascular disease, and several cancers. Carbohydrates are broken down into six-carbon glucose molecules, which are used for either building other compounds or for producing energy.

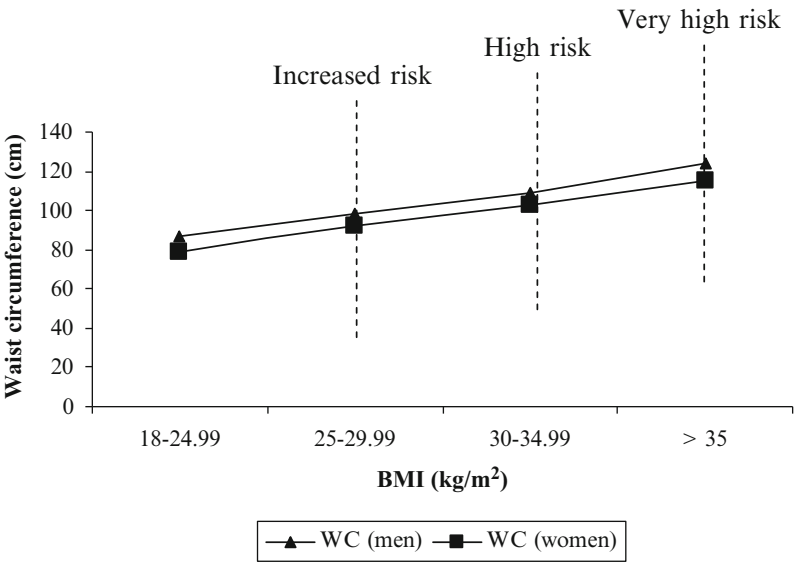

Fig. 119.2 Combination of BMI and waist circumference in identifying the risk for cardiometabolic disease (Ref: Klein et al. 2007)

1. *Glucose intolerance*: For optimum functioning, the body needs to maintain blood glucose levels within limits (80–100 mg/dl), with both high and low blood glucose levels being deleterious. Impaired glucose tolerance, also known as pre-diabetes, is a condition where fasting glucose values are between 100 and 124 mg/dl. Higher waist circumference seems to have a negative effect on glucose metabolism. In individuals with impaired fasting glucose levels, higher waist circumference indicates a greater risk for coronary artery disease than those with normal fasting glucose (St-Pierre et al. 2002). In a study conducted to investigate the effect of Roux-en-Y gastric bypass surgery in individuals with normal and impaired fasting glucose levels, it was observed that reduction in waist circumference, as a result of the surgery, was significantly associated with improvement in fasting glucose as well as insulin sensitivity (Gomez-Ambrosi et al. 2007).
2. *Insulin resistance*: Insulin resistance is a condition in which glucose uptake by insulin-sensitive tissues is diminished. The resultant hyperglycemia is compensated by an increased production of insulin by the pancreatic beta cells. Initially, increased secretion of insulin is effective, but gradually, beta cells are overburdened, and their function is adversely affected, leading to the development of type 2 diabetes. Insulin resistance is a strong predictor of type 2 diabetes and CVD risk (Schinner et al. 2005). When evaluating the risk for metabolic syndrome, the International Diabetes Federation included waist measurement as the first criterion in identifying individuals at risk for metabolic syndrome. This was controversial as some felt that insulin resistance was the most prominent factor in the metabolic syndrome and not waist circumference. However, insulin resistance and excess abdominal fat are highly correlated and visceral obesity seems to be the driving factor in the pathogenesis of insulin resistance (Bosello and Zamboni 2000).

Insulin resistance is highly prevalent in individuals who are abdominally obese (Despres and Lemieux 2006). A lower waist circumference (<100 cm) is believed to exclude the risk of insulin resistance in both men and women (Wahrenberg et al. 2005). Waist circumference was also found to be an independent predictor of insulin resistance in young individuals aged between 8 and 17 years (Lee et al. 2006). The homeostatic model assessment method (HOMA) is often used to estimate insulin resistance.

Table 119.3 Significant correlations between waist circumference and metabolic risk factors

	Correlation coefficient (r^2)	Population	References
Glucose	0.363–0.475	European and Chinese women	Lear et al. (2002)
Insulin	0.563–0.662	European and Chinese men and women	Lear et al. (2002)
HOMA*	0.521	Caucasians	Kressel et al. (2009)
Total cholesterol	0.298–0.452	European and Chinese men and women	Lear et al. (2002)
	0.344	European men	Han et al. (1995)
		European women	Han et al. (1995)
Triglycerides	0.378–0.655	European and Chinese men and women	Lear et al. (2002)
LDL* cholesterol	0.209–0.404	European and Chinese men and women	Lear et al. (2002)
HDL*	(–0.273) – (–0.369)	European and Chinese men and women	Lear et al. (2002)
	–2.1	Caucasians	Kressel et al. (2009)
	–0.269	European men	Han et al. (1995)
	–0.261	European women	Han et al. (1995)
Systolic blood pressure	0.336	European men	Han et al. (1995)
	0.372	European women	Han et al. (1995)
Diastolic blood pressure	0.371	European men	Han et al. (1995)
	0.374	European women	Han et al. (1995)

**HOMA* Homeostatic model assessment method,
**LDL* Low-density lipoprotein,
**HDL* high-density lipoprotein
**Only significant correlations ($p < 0.05$) are shown in the table

Waist circumference was significantly correlated with HOMA in Caucasians (Kressel et al. 2009), and glucose and insulin were also positively correlated with waist circumference (Lear et al. 2002). Table 119.3 shows the significant correlations between metabolic risk factors and waist circumference.

119.3.2 Lipid Metabolism

Lipids are preferred as sources of energy after carbohydrates. They are important as energy reserves. Increased waist circumference reflects increased visceral adipose tissue. Free fatty acids released from visceral adipose tissue can interfere with normal lipid metabolism by disrupting cholesterol and triglyceride metabolism.

1. Cholesterol: As described earlier, excessive lipolysis from expanded visceral adipose tissue releases free fatty acids into the portal circulation leading to a cascade of events contributing to increased production of triglyceride-enriched LDL cholesterol. By the further action of hepatic lipase, these LDLs tend to become small and dense which tend to damage vascular walls and are atherogenic in nature (Mathieu et al. 2009). Individuals with higher waist circumference tend to have higher levels of small and dense LDLs (Lemieux et al. 2000). Increased levels of small and dense LDLs are also associated with lower levels of HDL cholesterol. In individuals with larger waistline, HDL levels were found to be low. In addition, they were found to have higher levels of small HDL, indicating that small HDL particle size is another feature of dyslipidemia that accompanies visceral adiposity (Burns and Arslanian 2009). Also, oxidized LDL, a significant marker of atherosclerosis, was closely associated with waist circumference independent of BMI (Weinbrenner et al. 2006).

The fatty acid (main constituent of fats) composition has been related to metabolic disease risk. Polyunsaturated fatty acids (PUFA) have been associated with beneficial effects on lipid metabolism and blood pressure. Omega-3 fatty acids (n-3 PUFA) are known to improve lipid profile and reduce blood pressure, insulin resistance and inflammation (Lee et al. 2008). Studies conducted with plasma fatty acid composition have shown that waist circumference was positively correlated with saturated and trans fatty acids and negatively with PUFAs (Lee et al. 2008). Steffen et al. (2008) investigated fatty acid composition in plasma, cholesterol esters, and phospholipids in adolescents between 13 and 17 years of age in relation to metabolic disease risk factors. These children were classified as normal and overweight based on their BMI percentiles. Waist circumference was significantly higher ($p \leq 0.001$) in overweight as compared to normal weight children. Waist circumference was correlated positively with plasma stearic acid and inversely with linoleic and oleic acids, indicating an adverse fatty acid profile for children with higher BMI and larger waist circumference.

2. Triglycerides: The delivery of free fatty acids to the liver contributes to the synthesis of VLDLs enriched with triglycerides (Mathieu et al. 2009). Hypertriglyceridemia or increased triglycerides usually arises due to increased production or reduced clearance of VLDLs and tend to increase the production of small and dense LDLs. Individuals with increased waist circumference, small and dense LDLs, apolipoproteins B and triglycerides are known to be at high risk for coronary events. Lemieux et al. (2000) reported a clinical phenotype 'hypertriglyceridemic waist" which includes higher waist (≥90 cm) in conjunction with higher triglyceride (≥177 mg/dl) to indicate cardiometabolic risk. An important step in VLDL production is the production rate of apolipoprotein B (ApoB) (Lewis and Steiner 1996). Abdominal adiposity and impaired liver insulin signaling are known be associated with higher levels of ApoB. Excess abdominal fat also leads to increased deposition of triglycerides in liver (Jakobsen et al. 2007). Studies using waist circumference as a measure for abdominal obesity have shown a positive correlation between increased waist circumference and liver steatosis (Sabir et al. 2001).

   A study conducted by Han et al. (1995) used waist circumference categories to stratify the risk for metabolic disease, particularly hyperlipidemia and hypertension. They determined two action levels of waist circumference (based on an earlier study by Lean et al. (1995)) to identify people at health risk. Accordingly, action level 1 included men and women with waist circumference greater than or equal to 94 and 80 cm, respectively and action level 2 included men and women with waist circumference greater than or equal to 102 and 88 cm, respectively. The prevalence of total cholesterol, LDL cholesterol, and systolic and diastolic blood pressure increased with increase in action levels of waist circumference in both men and women. Waist circumference action levels can also be utilized to predict the risk of metabolic disease related to hyperlipidemia or hypertension (Han et al. 1995).

119.3.3 Protein Metabolism

Proteins are the least preferred sources of energy. Amino acids (breakdown products of proteins) are catabolized only when other sources of energy are not adequate. Abdominal obesity has been associated with alterations in glucose and lipid metabolism. However, not much is known about its effect on protein metabolism.

119.3.4 Hypertension

Greater visceral adiposity is known to be positively associated with hypertension, a major CVD risk factor (Mathieu et al. 2009). Visceral adipose tissue is known to express higher amounts of angiotensinogen which is converted to angiotensin, and is activated in hypertension (Mathieu et al. 2009). Blood volume as well as pressure is actively regulated by angiotensin II along with epinephrine, norepinephrine, atrial natriuretic peptide (ANP), and antiduretic hormone (ADH). Waist circumference is known to have a greater impact on blood pressure than BMI. It was observed that a decrease in waist circumference, and not BMI, was associated with a reduction in blood pressure and angiotensinogen in women (Engeli et al. 2005). Investigations into the usefulness of anthropometric measurements in predicting hypertension have shown that waist circumference is an independent risk factor for hypertension and is closely associated with it, particularly in men (Yalcin et al. 2005).

119.3.5 Inflammation/Endothelial Dysfunction

Increased lipolysis as a result of adipocyte hypertrophy has wide ranging implications. On the one hand, it causes the cell to become insulin resistant and on the other hand it induces the activation of proinflammatory cytokines such as interleukin 6 (IL6), interleukin 8 (IL8) and macrophage chemoattractant protein 1 (MCP1). Hypertrophic obesity also leads to the infiltration of macrophages into the adipose tissue, resulting in inflammation (Gustafson et al. 2009). In addition, biomarkers of endothelial dysfunction are known to increase with adipocyte hypertrophy (Burns and Arslanian 2009). These markers, intercellular adhesion molecule 1 (ICAM1) and E-selectin, play an important role in plaque formation and inflammation. In a study conducted in children, a higher waist circumference was associated with increases in ICAM1 and E-selectin (Burns and Arslanian 2009). The CRP is an acute phase reactant protein and is a sensitive marker of systemic inflammation. In a study in adolescents, waist circumference was positively associated with CRP and complement factors C3 and C4 (Warnberg et al. 2006). Higher waist circumference was also associated with oxidative stress and higher valvular inflammation in patients who were undergoing aortic valve replacement surgery (Cote et al. 2009).

Increased proinflammatory cytokines (due to increased visceral adiposity) may affect the integrity of the endothelial wall, which may also lead to microalbuminuria. Microalbuminuria is defined as urinary albumin excretion of 30–300 mg/24 h. It is a known cardiovascular risk factor and is known to predict the progression of diabetic nephropathy (Thoenes et al. 2009). In a large study of about 21,000 individuals, it was found that microalbuminuria was positively associated with waist circumference (Thoenes et al., 2009). However, the mechanism is not clear. Likewise, another risk factor for CVD, end stage renal disease (ESRD) is also affected by changes in waist circumference. It has been observed that patients with ESRD and larger waist circumference have high risk of death due to CVD as compared to those with smaller waistlines (Postorino et al. 2009).

119.3.6 Other Metabolic Diseases

Several other diseases are affected by an increase in abdominal obesity and waist circumference. Obesity is a risk factor for asthma, several types of cancer, osteoarthritis, restless leg syndrome, sleep

apnea, etc. Abdominal obesity, measured by waist circumference, has been associated with esophageal and breast cancer and cancer mortality (Steffen et al. 2009). Visceral obesity is known to affect pulmonary function. Of all anthropometric measurements, waist circumference was found to have the greatest impact on markers of pulmonary function (e.g., forced vital capacity, forced expiratory volume, total lung capacity, and vital capacity) (Wei et al. 2009). Waist circumference has been positively correlated with the incidence of asthma even in women with normal body weight (Von Behren et al. 2009). When compared with BMI, waist circumference was more strongly associated with asthma and its severity in children (Musaad et al. 2009). Larger waistlines have also been associated with osteoarthritis; individuals with a larger waist circumference having reduced cartilage volume increasing the risk for patello femoral osteoarthritis (Teichtahl et al. 2008).

119.4 Application to Other Areas of Health and Disease

119.4.1 Physical Fitness

An increased waist circumference is associated with decreased physical fitness. Increased physical activity, aerobic and cardio-respiratory fitness have been consistently associated with lower waist circumferences. In young adults, waist circumference was inversely associated with cardio-respiratory and neuromuscular fitness (Sakuragi et al. 2009). Increased waist circumference was also associated with lower maximal isometric and isokinetic knee extensor strength (Thomson et al. 2009). Likewise, in boys and adolescents, muscular and cardio-respiratory fitness were negatively associated with waist circumference. In adolescents, handgrip strength was positively associated with waist circumference (Moliner-Urdiales et al. 2009).

119.4.2 Quality of Life

Obesity, in general, negatively affects an individual's quality of life, particularly in women, and is considered to be a significant predictor of poor psychological well being and health-related quality of life. Health-related quality of life encompasses several aspects of lifestyle, including physical health, work-related health, routine life, sexual life, diet distress, and pain/discomfort. Abdominal obesity, as measured by waist circumference, was associated with a lower quality of life and increased ill health (Han et al. 2009) with women being affected more than men (Akinpelu et al. 2009).

119.5 Conclusion

Waist circumference is a simple anthropometric measurement that is practical and relatively easy to obtain in clinical settings and strongly correlates with abdominal obesity. Waist circumference is closely associated with alterations in carbohydrate and lipid metabolism. Waist circumference can be used to screen individuals who are at greater risk for metabolic diseases and raise awareness of the need for proper management of weight.

Summary Points

- Obesity, particularly abdominal obesity, is a major risk factor for several metabolic diseases.
- Waist circumference is a simple anthropometric measurement that correlates highly with abdominal obesity.
- Waist circumference is easily measured in clinical settings and requires no complicated equipment or calculations.
- Larger waist circumferences are associated with increased risk for metabolic alterations such as impaired glucose tolerance, dyslipidemia, hypertension, inflammation/endothelial dysfunction and atherosclerosis.
- The risk for diseases such as arthritis, some types of cancer and asthma also seems to increase with an increasing waist circumference.
- The quality of life and general physical fitness are adversely affected with an increase in waist circumference.
- Waist circumference is easy to measure and provides important information in identifying individual's at risk for metabolic disorders.

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Chapter 120
Waist Circumference for the Clinical Diagnosis of Metabolic Syndrome in the Japanese Population: Optimal Cut-Point to Predict Early Arteriosclerosis

Yuka Matoba, Toyoshi Inoguchi, Atsushi Ogo, and Ryoichi Takayanagi

Abstract Metabolic syndrome (MetS) has been proposed as a syndrome in an individual with clustered metabolic dysfunction including increased abdominal adiposity, raised blood pressure, raised triglyceride and/or reduced HDL cholesterol and raised fasting plasma glucose. At the time of writing, several definitions for clinical diagnosis of MetS have been proposed by different organizations. Clinical methods to evaluate visceral adiposity include abdominal computed tomography, body mass index, and waist and hip circumference; in which waist circumference is the most available, but is highly dependent on the ethnicity. Current MetS definitions include waist circumference as a surrogate marker for visceral adiposity and adapt cut-points of waist circumference for each ethnic group to optimize their predictive values. For Asians, the International Diabetes Federation (IDF), the American Heart Association and the National Heart, Lung and Blood Institute have provided the waist cut-points as 90 cm for men and 80 cm for women as recommended by the World Health Organization. By contrast, the previous IDF definition and the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome adopted waist cut-points of 85 cm for Japanese men and 90 cm for Japanese women which were derived from the cut-points of visceral fat area by computed tomography to identify clustered risk factors. After the MetS definitions were published, waist cut-points for the Japanese population have been re-evaluated in several studies. Our recent studies obtained optimal waist cut-points (87 cm for men and 80 cm for women) from the relation between waist circumference and risk factor clustering in a Japanese population. It showed superior sensitivity and specificity to the conventional IDF (90 cm), which is also the cut-points for Japanese women (90 cm), to predict intima-media thickening; it also agreed with the revised IDF definition (80 cm) for women. These studies suggest that the waist cut-points of 90 cm for men and 80 cm for women are relevant for Japanese population to define MetS with a short-term risk of development of atherosclerosis. Further studies with larger population and longer follow-up period may validate these waist cut-points for the clinical diagnosis of MetS with a substantial risk of cardiovascular events and/or onset of type 2 diabetes.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_120,

Abbreviations

BMI	Body mass index
BP	Blood Pressure
CT	Computed tomography
FPG	Fasting Plasma Glucose
HDL-C	High Density Lipoprotein Cholesterol
IL-6	Interleukin-6
IMT	Intima-media thickness
MetS	Metabolic syndrome
RF	Risk factor
TC	Total cholesterol
TG	Triglyceride
TNF-α	Tumor Necrosis Factor-α
WC	Waist circumference

120.1 Introduction

Metabolic syndrome (MetS) has been proposed as a syndrome in an individual with clustered metabolic dysfunction including increased abdominal adiposity, raised blood pressure, raised triglyceride and/or reduced HDL cholesterol and raised fasting plasma glucose (Alberti and Zimmet 1998). The predominant pathological states for MetS are visceral adiposity and insulin resistance, which contribute to a dyslipidemic state, prothrombotic profile and a state of inflammation, which increases the risk for type 2 diabetes and atherosclerotic cardiovascular diseases (Lakka et al. 2002; Dekker et al. 2005; McNeill et al. 2005; Kawamoto et al. 2005; Katzmarzyk et al. 2006; Isomaa et al. 2001; Takeuchi et al. 2005). At the time of writing, several definitions for clinical diagnosis of MetS have been proposed by different organizations. The American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) published its revised MetS definition in 2005 (Grundy et al. 2005). In the same year, the International Diabetes Federation (IDF) proposed a worldwide definition that recommends the ethnicity-specified waist circumference criteria for each region in consideration of the ethnic differences in the prevalence and characteristics of MetS (Alberti et al. 2005). The Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome has also published a definition exclusively for the Japanese population in 2005 (The Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome 2005). All the above definitions employed waist circumference as a surrogate marker for abdominal adiposity and defined its cut-points based on different rationales. In order to optimize MetS diagnosis for the specific ethnic group, each definition considers waist circumference criterion specific for Asians or for exclusively the Japanese population (Table 120.1). The purpose of this review is to describe the rationale of each cut-point of waist circumference employed in each MetS definition and to discuss how to determine the optimal waist cut-point for MetS diagnosis to identify subjects at high risk for future cardiovascular diseases.

120.2 Evaluating Visceral Adiposity for the Clinical Diagnosis of MetS

Visceral fat accumulation has long been suggested to cause an adverse metabolic profile with issues such as glucose intolerance, hypertension and dyslipidemia and to be associated with cardiovascular diseases (Eckel et al. 2005; Alberti et al. 2005; Despres and Lemieux 2006). The visceral adipose

Table 120.1 Feature of criteria for clinical diagnosis of metabolic syndrome for Asian or Japanese

Diagnosis	AHA/NHLBI (2005) Any three of the following five features	IDF (2005) Increased WC plus any two of the following five features	Japanese (2005) Increased WC plus any two of the following four features
WC (cm)	≥ 90 in men ≥ 80 in women for Asian	≥ 90 in men ≥ 80 in women for Japanese	≥ 85 in men ≥ 90 in women
FPG (mg/dl)	≥ 100 or On medication for elevated glucose	≥ 100 or On medication for elevated glucose	≥ 110 or On medication for elevated glucose
BP (mmHg)	Systolic ≥ 130 Diastolic ≥ 85 or On medication for elevated BP	Systolic ≥ 130 Diastolic ≥ 85 or On medication for elevated BP	Systolic ≥ 130 Diastolic ≥ 85 or On medication for elevated BP
Dyslipidemia (mg/dl)	TG ≥ 150 or On medication for elevated TG HDL < 40 in men HDL < 50 in women or On medication for reduced HDL	TG ≥ 150 or On medication for elevated TG HDL < 40 in men HDL < 50 in women or On medication for reduced HDL	TG ≥ 150 or HDL < 40 or On medication for elevated TG or reduced HDL

Above all definitions employed waist circumference as a surrogate marker for abdominal adiposity. Each definition accustoms waist circumference criterion specific for Asians or for exclusively Japanese. In Japanese definition, cut-points of 85 cm for men and 90 cm for women were decided as the respective values of the waist circumference correspond to 100 cm^2 of visceral fat area

tissue is now known to secrete pro-inflammatory (e.g., IL-6, TNF-α) and anti-inflammatory (e.g., adiponectin) cytokines and play a central role for developing insulin resistance and MetS (Ridker et al. 2003; Freeman et al. 2002; Bermudez et al. 2002).

1. Computed tomography

Computed tomography (CT) scanning is the most accurate method to evaluate the visceral fat. Theoretically, serial scanning may determine the volume of visceral as well as subcutaneous fat. Indeed, visceral fat area determined by CT at the umbilical level is well correlated with the clustering of risk factors, which is adopted for the concept of the Japanese definition (Japan Society for the Study of Obesity 2002). The weakness of the method, however, is the availability of the equipment and the exposure to radiation.

2. Body mass index

Body mass index (BMI), a well-known parameter determined by the weight and the height, has been widely used to describe obesity in clinical settings. Increased BMI is associated with an increased probability of metabolic abnormalities (Whitlock et al. 2009). The World Health Organization (WHO) generally defines obesity as BMI ≥ 30 kg/m^2, and overweight as BMI ≥ 25 kg/m^2. Since several studies have shown that Asians have higher amounts of body fat at lower BMI than Western populations, the Western Pacific regional office of the WHO, the International Association for the Study of Obesity (IASO) and the International Obesity Task Force (IOTF) collaborated to create the new recommendations for BMI cutoffs among Asian populations in 2000. In these recommendations, obesity is defined

as BMI ≥ 25 kg/m^2 and overweight is defined as BMI ≥ 23 kg/m^2 for Asians. Since BMI measures total body mass, it is largely influenced by structural divergence of the subject's body including ethnicity, muscularity and dominance of visceral or subcutaneous fat, which affects the accuracy of BMI, in order to evaluate the visceral adiposity.

3. Waist and hip circumference

Measuring waist and/or hip circumference is a simple and costless approach to estimate visceral adiposity. Yusuf et al. (2005) showed that waist circumference, hip circumference and waist hip ratio (WHR) were closely associated with the risk of myocardial infarction even after adjustment for risk factors other than BMI in a case control study with 27,000 participants. Winter et al. (2008) showed that waist circumference and WHR were strongly associated with the risk of stroke/TIA, independent of other vascular risk factors in a case–control study with 1,137 participants. More recently, in the EPIC-Norfolk study that followed subjects for 9 years, waist circumference was associated with an elevated CHD risk, whereas a large hip circumference appeared to be protective against CHD after adjusting for confounding variables including BMI. Above all, these studies suggested the predictive value of waist circumference for cardiovascular diseases that is associated with visceral adiposity, and thus, current definitions of MetS employ waist circumference as an indicator of visceral adiposity.

120.3 Ethnicity in Cut-Points for Waist Circumference

A number of studies have shown that the relationship of waist circumference and visceral adiposity is affected by age, gender and ethnicity (Han et al. 1997; Lemieux et al. 2006; Lemieux et al. 1996; Pascot et al. 1999; Hayashi et al. 2007; Despres et al. 2000; Misra et al. 2005). The National Institutes of Health clinical guidelines for obesity adopted the waist cut-points for central obesity as 102 cm for men and 88 cm for women in the USA (National Institutes of Health 1998). These cut-points were employed by ATP III to define central obesity and correspond approximately to a BMI of 30 kg/m^2, or clinical obesity, in European populations.

Although the WHO report in 1998 suggests that 94 cm in men and 80 cm in women should be the appropriate measures in Europeans, these cut-offs are not suitable for Asian populations. Asians appear to have higher morbidity at lower cut-points for waist circumference than do white Caucasians (Wildman et al. 2004; Deurenberg et al. 1998). The WHO Asian report suggested lower waist cut-points for Asians, 90 cm for men and 80 cm for women, because Asians have an increased propensity to abdominal obesity and they also have an absolute increase in risk at any particular waist measurement.

IDF adopted the waist cut-points for south Asians and Chinese, 90 cm for men and 80 cm for women, as recommended by the WHO and validated in a series of studies (Wildman et al. 2004; Tan et al. 2004). Also, for the Japanese, because of new supportive data, IDF has adopted the waist cut-points of 90 cm for men and 80 cm for women, instead of the original value of 85 cm for men and 90 cm for women that was derived from the Japanese waist criteria (The IDF consensus worldwide definition of the metabolic syndrome, available at http://www.idf.org/webdata/docs/MetS_def_update2006.pdf). The AHA/NHLBI also recommended the waist cut-points for Asian Americans, 90 cm for men and 80 cm for women, when they modified NCEP/ATP criteria in 2005 (Grundy et al. 2005). By contrast, the cut-points of the waist circumference in the Japanese definition are 85 cm for men and 90 cm for women that featured the larger waist cut-point for women rather than men (The Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome 2005) (Table 120.1).

These cut-points in the Japanese definition are derived from the relation with the visceral fat area as determined by computed tomography to identify individuals with multiple obesity-related diseases including hyperglycemia, dyslipidemia and hypertension (Japan Society for the Study of Obesity 2002).

120.4 Optimal Waist Cut-Points for Japanese Population

Current Japanese waist criterion was published in 2002 (Japan Society for the Study of Obesity 2002), which were adopted into the Japanese MetS definition. The Japanese waist cut-points were based on the report from the Examination Committee of Criteria for "Obesity Disease" in Japan, which showed that the optimal cut-point of visceral fat area determined by computed tomography (CT) for identifying individuals with plural obesity-related disorders, (1) hyperglycemia: FPG ≥110 mg/dl; (2) dyslipidemia: TC ≥220 mg/dl and/or TG ≥150 mg/dl and/or HDL-C <40 mg/dl; (3) hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. The number of disorders was greater than 1.0 at 100 cm^2 in a study sample that combined both men and women. Japanese waist cut-points 85 cm for men and 90 cm for women were decided as the respective values of the waist circumference in men and women which correspond to 100 cm^2 of visceral fat area. Based on this approach, the waist cut-point for Japanese women might be greater than that for men because women generally tend to have more subcutaneous fat than men.

Since the Japanese definition was published in 2005 (The Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome 2005), several studies have re-evaluated the cut-points for Japanese population; Hayashi et al. (2007) examined the waist cut-points based on the value of their visceral fat area separately in men and women using modified IDF definition in 639 Japanese-American subjects. In the study, they found that the optimal cut-points of visceral fat area differed by sex. They reported that the appropriate visceral fat area and waist circumference cut-points were 51.5 cm^2 and 81 cm (age ≦ 56 years) and 86.3 cm^2 and 89 cm (age >56 years) in women and 88.6 cm^2 and 90 cm (age ≦ 57years) and 96.1 cm^2 and 87 cm (age >57years) in men. Hara et al. (2006) reported that the waist cut-points to identify the subjects with multiple risk factors in the MetS definition were ~80 cm in women and ~85 cm in men, using the NCEP/ATP III definition in 692 general Japanese people. Also, Miyawaki et al. (Miyawaki et al. 2005) reported that the optimal visceral fat area and waist cut-points to identify the subjects with multiple risk factors of the MetS were 100 cm^2 and 86 cm for men and 65 cm^2 and 77 cm for women, respectively, using the Japanese definition in a study of 3,574 middle-aged general Japanese people.

Recently, we investigated the optimal waist cut-point to identify subjects with clustered metabolic dysfunction in general Japanese employees (Matoba et al. 2008). We reviewed cross-sectional data from 1,658 men and 1,116 women aged 49 ± 10 years and 47 ± 10 years respectively, who had annual medical checkup services provided by the companies that they work for. Waist circumference was measured at the level of the umbilicus. Blood pressure was measured at rest using an automatic sphygmomanometer. All blood samples were drawn after an overnight 10-hour fast. Mean carotid intima-media thickness (IMT) was measured by ultrasonography (SDU-2200, Shimadzu Co., Ltd., Kyoto, Japan) that was equipped with IMT measurement software (Intimascope, Media Cross Co., Ltd., Tokyo, Japan) (Yanase et al. 2006). We diagnosed MetS with waist circumference (WC) and at least two of the following risk factors, using the IDF definition: (1) blood pressure (BP), systolic ≥130 and/or diastolic ≥85 mmHg, (2) triglycerides (TG) ≥150 mg/dl, (3) HDL-cholesterol <40 mg/dl in men and <50 mg/dl in women, (4) fasting plasma glucose (FPG) ≥100 mg/dl; and using the Japanese definition: (1) blood pressure, same as the IDF, (2) triglycerides ≥150 mg/dl and/or HDL-cholesterol <40 mg/dl, (3) fasting plasma glucose ≥110 mg/dl.

Table 120.2 Basal data of the subjects

	Male		Female	
	MetS (+)	MetS (−)	MetS (+)	MetS (−)
Number (%)	415 (25.0%)	1,243 (75.0%)	34 (3.0%)	1,082 (97.0%)
Age (year)	50.4 ± 8.7*	48.2 ± 10.1	52.7 ± 9.1*	46.4 ± 10.4
BMI (kg/m2)	25.8 ± 2.8*	22.9 ± 2.7	28.6 ± 2.8*	20.8 ± 2.6
WC (cm)	93.2 ± 6.3*	84.3 ± 7.6	98.9 ± 7.4*	77.1 ± 7.9
SBP (mmHg)	125.2 ± 14.7*	113.0 ± 13.6	128.1 ± 14.2*	106.5 ± 14.8
DBP (mmHg)	78.0 ± 10.5*	69.5 ± 9.6	75.9 ± 39.8*	64.0 ± 9.9
FPG (mg/dl)	112.7 ± 30.0*	98.0 ± 14.8	105.8 ± 17.0*	91.2 ± 9.9
HbA1c (%)	5.5 ± 1.0*	5.0 ± 0.5	5.4 ± 0.6*	4.9 ± 0.4
TC (mg/dl)	211.7 ± 35.0*	204.5 ± 33.4	217.0 ± 35.0*	202.6 ± 35.2
TG (mg/dl)	216.6 ± 207.3*	116.1 ± 99.5	134.1 ± 63.8*	75.9 ± 39.8
HDL-C (mg/dl)	44.7 ± 10.0*	54.5 ± 12.5	51.0 ± 8.8*	65.2 ± 13.4
Mean IMT (mm)	0.639 ± 0.125*	0.592 ± 0.109	0.649 ± 0.10*	0.566 ± 0.10

In the MetS group, all of the following components, age, body mass index (*BMI*), systolic and diastolic blood pressure (*SBP*), fasting plasma glucose (*FPG*), HbA1c, total cholesterol (*TC*), triglyceride (*TG*), waist circumference (*WC*), carotid IMT were significantly higher and HDL-cholesterol (*HDL-C*) was significantly lower than non-MetS *$P<0.05$; vs. MetS (−) group

Table 120.3 Key Features of ROC curves and Youden index

1. Receiver operating characteristic (ROC) curve is a graphical representation of the relationship between the sensitivity and specificity of a measurement.
2. The area under the ROC curve indicates the appropriateness of the measurement.
3. Youden index is defined as maximum (sensitivity + specificity − 1), which is maximum vertical distance between the ROC curve and the diagonal line when equal weight is given to sensitivity and specificity.
4. Youden index provides the optimal threshold value of the measurement.

This table lists the key facts of ROC curves and Youden index
AUC area under the curve; *ROC curve* Receiver operating characteristic curve

The baseline characteristics of the study subjects are shown in Table 120.2. The prevalence of MetS as defined by IDF in men and women was25.0% and 3.0%, respectively, while that defined by the Japanese was 14.9% and 1.3%, respectively. In the MetS group, all of the following components – age, body mass index, systolic and diastolic blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglyceride, waist circumference, carotid IMT – were significantly higher and HDL-cholesterol was significantly lower than non-MetS (Table 120.2).

We plotted ROC curves to determine optimal waist cut-points (87 cm in men and 80 cm in women) to identify subjects with multiple risk factors with maximum sensitivity and specificity using the Youden index for both definitions (Table 120.3, Fig. 120.1a–d). Using the optimal cut point of 87 cm for men, the sensitivity and specificity were 68% and 62% for the IDF and 70% and 57% for the Japanese definition, whereas the cut point of 90 cm, compared with 87 cm, showed lower sensitivity of 51% for the IDF and 53% for the Japanese definition (Fig. 120.1a and b). Using the optimal cut point of 80 cm for women, the sensitivity and specificity were 74% and 70% for the IDF and 84% and 68% for the Japanese definition. The former IDF and Japanese cut point of 90 cm showed inadequate sensitivity of 33% for the IDF and 38% for the Japanese definition (Fig. 120.1c and d).

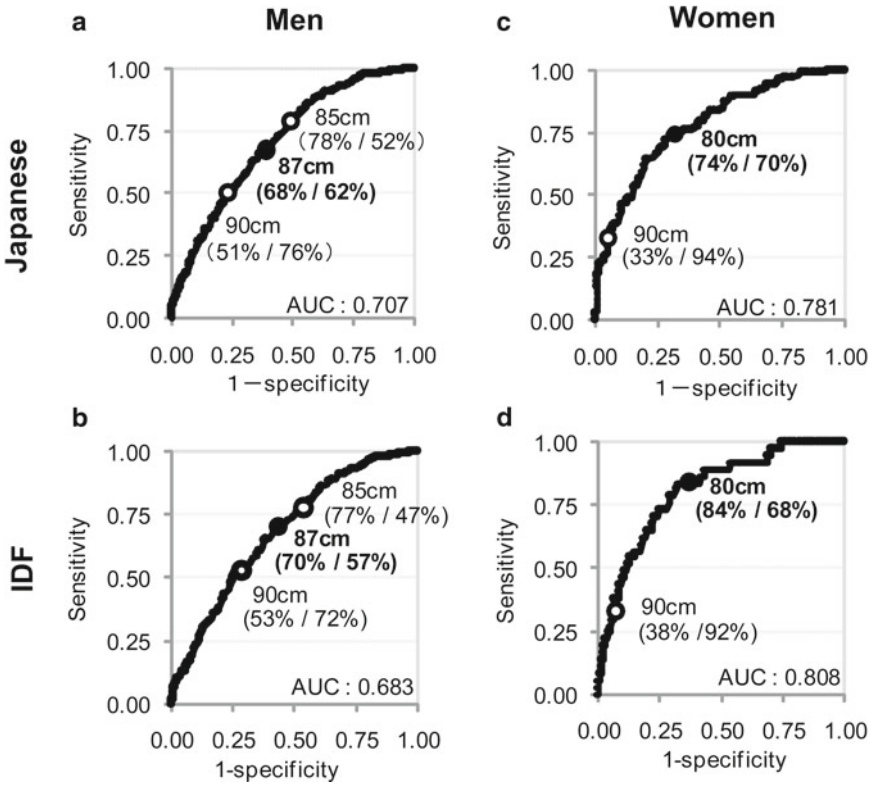

Fig. 120.1 ROC curves for waist circumference. ROC curves for waist circumference were plotted (**a**–**d**). Closed circles (●) on the ROC curve indicate the optimal cut-point with maximum sensitivity and specificity determined using the Yoden Index. Open circles (○) indicate the cut-point of the conventional and revised IDF waist cut-points. The numbers in parentheses under the waist circumference indicate sensitivity (%)/specificity (%) at each cut-point. The area under ROC curve is abbreviated to AUC

120.5 Validation of the Waist Cut-Points for MetS Diagnosis

Conceptually, the diagnosis of MetS would identify individuals at a high risk of cardiovascular diseases and type 2 diabetes. Indeed, waist cut-points and MetS diagnosis themselves are proven to predict future cardiovascular events (Wildman et al. 2004). In order to validate the above-determined waist cut-points, we divided the study subjects into subgroups by abdominal adiposity using the conventional and the optimal cut-point, and evaluated their predictability of increased intima-media thickness (IMT) (Matoba et al. 2008). Among 1,658 men, the cut-points of 85, 87, and 90 cm identified 25.0%, 21.9%, and 16.2%, respectively, of subjects with the metabolic syndrome, for the IDF definition; for the Japanese definition the cut-points were 14.9%, 13.4%, and 10.2%, respectively. In subgroups with abdominal adiposity, IMT increased significantly in metabolic syndrome subjects with multiple risk factors, suggesting the feasibility of the cut-points of 85, 87, and 90 cm (Fig. 120.2a and b). Among 1,116 women, the cut-points of 80 and 90 cm identified 7.0% and 3.0% of metabolic syndrome subjects, respectively, for the IDF definition and 2.8% and 1.3% of subjects, respectively, for the Japanese definition. In subjects with waist circumference ≥90 cm, there was no significant difference in IMT using either definition. In contrast, when we used the cut point of 80 cm, the IMT increased significantly in metabolic syndrome subjects (Fig. 120.2c and d), suggesting the feasibility

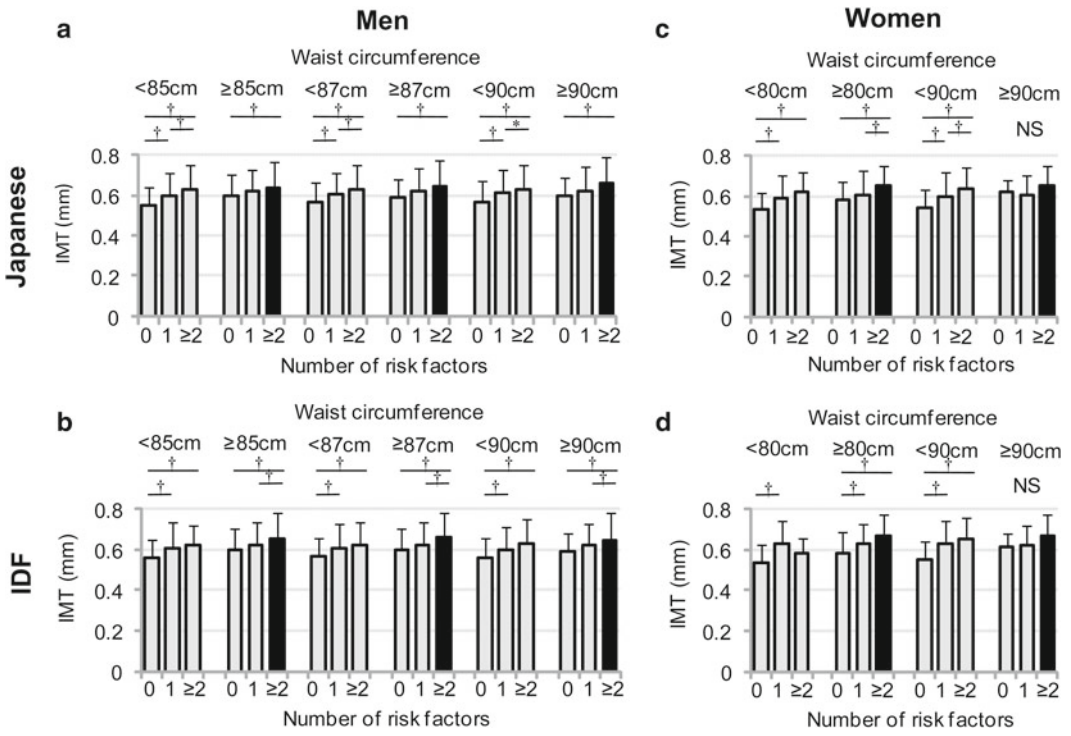

Fig. 120.2 Intima-media thickening in MetS subjects. Mean IMT were obtained in subgroups using the optimal or conventional waist cut-points and the IDF or the Japanese definition (**a**–**d**). Black bars indicate that the IMT increased significantly with the number of risk factors in subjects diagnosed as MetS

of the optimal cut-points (80 cm) and the revised IDF definition. The increasing IMT in metabolic syndrome subjects was more specific using the IDF definition (Fig. 120.2c and d).

In our subsequent study (Matoba et al. 2009), we followed up 769 men and 502 women of the above study subjects (means ± SD age: 48.8 ± 9.8 and 46.8 ± 10.4 years, respectively), for 1.2 ± 0.4 years under the hypotheses that MetS and an accumulation of individual risk factors predict future atherosclerosis. We excluded 107 subjects on medications for dyslipidemia. Subjects diagnosed as having MetS at baseline received instruction for lifestyle modification and were referred to a clinic if they had untreated hypertension, diabetes or dyslipidemia. We diagnosed MetS using the IDF definition for Japanese population. Student's *t*-tests were used to compare the mean basal IMT adjusted for age and the annual changes in IMT adjusted for age and basal IMT between the groups with or without MetS or the individual components of MetS. Multiple comparisons with Tukey's test were used to compare the mean IMT adjusted for age and the annual difference in IMT adjusted for age and basal IMT among four groups, namely subjects without risk factor and with 1, 2, and 3 or more risk factors (RF 0, RF 1, RF 2, and RF ≥3, respectively) diagnosed at baseline. Subjects were regrouped based on the MetS diagnosis at the baseline and at the time of follow-up; MetS (baseline/follow-up): MetS (–/–), (–/+), (+/–) and (+/+). The statistical analyses were performed using JMP 7.0 software (SAS Institute, Cary, 76 NC). Statistical significance was inferred at $P < 0.05$. At baseline, 108 (14.0%) males and 37 (7.3%) females had MetS. IMT was significantly greater in subjects of both sexes with MetS (Table 120.4). Some risk factor components of MetS were also significantly related to an increase in baseline IMT (WC, BP, TG, and HDL in males and WC, BP, TG, HDL, and FPG in females) after adjustment for age (Table 120.4). Increase in the number of RF including WC

Table 120.4 Baseline IMT adjusted for age relates with MetS and its risk factors

		Male			Female		
		N (%)	IMT (mm)	*P*	*N* (%)	IMT (mm)	*P*
MetS	−	661 (86)	0.601 ± 0.004		465 (93)	0.569 ± 0.003	
	+	108 (14)	0.631 ± 0.009	<0.001	37 (7)	0.633 ± 0.011	<0.001
WC	−	525 (68)	0.599 ± 0.004		335 (67)	0.566 ± 0.004	
	+	243 (32)	0.618 ± 0.006	0.005	167 (33)	0.589 ± 0.005	<0.001
BP	−	196 (25)	0.599 ± 0.004		441 (88)	0.567 ± 0.003	
	+	572 (75)	0.623 ± 0.007	0.001	61 (12)	0.618 ± 0.009	<0.001
TG	−	559 (73)	0.600 ± 0.004		467 (93)	0.571 ± 0.003	
	+	209 (27)	0.619 ± 0.006	0.009	35 (7)	0.607 ± 0.001	0.002
HDL	−	682 (89)	0.600 ± 0.003		453 (90)	0.569 ± 0.003	
	+	86 (11)	0.640 ± 0.010	<0.001	49 (10)	0.614 ± 0.009	<0.001
FPG	−	446 (58)	0.602 ± 0.005		442 (88)	0.571 ± 0.003	
	+	322 (42)	0.609 ± 0.005	0.282	60 (12)	0.594 ± 0.009	0.011
RF	0	208 (27)	0.589 ± 0.006		278 (54)	0.564 ± 0.004	
	1	255 (33)	0.598 ± 0.006		126 (25)	0.564 ± 0.006	
	2	172 (22)	0.610 ± 0.007	<0.05†	59 (12)	0.601 ± 0.008	<0.05†
	≥3	133 (17)	0.625 ± 0.008	<0.05†	39 (8)	0.629 ± 0.010	<0.05†

At baseline, 108 (14.0%) males and 37 (7.3%) females had MetS. IMT was significantly greater in subjects of both sexes with MetS. WC, BP, TG and HDL in males and WC, BP, TG, HDL, and FPG in females were also significantly related to an increase in baseline IMT after adjustment for age. Increase in the number of RF including WC was also significantly related to an increase in baseline IMT in males and females (RF 2 and RF ≥3 group). Statistical significance was inferred at $P < 0.05$.†; vs. RF0 group

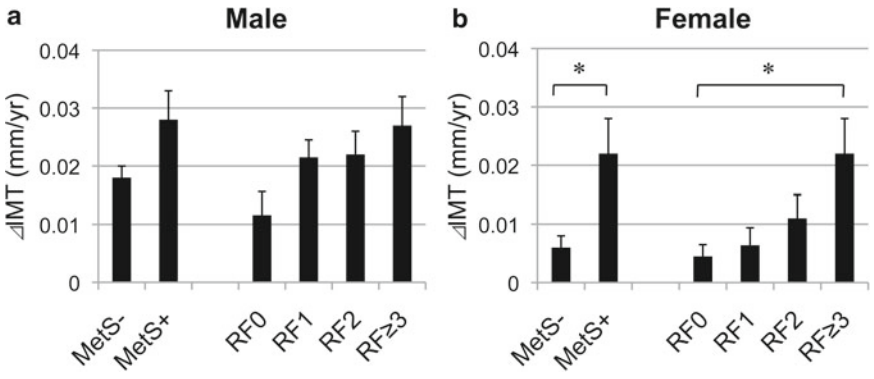

Fig. 120.3 Impact of MetS and its components on annual changes of IMT. Annual changes of IMT after adjustment for age and basal IMT in the groups with or without MetS and the groups of accumulation risk number of the MetS at the base line in males (**a**) and females (**b**)

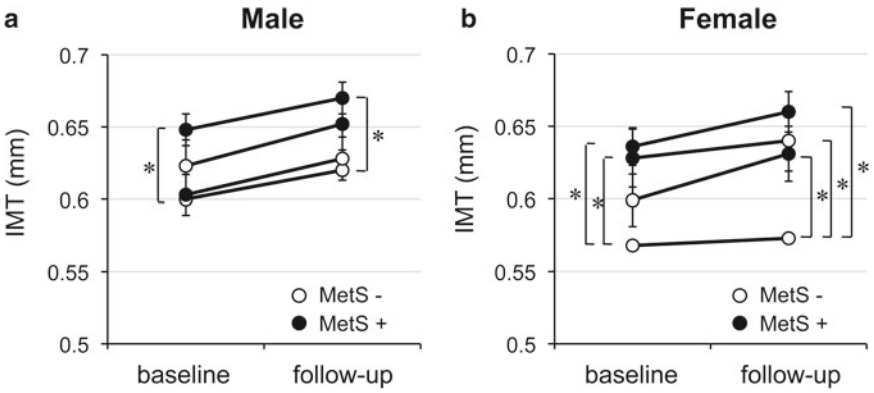

Fig. 120.4 Mean IMT after adjustment for age in the groups with or without MetS at the baseline and at the follow-up. In females, IMT at baseline was significantly greater in the MetS (+/–) and MetS (+/+) groups than in the MetS (–/–) group. Similarly, IMT at follow-up was significantly greater in the MetS (–/+), MetS (+/–) and MetS (+/+) groups than in the MetS (–/–) group. Data are means±SEM. *$P < 0.05$

was also significantly related to an increase in baseline IMT in males and females (RF 2 and RF ≥3 group) (Table 120.4). We analysed annual IMT increase in each subject after 1.2 ± 0.4 years follow-up. In both males and females, annual IMT increase tended to be larger in subjects with the MetS compared with subjects without MetS, and in subjects with an increasing number of RF (Fig. 120.3a and b). This difference was statistically significant in females (MetS+ and RF ≥3 group). Among individual RF, WC in males (0.017 mm/year vs. 0.027 mm/year, $P < 0.05$), WC in females (0.004 mm/year vs. 0.012 mm/year, $P < 0.05$) and HDL in females (0.006 mm/year vs. 0.020 mm/year, $P < 0.01$) were related to larger annual IMT increase. These results indicate that MetS as well as an increased number of individual risk factors are associated with an increased IMT at baseline, and that MetS predicts annual increase in IMT particularly in females when we used 80 cm waist cut-point just as provided for Japanese in the IDF definition. We analyzed baseline IMT and annual IMT changes based on a diagnosis of MetS at baseline and follow-up. In males, 635 (82.7%), 26 (3.4%), 40 (5.2%) and 68 (8.9%) subjects were diagnosed as MetS (–/–), (–/+), (+/–) and (+/+), respectively. Among the four groups, the IMT in the MetS (+/+) group was significantly greater than that in the MetS (–/–) group at baseline and at follow-up (Fig. 120.4a and b). In females, 452 (90.0%), 13 (2.6%), 11 (2.2%)

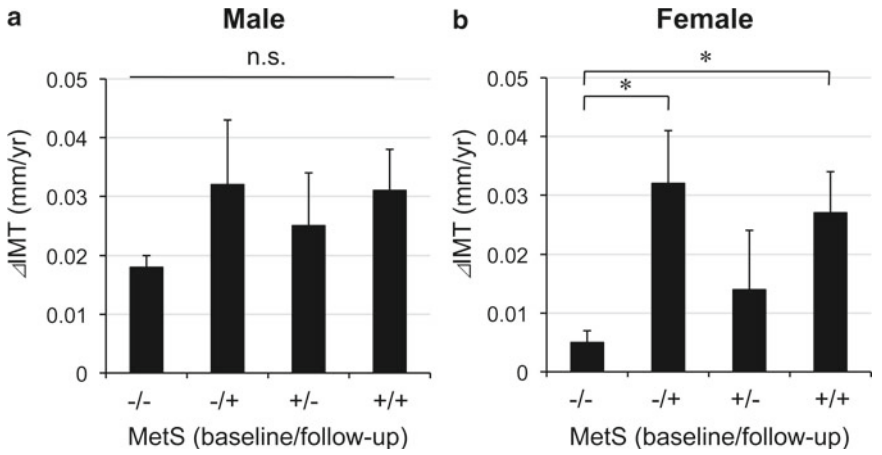

Fig. 120.5 Annual changes of IMT after adjustment for age and basal IMT in the groups with or without MetS at the baseline and at the follow-up. In females, the annual IMT change was significantly greater in the MetS (–/+) and MetS (+/+) group. Of interest was the fact that the annual increase in IMT in the MetS (+/–) females was not significantly different from that in the MetS (–/–) females. Data are means±SEM. *$P < 0.05$

and 26 (5.2%) subjects were diagnosed as MetS (–/–), (–/+), (+/–) and (+/+), respectively. IMT at baseline was significantly greater in the MetS (+/–) and MetS (+/+) groups than in the MetS (–/–) group (Fig. 120.4b). Similarly, IMT at follow-up was significantly greater in the MetS (–/+), MetS (+/–) and MetS (+/+) groups than in the MetS (–/–) group (Fig. 120.4b). Next, we assessed the annual IMT changes among these groups. In males, the annual IMT changes were not significantly different (Fig. 120.5a). In contrast, in females, the annual IMT change was significantly greater in the MetS (–/+) and MetS (+/+) group (Fig. 120.5b). Of interest was the fact that the annual increase in IMT in the MetS (+/–) females was not significantly different from that in the MetS (–/–) females, which may indicate a beneficial effect of medical intervention in MetS on IMT. These IMT changes were not significant in the same subjects when we used 90 cm as the waist cut-point for females.

120.6 Conclusions

MetS is a cluster of multiple metabolic risk factors based on visceral adiposity and insulin resistance, which retains future risk for cardiovascular diseases and type 2 diabetes. Diagnostic criteria proposed by the IDF, AHA/NHLBI and the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome of MetS include waist circumference as a surrogate marker of visceral adiposity and current definitions adopt cut-points of waist circumference for each ethnic group to optimize their predictive values.

Our data provided optimal waist cut-points for Japanese, 87 cm for men and 80 cm for women using relations with the clustered risk factors. The optimized waist cut-points showed superior sensitivity and specificity to the conventional IDF and the Japanese cut-point for women (90 cm) in order to predict intima-media thickening, and agreed with the revised IDF definition (80 cm) for women. Moreover, the follow-up study suggested that the presence of MetS determined by the optimal waist cut-points of 90 cm for men and 80 cm for women identified subjects with a short-term risk of development of atherosclerosis. Further studies with larger population and longer follow-up period may validate these waist cut-points for the clinical diagnosis of MetS with a substantial risk of cardiovascular events and/or onset of type 2 diabetes.

Summary Points

1. MetS is a cluster of multiple metabolic risk factors based on visceral adiposity and insulin resistance, which retains future risk for cardiovascular diseases and type 2 diabetes.
2. Clinical methods to evaluate visceral adiposity include abdominal computed tomography, body mass index and waist and hip circumference; in which waist circumference is most available but highly dependent on the ethnicity.
3. Current MetS definitions include waist circumference as a surrogate marker of visceral adiposity and adapt cut-points of waist circumference for each ethnic group to optimize their predictive values.
4. For Asian or Japanese people, the International Diabetes Federation, the American Heart Association and the National Heart, Lung and Blood Institute provided the waist cut-points of 90 cm for men and 80 cm for women.
5. The Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome adopted waist cut-points of 85 cm for men and 90 cm for women as the waist cut-points that derived from the cut-points of visceral fat area by computed tomography to identify clustered risk factors.
6. Several studies, including our recent studies obtained optimal waist cut-points, suggest that the waist cut-points of 90 cm for men and 80 cm for women are relevant for Japanese population to define MetS with a short-term risk of development of atherosclerosis.
7. Further studies with larger population and longer follow-up period may validate these waist cut-points for the clinical diagnosis of MetS with substantial risk of cardiovascular events and/or onset of type 2 diabetes as hard end-points.

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Chapter 121
BMI, Waist Circumference, and Metabolic Syndrome: Lessons from Japanese Perspectives

Masaru Sakurai, Tsuguhito Ota, Katsuyuki Miura, Hideaki Nakagawa, Shuichi Kaneko, and Toshinari Takamura

Abstract The prevalence of overweight and obesity in Japan is much lower than in Western countries: about 30% for Japanese men and 20% for Japanese women. Despite this low rate of obesity, the prevalence of metabolic abnormalities related to cardiovascular risk factors such as hypertension, dyslipidaemia, and diabetes is not lower in Japan than in Western countries. Visceral fat accumulation is also closely associated with metabolic abnormalities in the Japanese. Among the anthropometric variables, waist circumference is an indirect measure of abdominal fat accumulation. The waist circumference cutoff points for the Japanese have been proposed as 90 cm for women and 85 cm for men, which correspond to a 100-cm^2 area of visceral fat at the umbilical level on computed tomography imaging. However, subcutaneous fat strongly influences waist circumference in relatively lean Japanese women, and waist circumference does not effectively predict the existence of metabolic syndrome. In relatively lean Japanese women, BMI rather than waist circumference is reported to be more strongly associated with metabolic syndrome and may be more appropriate as an index for total and abdominal fat accumulation. Normal weight is associated with increased cardiovascular risk factors in Japanese. The difference in the association between obesity and metabolic abnormalities in Asian and Western countries may be due to genetic factors, different lifestyles, or sensitivity to metabolic disorders of obesity. Japanese have more total body fat and visceral fat than Caucasian men with the same degree of obesity, and the difference in body fat distribution also contributes to these differences. Furthermore, there is a J-shaped relationship between waist circumference and subsequent risk for type 2 diabetes in relatively lean Japanese; lower pancreatic B-cell function may also increase the diabetes risk in very lean Japanese. Recently, nonalcoholic fatty liver disease has been reported to be closely associated with metabolic syndrome in Western and Asian populations. Not only fat accumulation in the visceral area, but fat accumulation in the liver may also contribute to the development of metabolic syndrome. Therefore, when we consider the association between obesity indices, such as waist circumference and BMI, and metabolic syndrome, we should consider the gender/ethnic differences of these associations, insulin deficiency, and fatty liver-associated insulin resistance.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_121,

Abbreviations

BMI	Body mass index
OECD	Organisation for Economic Cooperation and Development
MetS	Metabolic Syndrome
DXA	Dual-energy X-ray Absorptiometry
FM	Fat mass
CT	Computed tomography
IDF	International Diabetes Federation
ROC	Receiver-Operator Characteristic
FPG	Fasting Plasma Glucose
RR	Rate ratio
HOMA	Homeostatic Model Assessment
HR	Hazard ratio
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis

121.1 Introduction

The prevalence of obesity is quite low in Japanese and Asian populations. About 30% of the Japanese are overweight (body mass index (BMI) ≥ 25 kg/m^2), but only 3.2% are obese (BMI ≥ 30 kg/m^2), whereas 32.2% of Americans are obese (Organisation for Economic Cooperation and Development (OECD) Health Data 2008). However, despite the low prevalence of obesity, the prevalence of metabolic abnormalities related to cardiovascular risk factors such as hypertension, dyslipidaemia, and diabetes is not lower in Japan than in Western countries (Ota et al. 2002; Yoon et al. 2006). These differences in the association between obesity and cardiovascular risk factors are derived from genetic factors, different lifestyles, different body fat distributions, and/or sensitivity of metabolic disorders to obesity, as compared to Western people. We should consider such racial/ethnic differences when evaluating the association between obesity and metabolic syndrome (MetS).

In this chapter, we first provide an overview of obesity in the Japanese and then discuss the gender differences in anthropometric variables, such as BMI and waist circumference, and their association with MetS in the Japanese population.

121.2 Epidemiology of Obesity and Metabolic Abnormalities in Japanese

The prevalence of overweight (BMI ≥ 25 kg/m^2) and lean (BMI < 18.5 kg/m^2) people and changes in these figures in the last three decades are shown in the results from the National Health and Nutrition Survey of Japan (Ministry of Health, Labour, and Welfare 2009; Fig. 121.1). The prevalence of overweight is much lower than in Western countries: about 30% for Japanese men and 20% for Japanese women. However, the prevalence of overweight has increased, especially in middle-aged Japanese men, and these trends are similar to other Asian countries (Ge 1997; Ko et al. 1997; Yoshiike et al. 1998). However, mean BMI has decreased in the last two decades in young women; lower body weight and its associated health problems, such as anaemia, eating

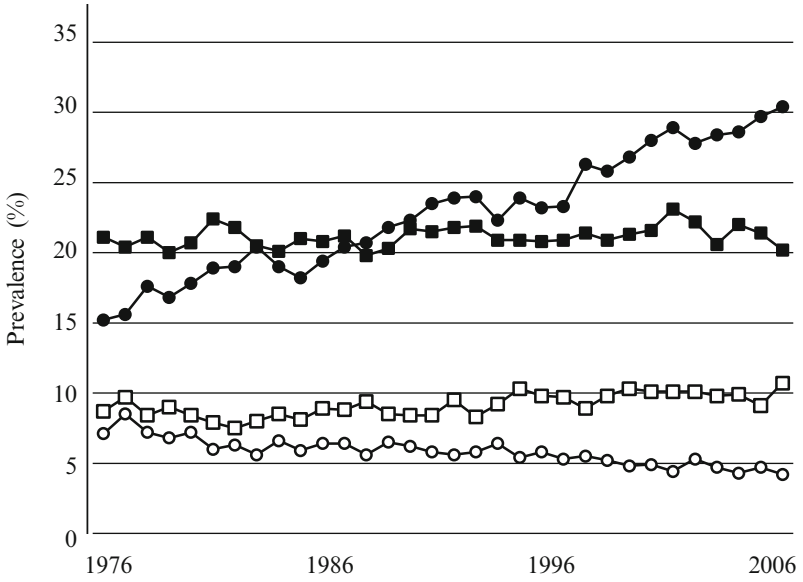

Fig. 121.1 Prevalence of overweight (BMI ≥25 kg/m^2) and lean (BMI <18.5 kg/m^2) people in the Japanese population: Results from the National Nutrition Survey (1976–2002) and the National Health and Nutrition Survey (2003–2007). (●) Overweight men; (■) overweight women; (○) lean men; (□) lean women

disorders, irregular menstruation, and reduced foetal growth in pregnancy, have become important problems in young Japanese women (Takimoto et al. 2004; Ministry of Health, Labour, and Welfare 2009).

Although the prevalence of obesity is much lower in Asian than Western countries, the prevalence of type 2 diabetes is similar (Yoon et al. 2006), suggesting that the association between obesity and metabolic abnormalities may be different in Asian and Western countries.

The relationship between obesity and metabolic abnormalities is also observed in relatively lean Japanese men and women. Ota et al. examined the relationship between BMI and metabolic abnormalities among 21,050 healthy Japanese men and women aged 35–60 years in a cross-sectional study (Ota et al. 2002, 2006). As BMI increased, systolic and diastolic blood pressure, total cholesterol, triglycerides, and fasting plasma glucose increased, and HDL-cholesterol decreased linearly (Fig. 121.2). Furthermore, increasing BMI was also associated with increasing alanine aminotransferase and uric acid, indicating that obesity is also associated with fatty liver disease and hyperuricemia (gout) in Japanese men and women. When participants were classified using the WHO obesity classification, all but one of the components were significantly higher (only HDL-C was lower) for the pre-obese participants (BMI of 25.0–29.9 kg/m^2) than the normal body weight participants (BMI of 18.5–24.9 kg/m^2) ($P < 0.001$). Furthermore, the mean levels of total cholesterol, fasting plasma glucose, systolic and diastolic blood pressure, and uric acid were higher, and HDL-cholesterol was lower in normal body-weight than in underweight participants (BMI < 18.5 kg/m^2). These results show that normal weight also involves increased cardiovascular risk factors in Japanese. In these reports, the BMI threshold for significantly increasing levels of metabolic variables such as blood pressure and serum lipid levels was around 21–23 kg/m^2. Because Asian people, including the Japanese, tend to have a higher risk for cardiovascular disease even with normal body weight, the WHO proposed the BMI cut-off points for pre-obesity as 23 kg/m^2 for the Asian population (WHO Expert Consultation 2004).

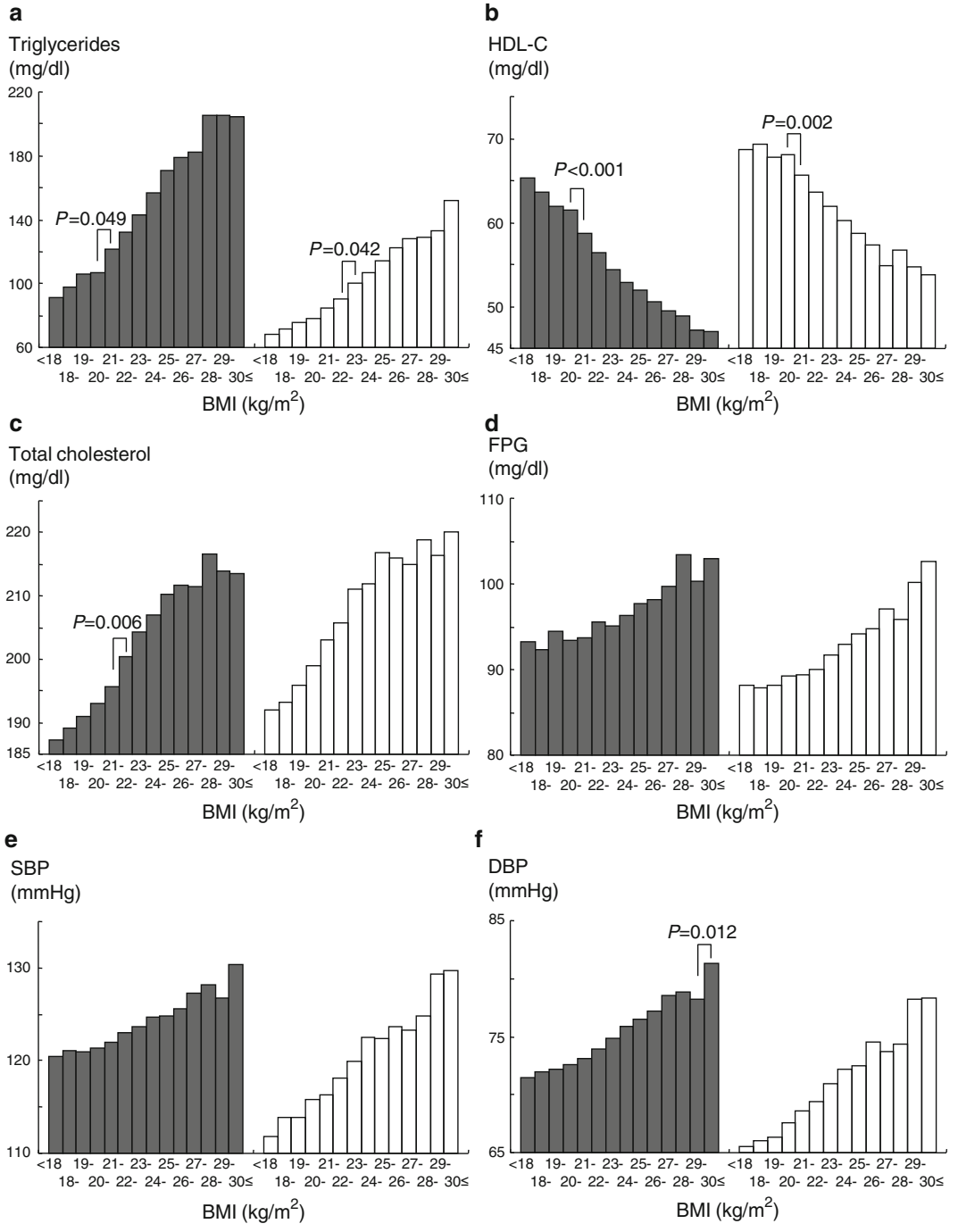

Fig. 121.2 BMI thresholds for the risk of metabolic syndrome. (**a**) Serum triglycerides; (**b**) serum HDL-cholesterol; (**c**) serum total cholesterol; (**d**) fasting plasma glucose; (**e**) systolic blood pressure; (**f**) diastolic blood pressure; (**g**) number of metabolic syndrome components defined by ATP-III; (**h**) alanine aminotransferase (Ota, Sakurai, and Takamura, unpublished data). Black column, men; white column, women. The values are means. (Ota et al. 2006)

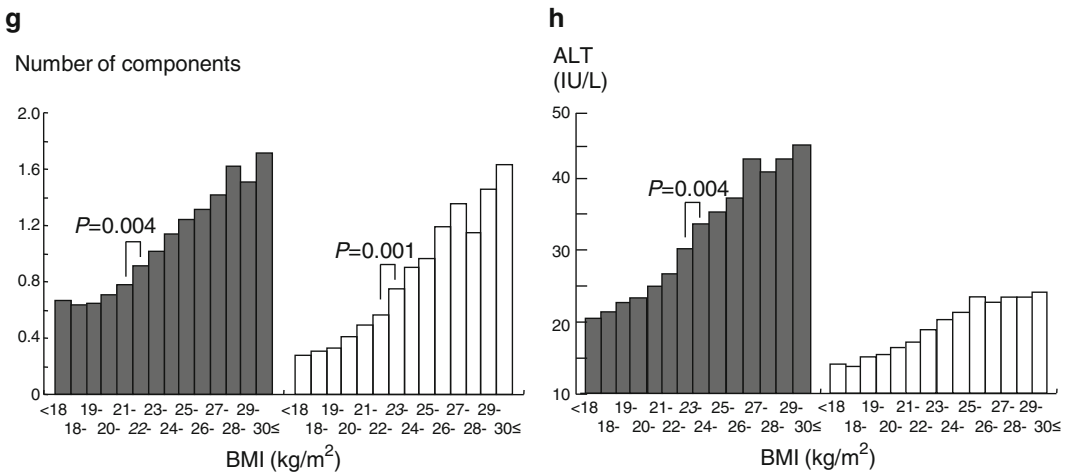

Fig. 121.2 (continued)

121.3 Visceral Adiposity and Metabolic Abnormalities in Japanese

Although obesity is less common in Japanese men and women, concealed abdominal fat may play an important role in the development of MetS. Ito et al. examined body fat distribution by dual-energy X-ray absorptiometry (DXA) in 2,728 Japanese men and women and showed that the percentage fat mass (FM) (trunk)/FM (legs) most accurately detected abnormalities in blood pressure, serum lipid levels, and fasting plasma glucose (Ito et al. 2003). Oka et al. examined the subcutaneous and visceral fat area at the level of the umbilicus using computed tomography (CT) in about 2,000 middle-aged Japanese men and women and reported that the visceral fat area was more closely associated with metabolic abnormalities than the subcutaneous fat area (Oka et al. 2010). Furthermore, the relationship between visceral fat area and metabolic abnormalities was significant even after adjusting for BMI and waist circumference, indicating that visceral fat accumulation is closely associated with metabolic abnormalities in relatively lean Japanese people.

Abdominal fat accumulation is considered an important etiological factor in the development of MetS. Among the anthropometric variables, waist circumference and variables associated with waist circumference, such as waist-to-hip ratio, are indirect measures of abdominal fat accumulation. Waist circumference is included as one of the key criteria for defining MetS. The Japan Society for the Study of Obesity defined a 100-cm^2 area for visceral fat at the umbilical level on CT imaging as a risk factor for cardiovascular disease in Japanese (The Examination Committee of Criteria for 'Obesity Disease' in Japan 2002). The waist circumference cutoff points for Japanese were then proposed as 90 cm for women and 85 cm for men, which correspond to a 100-cm^2 area of visceral fat at the umbilical level on CT imaging (The Examination Committee of Criteria for Metabolic Syndrome 2005). These cutoff points for Japanese are unique in that the value for women is larger than that for men, and they remain controversial. In contrast, the International Diabetes Federation (IDF) proposed a waist circumference cutoff point of 90 cm for men and 80 cm for women (Arberti et al. 2005), and some reports have proposed lowering the waist circumference cutoff point for Japanese women. Indeed, many studies have been conducted to re-evaluate the association between waist circumference and cardiovascular risk factors and have also proposed lowering the waist circumference cut-off points for Japanese women (Hara et al. 2006; Ohkubo et al. 2006; Oizumi et al.

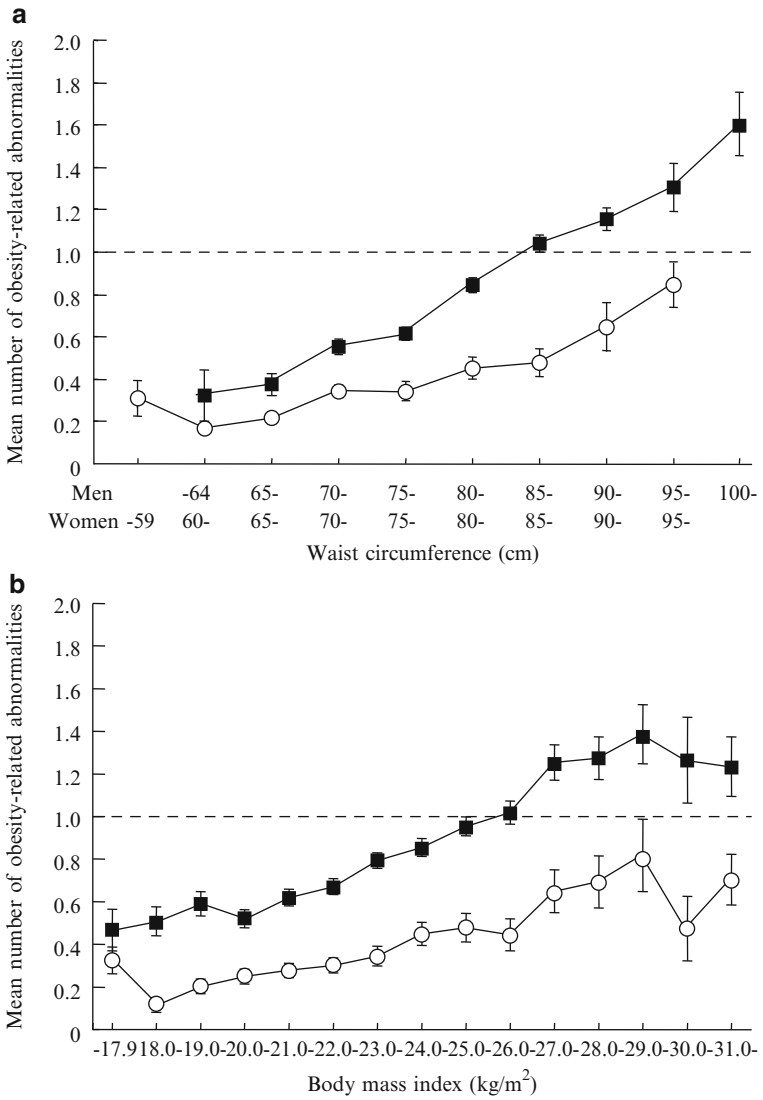

Fig. 121.3 The mean number of obesity-related abnormalities distinguished by waist circumference (**a**) or body mass index (**b**) in men (■) and women (○). Obesity-related abnormalities included hypertension, dyslipidaemia, and glucose intolerance. The horizontal dotted line shows the mean number of obesity-related abnormalities as 1.0. Data are presented as means ± standard errors (Sakurai et al. 2009a)

2006; Nishimura et al. 2007; Lee et al. 2007b; Miyatake et al. 2007; Ohnishi et al. 2008; Kato et al. 2008; Matoba et al. 2008; Narisawa et al. 2008; Oka et al. 2008; Sato et al. 2008; Shimajiri et al. 2008; Kashihara et al. 2009; Sone et al. 2009; Tabata et al. 2009; Yoshida et al. 2009). However, these reports determined the cut-off points only from receiver-operator characteristic (ROC) curves for waist circumference to predict one or more obesity-related metabolic abnormalities, and did not consider the absolute cumulative risk of metabolic abnormalities in Japanese women.

We evaluated the association between waist circumference and accumulation of cardiovascular risk factors in Japanese men and women (Sakurai et al. 2009a) and showed that in women, the mean number of complicated metabolic syndrome components was lower than one even in those with a waist circumference ≥90 cm, which is the abdominal obesity cut-off value for Japanese women (Fig. 121.3). This result suggests that Japanese women are resistant to obesity-related metabolic abnormalities or that waist circumference does not effectively predict the existence of MetS in relatively lean Japanese women.

Hara et al. (2006) and Ohkubo et al. (2006) proposed a waist circumference cutoff point for detecting MetS or insulin resistance in Japanese based on relatively small, older, and a somewhat higher-risk population. Both reports proposed lowering the waist circumference cutoff point for Japanese women to 76 cm because this value provided the highest sensitivity and specificity for detecting MetS. Theoretically, sensitivity and specificity (i.e., ROC curves) are not affected by the prevalence of the detected disease in various populations. For example, in our study, the positive predictive value was as low as 7.1% in a population of middle-aged Japanese women, which means that only 7.1% of women with a waist circumference of 73 cm or greater had metabolic abnormalities (Sakurai et al. 2009a). Therefore, such a cutoff point may not be suitable for a screening test in women. The low positive predictive value was caused by the low prevalence of metabolic abnormalities in middle-aged Japanese women, and possibly by the relatively higher resistance of Japanese women than that of Japanese men to obesity-induced metabolic abnormalities. As proposed in previous reports (Hara et al. 2006; Ohkubo et al. 2006), lower waist circumference cutoff points might detect more people with metabolic abnormalities with a higher sensitivity. However, in a population with a low prevalence of metabolic abnormalities, lower cutoff points would also result in a greater proportion of false positives, with more healthy women, in particular, being judged as at risk. Furthermore, because the mean number of complicated metabolic abnormalities was lower than one even in those with a waist circumference ≥95 cm, and even though the area under the ROC curve was lower in women than in men (Sakurai et al. 2009a), waist circumference would not effectively predict the existence of MetS in Japanese women.

121.4 Gender Differences in Anthropometric Indices Reflecting Obesity-Associated Metabolic Abnormalities in Japanese

Waist circumference is reported to be more closely related to metabolic abnormalities than BMI in many studies from Western countries. Results from urban Japanese men showed that waist-to-hip ratio, but not BMI, was linearly associated with HbA1c, and waist-to-hip ratio was positively associated with serum total cholesterol levels and inversely associated with HDL-cholesterol levels, even after adjusting for BMI (Iso et al. 1991). Similar stronger relationships between the variables associated with abdominal obesity (waist circumference and waist-to-hip ratio) and the prevalence of hypertension, diabetes, and accumulation of metabolic abnormalities have been reported in some cross-sectional studies with Japanese participants (Ito et al. 2003; Hsieh and Muto 2005; Huxley et al. 2008; Kato et al. 2008; Nakamura et al. 2008; Asayama et al. 2009). In contrast, some reports have shown that the association is similar for BMI and waist circumference (Nakamura et al. 2007; Obesity in Asia Collaboration 2008; Kondo et al. 2009), and some reports showed that the relationship to some metabolic abnormalities was stronger for BMI than waist circumference (Sakurai et al. 2006, 2008; Decoda Study Group 2008; Kondo et al. 2009).

We evaluated the gender difference of the association between anthropometric indices and metabolic abnormalities in 2,935 Japanese men and 1,622 Japanese women aged 35–59 years (Sakurai et al. 2006, 2008). As shown in Table 121.1, waist circumference was more strongly associated with high blood pressure, dyslipidaemia, and high fasting plasma glucose (FPG) in men, whereas BMI was more strongly associated with high blood pressure and dyslipidaemia in women. Although waist circumference was more strongly associated with high FPG in women, the association was weaker than the relationship between BMI and high blood pressure or dyslipidaemia. The rate ratio (RR) (95% confidence interval) of having two or more metabolic abnormalities by one standard deviation increment of each anthropometric variable was higher for waist circumference (RR, 1.85;

Table 121.1 The relationship between prevalence of metabolic abnormalities and anthropometric indices in men and women (Sakurai et al. 2006, 2008)

	Model 1						Model 2					
	Men			Women			Men			Women		
	χ^2	RR	95% CI	χ^2	RR	95% CI	χ^2	RR	95% CI	χ^2	RR	95% CI
High blood pressure												
Body mass index	61.2	1.36	1.26–1.47	52.4	1.55	1.38–1.75	0.4	1.05	0.91–1.20	27.5	1.62	1.35–1.94
Waist circumference	77.9	1.46	1.35–1.59	25.3	1.37	1.21–1.55	18.8	1.40	1.20–1.63	0.4	0.94	0.78–1.13
Dyslipidaemia												
Body mass index	200.8	1.85	1.70–2.01	26.3	1.50	1.28–1.75	15.1	1.35	1.16–1.57	1.9	1.19	0.93–1.53
Waist circumference	205.9	2.01	1.83–2.21	22.5	1.48	1.26–1.74	23.3	1.51	1.28–1.79	5.5	1.36	1.05–1.76
High fasting plasma glucose												
Body mass index	7.5	1.19	1.05–1.35	6.1	1.33	1.06–1.68	0.0	0.98	0.78–1.24	0.1	0.95	0.66–1.37
Waist circumference	11.3	1.26	1.10–1.45	11.9	1.50	1.19–1.88	3.8	1.29	1.00–1.66	5.6	1.56	1.08–2.25
Two or more metabolic abnormalities												
Body mass index	118.9	1.70	1.54–1.86	28.8	1.73	1.42–2.12	5.8	1.24	1.04–1.48	7.1	1.57	1.13–2.18
Waist circumference	126.3	1.85	1.66–2.06	20.9	1.64	1.33–2.03	16.7	1.51	1.24–1.83	0.6	1.14	0.81–1.61

Model 1, adjusted for age; model 2, adjusted for age and two anthropometric variables (each adjusted for the other)
RR are calculated for each anthropometric variable greater than 1 SD
Metabolic abnormalities were determined using the Japanese metabolic syndrome criteria
RR risk ratio; *95% CI* 95% confidence interval

[1.66–2.06]) than for BMI (RR, 1.70; [1.54–1.86]) in men, whereas it was higher for BMI (RR, 1.73; [1.42–2.12]) than for waist circumference (RR, 1.64; [1.33–2.03]) in women. When BMI and waist circumference were included simultaneously in a model, waist circumference showed a stronger association with the presence of metabolic abnormalities in men. However, in women, BMI showed an independent association, whereas waist circumference showed no significant association in women after adjusting for BMI.

At the same BMI, the percentage of body fat in Asians is 3–5% higher than in Caucasians (Deurenberg et al. 2002), and Japanese men have more visceral adipose tissue than do Caucasian men for the same waist circumference (Kadowaki et al. 2006). Thus, these body-fat distribution characteristics in Japanese influence the anthropometric indices of obesity. For example, Oka et al. measured visceral and subcutaneous adipose tissue using CT scans in 2,470 Japanese men and women and showed that the relationship with waist circumference or BMI was greatest for total (visceral plus subcutaneous) adipose tissue and subcutaneous adipose tissue and least for visceral adipose tissue (Oka et al. 2009). These results show that waist circumference does not always reflect visceral adipose tissue. Compared to those in men and women in Western countries and Japanese men, associations between waist circumference and metabolic abnormalities were weaker for Japanese women (Decoda Study Group 2008; Kondo et al. 2009), and these discrepancies may be due to differences in fat distribution. In relatively lean Japanese women, given the stronger influence of subcutaneous fat on waist circumference, BMI may be more appropriate than waist circumference as an index for total and abdominal fat accumulation.

121.5 J-Shaped Relationship Between Waist Circumference and Subsequent Risk for Type 2 Diabetes in Japanese

A linear association between the degree of obesity and the incidence of type 2 diabetes was reported in the Nurses' Health Study (Carey et al. 1997) and other cohort studies from Western populations (Wei et al. 1997; Folsom et al. 2000; Wang et al. 2005; Meisinger et al. 2006). In Western populations, insulin resistance and hyperinsulinemia are observed in subjects with impaired glucose tolerance, and a marked deterioration in insulin secretion precedes the onset of type 2 diabetes (Tripathy et al. 2000) (Fig. 121.4a). However, decreased insulin secretion precedes not only the onset of type 2 diabetes but also the onset of impaired glucose tolerance in Japanese

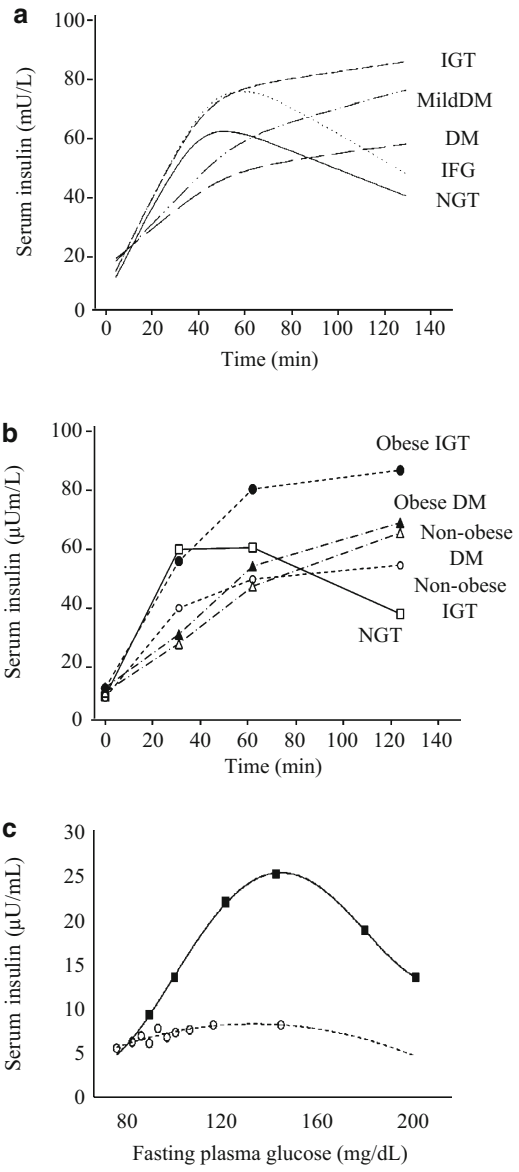

Fig. 121.4 The insulin response during OGTTs in Western and Japanese populations. Comparison of the results from the Botnia study (**a**) with 5,396 Finnish individuals (Tripathy et al. 2000) and our data of 689 Japanese individuals (**b**) (□ normal glucose tolerance, $n = 324$; ○ non-obese impaired glucose tolerance, $n = 86$; ● obese impaired glucose tolerance, $n = 86$; non-obese diabetes mellitus, $n = 73$; ▲ obese diabetes mellitus, $n = 59$. Sakurai and Takamura, unpublished data). Obesity is defined as BMI ≥25 kg/m^2. Fasting plasma insulin levels were compared to fasting plasma glucose levels in Western (■, De Fronzo et al. 1989, 1988) and Japanese populations (○; $n = 689$, Sakurai and Takamura, unpublished data) (**c**). *NGT* normal glucose tolerance; *IFG* impaired fasting glucose; *IGT* impaired glucose tolerance; *DM* diabetes mellitus

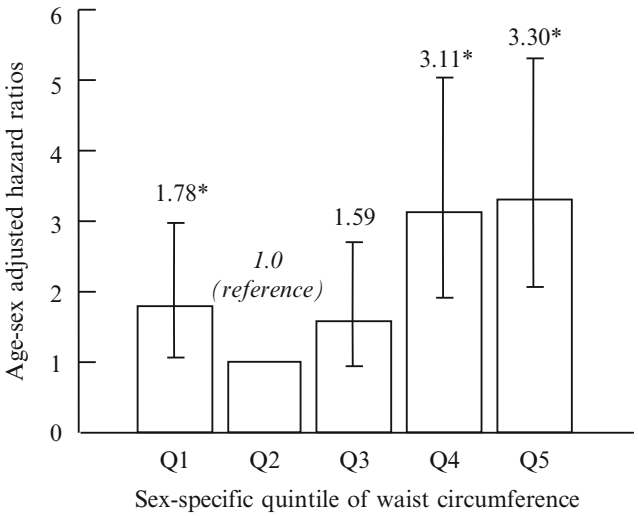

Fig. 121.5 Age- and gender-adjusted hazard ratios for the incidence of type 2 diabetes across the gender-specific quintile for baseline waist circumference. *$p < 0.05$ vs. second quintile (Sakurai et al. 2009b)

(Fukushima et al. 2004). Our data also showed that insulin secretion was reduced in subjects with impaired glucose tolerance compared to those with normal glucose tolerance, at least in non-obese Japanese (Fig. 121.4b), and compensatory higher insulin secretion was not observed in Japanese with higher fasting plasma glucose levels (Fig. 121.4c). Furthermore, the prevalence of type 2 diabetes is similar in Asian and Western populations, although the prevalence of obesity is much lower in Asian countries (Yoon et al. 2006). These findings suggest that the association between obesity and insulin resistance, as well as insulin secretion and the incidence of diabetes may be different in Asian from that in Western countries.

We examined the relationship between waist circumference and the incidence of type 2 diabetes in a Japanese cohort (Sakurai et al. 2009b). The participants were 3,992 employees (2,533 men and 1,459 women, aged 35–55 years) from a metal-products factory in Japan. During an 8-year follow-up, 218 participants developed diabetes. Age- and gender-adjusted hazard ratios (HR) across the waist circumference quintiles were 1.78, 1.00 (reference), 1.59, 3.11, and 3.30 (P for trend, <0.0001) (Fig. 121.5). The HR for the lowest quintile was significantly higher than that for the second quintile. Among participants with a waist circumference in the lowest quintile, the insulin secretion index Homeostatic Model Assessment (HOMA)-B was lower in those who developed diabetes than in those who did not (RR, 33.1; [24.1–45.0] vs. RR, 54.3; [37.9–74.6]) median [interquartile range], $P < 0.0001$), whereas the insulin resistance index HOMA-IR did not differ between the groups (Fig. 121.6). These findings suggest the existence of a J-shaped relationship between waist circumference and subsequent risk for type 2 diabetes in relatively lean Japanese individuals. Not only obesity, but lower pancreatic B-cell function may also increase the risk for diabetes in very lean Japanese.

121.6 Fatty Liver-Associated Metabolic Syndrome

It was recently reported that nonalcoholic fatty liver disease (NAFLD) is related to cardiovascular disease and to most cardiovascular risk factors, including diabetes, hypertension, hyperlipidaemia, and metabolic syndrome (Andre et al. 2007; Lee et al. 2007a; Devers et al. 2008; Adams et al. 2009). Insulin resistance and obesity are the two major risk factors underlying MetS, and they play a pivotal

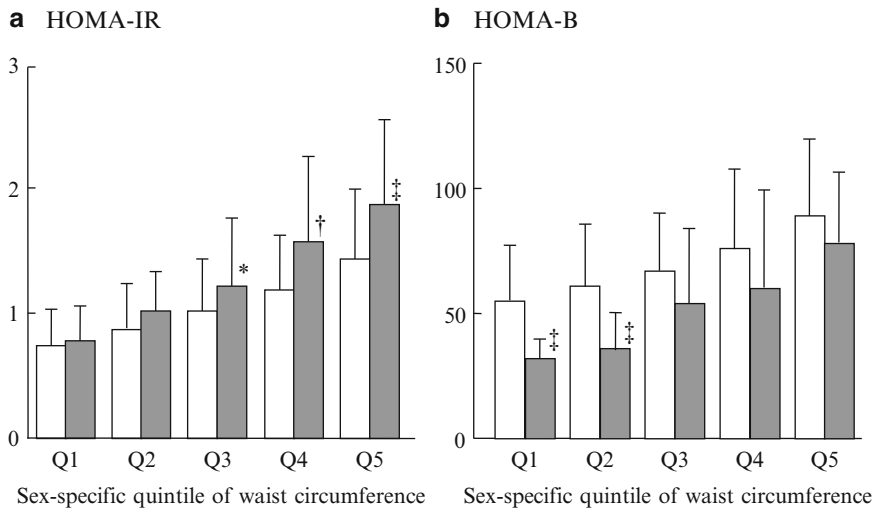

Fig. 121.6 Difference in baseline insulin sensitivity (HOMA-R, **a**) and beta-cell function (HOMA-B, **b**) between subjects who developed type 2 diabetes and those who did not across the gender-specific quintile for baseline waist circumference. *White column*, subjects who did not develop type 2 diabetes; *black column*, subjects who developed type 2 diabetes. Values are geometric means (*column*) and 75th percentiles (*error bar*). * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ vs. those who did not develop type 2 diabetes (Sakurai et al. 2009b)

role in the development of NAFLD and atherosclerosis. These confounding factors should be considered when evaluating the relationships among NAFLD, MetS, and atherosclerosis. We have shown that histological steatosis of the liver is an independent predictor for insulin resistance even after adjusting for BMI (Sakurai et al. 2007), suggesting that not only obesity (abdominal fat), but also fatty liver (hepatic fat deposition) is associated with insulin resistance and insulin resistance-related metabolic abnormalities. Insulin resistance and metabolic abnormalities are observed in the Japanese even with mild degrees of obesity, and one of the reasons for this discrepancy might be explained by the presence of NAFLD in these subjects. In Western people with a high prevalence of obesity, the impact of obesity is so strong on both NAFLD and metabolic abnormalities that it would be difficult to evaluate whether NAFLD itself increases the risk for MetS or cardiovascular disease beyond obesity. Data from lean NAFLD patients in Asia would provide insight into these questions.

NAFLD, especially nonalcoholic steatohepatitis (NASH), is a global issue that will determine the future development of liver cirrhosis, liver failure, and hepatocellular carcinoma. In a prospective evaluation of the histological course of liver pathology, we examined whether metabolic abnormalities were responsible for the histological changes observed in 39 Japanese patients with NAFLD who had undergone serial liver biopsies (Hamaguchi et al. 2010). The median follow-up time was 2.4 years (range, 1.0–8.5 years). Liver fibrosis improved in 12 patients (30.7%), progressed in 11 patients (28.2%), and remained unchanged in 16 patients (41%). In a Cox proportional hazard model, a decrease in HbA1c and insulin use were associated with an improvement in liver fibrosis independent of age, gender, and BMI. However, HbA1c was more strongly associated with the improvement in liver fibrosis than was insulin use after adjusting for each factor (chi-square; 7.97 vs. 4.58, respectively) (Hamaguchi et al. 2010). These findings suggest that tight glycaemic control, rather than weight reduction, may prevent histological progression in Japanese patients with NAFLD. Studies showing that liver fat content, much stronger than visceral fat mass, determines insulin sensitivity in humans (Stefan et al. 2008; Fabbrini et al. 2009), support a direct and major

role of fatty liver in the pathogenesis of insulin resistance. There is now world-wide effort going on in the scientific field aiming at studying the impact of fat accumulation in the liver as a cause for metabolic diseases. One of the links between fatty liver and metabolic abnormalities may be toxic lipids, such as free cholesterol (Matsuzawa et al. 2007) and saturated fatty acid palmitate (Nakamura et al. 2009), that cause inflammation and insulin resistance in the liver. We also hypothesized that in a manner analogous to adipose tissues, the liver may also contribute to the development of diabetes and insulin resistance through the production of secretory proteins, termed hepatokines. Of these, recently identified selenoprotein P, that is over-produced from the liver in face with over-nutrition state, may link over-nutrition and systemic insulin resistance, at least partly, by inactivating an AMP-activated protein kinase (Misu et al. 2010).

121.7 Conclusion

Obesity is an important medical and social problem in Japan, similar to other developed and developing countries. Obesity is closely associated with metabolic abnormalities and MetS in Japanese men and women. However, metabolic abnormalities are not always accompanied by a large waist circumference or high BMI. When we consider the association between obesity indices, such as waist circumference, BMI, and MetS, we should consider the gender/ethnic differences of these associations, insulin deficiency and fatty liver-associated insulin resistance.

Summary Points

- The prevalence of overweight is much lower in Japanese than in Western countries: about 30% for Japanese men and 20% for Japanese women.
- The prevalence of overweight has increased, especially in middle-aged Japanese men, and these trends are similar to trends in other Asian countries.
- Because Asian people, including the Japanese, tend to have a higher risk for cardiovascular disease even with normal body weight, the WHO proposed the BMI cut-off points for pre-obesity as 23 kg/m^2 for the Asian population.
- Abdominal fat accumulation is considered an important etiological factor in the development of MetS, even in relatively lean Japanese. The waist circumference cutoff points for Japanese were proposed as 90 cm for women and 85 cm for men, which correspond to a 100-cm^2 area of visceral fat at the umbilical level on CT imaging.
- Waist circumference does not effectively predict the existence of MetS in relatively lean Japanese women, because it does not strongly related to the prevalence of metabolic abnormalities.
- In relatively lean Japanese women, given the stronger influence of subcutaneous fat on waist circumference, BMI may be more appropriate than waist circumference as an index for total and abdominal fat accumulation.
- J-shaped relationship is observed between waist circumference and subsequent risk for type 2 diabetes in relatively lean Japanese individuals. Not only obesity, but also lower pancreatic B-cell function may also increase the risk for diabetes in very lean Japanese.
- Fatty liver is an independent predictor for insulin resistance even after adjusting for BMI, suggesting that not only abdominal fat, but also hepatic fat deposition is associated with insulin resistance and insulin resistance-related metabolic abnormalities.

Key Features

Table 121.2 Key features of abdominal fat accumulation

1. Body fat distribution contributes to obesity-related disease independent of overall adiposity.
2. The location of body fat has been used to delineate two body shapes; gynecoid versus android.
3. Android obesity is defined as having fat accumulation in the upper body, such as abdomen.
4. Gynecoid obesity is defined as having fat accumulation in subcutaneous area of the lower part of the body, such as hip and thighs.
5. Accumulation of abdominal fat is associated with more adverse metabolic and cardiovascular risk factors than is subcutaneous fat.
6. Abnormal regulation of adipocytokines caused by abundant abdominal fat is one of the important pathogenesis of obesity-related metabolic abnormalities.

Table 121.3 Key facts of Cox proportional hazard model

1. In most clinical situations, many variables act together to produce effects.
2. These variables would relate to each other, and also relate to the outcome of interest. The effect of one might be modified by the presence of others, and the joint effects of two or more may be greater than the sum of their individual effects.
3. "Multivariable analysis" is used to adjust for the effects of many variables to determine the independent effect of one.
4. "Cox proportional hazard model" is a type of multivariable technique used when outcome is the time to an event.

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Chapter 122
Anthropometry of Local Fat Reduction

Frank L. Greenway and Susan Pekarovics

Abstract Obesity is growing around the world in epidemic proportions. Diabetes follows obesity by approximately 10 years and the prevalence of diabetes is growing rapidly as well. Not only are diabetes and obesity associated with much suffering and disease, they are also expensive and threaten the economics of public health systems globally. Obesity medications give modest weight loss at best. Diet and lifestyle change are the basis of obesity treatment, and the growing obesity epidemic is testimony to their limitations. Obesity is a stigmatized condition. The fat in obesity is usually concentrated around the waist or at the hips and thighs. Women with lower body obesity become discouraged and may stop dieting, because fat is lost predominantly from their breasts which they often feel are too small, and not from their hips and thighs where they would prefer to lose it. Local fat reduction represents a way that people can direct the area from which fat is lost which gives them control over their own anthropometry. This ability can encourage subjects to remain in weight loss programs for longer periods of time, lose more weight and improve their health to a greater degree. There have been several approaches to local fat reduction. Invasive approaches include plastic surgery and liposuction. Mesotherapy, the injection of lipolytic stimulators or substances that destroy fat cells subcutaneously, is a less invasive method of removing fat locally. The least invasive approaches are low energy laser treatments that release fat from fat cells through the creation of pores in the cell membranes or topical creams containing lipolytic substances that cross the skin into the fat tissue. Although one might be tempted to dismiss all these methods as being cosmetic without any medical benefit, directing the areas from which fat is lost during a weight loss program is encouraging to many obese subjects, improves their self-image and gives them the motivation to continue losing weight for a longer period of time. Longer weight loss programs are associated with greater weight loss and greater health benefits. We hope this chapter allows a risk-benefit assessment of the different methods of local fat reduction. We also hope this chapter makes a case for the benefits of directing the area from which fat is lost during a weight loss program, potentially leading to longer and greater fat loss with a commensurate increase in medical benefits.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_122,

Abbreviations

AMP	Adenosine monophosphate
BMI	Body Mass Index
cc	Cubic centimeter
cm	Centimeter
GMP	Guanine monophosphate
IV	Intravenous
kcal	Kilocalorie
kg	Kilogram
LED	Light emitting diode
m	Meter
NIH	National Institutes of Health
nm	Nanometer
US	United States

122.1 General Consideration

Obesity is one of the most common disorders in medical practice, and among the most frustrating and difficult to manage. Little progress has been made in prevention or treatment, yet major changes have occurred in our understanding of its causes, and its implications for health and beauty.

We have learned that obesity is a chronic disease. Although the NIH consensus conference of 1985 came to that conclusion (1985), the concept did not become widely accepted until the discovery of leptin was made in 1994. The discovery of leptin was a paradigm-shifting discovery, since it identified a hormone that when missing resulted in massive obesity in both man and animals. As is typical with diseases that result from the lack of a hormone, obesity was reversed by leptin replacement therapy (Ravussin et al. 2002).

Thus, obesity is the most recent of the chronic diseases to be recognized as such. This puts obesity therapy at a severe disadvantage compared to hypertension and diabetes for which several effective medication therapies have been developed over the many years they have been recognized as physiologic regulatory disorders. In fact, many of the drugs for diabetes and hypertension can be combined. It is now unusual when hypertension or diabetes cannot be controlled, but doing so often requires a combination of multiple medications.

Obesity is growing at epidemic proportions, and the prevalence of diabetes follows an increase in the prevalence of obesity by about 10 years. Thus, just as the prevalence of obesity began to rise around 1980 in the United States, the prevalence of diabetes began to rise around 1990. Diabetes is a very expensive disease associated with much suffering and disability. In fact, diabetes and obesity each cost the US health care system over $100 billion per year.

122.2 Fat Distribution

Obesity stands apart from the other chronic diseases in that it is easy to diagnose and is stigmatized in our society. Even children point out the “fat man” or “fat woman” to their parents from across the street. This is much different than the case with hypertension or diabetes in which a blood pressure cuff or a laboratory test is needed for diagnosis. Women in particular are stigmatized by being obese.

Although women seem to be more tolerant of heavy men, the intolerance of men toward obese women can be observed on bumper stickers that proclaim "no fat chicks". Thus, it should be no surprise that 80% of people participating in clinical trials of candidate obesity pharmaceuticals are women. This almost certainly has to do with the stigmatization of obesity, since the abdominal fat distribution pattern in men carries greater medical risk than the fat distribution in women which includes fat on the hips and thighs where it carries no medical risk in addition to the accumulation of abdominal fat.

In the context of obesity being a condition that is easily diagnosed visually, is stigmatized particularly in women and has no effective pharmaceutical treatment, the obese person is often blamed for the condition instead of the abnormal physiology that is truly responsible. The obese individual becomes the victim and is accused of gluttony and sloth. Although the medical profession focuses upon the medical implications of obesity, women who suffer from the disease often are concerned about the distribution of their fat as much as its amount.

Many women tell their physicians that they try to lose weight with diet and exercise. They say although they do have some success in losing weight, the fat on their hips and thighs, which are the areas that give them the most concern from a cosmetic perspective, do not seem to get smaller. In fact, women who have heavy hips and thighs usually have small breasts and it is the breast area that seems to account for a disproportionate amount of fat loss. When men and apple-shaped women try to lose weight, their focus is on their waistline and fat that goes away from other areas does not encourage them as much to continue their weight loss program.

Thus, although local fat reduction for cosmetic purposes may not have direct benefits on the medical aspects of obesity, being able to direct the area from which the fat is lost may fulfill the cosmetic goals of obese individuals. Achieving these cosmetic goals can have very positive benefits on the person's self image. Such improvements in self-image can sustain the weight loss efforts causing greater fat loss which results in greater medical benefits. This chapter will be discussing the anthropometry of directed fat reduction in areas with the most cosmetic concern to the individual so afflicted. Although primarily a cosmetic change in anthropometry, the benefits of local fat reduction on self-image should not be underestimated, since this improvement in self-efficacy can result in redoubled efforts at weight loss resulting in a greater reduction in obesity with the accompanying greater improvement in obesity associated medical liabilities.

122.3 Definition and Measurements

Obesity is defined as an excess of adipose tissue. Accurate quantification of body fat requires sophisticated techniques not usually available in clinical practice. Physical examination is usually sufficient to detect excess body fat.

For clinical purposes in people with normal sedentary jobs, a quantitative evaluation of body fat is performed by calculating the Body Mass Index (BMI). Except in people who have an unusual body composition like body builders who have disproportionately large muscles, BMI is closely correlated with more accurate measures of adipose tissue like body densitometry. The BMI is calculated by dividing the body weight in kilograms by the height in meters squared.

Factors other than total fat, however, are medically important. Upper body obesity (excess fat around the waist and flank) is a greater health hazard than lower body obesity (fat in the thighs and buttocks). Obese patients with increased abdominal circumference (>102 cm in men and 88 cm in women) or with high waist-hip ratios (>1 in men and >0.85 in women) have a greater risk of developing diabetes mellitus, stroke, coronary artery disease, and early death than equally obese patients with lower ratios. Further differentiation of the location of the excess fat suggests that visceral fat

within the abdominal cavity is more hazardous to health than subcutaneous fat around and outside of the abdominal cavity.

Current US survey data demonstrate that 65% of Americans are overweight and 30.4% are obese. Women in the US are more apt to be obese than men, and African-American and Mexican-American women are more obese than non-Hispanic whites. The poor are more obese than the rich regardless of race.

Obese individuals often suffer from negative self-image. Many, even those with normal body mass index, resort to pharmacotherapy (lipase inhibitors, appetite suppressants), mesotherapy, and surgery (liposuction, apronectomy or gastric bypass) in order to remove excess adipose tissue. These treatments are associated with significant morbidity, even mortality. Therefore, surgery should be considered seriously before planning the procedure. Aesthetic physicians and plastic surgeons must understand the patient's personal request and ethnic identity as well as any universal ideal of proportions and contour that create the impression of beautiful thighs, waist or buttock. As we learn more about the physiology of obesity we are learning the reasons why fat is distributed in specific patterns. With understanding comes the potential to modify the physiology to change the typical fat distributions. Thus, we will next discuss the lessons we have learned about the physiology of body fat distribution.

122.4 Physiology of Body Fat Distribution

Fat cells give up their fat through a process known as lipolysis. There are two major lipolytic pathways. The traditional pathway involves the adrenergic receptors. Beta adrenergic receptor stimulation in this pathway mediates lipolysis. Activation of the beta adrenergic receptor stimulates adenylate cyclase through a stimulatory g-protein to generate cyclic AMP which activates hormone sensitive lipase through protein kinase A. Hormone sensitive lipase along with perilipins, adipose tissue glyceride lipase and monoglyceride lipase release glycerol and fatty acid from the fat cell (Fig. 122.1).

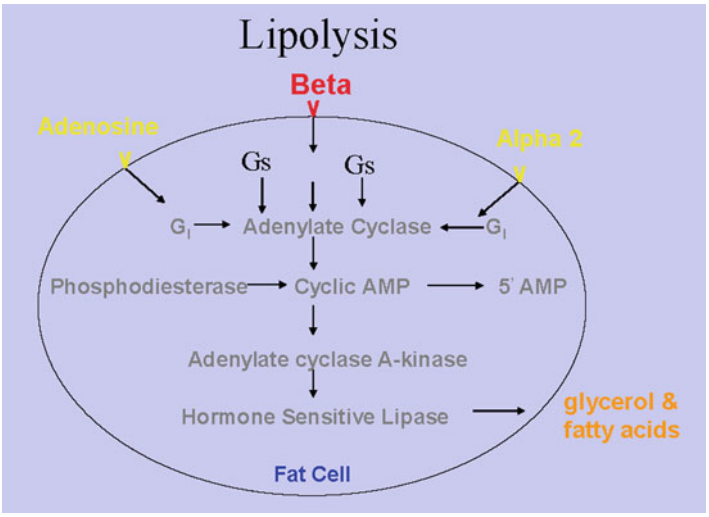

Fig. 122.1 Lipolysis. This illustration summarizes the lipolytic pathway characterized by beta-adrenergic stimulation of the fat cell. Stimulation through the beta receptor is inhibited by activation of the adenosine and alpha-2 receptors. Phosphodiesterase degrades cyclic AMP. Cyclic AMP acts to stimulate lipolysis through hormone sensitive lipase which releases glycerol and free fatty acids from the fat cell. (*AMP* adenosine monophosphate; *Gs* stimulatory G-protein; G_i inhibitory G-protein)

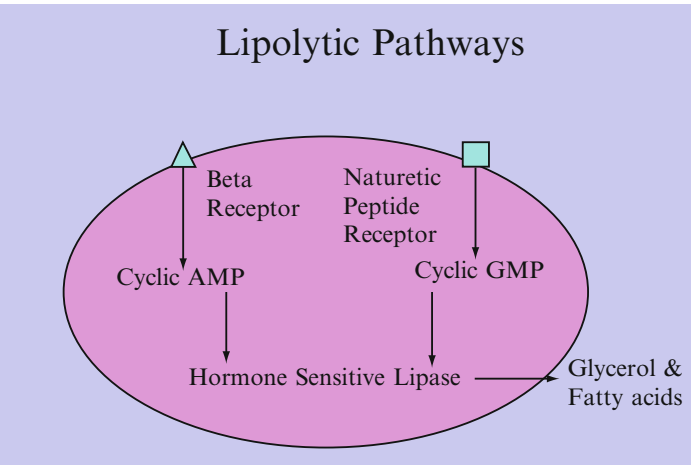

Fig. 122.2 Depiction of both major lipolytic pathway in the fat cell. Beta-adrenergic stimulation induces lipolysis through cyclic AMP while naturetic peptides stimulation does so through cyclic GMP. Both pathways simulate hormone sensitive lipase which results in the release of glycerol and fatty acid from the fat cell. (*AMP* adenosine monophosphate; *GMP* guanine monophosphate)

Cyclic AMP is broken down in the fat cell by phosphodiesterase 3B. Thus, lipolysis can be enhanced by phosphodiesterase inhibitors like xanthenes which also inhibit the adenosine receptor, an inhibitory receptor on the fat cell. The beta adrenergic receptor on the fat cell is inhibited through the stimulation of inhibitory g-proteins like adenosine, alpha-2 adrenergic receptors and other receptors. Thus, lipolysis can also be enhanced by inhibiting these inhibitory receptors. The alpha-2 adrenergic receptors become particularly important in body fat distribution, since they are induced by estrogen and are in higher concentrations in the hips and thighs of women accounting for their characteristic gynoid fat distribution.

The second lipolytic pathway that is quantitatively as important as the beta-adrenergic pathway is activated by naturetic peptides. Atrial naturetic peptide, the most efficient stimulator and this pathway, seems to be important in releasing fatty acids and glycerol during exercise. The naturetic peptide pathway uses cyclic GMP as a mediator, and although this pathway uses phosphodiesterase 5A to breakdown cyclic GMP, inhibiting this phosphodiesterase with sildenafil does not significantly enhance lipolysis in this pathway. Stimulation of this pathway by atrial naturetic peptide causes an intracellular increase of cyclic GMP which activates hormone sensitive lipase to cause lipolysis (Fig. 122.2).

Due to the fact that the naturetic peptides are large molecules that present challenges to transdermal transport and phosphodiesterase inhibitors are unable to achieve significant lipolytic stimulation of this pathway, the naturetic peptide pathway has not been utilized for local fat reduction or body re-contouring. We will, therefore, concentrate our discussion in the remaining part of this chapter on the beta-adrenergic pathway.

122.5 Ablative Topical Fat Reduction

Liposuction has been the gold standard ablative treatment of local fat reduction. Beside its quick and effective result, it carries high risk for general surgical complications (invasive procedures can lead to scarring, etc.) (Table 122.1).

Liposuction can aggravate unfavorable metabolic changes associated with obesity. It has been shown that the recovery of weight lost through these interventions is associated with body fat redistribution toward the visceral cavity, increasing metabolic risk factors for coronary artery disease such

Table 122.1 Local fat reduction

Modality	Risk	Efficacy
Plastic surgery	High	High
Liposuction	High	High
Mesotherapy	Medium	Medium[a]
Phosphatidylcholine-deoxycholate	Medium	Medium[b]
Low energy laser	Low	Medium
Creams	Low	Medium-high

[a]Studies scarce
[b]Inflammation and necrosis
Different modalities used to achieve local fat loss comparing their risks and efficacy

as insulin resistance and increased serum triglyceride level. Adding orlistat to patient's management immediately after surgery for 6 months (Montoya et al. 2009) showed no statistically significant decrease in visceral fat despite weight loss. On the contrary, abdominal liposuction in healthy normal weight or slightly overweight subjects improves the major lipoprotein components of obesity-associated dyslipidemia (Ybarra et al. 2008). This improvement occurs independently of insulin sensitivity.

Fat embolism after liposuction, despite its low incidence, is a life-threatening disorder. Although fat embolism is a multisystem illness, it affects mostly the cerebro- and cardiovascular system, the pulmonary structure and the skin. Many laboratory findings and clinical signs are characteristic but nonspecific, making the diagnosis difficult. There is no specific therapy for the fat embolism syndrome after liposuction so prevention, early detection and supportive therapy are important (Wang et al. 2008).

Combining liposuction with other procedures can increase aesthetic satisfaction and safety in local fat reduction. Circumferential dermo-lipectomy has been an effective means of reducing excess skin fat after massive weight loss; however, regions of residual mid-abdominal and epigastric fat frequently confer a suboptimal contour. Liposuction in association with lower body lift surgery has been regarded with caution, for fear of ischemia or necrosis of the undermined flaps as potential consequences. It has been shown that unlike standard dermolipectomy, the maintenance of a broad subcostal blood supply with selective direct undermining allows for liberal flap contouring with suction and the establishment of lower suture-line position (Kolker and Lampert 2009). With this technique liposuction can be safely used during lower body lift to maximize aesthetic outcomes.

Low-level laser-assisted liposuction (4-L), known as the Neira 4L technique, is an excellent adjuvant tool for the surgeon practicing liposculpture. A low-level laser is used to create a transitory pore in the cell membrane of the adipocyte to move fat from inside the cell to the intersticial space outside without killing the cell. 4-L has been performed successfully in in-vitro human adipose tissue cultures. It protects the patient from the surgical trauma of liposuction by protecting and preparing tissues for the surgery, modulating the inflammatory response to prevent short- and long-term side effects of surgery, improving the quality and quantity of the healing process by accelerating recovery time, diminishing secondary cicatrization, and preventing postoperative neuralgias.

Low level laser treatment without liposuction can be used alone to achieve a cosmetic body recontouring. The low level laser uses light at a wave length of 635–680 nm and uses energy levels that do not heat the tissue. Forty normal weight men and women were randomized to treatment for ten minutes with low energy laser light around the entire waist circumference twice a week for 4 weeks or a placebo condition in which the laser was inactivated. Each individual treatment reduced the waist

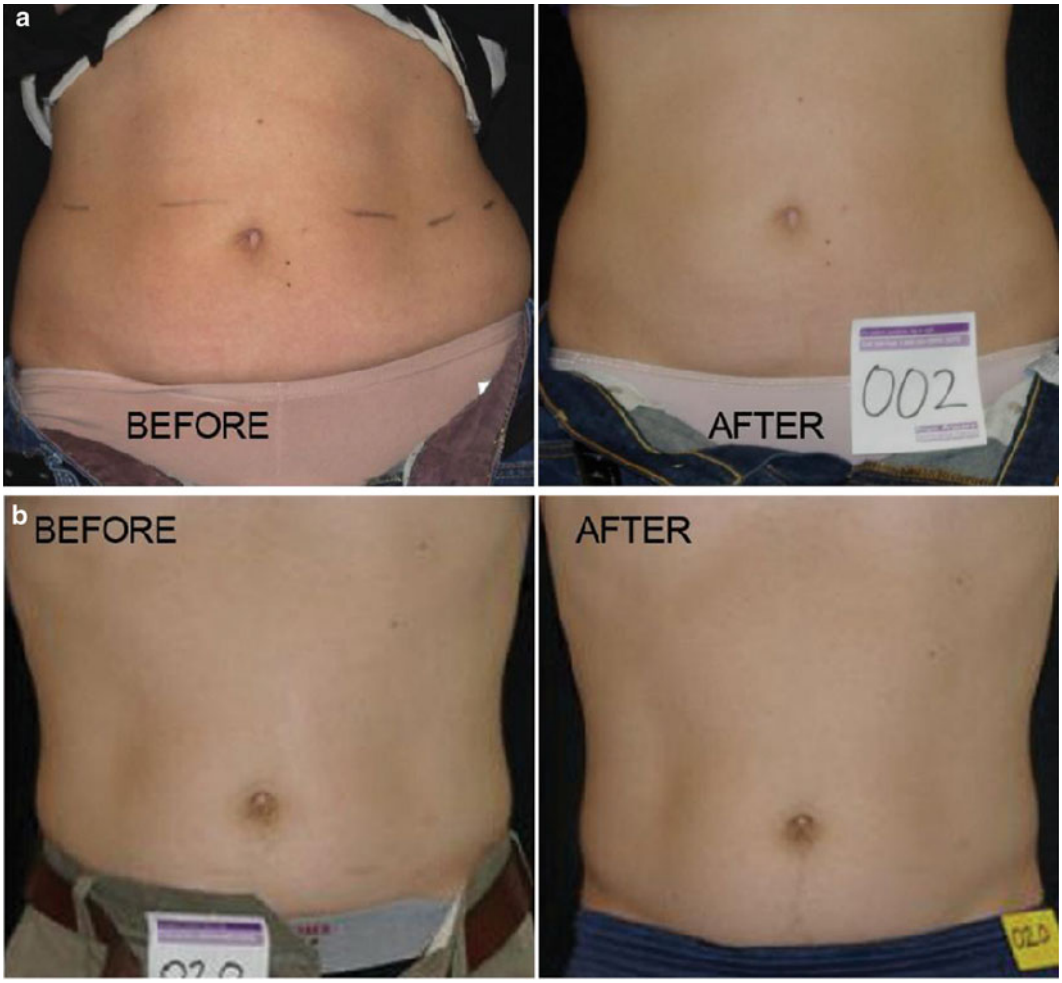

Fig. 122.3 (**a**) Lipolaser treatment to the waist of a female. Two 10-min treatments around the waist using a low energy laser each week for 4 weeks gave a cosmetically significant reduction in waist circumference in excess of 2 cm. (**b**) Lipolaser treatment to the waist of a male. Two 10-min treatments around the waist using a low energy laser each week for 4 weeks gave a cosmetically significant reduction in waist circumference in excess of 2 cm

circumference between 0.4 and 0.5 cm. The treatments were cumulative and those subjects who remained within 1.5 kg of their baseline weight lost an average of 2.2 cm from their waist which was statistically significant. The grading of standardized pictures by blinded observers detected a statistically and cosmetically significant improvement in appearance and body contour (Fig. 122.3a, b).

In-vitro studies to explore the mechanism by which the laser caused local fat reduction demonstrated that in the presence of serum, the laser released fat from the fat cells. It was demonstrated that serum was needed to achieve triglyceride release, that cell lysis was not involved, that the cells were not killed by the treatment, but their metabolism was impaired consistent with the demonstration of pores in the study by Neira et al. (Neira et al. 2002; Caruso-Davis et al. 2008). Thus, it would appear that the fat released from the fat cells returns to the venous circulation via the lymphatics in a similar manner to fat ingested during a meal.

122.6 Transitional Methods

The observation that denervation of adipose tissue results in lipoatrophy led researchers to postulate that chemodenervation using botulinum toxin may achieve the same result, i.e. fat loss (Lim and Seet 2006). Multiple methods were explored leading to potential selective fat loss. It was conceded that removal of subcutaneous fat does not, however, reduce the risk associated with metabolic syndrome, as visceral (intra-abdominal) fat is not reduced by the removal of subcutaneous fat.

The reduction of total adipose depots is considered to be the optimal management to reduce complications with obesity. These anti-obesity strategies are an attempt to achieve an overall weight loss and are unable to target specific adipose depots associated with morbidity. Utilizing localized and sustained delivery of drugs to provide for the selective ablation of adipose tissue offers promising results. This approach demonstrated control over the localization of tumor necrosis factor-alfa by performing blood analysis. It indicates the potential utility of the general tissue ablation approach for treatment of several pathologies (Richardson et al. 2003).

122.7 Mesotherapy

Mesotherapy was originally initiated in Europe using cutaneous injections of different compounds to treat local medical or cosmetic conditions. Although it was originally designed for pain relief, its aesthetic benefit, particularly its fat and cellulite removal potential, captured increasing attention in the US. Presumably due to its initial use for pain relief, mesotherapy solutions have traditionally included local anesthetics. Local anesthetics have been shown to decrease lipolysis by uncoupling cyclic AMP from hormone sensitive lipase. The lipolytic ingredients used by mesotherapists including isoproterenol, yohimbine, melilotus and aminophylline have been demonstrated to stimulate lipolysis, give greater lipolysis when combined as is done in the practice of mesotherapy, and are presumably effective in causing local fat reduction (Caruso et al. 2008). They should not be used with local anesthetics, however, and clinical trials to demonstrate effectiveness clinically are limited to a small study with injected isoproterenol (Greenway and Bray 1987).

Another treatment for local fat reduction is injectable phosphatidylcholine. Phosphatidylcholine alone has been demonstrated to stimulate lipolysis in vitro (Caruso-Davis et al. 2008) (Fig. 122.4). Phosphatidylcholine is usually combined with the emulsifier, deoxycholate when used clinically and this combination achieves cell lysis rather than lipolysis and has been used to remove small amounts of adipose tissue (Rotunda and Kolodney 2006) (Fig. 122.5). In animal studies (biologic model with rabbits) the phosphadidylcholine-deoxycholate injected group showed marked increase in the tissue necrosis, inflammatory exudation and fibrosis compared to a control group (Rittes et al. 2006).

Studies with human adipose tissue concluded that sodium deoxycholate induces an inflammatory reaction in subcutaneous human fat and dose dependent adipocyte lysis with acute pain and fibrosis. No systemic effect was detected. Further studies are needed to establish the appropriate dose-result ratio, frequency of administration and long-term safety (Yagima Odo et al. 2007).

The medicine Lipostabil-N has been used in Europe since 2002 to achieve reduction in the volume of small fat deposits by subcutaneous fat injections. Although Lipostabil-N was originally thought to stimulate lipolysis, due to the fact that it is combined with deoxycholate, it causes fat necrosis and an inflammatory response. The medicine has been authorized for IV use in the prophylaxis and therapy of fat embolism and liver diseases (Hasengschwandtner 2005).

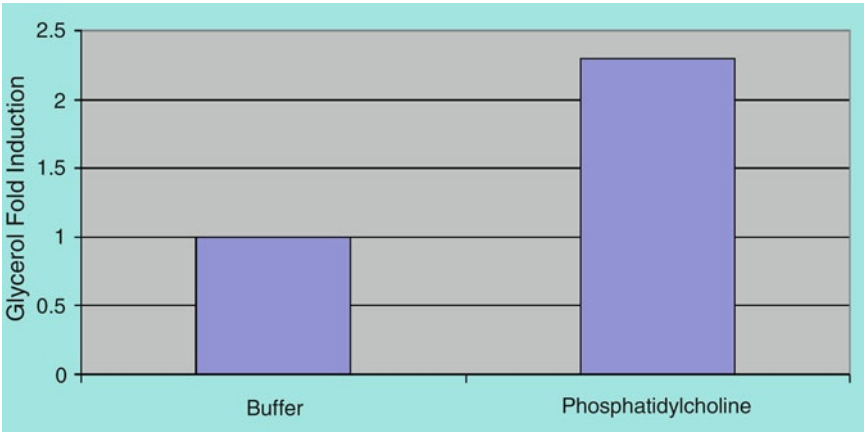

Fig. 122.4 Phophatidylcholine stimulation of lipolysis. Phosphatidylcholine alone stimulates lipolysis in human adipocytes in vitro

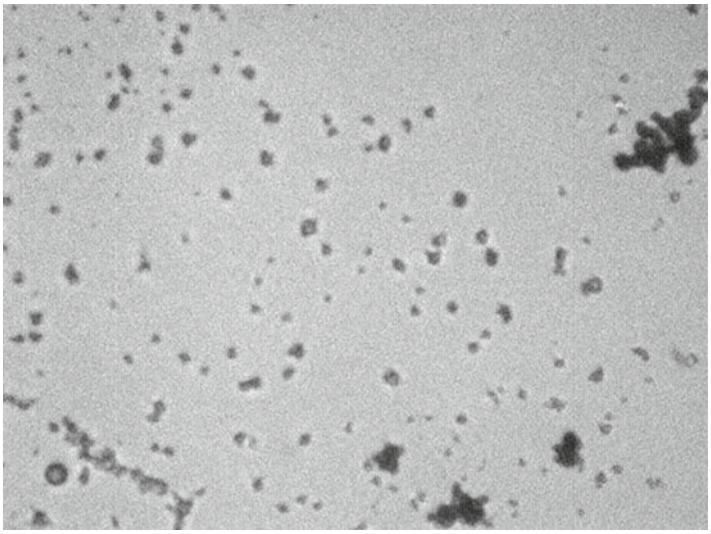

Fig. 122.5 Deooxycholate cell destruction. Deoxycholate, a detergent that is often used to solubilize phosphatidylcholine, causes cell lysis of human fat cells in vitro

Additional studies were conducted on lipomas (benign neoplasms of mature fat cells). Injections of phosphatidylcholine solubilized with deoxycholate have been used to reduce unwanted accumulation of fat. It was concluded that deoxycholate, rather than phosphatidylcholine, was the active ingredient. It was suggested that the low concentration deoxycholate may be a relatively safe and effective injectable treatment for small collections of fat (Rotunda et al. 2005).

A double-blind study was designed (Sasaki et al. 2007) to evaluate the efficacy and safety of a phosphatidylcholine based, cosmeceutical anti-cellulite gel combined with a light-emitting diode (LED) array at the wavelength of red (660 nm) and near infrared (950 nm), designed to treat thigh cellulites. The results of this study affirmed that treatment after 3 months achieved great improvement in cellulite appearance. However, 15 months after their course, a fraction of patients reverted back to their original condition, indicating the need for maintenance therapy.

122.8 Topical Preparations

122.8.1 Reducing Thigh Fat Preferentially: Proof of Concept

Thigh and buttock fat of women is more difficult to mobilize due to increased alpha-2 adrenergic receptor activity induced by estrogen. This fat is thought to be stored in that location to act as a storage site for calories to nourish a baby, since the receptor density changes during pregnancy and lactation to mobilize that fat. The high lipolytic threshold of women's thighs can be reduced to a level below that of fat tissue in other locations by a number of different mechanisms. Lipolysis can be stimulated locally by directly stimulating the beta adrenergic receptor using injectable isoproterenol. This approach was chosen for the proof of concept trial, since the concentration of isoproterenol needed to maximally stimulate lipolysis was known from in-vitro work. In-vitro studies documented that 10^{-5} Molar isoproterenol was well up on the plateau of the dose response curve. Small 0.2 cc injections using an insulin syringe at 4 cm intervals around the thigh circumference 3 times a week for 4 weeks gave a 1.4 cm greater loss of girth in the isoproterenol treated thigh than in the saline treated thigh, and this difference was statistically significant ($p < 0.05$) (Greenway et al. 1995).

122.8.2 Ointment Studies

Since the injection strategy involved the need to inject the back of the thigh which is hard to reach and since injections can be uncomfortable, this approach to local fat reduction was deemed impractical. Other strategies to lower the lipolytic threshold of the thigh include forskolin which directly activates the catalytic subunit of adenylate cyclase and achieves a similar result to stimulating the beta-adrenergic receptor directly with isoproterenol. A second strategy is use of yohimbine to inhibit the alpha-2 adrenergic receptor which inhibits the beta-adrenergic receptor through an inhibitory g-protein. A third strategy is to inhibit phosphodiesterase in the fat cell using a xanthene which will increase cyclic AMP in the cell by inhibiting its breakdown. The first trial combined all three mechanisms by including forskolin, yohimbine and aminophylline in a universal carrier, aquaphor, which has properties similar to vaseline. Applications of this ointment twice a day, 5 days per week for 4 weeks gave a 2 cm greater loss in girth in the thigh treated with the combination ointment compared to the control thigh treated with the ointment base which was statistically significant ($p < 0.05$) (Greenway and Bray 1987).

Since combination medications are more difficult to develop than ones that contain a single ingredient, it was decided to test the individual components of the three-component ointment. The first ointment tested contained yohimbine. The difference in thigh girth between the treated and untreated thighs was not statistically different. This occurred for two reasons. First, one of the subjects dropped out of the trial which left only 4 subjects. Secondly, we learned during this study that to get an accurate and reproducible thigh measurement, the thigh should be measured with the subject's weight on the leg being measured. This was not done in one of the subjects in the yohimbine trial and the lack of uniform muscle tension caused it to appear as if the control thigh lost more girth. Thus, the yohimbine trial was not a valid test, but it did inform future trials that thigh measurements should be done with weight supported on the leg being measured.

The forskolin ointment and the aminophylline ointment both gave more girth loss on the treated thigh compared to the thigh treated with the ointment base ($p < 0.05$) (Table 122.2). Since aminophylline was used at a much higher dose intravenously to treat asthma than the doses used for local

Table 122.2 Thigh girth reductions in excess of placebo using non-invasive local fat reduction (mean ± SEM)

Treatment	Treatment time	Girth loss (cm)	No. subjects
Ointment A+F+Y	4 weeks	2.03 ± 1.36	5
Ointment A	4 weeks	1.5 ± 0.77	5
Ointment F	4 weeks	1.0 ± 0.61	4
Ointment Y	4 weeks	0.75 ± 0.35	4
Ointment A 10%	5 weeks	0.77 ± 0.66	24
Cream A 2%	5 weeks	1.21 ± 0.31	12
Cream A 0.5%	5 weeks	3.08 ± 0.27	12

Girth loss from the thigh greater than placebo for several studies using topical ointment and cream (mean ± SEM)
A Aminophylline; *F* Forskolin; *Y* Yohimbine

fat reduction, and since much more is known about the safety of aminophylline compared to forskolin, a decision was made to limit further trials of topical fat reduction to aminophylline. Aminophylline was the chosen xanthene since it dissolved well in the ointment which was not the case for theophylline or caffeine which are much less soluble. Although the women participating in the trials felt that the ointment was an improvement over the injections, they preferred a cream rather than an ointment which had a tendency to make their clothes greasy.

122.8.3 Cream Studies

Attempts to change from an ointment to a cream used a readily-available cream base. Unfortunately, the aminophylline, which is two theophyllines joined by ethylenediamine, reacted with the cream base, caused the base to turn from white to yellow, did not work to cause fat loss and caused rashes. We discovered that ethylenediamine is a reactive molecule and a skin sensitizer. After going to a dermatologic specialty house to obtain a cream base that would stabilize the aminophylline, we had no further problems with rash or inactive cream.

The first trials we performed to evaluate creams and ointments for local fat reduction put all the subjects on a weight reduction diet to stimulate lipolysis. We performed a trial of a 0.5% aminophylline cream in a stabilizing cream base in which the subjects had the active cream applied to one thigh and the cream base applied to the other 5 days a week for 5 weeks. These subjects were not obese and they were not placed on a diet. At the end of 5 weeks the subjects lost 3 cm more girth on the thigh treated with the active cream compared to the thigh treated with the cream base. This difference was statistically significant ($p < 0.001$) and at 4 weeks the subjects lost approximately 1 in. more girth from the thigh treated with the active cream than from that treated with the cream base. In fact, the thigh treated with the cream base did not change during the trial (Fig. 122.6) (Table 122.2).

The trials done to evaluate the topical ointments and creams for their potential to cause local fat reduction had chemistry panels, complete blood counts and theophylline levels drawn. The laboratory studies did not detect any systemic toxicity and there was no detectable theophylline in the blood stream giving reassurance that the effect was occurring locally in the fat and not systemically. These studies confirmed that topical fat reduction can be achieved safely without diet or exercise in women's thighs (Greenway et al. 1995).

Local fat reduction in other body areas or in men by lowering the local lipolytic threshold was demonstrated in a study using aminophylline cream applied to the waist during a diet and exercise

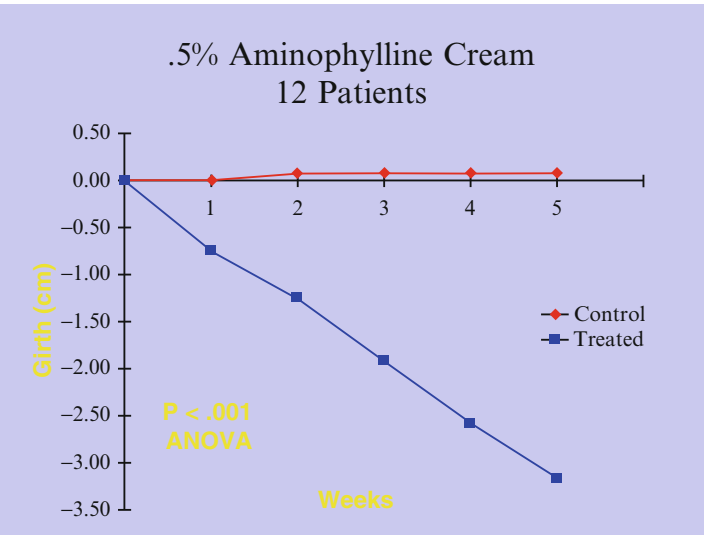

Fig. 122.6 Girth loss of thighs treated with 0.5% aminophylline cream or placebo cream. Women with a stable weight lost 3 cm more girth on the thigh treated with 0.5% aminophylline cream 5 days per week compared to the placebo treated thigh

Table 122.3 Waist girth when treated with 0.5% aminophylline cream compared to a control cream during a weight loss program with equal weight loss in both groups ($N = 50$, mean ± SEM)

Gender	Aminophylline (cm)	Control (cm)
Men	–9.4 ± 0.7	–4.7 ± 0.8
Women	–11.6 ± 0.6	–5.6 ± 0.6
Both	–11 ± 1.0	–5.0 ± 0.6

Girth loss from the waist using 0.5% aminophylline cream or a control cream during a weight loss program in which equal weight was lost in each group ($n = 50$, mean ± SEM)

program. Fifty overweight men and women with an apple shape and a waist to hip ratio of greater than 1 were randomized to treatment around the waist twice a day with 0.5% aminophylline cream or to no cream treatment. All subjects were treated with a 1,200 kcal/day balanced diet, encouraged to walk regularly and seen every 2 weeks in the clinic. At baseline the two groups had BMIs of 28.2 and 28.5 kg/m^2. At the end of the 12-week study the weights were 26.1 and 26.2 kg/m^2, respectively. Thus, there was no difference in weight loss between the two groups. Those treated with the aminophylline cream lost 11 cm from their waist while the group not treated with the cream lost only 5 cm. Thus, during weight loss one can direct the site from which the fat will be preferentially lost, since the weight losses of the two groups were not different while the difference in waist girth lost was more than double in the cream treated group, a change that was highly statistically and cosmetically significant ($p < 0.001$) (Caruso et al. 2007) (Table 122.3).

122.8.4 Botanical Extracts

The reduction of fat depots through the continued use of anti-cellulite botanical products depends on the availability of the active ingredients at the action site, the concentration of the ingredients in the formula and the physiochemical features particular to each ingredient. The botanicals used in topical products must have standardized extracts which insure that each phytomedicine will have the same

effect from batch to batch. Although the regulations are lax in the United States, many other countries have rules in place to ensure that all botanical products are standardized so their effect can be depended upon internationally. Currently, no evidence exists to verify the efficacy or define the ideal concentrations of botanical extracts for the treatment of local fat reduction. Therefore, additional scientific research is necessary before botanical cellulite treatments can be recommended (Hexsel et al. 2005).

122.8.5 Glycyrrhetinic Acid

Clinical observations in patients with Cushing's syndrome have highlighted the link between cortisol and central obesity. The circulating cortisol level is normal or reduced in obesity, but local regeneration of cortisol from inactive cortisone by 11-beta hydroxysteroid dehydrogenase type 1 has been studied as a pathogenic mechanism for visceral fat accumulation and its known association with insulin resistance and the medical problems associated with obesity. Human adipose tissue studies have confirmed that decreased 11-beta hydroxy steroid dehydrogenase type 1 activity can increase insulin sensitivity by reducing tissue-specific cortisol concentrations. Inhibition of 11-beta hydroxy steroid dehydrogenase type 1 may prove to be an important treatment for the metabolic syndrome associated with insulin resistance (Tomlinson et al. 2004).

Glycyrrhetinic acid, the active principle of licorice root, blocks 11-beta hydroxysteroid dehydrogenase type 1, thus reducing the availability of cortisol at the level of the adipocyte. Applying glycylrrhetinic acid cream on a female thigh showed significant reduction in the superficial fat layer. This local reduction in fat was most likely related to a block of 11-beta hydroxysteroid dehydrogenase type 1 at the level of fat cells. Glycyrrhetinic acid could be effectively used in reduction of unwanted local fat accumulation (Armanini et al. 2005).

122.9 Summary and Conclusions

Local fat reduction has been attempted by a number of mechanisms. These have ranged from invasive therapies like liposuction and plastic surgery to less invasive therapies like laser and injection approaches to non-invasive approaches with creams and ointments (Table 122.1). One might be tempted to dismiss such local fat reduction as a cosmetic approach inappropriate for consideration by the medical profession. We contend that this is a short-sighted view. The world is experiencing an obesity epidemic and an epidemic of type 2 diabetes that follows in its wake. Not only does this epidemic of obesity and diabetes carry with it much suffering, it is threatening economic health care systems around the world. Since obesity medications are modest in efficacy and surgery is appropriate for only the most obese, we must concentrate on strategies that will enhance the efficacy of diet and lifestyle change.

Obesity is stigmatized and almost all those that are overweight want to be lean. Most people, however, focus on one aspect of their body fat that disturbs them the most. Often it is the area most difficult to mobilize, like the thigh fat in women. When weight loss results in no change in the "problem thigh area" but causes fat loss in areas like the breast that these same women feel are too small, they become discouraged and give up trying to lose weight. If one could direct the body areas from which the fat would be lost, this might give people much more reinforcement for their efforts and

cause them to continue their weight loss programs over a longer period of time. The more fat that is lost, the greater will be the medical benefits. Thus, using a cream to cause weight loss from around the waist for those who want smaller waists could result in people feeling better about themselves with greater motivation to continue the weight loss program. Anything that will encourage additional fat loss will contribute to the public health of the nation involved.

Thus, anthropometry of local fat reduction is primarily a cosmetic area of research. One must not discount that addressing cosmetic concerns improves one's self image. The ability to direct the areas that fat is lost during a weight loss program could be a powerful motivator to continued fat loss and medical benefits. The most non-invasive of these cosmetic approaches like cream or a low level laser seem to have the best risk to benefit ratio. We hope that this chapter will encourage the medical profession to consider topical fat reduction in a new light and give consideration of its use to motivate weight loss that will lead to greater medical benefits.

122.10 Applications to Other Areas of Research

Topical fat reduction not only motivates obese patients to lose more weight by helping them to lose weight in the body areas that are most troubling to them, but is can be used as a purely cosmetic therapy as well. Many people who may not be obese feel that their thighs or waist are disproportionately large. Although this does not represent a medical problem, reducing fat in these "problem" areas can enhance the person's self-esteem and self-confidence. In fact, plastic surgeons use invasive procedures like liposuction to produce local fat reduction. Non-invasive procedures like low energy laser and topical creams offer reversible alternative treatments for local fat reduction with much lower risks than those carried by invasive techniques.

122.11 Practical Methods

122.11.1 Measuring Thigh Circumference

The thigh is measured two-thirds of the way from the top of the fibular head to the greater trocanter using a tape measure with a tensioning device attached that insures a constant tension on the tape. Once the measurement point on the thigh is located, a measurement from the floor is taken and recorded. Future measures are then taken in a horizontal plane parallel to the floor at the measured distance from the floor on the thigh. Body weight should be supported on the leg being measured, since this insures a reproducible amount of muscle tension and reduces variability of the measure.

122.11.2 Measuring the Waist

The waist is measured according to the recommendation of the United States National Institutes of Health. The waist is measured at the level of the iliac crest in a horizontal plane parallel to the floor using a tape measure with a tensioning device attached that will maintain a constant tension on the tape. The measurement is taken at the end of a normal expiration.

Summary Points

- Obesity is growing at epidemic proportions causing diabetes to increase in prevalence
- Obesity and diabetes are expensive diseases that are straining public health systems
- The mainstay of obesity treatment is diet and lifestyle change, but it is not working well, as evidenced by the growing obesity problem
- Obesity is stigmatized and easily diagnosed visually
- Many obese people want to lose fat in local areas like the waist or thighs
- A method that allows patients to direct the areas of their bodies from which the fat is lost encourages their attempt at weight loss
- By prolonging weight loss programs, more weight is lost and health benefits are commensurately increased
- Local fat reduction can be accomplished invasively by plastic surgery or liposuction
- Mesotherapy represents a minimally invasive method of local fat reduction
- The low energy laser and topical creams are non-invasive methods of local fat reduction
- Non-invasive methods seem to have the greatest cost to benefit ratio
- Local fat reduction gives more than cosmetic benefits
- Local fat reduction increases enthusiasm for the weight loss program and has the potential to prolong weight loss
- Longer weight loss programs result in greater weight loss and greater health benefits
- Local fat reduction is an opportunity to facilitate weight loss and achieve greater medical benefits

Key Facts About Liposuction

Liposuction is a technique in which a cannula is inserted under the skin of the body area from which one desires fat removal. Suction is applied to the cannula through which the fat is removed. This removal of fat changes the contour of the body area and is usually done for a more pleasing cosmetic appearance. There are several techniques through which liposuction can be employed. Dry liposuction is rarely used anymore, but was the original technique that was performed under general anesthesia. Wet liposuction uses a small amount of fluid containing a local anesthetic and a vasoconstrictor to minimize blood loss and can be performed in the office under sedation. Tumescent or super wet liposuction infuses or injects a solution into the fat tissue containing a local anesthetic and a vasoconstrictor. It is used for large volume liposuction under sedation, and is often done in an office setting. The fluid loosens the fat cells and reduces bruising. Laser or ultrasound assisted liposuction uses light or sound energy to lyse the fat cells and make them easier to suck out of the subcutaneous tissue.

Key Facts About Mesotherapy

Mesotherapy is a procedure in which materials are injected under the skin into fat tissue. The practice was initiated in France by Michael Pistor (1924–2003) and became recognized by the French Academy of Medicine as a specialty of medicine in 1987. Mesotherapy came more recently to the United States where it is used primarily as a cosmetic procedure to reduce fat locally. The procedure has been controversial in the United States due to the paucity of well controlled clinical

trials. Part of the controversy, however, may emanate from the plastic surgical community which views this procedure as a competitive business threat. There appear to be two general types of compounds that are injected by those practicing mesotherapy. One class of compounds stimulates lipolysis. Isoproterenol is one such compound, but mesotherapists use other less well-studied compounds as well. The second class of compounds lyse fat cells. Deoxycholine, a detergent, is one such compound.

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Chapter 123
Waist-to-Height Ratio and Obesity in Chinese

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Obesity is defined as a disease by the World Health Organization (WHO) and it increases the risk of chronic diseases such as cardiovascular disease, hypertension, type 2 diabetes, metabolic syndrome, dyslipidemia, chronic kidney disease, and some cancers. China, with a total population that accounts for one-fifth of the global population, is the world's most populous country and the largest developing country. China was once considered to have one of the leanest populations however, it has had an increasing prevalence of obesity over the past two decades because of an increase in family income, availability of food, and changes of lifestyle. In this chapter, we summarised recent researches regarding waist-height ratio and obesity focused on the optimal cut-off for obesity, ethnic differences, gender differences and the correlation to chronic disease.

123.1 Prevalence of Obesity Among Chinese

The prevalence of obesity has increased substantially over the last decades and the trend will continue not only in developed countries, but also in developing countries (Bray 1996; Feinleib 1985). About one-fifth of one billion overweight or obese people are Chinese (Keil and Kuulasmaa 1989) and the incidence of obesity in China has caught up with that of Western countries in the past decade (Wu 2006). It is believed that by 2020 there will be more obese people in China than in the United States, given the increase rates of obesity in past 15 years. The prevalence of obesity among Chinese (Wu 2006; Popkin et al. 1995; Chu 2005; Jia et al. 2002; Gu et al. 2005; Hwang et al. 2006; Ding 2008; Lin 2011) by time is summarized in Fig. 123.1. The prevalence of obesity (defined as BMI >=25) among men increased from 6.4% in 1989 to 26.9% in 2000 and 35% in 2005 and the prevalence of obesity among women increased from 4.3% in 1989 to 36.2% in 2000, kept at 21.4% in 2001, and 26.8% in 2005. The prevalence of obesity in men continuously increased in the past decade, but reached a peak at 2000 and kept stable around 20%. This was also observed to be higher in urban than rural areas (Lin et al. 2003; Ma et al. 2005; Huang 2008; Pan et al. 2008). Based on the survey of nutrition status among Chinese in a study before 2000, a BMI >= 27 or 28 was used to define obesity in later

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_123,

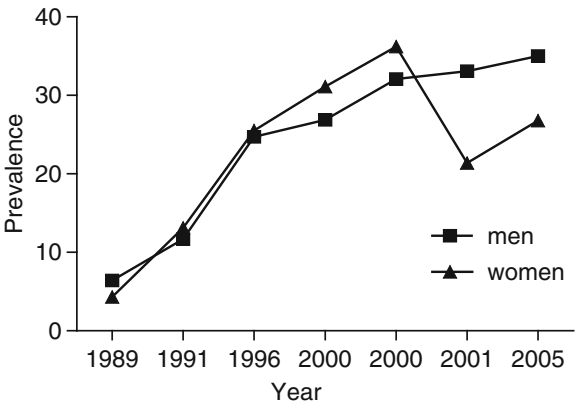

Fig. 123.1 Prevalence of obesity among Chinese from 1989 to 2005

studies (Ding 2008). It should be noted that in the following studies, the incidence of over-weight (BMI 24–28) and obesity (BMI >=28) that were previous partially classified as obesity increased to 29.9% in individuals older than 18 (Wu 2006). Meanwhile, the change of BMI cutoff also suggested that the average size of the Chinese population has increased in the last few decades.

123.2 Waist-Height Ratio and Obesity

Obesity indicates an excess of body fat. Central distribution of fat, i.e., excessive deposition of intra-abdominal fat, is an important cardiovascular disease risk factor (Bjorntop 1991; Larsson et al. 1984; Kissebah et al. 1982). The distribution of body fat can be measured using dual-energy X-ray absorptiometry (Mazess 1990), neutron activation analysis, electrical conductance, computerized tomography, ultrasound, infrared interactance, and magnetic resonance imaging (Lukaski 1987). Although there are several instruments to measure total body fat and its distribution (Mazess 1990; Lukaski 1987; Friedl et al. 1992), anthropometric measurements are the major measurements used in clinical practice. Body Mass Index (BMI) is one of the most widely used indexes of obesity and is used by WHO for the definition of obesity. The boundary value of BMI in the definition of obesity is different among different ethnic groups such as Asians and Caucasians (Misra 2003; Stevens 2003). The cutoff for Asians, suggested by WHO experts, is BMI = 23 (Choo 2002), but a Chinese working group suggested BMI = 24 (Zhou 2002). As obesity is important for its correlation with disease status including metabolic syndrome, cardiovascular disease, hypertension, diabetes, and total mortality (Gu et al. 2005; Fu et al. 2008; Despres 2001), other indices of obesity such as waist circumference (WC), waist to hip ratio (WHR), and waist to height ratio or waist to stature ratio (WheiR) had been proposed as assessments of obesity.

WheiR is a potential index of central obesity (Chien et al. 2004) and was suggested to be the best index of obesity in its association with chronic diseases such as metabolic syndrome risk factors (Hsieh et al. 2003). The advantages of WheiR are that it is cheaper and easier to measure and calculate and has the same boundary values for men and women (Hsieh et al. 2003; Ho et al. 2003), for different ethnic groups (Ashwell et al. 1996; Hsieh and Yoshinaga 1995), and for children and adults (Savva et al. 2000; Aswell and Hsieh 2005). The measurement of WheiR simply requires the knowledge of height (self-assessment is more stable and reliable than that of weight in the absence

of standard measuring equipment) and of waist circumference, requiring a tape measure rather than weighing scales (Aswell and Hsieh 2005).

123.3 Indices of Obesity and Disease

WheiR is more directly associated with central obesity compared with BMI and WC. Visceral distribution of body fat is an important risk factor for hypertension, diabetes, cardiovascular disease, chronic kidney disease, and cancers. The association between WheiR and disease may be explained by the association between central obesity and disease. We have summarized studies of the indices of obesity and disease among the general Chinese population (Table 123.1).

Ko et al. suggested that higher levels of BMI, WHR, WC, and WheiR are associated with risk of having diabetes mellitus or hypertension in Chinese as in Caucasians (Ko et al. 1999). However, the cutoff values of the anthropometric indices that define obesity are different from those for Caucasians. Zhang et al. studied 67,334 women without prior history of coronary heart disease, stroke, and cancer. BMI, WC, WHR, WHeiR, waist-to-sitting height ratio (WsHtR), and conicity index were positively associated with the risk of coronary heart disease including non-fatal myocardial infarction and fatal coronary heart disease. WHR was positively associated with the risk of coronary heart disease in both younger and older women with a relative risk of 3.2 (1.1–9.1) for the young and 2.9 (1.0–8.4) for the elderly (Zhang et al. 2004). WheiR had the best association with cardiovascular disease risk factors including blood pressure, total cholesterol, high density lipoprotein, low density lipoprotein, triglyceride, fasting glucose, 2-h glucose, fibrinogen, apolipoprotein B, fasting insulin, coronary heart disease, angina, diabetes, dyslipidemia, and stroke (Ho et al. 2003). WheiR as an index of central obesity is also associated with increasing risk of chronic kidney disease. Every 0.1 increase in WheiR is associated with a 2.74 time increase of chronic kidney disease risk (95% confidence interval 1.18–6.72) (Lin et al. 2007). Zhou et al. studied 13,558 men and 15,521 women and found that indices of obesity including BMI, WC, WHR, WheiR, and conicity index were positively correlated with blood pressure and hypertension. After adjusting for age, WheiR in men and BMI in women had the greatest association with hypertension, irrespective of the statistical method used (Zhou et al. 2009).

Table 123.1 Indices of obesity and disease in Chinese population

Indices	Disease	Study population	Major findings	References
WHR, BMI, WC, WheiR	Coronary heart disease risk	Women	WHR for young and old women WheiR, BMI, WC for young women	Zhang et al. (2004)
WHR, BMI, WC, WheiR	Cardiovascular risk factors	Men and women	WheiR is the best indicator	Ho et al. (2003)
WHR, BMI, WC, WheiR	Chronic kidney disease	Men and women	WheiR is the best indicator especially in women	Lin et al. 2007
WHR, BMI, WC, WheiR	Hypertension, diabetes, dyslipidaemia or albuminuria	Men and women	All indices are significant	Ko et al. (1999); Lin (2011)
WheiR, BMI	Hypertension	Men and women	WheiR in men and BMI in women	Zhou et al. (2009)

BMI body mass index, *WC* waist circumference, *WHR* waist to hip ratio, *WheiR* waist to height ratio

Table 123.2 Cut-offs of waist to height ratio for obesity related disease

Disease	Cut-off	AUC	Specificity	Sensitivity	References
Chronic kidney disease	0.54	0.612	50.7	72.9	Lin et al. (2007)
Coronary heart disease	0.51	0.66	82.8	60.3	Ho et al. (2003)
Hypertension	0.51	0.82	71.7	64.5	Ho et al. (2003)
Diabetes	0.52	0.78	77.5	64.2	Ho et al. (2003)
Stroke	0.52	0.64	81.8	61.5	Ho et al. (2003)

AUC area under the Receiver Operating Characteristic curve

123.4 Cutoff of Waist to Height Ratio in Association with Disease

The optimal cut-off of WheiR was 0.5 among Caucasians in association with cardiovascular risk (Srinivasan et al. 2009), and Japanese (Hsieh et al. 2003) in association with metabolic syndrome risk factors. The same cut-off can be applied to Chinese in association with disease and is similar to that of Caucasians. The optimal cut-offs for obesity related disease in Chinese population are listed in Table 123.2. The optimal boundary values in different diseases were very close to 0.5, such as 0.54 for chronic kidney disease, 0.51 for coronary heart disease, 0.51 for hypertension, 0.52 for diabetes, and 0.52 for stroke (Ho et al. 2003; Lin et al. 2007). The area under the receiver operating characteristic curve (AUC) indicated the ability of WheiR to discriminate between alternative states of disease over health condition (Zweig and Campbell 1993). Higher AUC values (between 0.5 and 1) indicated better accuracy of WheiR in predicting disease. It should be noted that the cut-off of WheiR determines its specificity and sensitivity in predicting disease. For example, a cut-off of 0.54 in predicting chronic kidney disease results in a sensitivity of 72.9% suggesting that individuals with WheiR less than 0.54 can be used to exclude the risk of chronic kidney disease. A lower cut-off of WheiR such as 0.5 revealed a higher sensitivity (76.5%) and a lower specificity (47%). Therefore, the optimal cut-off of WheiR may be dependent on the purpose of its clinical use. Of interest is that WheiR is more important for Chinese women in predicting chronic kidney disease than men and that the number of metabolic syndrome risk factors is more correlated to the risk of chronic kidney disease (Lin et al. 2007). The cutoff of WheiR is not different between Chinese and Caucasian populations, but the clinical usefulness of WheiR may be different among genders and different age groups.

123.5 Waist to Height Ratio and Obesity in Women

The difference between the measurement of BMI and WheiR is its association to central obesity. Women had a more consistent correlation between waist circumference and abdominal visceral fat than men (Stewart et al. 2003; He et al. 1999). WheiR had a different prognostic value in women such as the presence of proteinuria in diabetic women (Tseng 2005) and the increase of chronic kidney disease risk (Lin et al. 2007). Zhang et al. (2004) studied coronary heart disease risk in 67,334 women aged 40–70 years without prior history of coronary heart disease, stroke, and cancer and found that waist height ratio is associated with coronary heart disease risk among women less than 55. The association between waist to hip ratio and mortality was studied in the ShanghaiWomen's Health Study (Zhang et al. 2007a, b), a population-based, prospective cohort study of Chinese women aged 40–70 years enrolled from December 28, 1996, through May 23, 2000, 95% of whom had a body mass index less than 30. A total of 1,456 deaths occurred in an average follow-up of 5.7 years. The relative risks of total mortality comparing the extreme waist-hip ratio quintiles were 2.36

(95% CI, 1.71–3.27), 1.60 (95% CI, 1.10–2.34), and 1.46 (95% CI, 0.97–2.20) for women with a BMI of less than 22.3, 22.3–25.1, and 25.2 or greater, respectively.

123.6 Waist to Height Ratio and Obesity in Children

The definition of obesity in children is even more complex. The often-used 85th and 95th percentile cut off points for BMI in children were arbitrarily determined and not directly based on evidence linking this level of fatness to adverse health outcomes.

The reason for the devastating obesity increase rate in China is the vast number of Chinese children and youth with obesity. The combined prevalence of overweight and obesity for the 7 to 18 years old Chinese increased from 1.6% to 23.6% for males and from 1.8% to 13.6% for females in the coastal big cities between 1985 and 2000. In 2005, the prevalence of combined overweight and obesity in the northern coastal big cities of China reached 32.5% and 17.6% for male and female youth respectively (Ji and Cheng 2008). Obese children grow up to be obese adults (Cheng 2007). Childhood obesity is becoming one of the public health problems of high priority in China.

General obesity indicator BMI is still one of the most commonly used anthropometric indices in current scientific research and the obesity index of choice according to the World Health Organization (WHO), International Association of the Obesity (IASO) and International Obesity Task Force (IOTF), although controversies exist on the cutoff values in different ethnic populations, the level of understanding is limited among the general public and BMI cannot provide information on fat distribution. Zhang et al. (2008) studied the cardiovascular risk factors in overweight and obese Chinese children, and found that even according to the reference established by the working group on obesity in China (WGOC), BMI underestimated the prevalence of childhood obesity in population-based screening programs, and the overweight children identified by Chinese BMI have presented the metabolic abnormalities like increase levels of TG, LDL-C, apo B, and insulin, lower levels of HDL-C and apo A. As Asian people tend to central obesity at lower levels of BMI than white populations and central obesity in both adults and children is related to cardiovascular risk factors (Han et al. 1995; Kelishadi et al. 2007), more informative anthropometric indicators are of special value when population-based health survey is conducted in Chinese children.

In recent years, as the increasing literature showed the superiority of waist to height ratio (WheiR) as an anthropometric index for obesity and cardiovascular risks prediction when compared with BMI, waist circumference (WC) and waist to hip ratio (WHR) in Chinese adults (Ho et al. 2003), Japanese adults and children (Hsieh et al. 2003; Hara et al. 2002), European adults (Ashwell et al. 1996) and Greek-Cypriot origin children (Savva et al. 2000), research was also performed in Chinese children.

Yan and colleagues (Lin et al. 2006) compared the association of cardiovascular risk factors with WheiR, BMI, and WC in Chinese children including 389 Han and 272 Uygur ethnic children aged 7–18 years, stratified by age, sex, and ethnicity from a school-based cross-sectional study in Xinjiang Uygur Autonomous Region (North-west area of China). After partial correlations (r) and linear regression analysis (R^2) was performed, the authors concluded that in Chinese children, WheiR was a better indicator of lipids and BMI was superior to indicate blood pressure, while WC was the best indicator of fasting glucose. Liao et al. (2008) measured the WheiR, BMI, upper arm circumference, and sitting height of 962 children aged 6–18 years from elementary and middle school in Beijing, and discussed the relationship between anthropometric indices and dyslipidemia in Chinese children. Their data revealed that WheiR together with BMI were the risk factors for dyslipidemia in Chinese children.

Two studies compared WheiR, WC, and BMI in Chinese children to evaluate the accuracy and simplicity of these anthropometric indexes. Weili et al. (2007) enrolled a sample of 2,055 Han and

2,132 Uygur ethnic children aged from 8 to 18 years in Xinjiang Uygur Autonomous Region, with overweight and obesity identified by BMI, aiming to suggest the optimal thresholds of WheiR for overweight and obesity by gender, analyze the correlation between age and WheiR, and make a comparison with that of BMI. As there were minor differences between the two ethnicities shown in this study, the author combined the data of Han and Uygur children. Results showed that the area under curve of WheiR for diagnosing overweight and obesity were both over 0.90 in male and female children, superior to those of WC. Based on their data, the threshold to identify overweight in both genders was 0.445 (with sensitivity and specificity >0.8); the threshold for obesity determination was 0.485 in male and 0.475 in female (with sensitivity and specificity >0.90). Association with age was found as much weaker for WHEIR (r = -0.108 for boys and 0.035 for girls) when compared with BMI (r = 0.413 and 0.39 for boys and girls respectively). Based on their finding, the authors concluded that WheiR is a simple, accurate, and non-age-dependent index to screen overweight and obesity in children and adolescents.

Sung et al. (2008) found that WheiR is a relatively age-independent anthropometric index by analyzing the body measurements of 14,842 Chinese children aged 6–18 years in Hong Kong (south China) in a cross-sectional study. The authors provided age- and sex-specific reference values for WheiR and WC, and found that WC was relatively larger in boys than girls and increased with age, although to a smaller extent after 14 years in girls; meanwhile, WheiR was slightly larger in boys than girls and decreased with age in both genders, particularly up to age 14 and then remained almost constant. For children aged 14–18 years, WheiR 0.5 corresponded to the 95th percentile for boys and the 97th percentile for girls. Their data also showed that WC correlated better with BMI than WheiR (r = 0.93, 0.91 cf. 0.65, 0.59 for boys and girls respectively). As the public health tool, WheiR failed to offer major advantages over WC for Chinese children in this study in that WheiR cannot avoid the need for age-related reference range. Considering its better correlation with BMI and it being easy-to-use, the authors recommended WC as a more convenient parameter for central fat estimation rather than WheiR in Chinese children.

WheiR has been shown as correlated with CV risk markers among children in studies concerning several ethnic populations, a few of which suggested that WheiR was an anthropometric index independent of age and sex. Based on these advantages, WheiR was proposed as a convenient alternative anthropometric index to assess central obesity in children as it was normalized for growth and obviated the need for age reference charts during application. Moreover, "Keep your waist circumference to less than half your height" (WheiR cutoff value 0.5) seems to be an attractive simple health target for the public.

Considering the dramatic differences of climates, life style, and ethnic composition between regions of this vast country, the conflicts between the conclusions of two major surveys with relatively large sample sizes among Chinese children might be the results of variability between regions and ethnic factors, suggesting further direct confirmatory evidence from comparative correlations with central obesity and cardiovascular risk factors in children of different age and ethnic origins will be mandatory before the WheiR cutoff of 0.5 is universally accepted as the alternative screening tool for population-based health survey.

123.7 Waist to Height Ratio and Obesity in Chinese Elderly

To date, there are few studies designed specifically for Chinese elderly population to discuss the value of WheiR in obesity measurement and cardiovascular risk prediction. Some studies incorporated the data of elderly people into the major results to evaluate WheiR in adults of all ages.

As a result, it is difficult to get a full-spectrum view of WheiR in elderly population from the current published data.

Huang et al. (2002) studied the relationship between anthropometric measurements and cardiovascular risk factors in 38,556 Chinese people of Taiwan, 1,013 of which, including 528 male and 485 female, were 65 years old or above. The authors measured BMI, WheiR, WC, and WHR, and assessed their relationships with blood pressure, glucose, and lipid profiles. Surprisingly, this study failed to find significant trends by different WheiR groups in hypertension, hypercholesterolemia, and LDL cholesterol elevation in elderly women, nor hypercholesterolemia and LDL cholesterol elevation in elderly men. Similarly, the relationships with other anthropometric indices were also statistically inconsistent for lipid profiles. Meanwhile, the four anthropometric indices were found to be closely related to cardiovascular risk factors in adults of both genders below 65 years.

This difference of WheiR's role in cardiovascular risk prediction among different age groups might imply that the value of anthropometric indices in elderly Chinese deserve further demonstration. Or more likely, the discrepancy was due to the relatively small sample size of senior subjects in that study, as was discussed by the authors.

In summary, further evidence is urgently needed before the importance of WheiR in the Chinese elderly is established, considering the lack of specific data concerning this population.

123.8 Conclusion

Waist to height ratio can be an important indicator of central obesity in Chinese and is associated with chronic diseases such as hypertension, cardiovascular disease, diabetes, metabolic syndrome, and chronic kidney disease. The optimal cutoff of WheiR is 0.5 for general population and children. However, small differences exist in genders and age groups in the optimal cut-off. The optimal cut-off of WheiR may be slightly different in cardiovascular disease, diabetes, hypertension and chronic kidney disease. More interventional studies are needed to determine if treatment of central obesity decreases risks of chronic disease.

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Chapter 124
Diagnosis of Obesity Using Anthropometric Indices in Urban Populations: Brazilian Perspectives

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Abstract There is a consensus in the literature that the etiology of obesity is multifactorial, caused by interaction of several factors. The parameter used for diagnosis is established by the WHO and defined by the body mass index (BMI), obtained by calculating the ratio between body weight (kg) and square of the height (m^2). An adult is considered obese when for BMI greater than or equal to 30 kg/m^2. In Brazil, an increase in obesity has been observed in all regions, especially in the South and Southeast regions, and more in urban than rural areas. This evolution is concomitant to a nutritional transition process, showing great change in the Brazilian diet pattern. Decrease in malnutrition and increase in obesity in adults were identified when two national surveys were compared: The National Study on Family Expenses [*Estudo Nacional sobre Despesas Familiares*] (1974/1975) and the National Health and Nutrition Survey [*Pesquisa Nacional de Saúde e Nutrição*] (1989). The evolution of obesity in Brazil took place in a relatively short time, and controlling it became a priority in the country public health policies. Among the several factors that determine obesity, are urbanization, which has changed diet patterns; sedentary lifestyle, which has contributed to weight excess; and a change in nutritional indicators. Hence changes in diet patterns indicate urgency in directing health and nutrition policies towards minimizing the problem of obesity in adults in Brazil.

Abbreviations and Acronyms

AMA	Arm Muscle Area
AMC	Arm Muscle Circumference
BIA	Bioelectrical Impedance
BMI	Body Mass Index
CNCD	Chronic Non-Communicable Diseases
DEXA	Hydrostatic Weighing and Dual-Energy X-Ray Absorptiometry
ECLAC	Commission for Latin America and the Caribbean
ENDEF	National Study on Family Expenses
HDI	Human Development Index
HDL	High Density Lipoprotein
IBGE	Brazilian Institute of Geography and Statistics

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_124,

ILO	International Labor Organization
INAN	National Health Institute of Diet and Nutrition
MS	Metabolic Syndrome
NIDDM	Non-Insulin Dependent Diabetes Mellitus
PNSN	National Health and Nutrition Survey
POF	Familiar Budget Survey
PPV	National Survey on Standard of Living
ROC	Receiver Operating Characteristic Curve
UNDP	United Nations Development Program
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

124.1 Introduction

The morbidity and mortality patterns in the Brazilian population have undergone changes since the 1960s (Monteiro et al. 2000), and understanding of their behavior is based on concepts from the epidemiological transition, nutritional transition, and demographic transition.

With regard to the epidemiologic transition, changes in the population morbidity and mortality patterns were observed, with reduction of infectious diseases and rapid increase of chronic non-communicable diseases (CNCDs), which stand out as causes of death. Increase in life expectancy and aging of population in developing societies further raise the likelihood of the onset of CNCD.

Regarding nutrition disorders and diet- and nutrition-related diseases, an important drop in the prevalence of malnutrition/low weight has been observed in all age groups and regions. This is especially true in children aged 0–5 years, during the past decades, which was followed by an increase in the overweight and obesity rates in all regions and age groups, with special focus on women from lower social and economic levels.

The demographic transition resulted in changes in the trends of morbidity and mortality and fecundity patterns. These caused changes in the population structure in which there was a decrease in high morbidity and mortality due to infectious diseases, but a high predominance of chronic non-communicable diseases, which was observed to alter how a population falls prey to disease and how it dies.

The nutritional transition, following the same logic of the previously mentioned transitions, is also a process of sequential change associated with diet and nutrition patterns. It is influenced by economic, social, and demographic change, modifying the diet and nutrition profile in the context of the population's health–disease process (Monteiro et al. 2000).

In Brazil, there were two national nutrition surveys, conducted in the 1970s and 1980s: the National Study on Family Expenses (ENDEF) and the National Health and Nutrition Survey (PNSN). The former was carried out during 12 months between 1974 and 1975 and comprised a sample of 55,000 households. This study assessed the nutrition conditions, establishing diet consumption and family expenses (Brazil 1975). The PNSN was conducted in 1989 by the former National Institute of Diet and Nutrition [*Instituto Nacional de Alimentação e Nutrição*] (INAN), in partnership with the Brazilian Institute of Geography and Statistics [*Instituto Brasileiro de Geografia e Estatística*] (INAN 1990). It was a household-based transversal study, with a stratified and probabilistic-type sampling of approximately 63 million Brazilians, encompassing 14,455 households. Its main objective was to assess the population nutrition condition, in addition to obtaining information on the

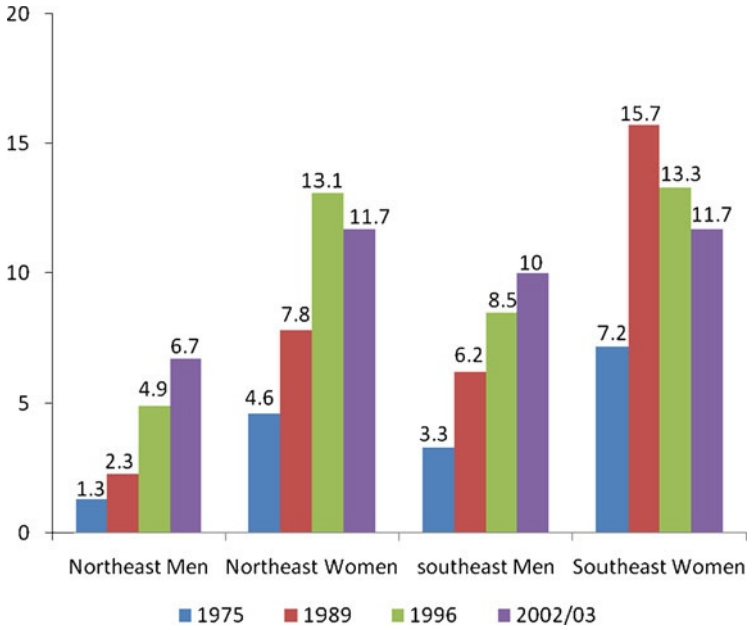

Fig. 124.1 Temporal evolution of obesity prevalence (BMI ≥ 30 kg/m^2) in northeast and southeast of Brazil (1974/1975, 1989, 1996, and 2002/2003) (Source: IBGE, National Study on Family Expenses (ENDEF) 1974–1975; National Institute of Food and Nutrition, National Health and Nutrition Survey (PSNS) 1989; Sociedade Civil Bem-Estar Familiar no Brasil, National Survey on Demographics and Health (PNDS) 1996 and 2006; and IBGE, Department of Surveys, Coordination of Work and Income, Family Budget Survey (POF) 2002–2003 (Based on Batista Filho and Rissin 2003; IBGE/MP/MS 2004))

household health condition, income, occupation, and participation in government-sponsored diet and nutrition programs.

An inversion in the nutrition indicators that evaluate the Brazilian population nutrition profile was found in these surveys. According to the ENDEF, the weight deficit in the adult Brazilian population was 24% for men and 26% for women, and obesity was 2% for men and approximately 7% for women (Brazil 1975).

The PNSN also showed changes in nutrition indicators, with a reduction of 15% in low weight for men and of 16% for women, and obesity rates were 5% among men and 12% among women during the same period. A significant reduction of low weight was identified in the 15-year interval between both surveys.

Still, according to these studies, there was a 50% drop in weight deficit for both genders. This is contrary to what was observed regarding overweight, which affected approximately 32% of 27 million Brazilian adults, corresponding to 27% of 11 million men and 38% of 16 million women.

The National Survey on Standard of Living [*Pesquisa Nacional sobre Padrões de Vida*] (PPV), conducted between 1996 and 1997, revealed an increase of obesity in all educational levels for the male population. For females, the ratio was similar to that of the male population during the period between 1974/1975 and 1989. Between 1974/1975 and 1995/1996, a continuous trend of increase in obesity was observed only among women in the low educational level and also stabilization, or even reduction in obesity, among women in the high educational level.

According to data from the Familiar Budget Survey [*Pesquisa de Orçamento Familiar*] (POF), from 2002 to 2003, overweight was diagnosed in 41.1% of men and in 40% of women, and, of this group, 8.9% of men and 13.1% of adult women were obese (Fig. 124.1).

124.2 Distribution of Obesity in Brazilian Regions

According to Coitinho et al. (1991), the country's several geographic regions show social differentiations in distribution of obesity. These authors found higher prevalence of overweight in the more economically developed regions of the country and in the higher income levels, but an increased trend of obesity is already observed in the poorer regions and lower income levels.

To better understand the obesity distribution in Brazil, which is 8.5 million km^2, it is necessary to know some of the country's characteristics and the Human Development Index (HDI). The HDI is an index created by the United Nations Development Program (UNDP) and calculated for several countries since 1990. Originally intended to measure the differences between countries, it was adapted also to be applied to states and cities (Table 124.1). The index ranges from 0 to 1. The closer the index is to 1, the better is the quality of human life. The most recent HDI ranking of the Brazilian states shows a country divided in half. Figure 124.2 reveals that, in 2005, the highest HDIs are from 11 states in the South, Southeast, and Midwest regions, with the Federal District ranked first.

On the other hand, the lowest values of HDI are in the nine states in the Northeast region. No state in this region has a HDI higher than that of any other part of the country, according to the report *Employment, Human Development and Decent Work – Recent Brazilian Experience*, recently launched by three United Nations agencies: the Economic Commission for Latin America and the Caribbean (ECLAC), International Labor Organization (ILO), and the United Nations Development Program (UNDP) Programa de las Naciones Unidas para el Desarrolo (PNUD 2004).

Between 1991 and 2005, the HDIs of all states in the country improved. The Northeast region, which registers the lowest values since the last decade, was however, the region with the highest increase (16.3%) of the index. The Southeast and the Midwest had HDIs increased by 10.9%. The South, which maintained its three states among the six highest HDIs since the past decade, showed the lowest increase in the index (8.5%). Of the ten states with the highest variation in the HDI, nine are from the Northeast region.

This situation, showing a country in which the HDI is lower in the North/Northeast regions and higher in the Southeast, South, and Midwest regions, can be explained by the economic geography of Brazil, in which production, economic activity, and income are still much more concentrated in these regions. The recent increases in the HDI were attributed to education according to the report (PNUD 2004), and education is one of the three HDI dimensions (income, education, and longevity). In all states, the education dimension showed the highest increase between 1991 and 2005. The HDI–education evolution – and, less noticeably, that of the HDI–longevity – contributed to considerably reducing the difference in development levels between the Brazilian regions (Fig. 124.2).

According to Coitinho et al. (1991), the highest percentage of overweight was in the South region. This region is the smallest in area, comprising 7% of Brazil and 15% of the population. Five million adults are overweight, with higher prevalence in urban areas. This difference is more noticeable in males, with 4% in rural areas and 8.6% in urban areas. Among women, the indices are practically the same for both rural and urban areas, with 15% and 14.6%, respectively.

In absolute terms, the Southeast region occupies 11% of Brazil and has 45% of population, which is the most populated in the country. It has ten million overweight adults and roughly 3.5 million obese individuals, making up the critical picture of the country. In this region, the obesity is more frequent in females (13%) than in males (5%). The indices are higher for female population in urban areas (13.7%) as compared to rural areas (11.4%). However, decreased obesity rate is a trend observed among higher-income women in this region (Monteiro & Conde 2000).

Table 124.1 Criteria to classification of Human Development Index (HDI)

Criteria	Classification
≥0.90	Human developing higher
0.80–0.89	Human developing high
≥0.50–0.79	Human developing medium
<0.50	Human developing low

Fig. 124.2 Distribution of Human Development Index in Brazilian regions in 2005. (Source: IBGE 2009)

The North region comprises the largest area and occupies 45% of Brazil, with only 7% of population. The lowest economic development is found in this region, and the number of adults with excess weight reaches 34% of total population, with differences between sexes, and it is higher in women (10%) than in men (6%).

The Midwest region corresponds to 18% of Brazil, and excess weight affects 31% of adult population: 10% of females and 4% of males. Unlike other regions, the highest frequency is observed in women residing in rural areas (10.5%) and in men in urban areas (5.6%), as compared to rural areas (1.8%) (Cointinho et al. 1991).

The Northeast region occupies 18% of Brazil and has the largest number of states. Twenty-four percent of the adult population in the region has excess weight (Cointinho et al. 1991). The highest incidence is found in the female group (7%) as compared to males (2%), and it is an urban problem for both men and women.

Hence, it could be concluded that obesity in Brazil is more present in the urban context, and the rates are slightly higher in urban than in rural areas throughout all regions. In urban areas, the problem of excess weight is more significant in females (12%) than in males (6%).

124.3 Factors that determine obesity in Brazil

According to Peña and Bacallo (2006), determining obesity may be different among the poorest and wealthiest people in the same country, or in developed and developing countries. Therefore, these differences must be taken into account since there are some factors that contribute to this condition.

Genetics, although not fully elucidated, seems to have a mechanism of metabolic adjustment in poor obese individuals. Thus, people exposed to inappropriate or fluctuating food consumption, in whom food intake alternates with no intake, seem to be able to efficiently use the energy and fat when the food supply is regular and available, which could lead to increased prevalence of overweight and type II diabetes mellitus – non-insulin dependent diabetes mellitus (NIDDM) (Peña and Bacallo 2006).

Some factors, such as living and environmental conditions (political, economic, social, cultural and physical) are considered as important influence in determining urban obesity in Brazil. The sociocultural factors as violence, lack of infrastructure and education for health as determinants, in addition to lack of physical activities. A negative effect in economic growth, observed in the 1980s, in Brazil, led to poor income distribution, and together with stabilization measures of economic plans, contributed to increase poverty and to intensify its extreme forms in the Brazilian population. Social inequality among these population groups and rural exodus to large metropoles, besides sedentary lifestyle, aggravated even more this situation (Gigante et al. 2006).

Distant acculturation influenced by the food industry, induces people to take habits and lifestyles that are not adequate for their region and style, making the low-income groups having conflicts between their real life and that projected they identify with, thus assuming Western food habits. In general, they comprise groups with less cultural and social opportunities, living in violent and unsafe environments and who suffer from micronutrient deficiency and overweight, and pose a higher risk of developing infectious and chronic diseases.

In regard to the factor sex, women are more vulnerable for having fewer opportunities, taking more social responsibilities and underestimating their body image. Some factors related to the female reproductive cycle, such as age at menarche, gestational weight gain, number of children, interval between deliveries, duration of breastfeeding and menopause are also considered as determinants of female obesity (Ministério da Saúde 2006).

In addition to other factors, the newest challenge is to face the dynamic relation between poverty and obesity in Latin America and the Caribbean as observed by the United States Agency for International Development (USAID) and also reported in Brazil.

124.4 Applications to Other Health and Disease Areas

The metabolic syndrome (MS), also known as syndrome X, insulin-resistance syndrome, deadly quartet, or plurimetabolic syndrome, is characterized by a group of risk factors related to insulin resistance and abdominal obesity (Gomes 2006).

Although there is no consensus in the national and international literature in the diagnosis of MS, it is assumed that the individuals who meet three or four of the following criteria are considered as suffering from this syndrome: (1) abdominal obesity, (2) hypertriglyceridemia, HDL cholesterol <40 mg/dL in males and <50 mg/dL in females, (3) blood pressure 130/85 mmHg, and (4) fasting glucose ≥110 mg/dL.

It is estimated that 24% of the adult population in the USA and 50–60% of population aged over 50 have metabolic syndrome. The projection for 2010 is that 50–70 million or more Americans will have some manifestation of this syndrome.

However, there is scarce information about this syndrome in the adult population in Brazil. However, there are some studies in specific populations using centralized obesity indicators, such as waist and hip circumferences, waist circumference, BMI, and percentage of fat (%F), to predict the presence of metabolic syndrome in adults.

A study conducted by Pontes et al. (2008), with women aged 27–29 years, showed mean values above the normal nutritional standards in BMI, percentage of body fat and presence of MS.

Another study performed by Gomes et al. (2006) demonstrated that BMI ≥ 25.0 kg/m^2 was the best predictor of altered abdominal circumferences in females, when assessing the area under the ROC curve. In males, a BMI ≥ 25.0 kg/m^2 was the best predictor in presence of abdominal circumference for cardiovascular risk, whereas the circumference of metabolic syndrome occurred in those with a BMI ≥ 30.0 kg/m^2.

A third study used the waist-to-hip ratio (WHR) and the waist circumference (WC) and showed that the WHR, with alteration, has a significant association with metabolic syndrome, such as hypertension and low HDL-cholesterol levels, but the WC had significant association only with isolated arterial hypertension. However, both indicators present a strong association with concomitant presence of two or more changes related to MS (Martins & Marinho 2003).

The literature reports that the most accurate cutoff points are sometimes greater or smaller than those established by the World Health Organization, thus hindering interpretation of results in other populations. Very often, these indicators present low sensitivity and low specificity, when compared to American reference measures, mainly for cardiovascular risk, although validation of these indicators is reported in specific studies.

124.5 Practical Methods and Techniques

According to Himes (2006), the anthropometric indicator to assess obesity demands answers to three questions, as follows:

- What is the specific purpose of identifying those overweight or obese?
- Which anthropometric indicator meets this purpose?
- Which is the best cutoff point for the indicator?

The indicator to use should be one that maximizes both sensibility (proportion of those who become ill and are correctly identified by the indicator) and specificity (proportion of those who are not ill and are correctly identified by the indicator) relative to a specific result, that is, the risk of being ill subsequently. This method produces an indicator with the best general efficiency, or the correct classification of individuals in relation to expected result (Himes 2006).

Practice related to implementation of anthropometric assessments in public health units is a decisive factor in selection of the most appropriate anthropometric indicator. Location, facilities, and team have important implications on the demands of equipment, training, quality control, and reliability of the measurements.

Cultural acceptance of measurements, frequency of visits required, and transport may bring some limitations to the target groups, but anthropometric indicators are considered more feasible (Himes 2006).

Different cutoff points of the same indicator are associated with diverse sensibility and specificity points. Theoretically, there may be many claims to select a cutoff point based on maximum sensibility, maximum specificity, or maximum efficiency of an indicator or screening, depending on the purpose.

In practice, the variety of probable purposes for the anthropometric indicators of overweight or obesity in public healthcare facilities suggests that, in most cases, the indicators should be selected based on maximum specificity.

Although it seems to be controversial, using specificity rather than sensibility corresponds to identifying who could be ill through calculation of the predictive positive value (PPV) or the proportion of individuals considered at risk by the indicator (Himes 2006).

Among the several indicators are used to evaluate body fat, the WHO recommends, from 1995, the body mass index (BMI) in kg/m^2, as the anthropometric indicator for adults aged under 60 years. The main reasons for such a recommendation include the fact that: (1) they are measures routinely collected; (2) they have good reliability; (3) pieces of equipment used to measure are easily acquired; (4) there is no need for ideal weight reference specific for that population; (5) it is valid in relation to morbidity and mortality; and (6) the standard report categories and the tables and normograms for calculations are provided by the World Health Organization.

The several cutoff point levels for overweight, based on the BMI, are for grade I: 25–29.99); for grade II: 30–39.99; and for grade III: over 40; moreover, they have not been assessed for other purposes apart from determining the total subsequent mortality (WHO 1995).

There are other indicators to evaluate body fat that can be used to consider total fat and its distribution. Such indicators are: (1) circumference of the arm, waist, and hip; (2) proportion of the circumferences (waist-to-hip); (3) tricipital, bicipital, subscapular, and suprailiac skinfold thickness; (4) sum of skinfold measurements; (5) proportion of skinfolds (tricipital and subscapular); and (6) equations to predict total body fat.

The circumferences are influenced by fat mass, muscle mass, and size of bones. It is possible to measure several body circumferences, including the main ones, as follows: mid-upper-arm circumference and its combination with the tricipital skinfold thickness enables calculating, by means of formulas, the arm muscle circumference (AMC), the arm muscle area (AMA), and bone-free arm muscle area, which correlate with total muscle mass, thus assessing the protein nutritional status.

Some studies analyzed the association of diet and development of central adiposity (Koh-Banerjee et al. 2003), and others showed gain in waist circumference (WC).

The association of food patterns with excess weight has been the object of several studies, indicating a positive association between these food patterns and global and central obesity (Sichieri et al. 2003). For other authors, this relation is not clear (Quatromoni et al. 2002; Togo et al. 2004).

Waist circumference (WC) is used due to its low cost and relatively simple measurement, and it is one of the indicators to assess composition of total body fat and its relation with chronic diseases. It classifies adiposity and has been recently used to evaluate cardiovascular risk for predicting visceral fat, which is responsible for metabolic and cardiovascular alterations (Freitas et al. 2007).

In a study conducted by Freitas et al. (2007) the use of BMI and WC was very precise in evaluating obesity in the urban mixed-race population, except for men aged under 40 years. These two indicators have a good discriminatory power according to the ROC curve, independent of age and sex (Fig. 124.3), and the lower estimates of BMI cutoff points compared to the international standards were observed in this study, according to sex and sex/age.

Similar results were reported by other authors in studies of specific population groups, in whom the cutoff points varied according to sex and age (Stanforth et al. 2004; Movsesyan et al. 2003; Aronne and Segal 2002; Pitanga and Lessa 2005; Sánches-Castillo et al. 2003). When the values

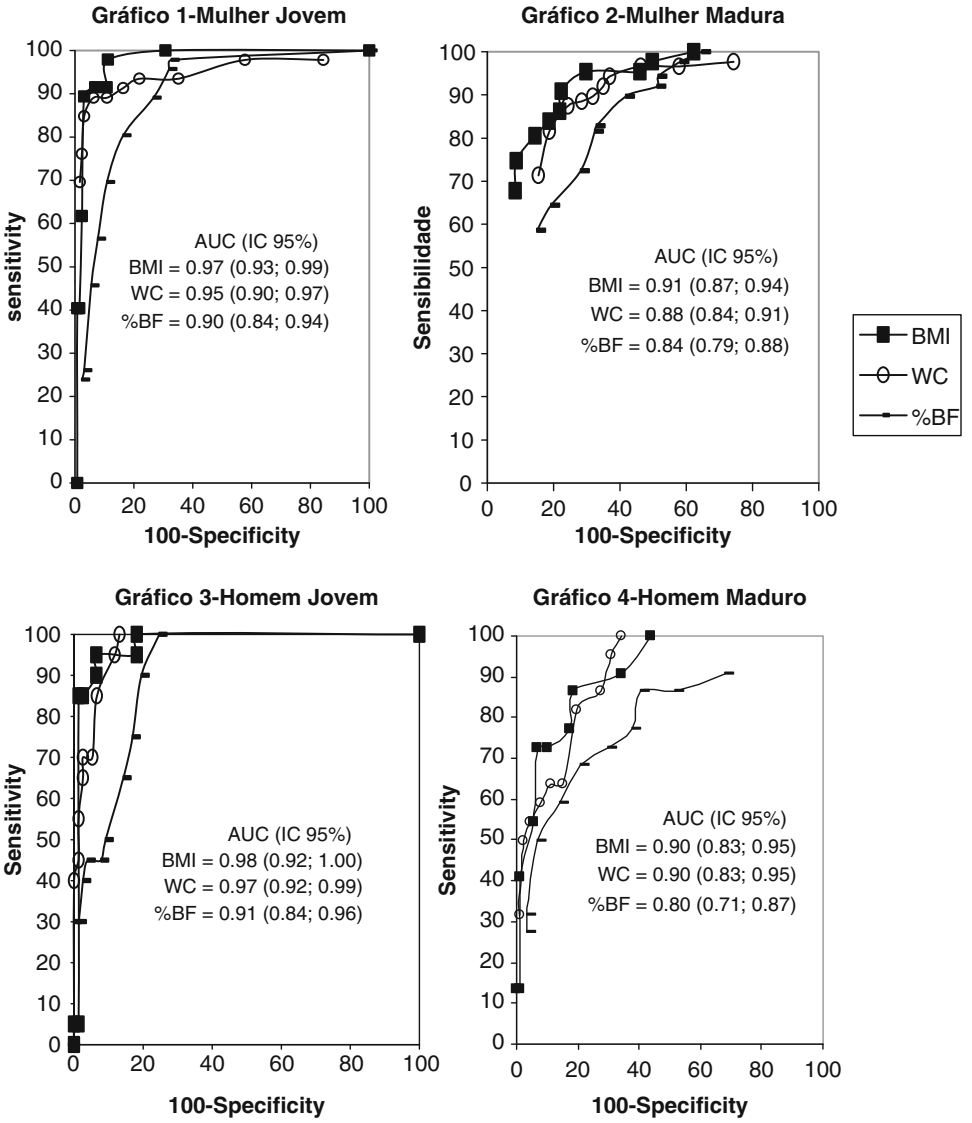

Fig. 124.3 Receiver operating characteristic curves of anthropometric predictors in the urban population of Ouro Preto City, Brazil aged 20–79 years, by sex and age (*AUC* area under the curve, *CI* confidence interval, *BMI* body mass index, *WC* waist circumference, *%BF Siri* percentage total body fat estimated with Siri's equation)

recommended by the NIH and WHO (National Institutes of Health 2000) were used to define obesity, an increase in specificity for men and women (98.8% and 94.2%, respectively) and a significant drop in sensibility (33.3% and 60.4%, respectively) was observed.

The rise in the number of false-negatives, that is, obese individuals who were not considered as such, led to an underestimated rate of obesity of 57.2% and 29.9% for men and women, respectively, regardless of age. Similar under-reporting estimates were reported by Frankenfield et al. (2001), using the same cutoff points recommended by the WHO to estimate obesity in white individuals (Table 124.2).

According to Rezende et al. (2007), the WC is widely used to differentiate gynecoid and android fat distribution, and, like the BMI, it is able to predict the incidence of diabetes. Moreover, the waist–

Table 124.2 Values of sensibility (Sn) and specificity (Sp) of the cutoff points for obesity, according to reference method and reference standards. Ouro Preto-MG, Brazil

	Female			Male		
Index	Cutoff point	Sn	Sp	Cutoff point	Sn	Sp
BMI (kg/m^2)						
Ouro Preto	**27.5**	90.3	82.6	**26.3**	90.5	86.6
Reference[a]	**30.0**	60.4	94.2	**30.0**	33.3	98.8
Age						
<40 year	26.0	97.9	88.5	26.3	95.0	93.5
≥40 year	28.0	90.8	77.7	26.3	86.4	81.6
WC (cm)						
Ouro Preto	**86.0**	91.0	75.7	**89.5**	92.9	79.1
Reference[b]	**88.0**	82.7	79.5	**102.0**	33.3	98.8
Age						
<40 year	84.0	89.1	93.7	86.0	100	86.8
≥40 year	90.0	87.4	75.7	89.0	100	65.5
BF Siri (%)						
Ouro Preto	**37.0**	78.9	73.6	**21.9**	92.9	66.5
Reference[c]	**35.0**	92.5	57.8	**25.0**	61.9	86.6
Age						
<40 year	34.0	97.8	67.2	22.5	100	75.3
≥40 year	37.4	82.8	67.1	24.5	68.2	79.3

[a] WHO
[b] NIH
[c] Lohman

hip ratio is able to predict diabetes with other indices, BMI and WC, and it has better inverse association with low HDL-cholesterol levels than waist circumference.

There are more than 100 equations to estimate body fat based on skinfolds, and some studies, such as that performed by Durnin and Wormersley (1974) and Jackson et al. (1980) in population groups, verified the validity of equations. Nonetheless, Rezende et al. (2007) demonstrated the existence of low accuracy due to ethnicity, level of physical activities, and amount of body fat, when these equations are used in other population groups.

The studies on the Brazilian population to validate these equations and that were cited by Rezende et al. (2007) showed that the samples were often small and with a very specific population group. For this reason, the equations of Durnin and Wormersley (1974) and of Jackson et al. (1980) are still used, even though the specific and general equations of Durnin and Wormersley underestimate the percentage of fat measured by hydrostatic weighting. Hence, one must bear in mind that the equations found in the literature have gone through a validation process for specific groups and should not be generalized, which hinders their use in other populations, unless they are proven.

Other indicators to assess body composition, such as hydrostatic weighing and dual-energy X-ray absorptiometry (DEXA), are considered gold standards and have the disadvantage of low applicability and high cost for population studies.

Bioelectrical impedance (BIA) has been used to assess body composition through two techniques – bipolar measurement in lower and upper limbs or tetrapolar, measuring the whole body. These techniques are based on conduction of a low-intensity electrical current, applied by cables connected to electrodes or conducting surfaces that are in contact with the skin.

Although easy to be used and presenting high reproducibility, they provide less precise data depending on the body's hydroelectrolytic balance, which alter due to intense physical activity, use of alcohol, and edema or fluid retention.

Another disadvantage is that these devices provide values of fat mass, lean mass, and body water by means of predictive equations adjusted by sex, age, weight, and height. For each device, there are prediction equations that vary and are valid only for the study population, thus making it necessary to validate them for other population groups.

Although this technique is not invasive, inexpensive, and highly reproducible, the studies showed that validation of the equations presented body composition values that were very different from those found according to the standard methods (Sun et al. 2005), both with bipolar and tetrapolar techniques. On the other hand, when compared to anthropometric equations, there were fewer errors in tetrapolar bioelectric impedance than in Durnin and Wormersley (1974) and Jackson et al. (1980) equations.

In three studies performed in Brazil (Carvalho & Pires-Neto 1999; Marques et al. 2000; Glaner 2005), the difficulty to validate the tetrapolar BIA for the Brazilian population is evident due to diverse characteristics of the groups evaluated and the use of different equations, in addition to scarcity of studies with this approach.

Rezende et al. (2007) reported that some studies with bipolar or tetrapolar BIA showed no differences in fat percentage obtained by hydrostatic weighing or by some BIA models. However, the same authors demonstrated that superior and inferior bipolar BIA models were not adequate to assess fat body as compared to DEXA. Since there are data still unclear, further epidemiological investigations on the use of BIA are necessary.

124.6 Conclusion

In Brazil, the studies show that obesity affects urban area populations more, followed by high-income- and low-income groups in rural areas. There is an urgent need for studies to validate indicators that can provide early detection of possible harm to health, primarily obesity, and to be preventatively used in individuals and collectivities. The literature is scarce in this type of studies in Brazil; it is necessary to define possible indicators to determinate factors that contribute to the onset of chronic non-communicable diseases.

Nowadays, in developing countries, the same agenda is shared with both excess and deficiency, obesity and malnutrition; thus, it is necessary to establish more efficient programs to change the predominant idea that conditions related to malnutrition have more impact in developing countries than obesity.

Summary Points

- *Introduction*: In Brazil, a decrease in prevalence of malnutrition/low weight has been observed in all age groups and regions, followed by a rise in overweight and obesity rates in all regions and age groups, with special focus on women from lower social and economic levels.
- *Obesity distribution in Brazilian regions*: The distribution of obesity in the country shows social differentiations in several geographic regions. A higher prevalence of overweight was found in the more economically developed regions and in the higher income levels, but a trend of obesity increase is already observed in the poorer regions and lower income levels.
- *Factors that determine obesity in Brazil*: Several factors determine obesity in developed and developing countries, and there are differences between poor and wealthy peoples in the same country.
- *Applications to other health and disease areas*: Metabolic syndrome (MS), also known as syndrome X, insulin-resistance syndrome, deadly quartet, or plurimetabolic syndrome, is character-

ized by a group of risk factors related to insulin resistance and abdominal obesity and is generally a consequence of obesity.
- *Practical methods and techniques*: Among the several indicators used to evaluate body fat, the WHO recommends the body mass index (BMI), in kg/m^2, as the anthropometric indicator for adults aged under 60 years.
- *Conclusion*: In Brazil, the studies show that obesity affects primarily urban-area populations followed by high-income groups in rural areas and low-income brackets in rural areas.

Key Points

Key features of prevalence of obesity in adults in northeast and southeast of Brazil (Fig. 124.1).

- BMI of 18.5–25 may indicate optimal weight, a BMI lower than 18.5 suggests the person is underweight, while a number above 25 may indicate the person is overweight; a BMI below 17.5 may indicate the person has anorexia nervosa or a related disorder; a number above 30 suggests the person is obese (over 40, morbidly obese).
- Figure lists the key facts of evolution of obesity prevalence (BMI ≥ 30 kg/m^2) in northeast and southeast of Brazil through surveys conducted in 1974/1975, 1989, 1996, and 2002/2003.

Key features of Human Development Index in the Brazilian regions (Fig. 124.2).

- HDI is defined as a measure to compare the characteristics as richness, education, and life of expectancy of the population of a country. This is a pattern of assessing the welfare of a population. It is used to identify if the country is developed, is developing or subdeveloped and also to assess the impact of economic politics on the quality of life.
- Figure shows that, in 2005, the 11 states with the highest HDI in Brazil are from states in the South, Southeast, and Midwest regions, with the Federal District ranked first.

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Chapter 125
Presurgical Assessment of Intra-abdominal Visceral Fat in Obese Patients

Angela Falbo and Stefano Palomba

Abstract To date, obesity is simply defined as body mass index (BMI) higher or equal to 30 kg/m2 (National Heart, Lung, and Blood Institute/National Institutes of Diabetes and Digestive and Kidney diseases 1998). Although BMI is widely accepted as a marker of adiposity in population-based studies, and is recognized as an instrument to diagnose obesity for all age groups, it should be more properly seen as an index of weight excess, rather than body fatness.

Abbreviations

AFI	Abdominal wall fat index
BMI	Body mass index
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
LADG	Laparoscopy-assisted distal gastrectomy
MRI	Magnetic resonance imaging
P	Preperitoneal fat layer
RCT	Randomized controlled trial
RR	Relative risk
S	Subcutaneous fat layer
SC	Subcutaneous
SF	Subcutaneous fat
SPAIR	Spectral attenuation with inversion recovery
THRIVE	3D T1-high-resolution isotropic volume examination
VF	Visceral fat
WC	Circumference of the waist
WHO	World Health Organization
WHR	Waist-to-hip ratio

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_125,

125.1 Introduction

To date, obesity is simply defined as body mass index (BMI) higher or equal to 30 kg/m^2 (National Heart, Lung, and Blood Institute/National Institutes of Diabetes and Digestive and Kidney diseases 1998). Although BMI is widely accepted as a marker of adiposity in population-based studies, and is recognized as an instrument to diagnose obesity for all age groups, it should be more properly seen as an index of weight excess, rather than body fatness. In fact, BMI measurement does not provide information on body composition or distinguish between fat and fat-free mass or between deep and subcutaneous abdominal fat.

The deep abdominal fat, also known as organ fat or intra-abdominal fat or, more simply, visceral fat (VF), is located inside the abdominal cavity, packed in between internal organs and torso, as opposed to subcutaneous fat, which is found underneath the skin, and intramuscular fat, which is found interspersed in skeletal muscle (Fig. 125.1). Fat in the lower body, as in thighs and buttocks, is subcutaneous, whereas fat in the abdomen is mostly visceral. This is composed of several adipose depots including mesenteric, epididymal white adipose tissue and perirenal depots. An excess of visceral fat is known as central obesity, or "belly fat," in which the abdomen protrudes excessively.

According to the National Institutes of Health, the number of overweight and obese has continued to increase since 1960, a trend that is not slowing down. Today, obesity affects nearly one-third of the adult American population, about 30.5% of adult Americans, with a prevalence slowly

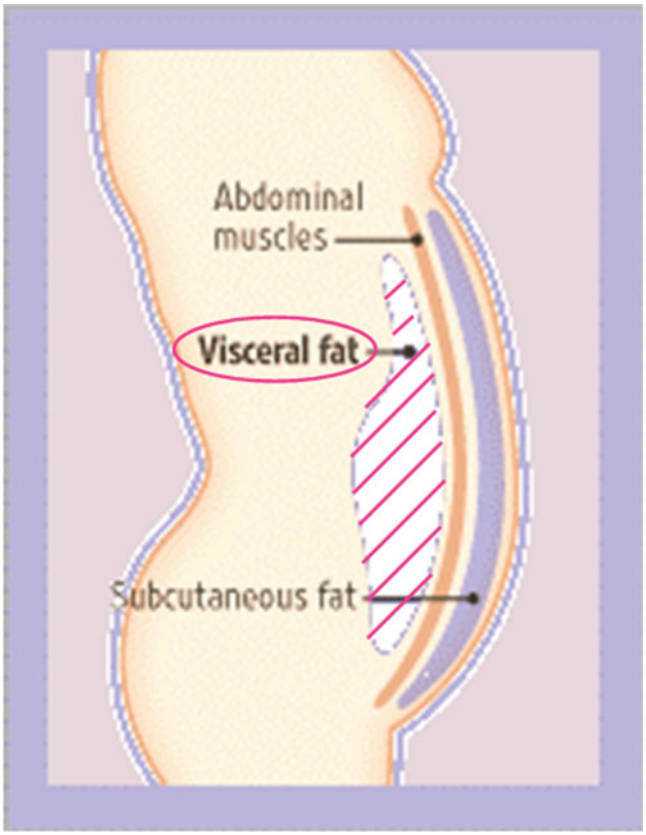

Fig. 125.1 Localization of intra-abdominal visceral fat

growing also in European countries, where the figure is 15–20% (Fig. 125.2). The latest figures published in 2005 state that 22% of men and 24% of women are now obese and projected figures expect those numbers to rise to 60% of men and 50% of women, with a diagnosis of clinical obesity by 2050.

At the present, obesity, and in particular abdominal obesity, represents a very expensive condition due to direct and indirect costs. In fact, each year, obesity causes at least 300,000 excess deaths in USA, and the healthcare costs of American adults with obesity amount to approximately $100 billion (Andreyeva et al. 2010).

There is substantial evidence supporting the notion that a great amount of VF is predictive of insulin resistance and of the presence of related metabolic abnormalities, commonly referred to as the metabolic syndrome (Wajchenberg 2000; Despres and Lemieux 2006; Schneider et al. 2007). Moreover, regardless of BMI, patients with increased VF usually have an atherogenic lipid profile, high fasting serum glucose and insulin levels, and high blood pressure, all metabolic factors participating in the atherosclerotic process. These factors, in turn, contribute to the occurrence of coronary heart disease, stroke, as well as peripheral vascular diseases (Wajchenberg 2000; Despres and Lemieux 2006; Schneider et al. 2007).

Other than medical diseases, patients with visceral obesity undergo more frequently surgery due to: (1) the effectiveness of bariatric surgery in weight loss and complete resolution or improvement of obesity-related risks (Buchwald et al. 2004) and comorbidities and (2) risk of some common adult cancers (Renehan et al. 2008). In this regard, a recent meta-analysis (Renehan et al. 2008) showed that, in men, a 5 kg/m^2 increase in BMI was strongly associated with esophageal adenocarcinoma [relative risk (RR) 1.52, $p < 0.0001$] and with thyroid (RR 1.33, $p = 0.02$), colon (RR 1.24, $p < 0.0001$), and renal (RR 1.24, $p < 0.0001$) cancers, whereas, in women, close associations between a 5 kg/m^2 increase in BMI and endometrial (RR 1.59, $p < 0.0001$), gallbladder (RR 1.59, $p = 0.04$), and esophageal adenocarcinoma (RR 1.51, $p < 0.0001$), and renal (RR 1.34, $p < 0.0001$) cancers were observed.

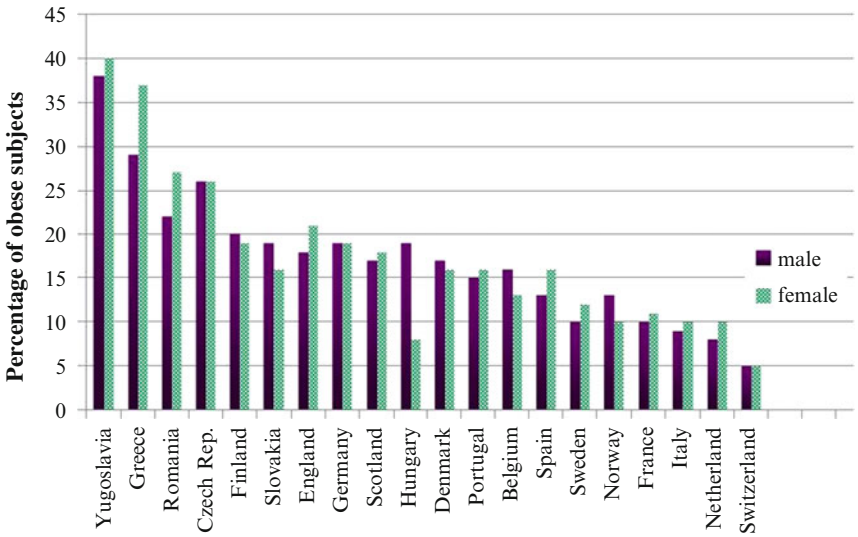

Fig. 125.2 Distribution of obesity in several European countries

125.2 Obesity and Surgical Risk

In each surgical procedure, anesthesia is the first step to be safely overcome. Obesity can present significant problems for anesthesiologists, including difficult airway management, intravascular access, pulmonary aspiration, monitoring, and choosing appropriate medications (Adams and Murphy 2000).

The main organ systems impaired, concerning anesthesia, in obese patients are the cardiovascular and respiratory systems. In fact, because of the restrictive ventilatory effects of obesity, these patients show an overall decrease in total lung capacity due to both decreased functional residual capacity and decreased expiratory reserve volume. Consequently, arterial hypoxemia, ventilation–perfusion mismatch and right-to-left shunting are often shown in these patients. In addition, obese patients require increased cardiac output to maintain pulmonary and systemic circulations. Since increased left-ventricular blood volume and systemic hypertension are common in these patients, complications of chronic, increased afterload, which translates into increased cardiac work and increased oxygen demands often occur (Adams and Murphy 2000; Tantawy 2008).

Apart from cardiovascular and pulmonary issues, several perioperative and postoperative complications, such as renal diseases, atelectasis, pneumonia, wound infections, sleep apnea-related problems, and thrombo-embolic events, are more common in obese patients (Candiotti et al. 2009).

125.3 Surgical Approach in Obese Patients

The choice of a specific surgical approach in obese patients is crucial. Specifically, in women, more and more data have demonstrated that the vaginal approach is superior to others in terms of intra- and postoperative complications (Sheth 2010). Moreover, the abdominal access in several diseases is needed.

In the early development of laparoscopic techniques in surgery, obesity was considered a relative contraindication. In fact, there are technical challenges specific to laparoscopy and which are particularly important for obese patients. They include adequate insufflation of the peritoneal cavity, trocar insertion, maintenance and physiologic complications of the pneumoperitoneum, and reduced pelvis visualization due to limited exposure.

Anesthesiologic complications are more common in obese patients during laparoscopic surgery because CO_2 insufflation of the peritoneal cavity causes cephalad displacement of the diaphragm, increased peak inspiratory pressure, decreased functional residual and vital capacity, and increased intrathoracic pressure. As a result of these pulmonary changes, patients who undergo laparoscopy are at risk of atelectasis and of decreased arterial oxygenation.

At the moment, techniques, instrumentation, and knowledge of physiology associated with laparoscopic procedures have improved and some contemporary series have shown that obese patients can undergo laparoscopic procedures safely with reduced patient morbidity compared with open surgery (Lamvu et al. 2004). In particular, although minor technical modifications (i.e., proper trocar-site selection and greater insufflation pressures) were necessary, the benefits of the minimally invasive laparoscopic approach were preserved in the obese population undergoing laparoscopic radical nephrectomy (Fugita et al. 2004). Other data show that laparoscopic surgery can be safely applied to obese patients with colorectal diseases requiring colectomy. Recent data indicate that, although obesity is associated with a high conversion rate, laparoscopic colorectal surgery is feasible and effective in both obese and non-obese patients and that obese patients, who are thought to be at increased risk of postoperative morbidity, have the similar benefit of laparoscopic surgery as non-obese patients with colorectal disease (Schwandner et al. 2004; Leroy et al. 2005).

During the past 10 years, we contributed to increasing use of the laparoscopy also for treating gynecological malignancies, especially for early stage endometrial cancer, which typically occurs in

obese women. Safety data have demonstrated that the laparoscopic approach to this cancer is a well-standardized procedure with the same indications and limits of the laparotomic one. No difference between the laparotomic and the laparoscopic approach was observed in terms of feasibility, safety, recurrence and survival rate and several advantages over the traditional open approach was noted in patients who received laparoscopy. Complications rate, postoperative pain, duration of hospital stay and length of time needed to return to full activity and/or work, and quality of life resulted in significantly improved after laparoscopic surgery (Palomba et al. 2007).

Notwithstanding these benefits of the laparoscopic approach over the laparotomic one, a significant proportion of laparoscopies are commonly converted to abdominal surgery. The laparotomic conversion rate, in obese subjects, in fact, is higher when compared with normal-weight or overweight patients, even if the morbidity and length of hospitalization associated with the procedure seem to be similar to those among women with lower BMI (Palomba et al. 2007).

Also in patients undergoing coronary artery bypass surgery, obesity does not affect the risk of perioperative death and other adverse surgical outcomes compared to normal-weight, even if obese patients appear less likely to be selected for surgery than normal-weight patients (Reeves et al. 2003).

A recent study demonstrated that obesity, and particularly VF, was strongly, and significantly, correlated with both operation time and operative blood loss in subjects who received laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer, even if there was no significant difference in the rate of postoperative complications or conversions to open laparotomy between the approaches. According to their results, authors concluded that VF was significantly correlated with operative difficulties during LADG, and that it appears to be a possible risk factor in laparoscopy that should be considered when making a decision about treating early gastric cancer with LADG (Ueda et al. 2009).

Finally, concerning the gynecologic oncology field, although several studies (Kadar 1995; Eltabbakh et al. 1999, 2000; Holub et al. 2000, 2001; Scribner et al. 2001; Bai et al. 2002; Obermair et al. 2005) demonstrated that the laparoscopic approach to gynecological malignancies is feasible and has many advantages, the laparotomic conversion rate in obese subjects seems to be higher when compared with normal-weight or overweight patients (Kadar 1995; Eltabbakh et al. 1999, 2000; Holub et al. 2000, 2001; Scribner et al. 2001; Bai et al. 2002; Obermair et al. 2005). In particular, in a recent randomized controlled trial (RCT) comparing the laparoscopic and laparotomic approach to early stage endometrial cancer, we observed a 12.5% of laparotomic conversions, of which 7.5% were early laparotomic conversion due to anesthesiologic indication. A subanalysis of these data (Palomba et al. 2006) showed that all patients who were early converted to laparotomy were obese, even if their BMI was similar to those measured in obese patients who successfully completed the laparoscopic interventions. Furthermore, patients converted to laparotomy had significantly higher VF amount (Palomba et al. 2006). In a successive study (Palomba et al. 2007), it was confirmed that the only one discriminating parameter that was related to early laparotomic conversion in women with early stage endometrial cancer was the VF.

125.4 Presurgical Assessment of Obesity

125.4.1 Anthropometric Measurements

Body weight and BMI can be easily measured and therefore are frequently used in large-scale epidemiologic studies and in the clinical practice. BMI is measured as the ratio between the weight and the square of the height, where weight is measured at a standard balance beam scale to the nearest

0.1 kg with patients wearing light clothing and height is measured barefoot using a statiometer to the nearest 0.1 cm.

All anthropometric measurements are always obtained with the patients in a standing position with relaxed abdomen, arms at their sides, and joined feet (Yanovski 1993).

According to this widely used measurement, normal-weight patients are defined as subjects with a BMI ranging from 20 to 25, whereas a BMI > 25 ≤ 30 identifies overweight subjects, BMI > 30 ≤ 40 means obesity, and BMI values >40 are synonymous of morbid or severe obesity (National Heart, Lung, and Blood Institute/National Institutes of Diabetes and Digestive and Kidney diseases 1998).

Major limitations of this measure are that the BMI does not distinguish between fat mass and muscle (lean) mass, both weight and height are surrogate measures of body size, and the body weight and the BMI provide no information regarding the nature of body fat distribution (Chen et al. 1993).

On the other hand, the World Health Organization (WHO) (World Health Organization 2000) has agreed on an international standard for identifying overweight and obesity in adult populations using the BMI, but, increased risk of cardiovascular disease has been found in individuals presenting with a distribution of excess fat in the abdominal region, leading to an insulin resistance state.

Among the anthropometric indices usable to obtain a measurement of body composition, the waist-to-hip ratio (WHR) is the most reliable to reflect the regional distribution of adipose tissue in the body. WHR is calculated as the ratio between the circumference of the waist (WC) and the circumference of the hip (considered as the maximal extension of the buttocks). A WHR of 0.8 for women and 1.0 for men correlates strongly with general health and fertility. Women with values within 0.8 have optimal levels of estrogen and are less susceptible to major diseases, such as diabetes, cardiovascular disorders and ovarian cancers. Men with WHR around 1.0, similarly, are more healthy and fertile with less prostate cancer and testicular cancer. Even if not universally recognized (Taylor et al. 2010), WHR, rather than BMI, seems to be the more appropriate yardstick for overall mortality risk stratification of older adults (Srikanthan et al. 2009). Furthermore, that indicator of VF does not distinguish between subcutaneous (SC) and VF volume, thus is s poor predictor of changes in VF.

WC alone is another parameter widely used to evaluate obesity, with particular regard to abdominal obesity. On the basis of WC measurement, WHO (World Health Organization 2000) identifies two levels of abdominal obesity in Europids, depending on risk for metabolic complications: increased risk, that is, WC >94 cm in men and >80 cm in women, and substantially higher risk, that is, >102 cm in men and >88 cm in women. More recently, the WC was also introduced as one of the criteria for clinical diagnosis of the metabolic syndrome (Alberti et al. 2005). However, gender and ethnic variations have been proposed for identifying cutoff values (Alberti et al. 2005).

WC is considered as the smallest circumference of torso, measured at the end of a normal expiration, with the measuring tape positioned at the level of noticeable waist narrowing (Fig. 125.3). When narrowing cannot be determined, the circumference is measured at the level of the lower floating rib. For hip circumference, the tape would be positioned around the hips at the level of the symphysis pubis and the greatest gluteal protuberance (Dobbelsteyn et al. 2001). Tips for accurately measuring WC are to ensure that the tape is snug but does not push tightly into the skin, and to measure waist circumference after breathing out normally, without "sucking in" the stomach.

Several data (Balkau et al. 2007) showed the implications of WC in impairing the long-term cardiometabolic risks. WC was also indicated as possible marker of surgical complications in patients undergoing laparoscopic colorectal surgery (Nitori et al. 2009). Moreover, in a recent crossover study (Wei et al. 2010), WC was demonstrated to have the greatest impact on pulmonary function in obese patients undergoing bariatric surgery. These findings confirmed the repercussion of central obesity on the postoperative complication rate and the need of more intensive post-operative care. That result was also found in normal-weight and overweight subjects (Chen et al. 2007).

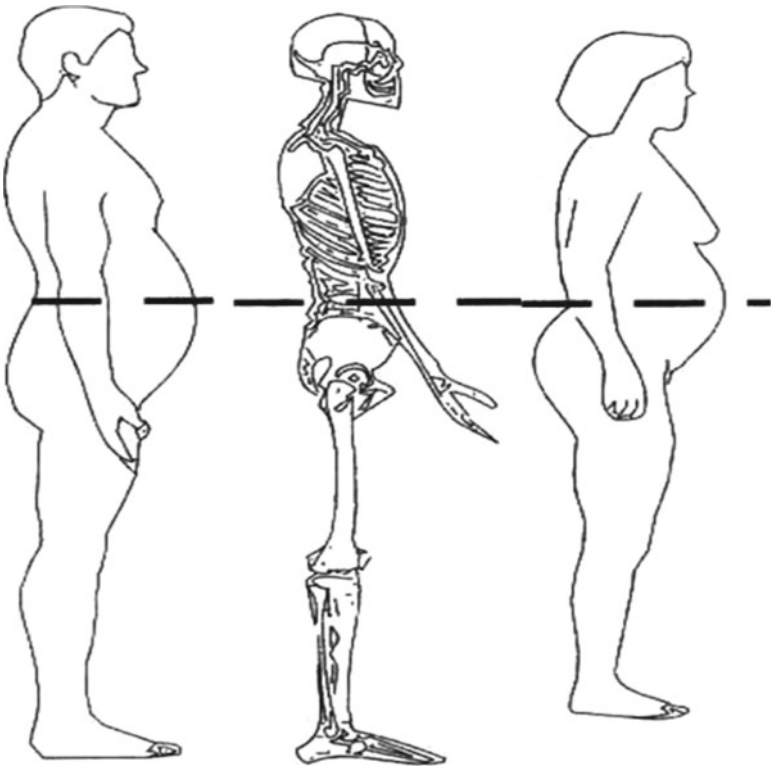

Fig. 125.3 Method for measuring waist circumference

In a recent study (Dobbelsteyn et al. 2001) designed to determine and comparatively evaluate cutoff points of WC, BMI, and WHR with respect to their ability to individually or collectively predict a number of cardiovascular risk factors at different ages, including multiple risk factors, the authors concluded that WC is probably the best single anthropometric measure for identifying individuals with cardiovascular disease risk factors, with many advantages over both BMI and WHR, that is, the simplicity by which it may be used in a clinical setting, and the ease of interpretation. In fact, WC assessment requires only the use of a tape measure, reducing the expense of the equipment needed to measure height and weight and, thanks to requiring a single measurement as opposed to the ratio of two measures, it is less susceptible to measurement and calculation errors (Dobbelsteyn et al. 2001).

Regarding surgical risk, several studies used anthropometric measurements for stratifying population on the basis of increased risks. To our experience, these indices have a weak value in predicting complications and conversion (Palomba et al. 2006, 2007). In particular, in a recent study aimed to evaluate any relationship between preoperative assessments and early laparotomic conversions in obese patients who receive laparoscopic surgery for clinical early stage endometrial cancer, we confirmed that a significant percentage subjects were converted to laparotomy for anesthesiologic reasons (Palomba et al. 2007). Furthermore, neither BMI nor other anthropometric measurements, such as WC or WHR, were predictors for anesthesiologic complications during laparoscopy in our sample (Palomba et al. 2007). In fact, no difference in any anthropometric evaluation was detected between patients who stopped the surgical intervention laparoscopically and those who had an early laparotomic conversion for anesthesiologic reasons.

125.4.2 Imaging

Numerous imaging techniques have been developed to assess VF, even if more of them are used only in experimental settings and do not have any application in the clinical practice.

Computed tomography (CT) and magnetic resonance imaging (MRI) was used as excellent tools for quantifying fat-tissue areas. However, these imaging techniques are expensive, MRI is time consuming and CT exposes patients to ionizing radiation. On the other hand, ultrasonography was also proposed as a simple procedure for estimation of the amount of VF, showing its effectiveness in both clinical and research settings.

125.4.2.1 Ultrasonography

During the years, several methods were proposed for assessing the distribution of fat tissue by ultrasonography.

In 1993, a study was conducted to establish a new index of regional fat distribution using ultrasound examination. The thicknesses of the preperitoneal fat layer (P) and subcutaneous fat layer (S) in the abdomen were measured by ultrasonography and the P/S ratio was calculated. The ratio of the maximum thickness of preperitoneal fat to the minimum thickness of subcutaneous fat was termed the abdominal wall fat index (AFI). AFI was shown to be positively correlated with metabolic impairment, suggesting that it may be a new indicator of VF deposition and may reflect lipid metabolism and glucose metabolism disorders (Suzuki et al. 1993).

Unfortunately, the first proposals failed to have a wide clinical application due to the trouble and complexity required to obtain these values.

More recently, Armellini et al. (1997) proposed the use of the sonographic intra-abdominal depth as a useful and simple indicator of VF amount. In particular, the probe is located 1 cm from the umbilicus in a transverse plane and measurements of VF and SF are taken and expressed in centimeters. SF is defined as the distance between the skin and the abdominal fascia, whereas VF is defined as the distance between the internal face of the rectus abdominis muscle and the anterior wall of the aorta (Fig. 125.4a). The VF to SF ratio (VF/SF) can be also calculated as an adjunctive parameter. However, the main difficulty of the Armellini method consists in the problem to have always a clear view of the aorta.

For these reasons, variants to that method have been successively proposed (Koda et al. 2007). Other authors (Koda et al. 2007) measured the distance from the internal face of the rectus abdominis and the anterior wall of the vertebra since it is more easily visible (Fig. 125.4b) and standardized ultrasound intra-abdominal thickness by height.

In clinical use, ultrasonographic fat indices result cheaper and easier than MRI or CT when used for assessing of fat distribution. In fact, sonographic intra-abdominal thickness seems to correlate well with abdominal fat area. In addition, the ultrasonographic measurements of the intra-abdominal muscle–vertebra distance seem to be a valid method in assessing the amount of VF as compared to L4–L5 adipose tissue area considered as a gold standard.

The high concordance of ultrasonography with CT was confirmed in a recent study (Palomba et al. 2007) showing also important clinical implications of that inexpensive, quick, and safe tool. In particular, in obese patients with endometrial cancer undergoing laparoscopy, we demonstrated that both ultrasonographic and CT procedures for assessing VF are useful in giving an estimation of the conversion risk. In fact, VF assessment by ultrasound and CT are strongly related (Fig. 125.5).

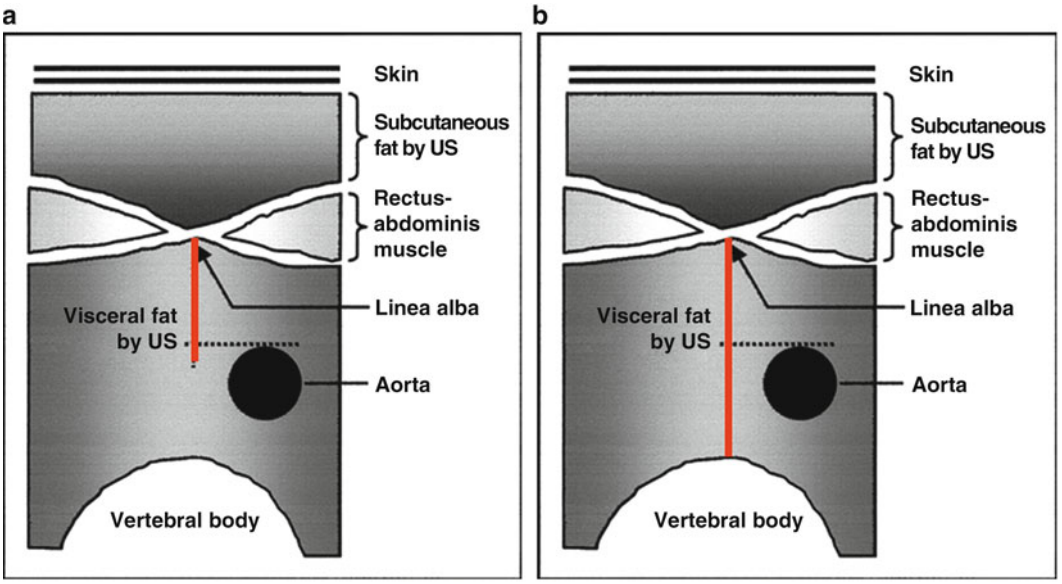

Fig. 125.4 Sonographic intra-abdominal depth by using two different indices for visceral fat amount (**a**) Classic Armellini method (**b**) Variant for sonografic visceral fat measurement

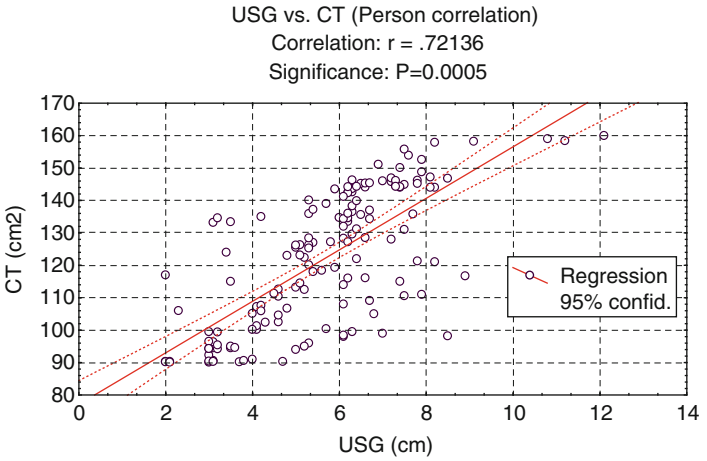

Fig. 125.5 Relationship between ultrasound and computerized tomography indices for visceral fat measurement

125.4.2.2 Computerized Tomography

CT is the most accurate and reproducible technique for assessing body fat and for quantifying the abdominal adiposity. It has been demonstrated to be an accurate and precise technique for measuring soft-tissue composition and for differentiating between visceral and subcutaneous fat in a cross section of the body.

Subjects are placed in the supine position with their arms above their head and legs elevated with a cushion to reduce the curve in the back and at the end of a normal exhalation. VF amount is evaluated using a single tomographic slice with a thickness of 0.5 mm at the L4–L5 level just before the appearance of the common iliac arteries. Specifically, the fields of interest consist of complete intra-abdominal

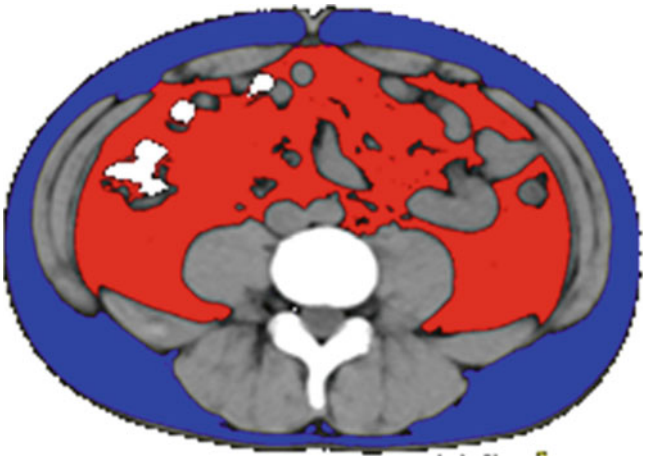

Fig. 125.6 Estimation of visceral fat by computerized tomography

region, and the extension of this area is considered as estimation of the VF (VF-CT) (Fig. 125.6). The intra-abdominal region is defined using the visceral surface of the following structures: rectus abdominis muscles with the linea alba on the midline, internal oblique muscles, psoas major muscles, quadratus lumborum muscles, inferior vena cava, and abdominal aorta (Lamvu et al. 2004).

Binary logistic regression analysis examining the relationship between VF, as an independent variable, and a laparoscopy successfully completed or early converted, as a dependent variable, showed the closest correlation ($r = 0.781$, $p = 0.008$) by using the VF-CT with an RR of 2.2 (Palomba et al. 2007). However, no cutoff value was calculated in order to give any suggestion in the clinical practice for reducing the laparotomic conversions in obese patients (Palomba et al. 2007).

Therefore, CT should be proposed to subjects scheduled for imaging evaluations before surgery, without adjunctive costs and risks.

125.4.2.3 Dual-Energy X-Ray Absorptiometry

An alternative method for measuring total body soft-tissue composition is dual-energy X-ray absorptiometry (DXA), based on the exponential attenuation of X-rays at two energies as they pass through body tissues. DXA provides accurate and precise measurements of fat, bone mineral content and fat-free soft tissue in the total body and in specific regions.

Because DXA is able to provide measurements at two dimensions, it is not possible to differentiate directly between VF and SF. Furthermore, VF is evaluated with that method either by using the standard trunk region or by manually defining a subregion at the abdomen. These subregions correlate with VF with small intra- and inter-operator variation (Snijder et al. 2002).

A recent study (Snijder et al. 2002) showed that DXA is useful in measuring total abdominal fat in elderly men and women when a single-slice CT is used as a gold standard, although it seems to underestimate total abdominal fat, in particular, when it is less. Furthermore, DXA is not superior to anthropometric measurements in prediction of visceral fat by CT (Snijder et al. 2002).

125.4.2.4 Magnetic Resonance Imaging

MRI compares well with CT-measured fat and both techniques have a similar accuracy in comparison with chemical analysis. Compared to CT, the risk of radiation exposure is really reduced by MRI

using a single planimetric evaluation obtained at the umbilical level with a successive process of 3D images. With the spectral attenuation with inversion recovery (SPAIR) water-suppression THRIVE (3D T1-high-resolution isotropic volume examination) technique, water can be selectively inverted, and when the T1-relaxation of the water signal reaches the null point, only the fat signal is excited by impression of the excitation pulse. Thus, MRI allows the estimation of adipose tissue, skeletal muscle, and other internal tissues and organs. In particular, MRI allows the quantification of the distribution of adipose tissue into visceral, subcutaneous, and more recently intermuscular depots.

The main limitation of MRI is the high costs in scan acquisition and processing of data. Claustrophobic persons cannot be scanned, and large individuals cannot fit within field of view. In addition, neither MRI nor CT is capable of accommodating very large persons, as the field of view for most MRI scanners is limited to 48 × 48 cm.

125.5 Conclusions

A presurgical assessment of VF should always be done in obese patients to estimate the risk of complication and to assess the risk of laparotomic conversion in patients scheduled for laparoscopic surgery (Table 125.1).

Anthropometric measurements are cheap and easy to perform but have a low value in the prediction of these surgical risks. On the other hand, imaging assessment of VF is useful, with significant relationship with surgical complications and, in particular, early laparotomic conversion for patients undergoing laparoscopic surgery.

An increased VF in obese and overweight patients should be considered as an adjunctive risk factor to identify a subgroup of patients with high risk conditions. In these patients, more accurate cardiopulmonary and anesthesiologic evaluations should be done in order to reduce the incidence not only of surgical complications but also of critical care during the postoperative period.

Summary Points

- Obesity, and, specifically, visceral obesity, is closely related to metabolic, cardiovascular and respiratory abnormalities, an increased risk for surgical intervention and of adult cancers.
- An increased visceral fat correlates with higher risks for both surgery and anesthesiology managements.
- In obese subjects, laparoscopic procedures seem to improve patient morbidity, even if an increased visceral fat is related to a higher laparotomic conversion rate.
- The body mass index is an accurate measure for obesity, even if it does not give any information regarding the body percentage of fat and lean mass. Similarly, no distinction between visceral and subcutaneous fat can be obtained by using this index.
- Waist-to-hip ratio and waist circumference are both indices of regional distribution of adipose tissue in the body.
- Neither body mass index nor waist-to-hip ratio nor waist circumference is an accurate predictor for anesthesiologic complications during laparoscopy.
- Ultrasonography is a cheap and simple tool for the assessment of fat distribution.
- Computerized tomography is the most accurate and reproducible technique for assessing body fat and for quantifying abdominal adiposity.

- Visceral fat assessment by using computerized tomography should be proposed to subjects scheduled for presurgical imaging evaluation without adjunctive costs and risks.
- In obese women undergoing laparoscopic treatment of early stage endometrial cancer, visceral fat, assessed with ultrasonography and with computerized tomography, is an accurate predictor for the laparotomic conversion risk.

Key Features

Table 125.1 Key features of the presurgical assessment of intra-abdominal visceral fat

1. In obese patients, a preliminary assessment of visceral fat is needed in order to prevent intra- and post-operative complications.
2. Visceral fat is the main factor related to early laparotomic conversion due to anesthesiology complications in patients undergoing laparoscopy.
3. Anthropometric measurements are reproducible, cheap and easy to perform, but they have a poor predictive value for anesthesiology complications.
4. Ultrasonography and computerized tomography are two noninvasive and accurate methods for evaluating visceral fat. Thus, they can be used for predicting an increased risk of surgical complications, including laparotomic conversion.
5. Other imaging techniques, as well as dual-energy X-ray absorptiometry and magnetic resonance imaging, do not have a favorable cost–efficacy ratio when compared to ultrasonography and computerized tomography.

This table lists the key points of the presurgical evaluation of intra-abdominal visceral fat in obese patients

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Part XIX
Anthropometry in Diabetes

Chapter 126
Maternal Anthropometric Indices and Gestational Diabetes

Edwina Yeung, Yiqing Song, and Cuilin Zhang

Abstract The prevalence of gestational diabetes (GDM) has been on the rise worldwide. GDM is glucose intolerance first detected in pregnancy and heightens the risk of caesarian section, prematurity and neonatal mortality, to name a few of its consequences. Greater prepregnancy BMI is a strong risk factor for GDM with evidence that overweight doubles its risk and obesity triples it. Other anthropometric risk factors of GDM reviewed in this chapter include low birth weight, short stature or leg length, increased abdominal adiposity (by waist circumference or waist-to-hip ratio), excessive total adiposity by skinfolds, greater gestational weight gain, and postpartum weight retention. Due to the strong association between prepregnancy BMI and the risk of GDM, these other anthropometric risk factors were also evaluated for whether there is evidence that they can delineate risks apart from that related to BMI; that is, whether they have clinical relevance independent of pregravid BMI. Scarce evidence was given that measures of total adiposity by skinfolds add to discriminating participants at risk for GDM that may not have been determined by prepregnancy BMI. Measures of central adiposity by waist and hip circumferences may have added information. Difficulties in measurement may preclude their use in clinical practice as they require some technical training to obtain valid and reliable values. Short stature or leg length and low birth weight, were factors that remained associated with increased risk of GDM independent of BMI but these associations were weak. Investigations of these associations, however, support the developmental origins of human disease hypothesis and generate evidence that early life risk factors may be important for future health. Gestational weight gain has been regarded as not to be a determinant of GDM by the Institute of Medicine, and review of the studies to date supports their conclusion, although there is some evidence that it is still relevant for development of less severe forms of hyperglycemia in pregnancy. Lastly, post-partum weight retention may increase the risk of GDM in subsequent pregnancies but this is through the mechanism of BMI. In conclusion, anthropometry does play a significant role in the development of GDM and investigations of its measures may bring about greater understanding of the etiology of the disease, even if not all measures are suitable for clinical use.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_126,

Abbreviations

ADA	American Diabetes Association
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CI	Confidence interval
CT	Computer tomography
CVD	Cardiovascular disease
Dx	Diagnosis
DXA	Dual energy x-ray absorptiometry
GDM	Gestational diabetes
GH	Growth hormone
GWG	Gestational weight gain
HOMA-IR	Homeostasis model of insulin resistance
ICC	Intra-class correlation coefficient
ICD-9	International Classification of Diseases, 9th edition
IGF-1	Insulin-like growth factor-1
IGT	Impaired glucose tolerance
IOM	Institute of Medicine
MRI	Magnetic resonance imaging
NDDG	National Diabetes Data Group
NHANES	National Health and Nutrition Examination Survey
NGT	Normal glucose tolerance
NHSII	Nurses' Health Study II
OGTT	Oral glucose tolerance test
OR	Odds ratio
PE	Preeclampsia
PNSS	Pregnancy Nutrition Surveillance System
ROC	receiver operating characteristic
RR	Relative risk
SCAT	Subcutaneous adipose tissue
SD	Standard deviation
T2D	Type 2 diabetes
TSF	Total skinfolds
US	United States
VAT	Visceral adipose tissue
WC	Waist circumference
WHO	World Health Organization
WHR	Waist to hip ratio

126.1 Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance with first onset or diagnosis during pregnancy (ADA 2009) (Table 126.1). Failure to resolve the condition postpartum may be an indication of undiagnosed preexisting type 2 diabetes (T2D) in the mother, rather than GDM. The pathology of

Table 126.1 Key facts of gestational diabetes mellitus

- Gestational diabetes mellitus is high blood sugar that starts or is first diagnosed during pregnancy
- Pregnant women with GDM usually do not have any severe symptoms prior to their diagnosis and their sugar levels return to normal after the delivery
- American Diabetes Association and American Society of Obstetrics and Gynecology recommend screening pregnant women at low risk for GDM between the 24th and 28th week of pregnancy, which involves blood taken and measured for glucose after fasting overnight and at an hour after the woman ingests a glucose dose (usually 50 g of sugar)
- Depending on the blood sugar levels, women then may go on to be tested with a lengthy diagnostic test (i.e., oral glucose tolerance test). Different doctors will screen and diagnose GDM using different cut-points for what is regarded as "high" glucose levels and with different glucose doses (see Table 126.2 for various diagnostic criteria)
- GDM affects about 3–7% of all pregnancies. It has been found to occur more among women who are ethnic minorities have a parent with type 2 diabetes, are older than 25 years when pregnant, or are overweight
- It leads to greater risk of the baby being born very large (i.e., macrosomia), which creates difficulties at birth including physical injury to the baby and increased need to have a C-section for the mother (see Table 126.3)
- There is some evidence that GDM has longer lasting effects, with increased risk to both the mother and child to have type 2 diabetes in the future
- Prevention or early detection of GDM is vital to avoid pregnancy complications and future risk of type 2 diabetes

This table lists some key facts regarding the characteristics and epidemiology of gestational diabetes mellitus

Table 126.2 Criteria for diagnosis of gestational diabetes mellitus

Measure	WHO	ADA	Carpenter & Coustan	NDDG
OGTT dose (g)	75	75 (or 100)	100	100
Fasting glucose (mg/d)	126	95	95	105
1-h glucose (mg/dl)	–	180	180	190
2-h glucose (mg/dl)	140	155	155	165
3-h glucose (mg/dl)	–	n/a (140)[a]	140	145
Diagnostic criteria	*1 of 2*	*2 of 3*	*2 of 4*	*2 of 4*

This table provides the multiple diagnostic criteria for GDM used worldwide. Although the WHO criterion requires only one measurement of glucose to be above the cut-point listed, the other criteria require at least two measurements to be above the values indicated (NDDG 1979; Carpenter and Coustan 1982; WHO/IDF 2006; ADA 2009)
OGTT oral glucose tolerance test, *WHO* World Health Organization, *ADA* American Diabetes Association, *NDDG* National Diabetes Data Group
[a]ADA criteria either by 75- or 100-g OGTT with 3-hr cutoff only applicable for the 100-g test

GDM has been discussed extensively in other works (Buchanan and Xiang 2005; Metzger et al. 2007; Reece et al. 2009) and is reviewed briefly here. Pregnancy naturally increases insulin resistance. This increase is hypothesized due to both increased maternal adiposity and placental hormones, (Buchanan and Xiang 2005) and functions to provide necessary nutrients to the fetus. Failure to compensate for this increase in insulin resistance through increased insulin secretion by expansion of β-cells of the pancreas leads to abnormally high glucose levels in the blood which marks GDM (Buchanan 2001). It is believed that women who develop GDM already have decreased β-cell capacity for insulin secretion prior to pregnancy and that the pregnancy unmasked this defect (Buchanan 2001). Multiple factors may contribute to β-cell dysfunction, including mutations in genes involved in insulin secretion.

GDM is commonly diagnosed at the third trimester of pregnancy (i.e., 24–32 weeks' gestation) by oral glucose tolerance test. The diagnostic criterion used varies in different areas of the world (Table 126.2). It has been estimated that GDM affects 3–7% of pregnancies in the USA and occurs more frequently among ethnic minorities (Dabelea et al. 2005). Similarly, it is estimated to affect

Table 126.3 Maternal and perinatal/neonatal complications from GDM

Maternal
• Cesarean section
• Preeclampsia
• Postpartum type 2 diabetes
Perinatal/neonatal
• Macrosomia
• Birth injury
• Shoulder dystocia
• Metabolic complications
◦ Hypoglycemia
◦ Hyperbilirubinemia
◦ Hypocalcemia
◦ Erythremia
• Polycythemia
• Prematurity
• Respiratory distress syndrome
• Mortality
• Increased risk of obesity and type 2 diabetes later in life

This table lists the complications that occur to both the mother and the baby from GDM (2004)

3–5% of pregnancies in the UK (Ben-Haroush et al. 2004). Worldwide estimates of GDM prevalence are unclear, as screening and diagnostic practices affect estimates. Nevertheless, even at the lowest estimate of 3%, the burden of GDM is considerable, as it is associated with increased risk of complications to both mother and fetus (Table 126.3) including cesarean section, preeclampsia, prematurity, macrosomia, shoulder dystocia, and perinatal mortality. Using US National Hospital Discharge Survey data, which included information on 27,000 maternal–child pairs, Chen et al (2009) estimated that GDM increased mean health-related expenditures by $3,305 per pregnancy and, additionally, $209 for the first year of life for the infant born to the GDM mother. Extrapolating this information to the 180,000 GDM pregnancies that occurred in 2007, the authors concluded that over $600 million was spent in additional medical care due to GDM. These costs, however, do not incorporate the increased costs at later life of both the mother and child. For example, after the index pregnancy complicated by GDM, the cumulative incidence of diabetes ranged from 2.6% to over 70% in studies that examined women 6 weeks postpartum to 28 years postpartum (Kim et al. 2002). This increase in diabetes risk associated with GDM is similar, regardless of ethnic subgroups or maternal age, although body mass index (BMI) at GDM diagnosis and subsequently at T2D diagnosis does play a role (Bellamy et al. 2009).

Anthropometry, especially body mass index (BMI), is a predominating risk factor for GDM. Other maternal anthropometric measures have also been investigated in relation to GDM development including maternal birth weight, central adiposity (e.g., waist and hip circumferences), skinfold thickness, height, leg length, pregnancy weight gain, and postpartum weight retention. Conversely, GDM may also affect changes in anthropometry after pregnancy including increased postpartum weight retention. The following chapter will review the evidence of these anthropometric measures as risk factors for GDM.

126.2 Maternal Anthropometry and GDM

126.2.1 Practical Methods and Techniques for Measurement of Anthropometry in Pregnant Women

Some methods to measure anthropometry may not be feasible in pregnant women due to safety concerns. In general, most methods are similar to those used in non-pregnant individuals (McCarthy et al. 2004). Pre-pregnancy measures of anthropometry may be more ideal markers of risk, as they are less likely to be misclassified due to pregnancy (e.g., waist circumference due to fetal growth vs. maternal growth). However, most women come for their clinical visit after the onset of pregnancy, which makes it a more convenient window for evaluation. Measures taken during pregnancy need to take into consideration the length of pregnancy at the time of measurement to correctly account for anthropometric changes that occur due to pregnancy. Anthropometric changes could also independently be a risk factor for GDM, in addition to static measures at any one time point (e.g., pregnancy weight gain).

126.2.2 Body Mass Index

Obesity is a top global concern in the twenty-first century. Pregnancy is not an exception, with an alarmingly high proportion of women beginning their pregnancy overweight or obese. In USA, this has been estimated to be 45% of all pregnant women (Gunderson. 2009). Pregravid BMI is a major risk factor for GDM, and determines risk much more strongly than even maternal age, ethnicity, birth weight, or diet (Radesky et al. 2008). Table 126.4 highlights the key points on BMI and GDM risk.

BMI is defined as weight (in kilograms) divided by height (in meters) squared. It has been used by the World Health Organization (WHO) to categorize individuals as normal (20–24.9 kg/m^2), overweight (25–29.9 kg/m^2), stage 1 obese (30–34.9 kg/m^2), stage 2 obese (35–39.9 kg/m^2), or stage 3 obese (≥40 kg/m^2). BMI remains an important risk factor for GDM, both because of its increase in prevalence over recent years and as it is a modifiable risk factor compared to other established risk factors (e.g., family history).

A meta-analysis of 70 studies (published between 1977 and 2007), which included 671,945 women, found that the prevalence of GDM increased in a dose-dependent manner by BMI (Fig. 126.1) (Torloni et al. 2009). Compared to normal-weight women, the combined odds ratio

Table 126.4 Key points of BMI and GDM Risk

1.	BMI, which accounts for weight and height, is a fairly good marker of total adiposity except among individuals who have high lean muscle mass. These individuals tend to be heavier even though they are lean. Its measurement, however, is simple and reliable, with the use of a standard scale and stadiometer
2.	The causal evidence between BMI and the development of GDM is fairly strong and consistent across many observational studies. Compared to women with normal pre-pregnancy BMI (BMI<25 kg/m^2), women at greater BMI who are overweight (BMI 25–30) or obese (≥30) can have two to six times greater risk of GDM during pregnancy. Studies of bariatric surgery have demonstrated that weight loss can decrease the risk of GDM, which further supports causality
3.	Excess adiposity is tied to development of GDM through affecting insulin resistance and pancreatic beta-cell function through multiple pathways including dysregulation in production of adipokines (e.g., adiponectin and leptin) and inflammatory cytokines (e.g., C-reactive protein and tumor necrosis factor-alpha)

This table lists the key points that highlight the findings on maternal BMI and GDM risk

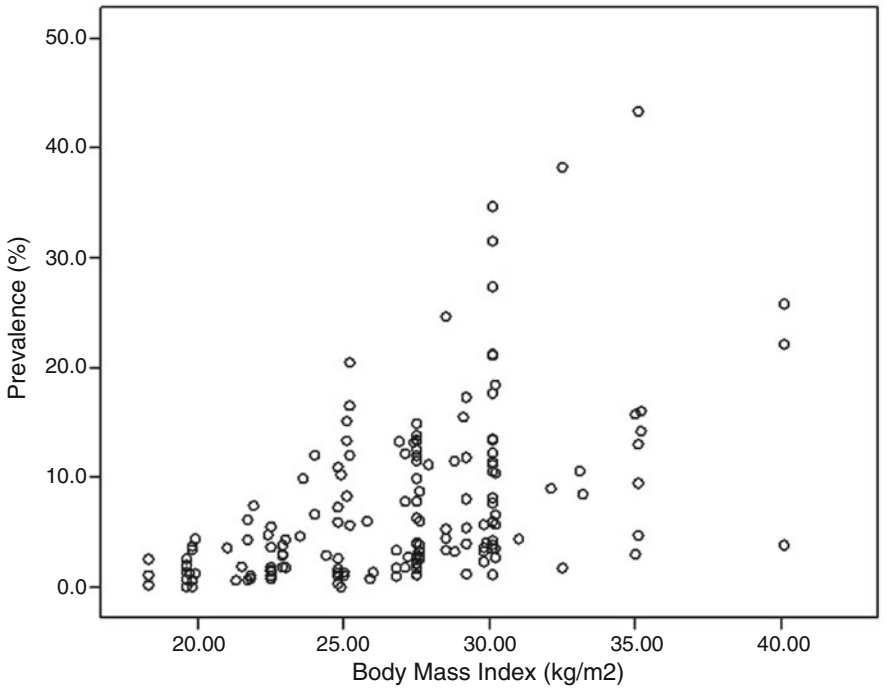

Fig. 126.1 Prevalence of GDM according to initial maternal BMI. Prevalence of GDM by pre-pregnancy BMI using information from 56 cohort studies (165 comparisons) that provided raw data with information from a total of 631,763 women. Estimating the risk of GDM in a linear fashion, each one unit increase in BMI increased the risk of GDM by 0.92% (95% CI 0.73–1.10). Extrapolating this to one category increase in BMI (i.e., 5 units) would result in 4.6% increase in GDM (Reproduced with permission from Obesity Reviews. Copyright 2009, Blackwell Publishing, Torloni et al. 2009)

(OR) and 95% confidence interval (CI) for GDM was 1.97 (95%CI: 1.77–2.19) among overweight women, 3.01 (95%CI: 2.34–3.87) among obese women, and 5.55 (95%CI: 4.27–7.21) among morbidly obese women (Torloni et al. 2009). Figure 126.2 shows all the studies and the pooled odds ratio of non-obese versus obese women for risk of GDM. No significant heterogeneity in associations was found for studies by method of assessing BMI (i.e., self-report vs. measured), region of study (i.e., North America, Western Europe, or Latin America/Middle East), prevalence of GDM (i.e., <5% or >5%), and study sample size. However, a difference was found by diagnostic criteria used ($p = 0.02$ for heterogeneity), with a stronger association found for studies which diagnosed GDM based on the 100-g OGTT (pooled OR: 4.19 (95%CI: 3.46–5.08)) compared to the 75-g OGTT (pooled OR 2.86 (95%CI: 2.25–3.62)).

Obesity is implicated in the pathogenesis of GDM via multiple mechanisms. As mentioned earlier, insulin resistance increases naturally during pregnancy. Overweight or obesity also increases insulin resistance through obstructing the insulin signaling pathway. For individuals with insulin resistance, the binding of insulin secreted from pancreatic β-cells to glucose transporters in muscle and liver cells does not trigger the adequate response required for glucose transport. Thus, glucose levels in the bloodstream remain high, which leads to negative effects for the mother and for the fetus exposed.

Adipose tissue, until recently, has been viewed as only storage units for excess lipids. However, recent breakthroughs have demonstrated that they are highly active endocrine tissues, secreting hormones called adipokines that have wide-ranging effects including those on appetite and insulin resistance (Berg and Scherer 2005). Excess adiposity, however, leads to dysregulation of these hormones,

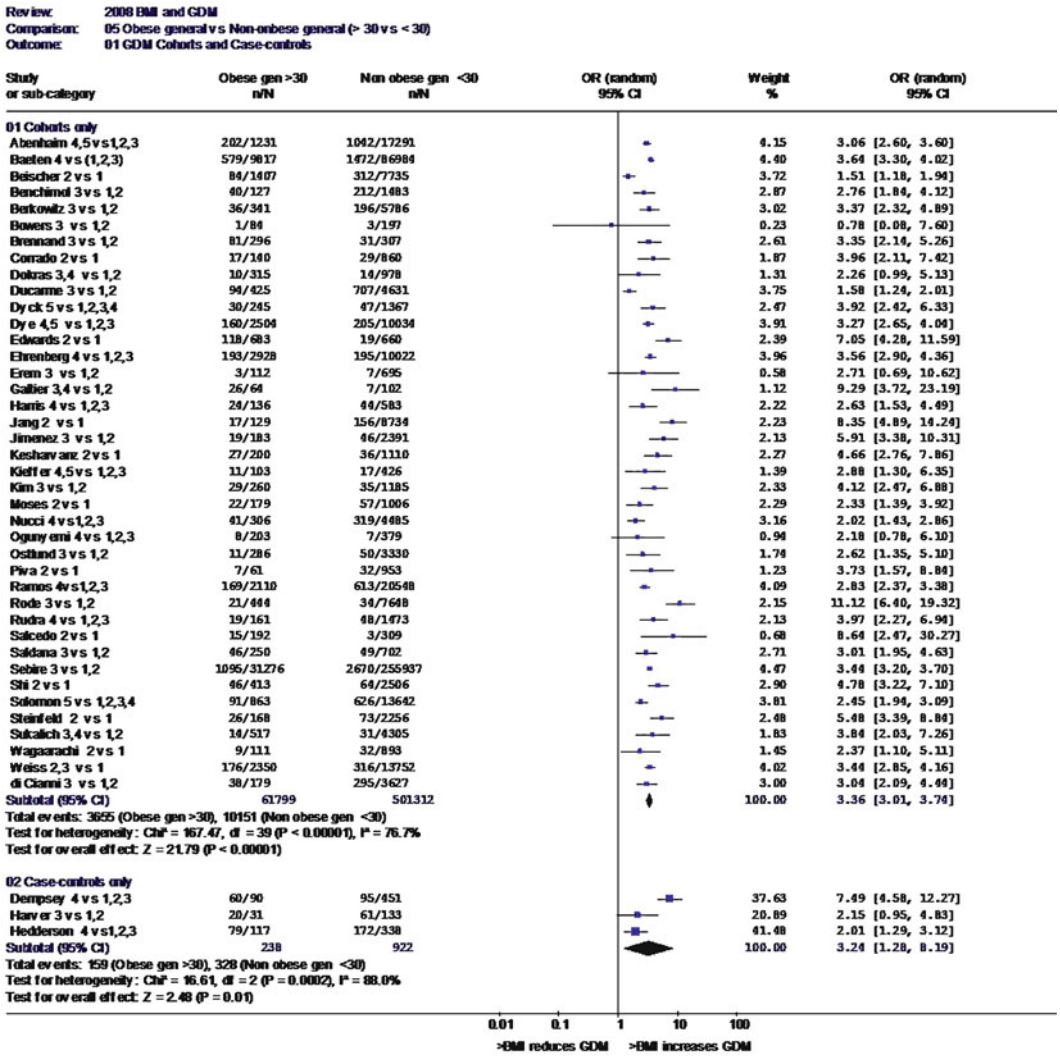

Fig. 126.2 Risk of GDM in obese and non-obese women in a meta-analysis. Meta-analysis of 40 cohort and three case-control studies on risk of GDM by pre-pregnancy obesity status (BMI>30 kg/m^2). Studies published between 1977 and 2007 were located from four databases (MEDLINE, EMBASE, CINAHL, and LILACS) (Reproduced with permission from Obesity Reviews. Copyright 2009, Blackwell Publishing, Torloni et al. 2009)

which subsequently generates metabolic imbalances stemming from lack of satiety in response to meals or to increasing inflammation. Levels of cytokines involved in inflammation, such as C-reactive protein, have been linked to increased risk of GDM (Wolf et al. 2003). As the understanding of these different molecular pathways becomes clear, interventions targeted at specific pathways may arise.

However, weight loss prior to pregnancy will likely remain the most important intervention in preventing GDM among overweight and obese women. Obese women who conceived post-bariatric surgery have a decreased risk of GDM (Guelinckx et al. 2009). Weight loss by less drastic methods between pregnancies of women who weighed over 200 lbs in their first pregnancy has also shown to significantly decrease the risk of GDM (Glazer et al. 2004). Of 4,102 women captured in the

Washington State Longitudinal Birth Database, women who lost at least 10 lbs of weight before their second pregnancy had 37% less risk of GDM compared to women who remained at the same weight (±10 lbs) (Glazer et al. 2004).

126.2.3 Central Adiposity and Its Measurement

Body fat distribution has been demonstrated to be more closely related to metabolic disorder than total adiposity (Ibrahim 2009). Upper body or android (i.e., "apple" shape) obesity leads to greater risk of CVD and T2D than peripheral or gynoid (i.e., "pear" shape) obesity (Ibrahim 2009). Individuals with android obesity have more visceral adipose tissue (VAT) than those with peripheral adiposity who store excess energy to a greater extent in their subcutaneous depots (SCAT). Anatomical, structural, and molecular differences between visceral and subcutaneous adiposity help to explain how the two depots affect metabolic risk (Ibrahim 2009). Specific measurements of VAT and SCAT require computed tomography (CT) or magnetic resonance imaging (MRI) to differentiate between the two adipose depots in the abdominal region. However, anthropometric measurements of central adiposity have been found to be effective alternatives to measures by CT or MRI, which are prohibited in pregnant women and thus impossible for studies of GDM.

Central adiposity can be assessed via measurements of waist (WC) and the ratio of waist to hip circumferences (WHR). These circumferences are typically measured by tape measure and may be more subject to measurement error than measures of height and weight. Moreover, it would be ideal to have pre-pregnancy measurements to ensure that measures are not due to fetal or placental mass. Various methods for measurement of WC have been used in research, from taking the narrowest waist to use of anatomical landmarks for its measurement (Ross et al. 2008). The National Health and Nutrition Examination Survey (NHANES), for example, measures WC at the uppermost lateral border of the right ilium (IC) and its protocol has been adopted by various organizations for defining abdominal adiposity. Even though as a continuous measure, methods of measurement do not seem to affect its association with mortality or morbidity including diabetes risk, it may be important to note the method of measurement for comparison between study means (Ross et al. 2008). For hip girth, the tape measure is placed at the level of the symphysis pubis and is run down to determine the site of the maximal protrusion of the gluteal muscles. The WHR additionally provides information on the distribution of adiposity (i.e., upper vs. lower). Despite being more technically involved, previous studies have shown that trained personnel could conduct these measurements with high reliability. Among a large group of women, measurements of waist, hip, and WHR had intraclass correlation coefficients (ICC) of 0.89, 0.81, and 0.74, respectively (Sonnenschein et al. 1993).

Despite the concern that measurement of waist after pregnancy onset is biased by fetal growth, the first trimester visit remains an important access point for clinicians. Thus, of note is that Branchtein et al. (1997) investigated the longitudinal changes in waist by uterine height and concluded that measurements conducted before the 26th week of gestation should reflect mainly central fat deposition rather than fetal growth. Valid measurements of WC can therefore be conducted early in pregnancy.

126.2.4 Evidence for Central Adiposity and GDM Risk

Given the strong association between BMI and GDM as discussed above, it would be important to determine whether waist or WHR is an independent predictor of GDM after accounting for BMI. However, the findings seem to be conflicting on the subject. Table 126.5 reviews the evidence of the

Table 126.5 Studies of the association between central adiposity and GDM

Author (year)	Study design	Study period	GDM diagnostic criteria	Controls/cases	Assessment	Mean (SD) age; BMI; WHR	Covariates adjusted for in statistical models	Associations with risk of GDM
Zhang et al. (1995)	Prospective US cohort study (CARDIA) with pre-pregnancy visits	1985–1993	Self-report	720/44	Measured waist (minimal abdominal girth) and hip (maximal protrusion)	Not given	age-adjusted and multivariate adjusted (age, race, BMI, family history, and parity) relative risks	Age-adjusted highest vs. lowest tertile: WC: RR = 2.31 Hip: RR = 2.44 WHR: RR = 2.61 Multivariate adjusted for WHR: T3 vs. T1: 4.02 (95%CI: 1.50–10.77) T2 vs. T1: 2.74 (1.02–7.35) BMI not associated after adjust for WHR (p-trend = 0.16)
Branchtein et al. (1997)	Two general prenatal care units in Brazil at 21–28 weeks gestation	1991–1993	WHO	1025/4 (71 with impaired glucose tolerance)	Measured in duplicate – waist (minimal abdominal girth), hip (maximal protrusion)	27.8 (6) yrs; 23.9 (4) kg/m^2 pre-pregnancy; 0.84 (0.06)	age, height, skinfold thickness, ambient temperature, parity, clinic	2-h glucose levels as outcome rather than GDM due to few cases; 1 SD increase in WHR = 0.11 mmol/l increase in 2-h glucose. 1 SD increase in WC = 0.13 mmol/l increase in 2-h glucose

(continued)

Table 126.5 (continued)

Author (year)	Study design	Study period	GDM diagnostic criteria	Controls/cases	Assessment	Mean (SD) age; BMI; WHR	Covariates adjusted for in statistical models	Associations with risk of GDM
Wendland et al. (2007)	Expanded above for six sites (Brazilian Study of GDM)	1991–1995	WHO	4735/354	Measured in duplicate – waist (minimal abdominal girth)	27.6 (5) yrs; 23.2 (4) kg/m^2 pre-pregnancy; waist = 81.7 (8) cm	Unadjusted ORs (calculated from authors' prevalences)	Quintiles of WC: Q5 vs. Q1: 2.91 (95% CI: 2.07–4.08); Q4 vs. Q1: 1.54 (1.07–2.23); Q3 vs. Q1: 1.04 (0.70–1.55), Q2 vs. Q1: 0.90 (0.59–1.35); ROC AUCs: pregravid BMI = 0.615 WC = 0.621
Madhavan et al. (2008)	Consecutive patients from gynecology unit at ≤12 weeks gestation in India	2005–2006	ADA	106/8	Measured waist (midpoint between iliac crest and lowest rib) and hip (widest area)	26 (4) yrs; 21.6 (4) kg/m^2; 0.85 (0.03)	Stratified by both BMI and WHR in subgroup analyses	WHR >0.85: OR = 12.05 (1.82–77.43); BMI > 23: OR = 7.5 (1.61–34.31). Subgroup: WHR more strongly a risk factor among heavier women (BMI > 23); By ROC, BMI a better determinant of GDM than waist or WHR

Yeung et al. (2009)	Prospective US cohort study (NHSII) with pre-pregnancy data	1989–2001	Self-report	4981/264	Self-reported waist (measured at navel) and hip circumferences (maximal protrusion)	30 (3) yrs; 23.0 (4) kg/m^2; 0.78 (0.08)	age, race, BMI, smoking, parental history T2D, age of first birth, parity and physical activity	Quintiles of WHR: Q5 vs. Q1: 2.12 (95% CI: 1.38–3.26); Q4 vs. Q1: 2.03 (1.30–3.17); Q3 vs. Q1: 1.51 (0.94–2.42), Q2 vs. Q1: 1.50 (0.94–2.39); Quintiles of WC Q5 vs. Q1: 1.88 (95% CI: 1.14–3.09); Q4 vs. Q1: 1.90 (1.20–3.00); Q3 vs. Q1: 1.47 (0.84–2.56), Q2 vs. Q1: 1.05 (0.64–1.79)

This table describes the study characteristics and summarizes the findings from literature on maternal central adiposity and GDM risk. The articles were located by a MEDLINE search conducted in September 2009. Mean (standard deviation) are noted where authors made information available

ADA American Diabetes Association, *CARDIA* Coronary Artery Risk Development in Young Adults, *BMI* body mass index, *CI* confidence interval, *GDM* gestational diabetes mellitus, *mmol/l* millimoles per liter, *NHSII* Nurses' Health Study II, *SD* standard deviation; *WC* waist circumference, *WHO* World Health Organization, *yrs* years

five studies published to date that have investigated central adiposity and development of GDM (Zhang et al. 1995; Branchtein et al. 1997; Wendland et al. 2007; Madhavan et al. 2008; Yeung et al. 2009). Of these studies, the CARDIA and NHSII studies investigated these associations using pre-pregnancy measurements and found that larger waist and WHR were significantly associated with increased risk of GDM (Zhang et al. 1995; Yeung et al. 2009). In CARDIA, compared to women in the lowest tertile (WHR 0.629–0.705), women in the highest tertile (WHR 0.743–1.02) had four times the risk of GDM even after adjusting for BMI, leading the investigators to conclude that WHR may be a better marker for GDM risk than BMI (Zhang et al. 1995). Significant associations with GDM risk were seen for both WC and WHR in NHSII after adjusting for BMI (Yeung et al. 2009). Findings from Branchtein et al. (1997) using 2-hr glucose levels among pregnant women undergoing OGTT as outcome demonstrated that women with higher WHR or WC had higher glucose levels, even after accounting for adiposity by skinfold thickness. However, a follow-up study in the same Brazilian cohort by Wendland et al. (2007) did not give sufficient evidence for these associations with GDM. Although crude ORs for GDM increased by increasing quintiles of WC, the investigators did not provide results from a BMI-adjusted model or results by WHR due to the lack of information on hip circumference. However, area under ROC curves were virtually the same (AUC ~0.6) by WC or BMI for discriminating women with GDM, leading the authors to conclude that both measures carry similar clinical information (Wendland et al. 2007). Lastly, a pilot study in India found an interaction between WHR and BMI, with WHR being a stronger risk factor among women who are heavier (Madhavan et al. 2008). From their analyses using ROC curves, BMI was found to be better than WHR or WC at predicting GDM case status (Madhavan et al. 2008). These findings, however, were based on only eight GDM cases. Taken together, these five studies suggest that WC and WHR are determinants of GDM though how much information they may add to clinical practice, in addition to BMI, remains unclear.

The CARDIA study showed results by hip circumference, with greater risk by increasing tertiles (Zhang et al. 1995). This finding, however, is in contradiction with what was observed in NHSII which found no association and in type 2 diabetes literature, where larger hip circumference has generally been found to be associated with decreased risk of T2D after accounting for total adiposity (Parker et al. 2009; Yeung et al. 2009). Biologically, hip circumference, as a surrogate measure of SCAT, should be protective after accounting for total adiposity. Clearly, more research is need for understanding how these anthropometric variables of central adiposity relate to development of GDM.

126.2.5 Maternal Body Composition

Measurement of skinfolds is one method by which investigators have assessed body composition without the use of tests, such as dual energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA), that are potentially harmful for the fetus in pregnant women. Multiple measurements of skinfolds need to be conducted and care taken that the pressure exerted on the calipers was consistent for all measurements. There are undoubtedly a number of limitations to use of skinfolds, including low reliability and unavailability of some sites that would be difficult to measure in later pregnancy. However, given the lack of other safe methods to estimate total body fat during pregnancy, these measures remain important to consider for investigation of GDM.

Fat accretion and rates of subcutaneous fat accumulation during normal pregnancy by skinfolds have been documented extensively (Taggart et al. 1967; Forsum et al. 1989; Sidebottom et al. 2001). Taggart et al. measured multiple skinfolds throughout pregnancy in 84 pregnant women (Taggart et al. 1967). Measurements were made in triplicate by the first author for the whole study at seven

sites (coefficient of variation, CV), including the triceps (4%), biceps (12%), scapula (4%), costal (6%), suprailiac (11%), mid-thigh (3%), and knee-cap (5%) (Taggart et al. 1967). Analyses were conducted standardized to weeks 10, 20, 30, and 38 weeks of gestation. Total skinfolds (TSF) increased to a greater extent in nulliparous than multiparous women (Taggart et al. 1967). Skinfolds did not increase as greatly among women who were obese (Taggart et al. 1967).

The relationship between body fat by skinfolds and GDM has been explored in several studies (Ehrenberg et al. 2003; Kale et al. 2005; Yilmaz et al. 2009). Of these, two were cross-sectional, with measurements of skinfolds by GDM status only conducted at one point in time (Kale et al. 2005; Yilmaz et al. 2009). Yilmaz et al. (2009) found that women with GDM (n = 56) had greater total body fat by sum of skinfolds compared to women with normal pregnancy (n = 42) at 26–36 weeks' gestation (22.0% vs. 20.8%, p = 0.007). Kale et al (2005) measured maternal skinfolds within 24 h of delivery and similarly found that the sum of skinfolds was greatly increased among GDM mothers (98.4 vs. 61.4 mm, $p < 0.001$) and that this difference was true even among lean women (BMI < 25 kg/m^2), though no data were shown. The only longitudinal study conducted (n = 19 GDM, 33 NGT) with measurements taken at 12–14 and at 33–36 weeks concluded that pre-pregnancy body fat had a greater influence on accumulation of body fat than GDM status (Ehrenberg et al. 2003). Findings from these studies suggest that subcutaneous fat by skinfolds' measures is increased in women with GDM. However, no strong evidence has been given that this information is advantageous in predicting risk of GDM over risks associated with pre-pregnancy BMI.

126.2.6 Maternal Height

Eight of ten studies have found that maternal height is inversely related to the risk of GDM even after accounting for pre-pregnancy weight and other GDM risk factors (Table 126.6) (Jang et al. 1998; Anastasiou et al. 1998; Kousta et al. 2000; Branchtein et al. 2000; Innes et al. 2002; Tabak et al. 2002; Yang et al. 2002; Di et al. 2003; Kale et al. 2005; Rudra et al. 2007; Yeung et al. 2009). The two studies which did not find a significant association may have been influenced by methodological problems regarding the selection of cases and controls from different hospitals and time periods (Tabak et al. 2002; Kale et al. 2005). One early study that looked at this association explicitly was conducted in a cohort of Korean women (n = 8863, 1.9% GDM) and found that women in the lowest quartile of height (≤157 cm) had twice the risk of GDM as women in the highest quartile (≥163 cm), even after adjusting for age and BMI (Jang et al. 1998). Despite differences in mean height by race, the magnitude of association was similar in Brazilian (adjusted OR = 1.60, p = 0.005) and American (adjusted OR = 1.76, p = 0.002) women, when comparing highest to lowest cohort-specific quartiles of height (Branchtein et al. 2000; Innes et al. 2002). In absolute differences, women with GDM were, on average, 1–3 cm shorter than women who did not develop GDM.

One factor of note that might not have been adequately addressed by most of the studies, however, was a birth cohort effect. To capture enough GDM cases for the studies, periods of 5–6 years of screening were used, which introduces the possibility of birth cohort effects that considering for maternal age may not properly account for. For example, a 25-year-old woman screened in 1995 would be born in an earlier birth cohort than a 25-year-old woman screened in 2000. In fact, the woman screened in 1995, born in 1960, may be shorter due to the increasing trend in height over time (Jang et al. 1998). Nevertheless, two studies that investigated the birth cohort effect on these associations found that the inverse height association remained significant even after stratifying the sample by birth cohort, despite taller height being found in women born in more recent times (Jang et al. 1998; Anastasiou et al. 1998).

Table 126.6 Studies of the association between height and GDM

Author (year)	Study design	Study period	GDM diagnostic criteria	Race/Ethnicity	Sample size (controls/cases)	Age; BMI; height	Covariates adjusted for in statistical models	Associations with risk of GDM or difference in height by GDM status
Jang et al. (1998)	Cross-sectional at 24–28 weeks' gestation from single hospital with universal screening	1991–1994	NDDG	Korean	8863/168	28.5 (3) yrs; 20.1 (2) kg/m^2; 160.0 (4) cm	age, pre-pregnancy weight, pre-pregnancy BMI, parental history, parity, and weight gain	GDM vs NGT: OR by height quartiles: Q4 vs. Q1: 2.04 (95% CI: 1.37–3.03) Q3 vs. Q1: 1.50 (0.91–2.46) Q2 vs. Q1: 1.15 (0.66–2.03)
Anastasiou et al. (1998)	Cross-sectional at 24–32 weeks' gestation from single hospital with women referred to for screening	1990–1996	NDDG	Greek	2087/685	29.5 (6) yrs; 24.8 (5) kg/m^2; 161.0 (6) cm	age, weight, education, and one abnormal glucose value	GDM vs. NGT: −2.52 cm (95% CI: −3.06 to −1.98)
Kousta et al. (2000)	Case-control at median 22 months postpartum; ten hospitals for cases; one hospital with universal screening for controls	1997–1999	WHO	European (W), South Asian (SA), Afro-Caribbean (B)	470/346 (W: 282/169, SA: 94/102; B: 94/75)	29–40 yrs; 23–30 kg/m^2 postpartum; 155–165 cm	stratified by ethnicity	GDM vs. NGT: W: −2.4 cm (162.9 vs. 165.3, $p < 0.0001$) SA: −3.0 cm (155.2 vs. 158.2, $p < 0.0001$) B: −1.5 cm (162.2 vs. 163.7, $p = 0.10$)

Tabak et al. (2000)	Cross-sectional analysis of two cohorts; one case only (n = 186)	1999–2000 & 1985–1990	WHO	Hungarian	517/280	27.2 (5) yrs; 23.4 (4)kg/m^2; 165.1 (6) cm	year of birth	GDM vs. NGT: unadjusted difference = –3.2 cm ($p < 0.0001$); adjusted difference = 0.3, $p = 0.70$
Branchtein et al. (2000)	Cross-sectional at 21–28 weeks' gestation from multiple general prenatal care units	1991–1995	WHO	Brazilian (white, black or mixed)	4973/ not given	27.8 (6) yrs; 23.4 (4) kg/m^2; 155.7 (7) cm	age, obesity, family history, race, education, gestational age, parity, referral, waist, and ambient temperature	Adjusted OR by height quartiles: Q4 vs. Q1: OR = 1.60 ($p = 0.005$) Q3 vs. Q1: OR = 1.12 ($p = 0.52$) Q2 vs. Q1: OR = 1.02 ($p = 0.91$)
Innes et al. (2002)	Case-control of women with first pregnancy using New York State Department of Health registry data	1994–1998	ICD-9 (648.0)	81% White, 12% Black, 5% Hispanic, 2% Other	22955/440	21.1 (4) yrs; median: 22.9 kg/m^2; median: 165 cm	age, race, and education, employment, maternal diabetes, pre-pregnancy weight, alcohol, and smoking	Adjusted OR by height quartiles: Q4 vs. Q1: OR = 1.76 (95%CI: 1.25–2.46) Q3 vs. Q1: OR = 1.15 (0.82–1.61) Q2 vs. Q1: OR = 1.53 (1.11–2.10)
Yang et al. (2002)	Cross-sectional at 26–30 weeks' gestation of all women screened from six Tianjin districts	1998–1999	WHO	Chinese	9109/174	26.8 (3) yrs; 21.2 (3) kg/m^2; 161.7 (5) cm	age, pre-pregnancy BMI, weight gain, family history, and smoking	Adjusted OR per cm increase in stature = 0.96 (95% CI: 0.93–0.99)

(continued)

Table 126.6 (continued)

Author (year)	Study design	Study period	GDM diagnostic criteria	Race/Ethnicity	Sample size (controls/cases)	Age; BMI; height	Covariates adjusted for in statistical models	Associations with risk of GDM or difference in height by GDM status
Di et al. (2003)	Cross-sectional at 24–28 weeks' gestation from single site with universal screening	1995–2001	Carpenter & Coustan	Italian	3473/333	31.1 (5) yrs; 22.5 (4) kg/m^2; 164 (6) cm	age, parity, family history, pre-pregnancy BMI, and weight gain	GDM vs. NGT: adjusted difference = −2.60 (p = 0.02)
Kale et al. (2005)	Retrospective case control from two hospitals (all controls from second hospital in 1998)	1998–2003	WHO	Asian Indian	315/268	25.6 (4) yrs; median: 21.9 kg/m^2; 153.0 (6) cm	age, parity and gestation at delivery	Height of GDM women vs. non-GDM women: 154.4 vs. 153.0 (p>0.05 after adjustment)
Rudra 2006	Orospective Omega Study cohort with two site hospitals in Washington, USA	1996–2002	NDDG	85% White, 2% Black, 3% Hispanic, 7% Asian, 3% Other	1644/67	71% between 20–34 yrs; 66% with BMI 19.8–26.0 kg/m^2; and unknown height	age, race, education, pre-pregnancy BMI	RR by categories of height with ≤160 cm as reference: vs. 161–165 cm: 0.54 (95% CI: 0.30–0.97) vs. 166–170 cm: 0.43 (0.23–0.82) vs. >170: 0.26 (0.11–0.59)

This table describes the studies on maternal height and GDM risk identified from MEDLINE in September 2009. Mean (SD) are given where authors made information available for age, BMI, and height

BMI body mass index, *GDM* gestational diabetes mellitus, *ICD-9* International Classification of Diseases, 9th edition, *NDDG* National Diabetes Data Group, *NGT* normal glucose tolerance, *OR* odds ratio, *p* p-value, *RR* relative risk, *SD* standard deviation, *WHO* World Health Organization, *yrs* years

A few hypotheses have been proposed as to the mechanism explaining the relationship between height and GDM. Insulin secretion impairment prior to puberty could have affected growth directly or indirectly via growth hormone and related factors (i.e., GH/IGF-1 axis) (Anastasiou et al. 1998). Puberty is known to be a time of increased insulin resistance (Goran and Gower 2001), thus underlying the fact that insulin secretion impairment may have resulted in short stature. Another mechanism hypothesized is that reduced fetal growth affected both pancreatic development and height potential. Evidence for this hypothesis comes from findings that socioeconomic status is associated with both factors. Branchtein et al. (2000) found that the inverse association of height with GDM risk was significant only among women with greater fat mass as determined by skinfold thickness, suggesting that early fetal or childhood malnutrition was at work to decrease height but led to more weight gain in later life. Lastly, common pleiotropic genes regulating both height and glucose intolerance may also play a role in this association. These hypotheses suggest that the relationship is not causal, but rather that height is a proxy of insulin secretion impairment due to either the direct effect of that impairment on height or factors which influence both insulin secretion and height.

126.2.7 Maternal Leg Length

Height may be a reflection of shorter leg length. It is generally accepted that shorter leg length is the result of growth delay in childhood due to a suboptimal early life environment which could arise from socioeconomic deprivation (Kim et al. 2008). A birth cohort of 2,879 British adults followed since childhood has demonstrated that breastfeeding and energy intake at 4 years of age were significant determinants of leg length (Wadsworth et al. 2002). In terms of measurements of leg length (i.e., femur and tibia length), most studies have taken the difference between standing (head to toe) and sitting heights (head to buttocks). Others have also looked at relative leg length, including leg to height ratio or leg to trunk length ratio.

Three studies have investigated the association between leg length and GDM development. In one study from Wollongong, Australia ($n = 161$ controls, 61 cases), the association between shorter stature and GDM was specifically attributed to shorter leg length (−3.2 cm), with no difference in trunk length ($p = 0.36$). (Moses and Mackay 2004) Findings were similar from a study of 831 healthy women from Kunming, China (163 cases), where GDM was associated with shorter leg length (−0.80 cm), leg to height ratio (−0.3%), and leg to trunk ratio (−0.4%) (Ma et al. 2007). A cross-sectional study using the National Health and Nutrition Examination Survey (NHANES) III cohort found that leg length tended to be 1 cm shorter among women who reported a history of GDM, although this difference did not reach significance ($p = 0.18$) due to the few number of cases ($n = 85$) (Kim et al. 2008). In summary, shorter height and leg length are both significantly, albeit weakly, associated with risk of GDM. Further studies are needed to tease apart the exact mechanisms. Although it is unlikely that such data would be used in clinical practice due to their weak associations with GDM, these observations have led to a greater emphasis on life-course risk factors of GDM and highlight the significant role of childhood environment on future risk of chronic conditions.

126.2.8 Birth Weight

Other markers of developmental inadequacy may also play a role in GDM. Low birth weight has been established as a risk factor for many conditions including type 2 diabetes as another chapter in

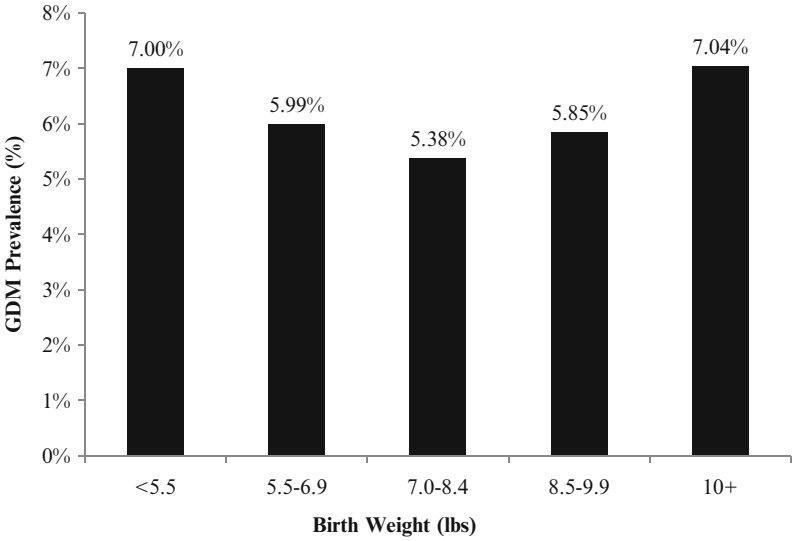

Fig. 126.3 Prevalence of GDM by birth weight among 19,018 women from the Nurses' Health Study II (unpublished results). A U-shaped association was observed between maternal birth weight and GDM prevalence using unpublished data in the Nurses' Health Study II (1991–2001). The prevalence is estimated from women who reported having a singleton birth with no previous history of diabetes (type 1 or 2 or gestational), CVD, or cancer

this book also addresses. The prevalence of GDM by maternal birth-weight categories from a US cohort of women from the Nurses' Health Study II exhibits a similar pattern (Fig. 126.3). A systematic review of eight studies assessing the association between maternal birth weight and GDM have demonstrated that the association is either linear inverse or J-shaped, with increased risk at both low and high birth weights (Pettitt and Jovanovic 2007).

One study conducted using New York state birth registry data ($n = 23{,}314$) found that the J-shape disappears after adjusting for family history of diabetes and that high birth weight was no longer significantly associated with increased risk of GDM (Innes et al. 2002) (Refer to Table 126.3 on height and GDM for more details of the study.). This finding is consistent with what is known about maternal hyperglycemia leading to greater risk of macrosomia in the offspring. Adjusting for parental diabetes then took into account those infants born to women who may have had diabetes during their pregnancy and therefore had children who were larger (i.e., macrosomic). The risk among women born 10 lbs or greater also became non-significant after adjustment for various risk factors including parental T2D history, in the NHSII (Yeung et al. 2009). Nevertheless, high birth weight remains a strong predictor of future GDM risk that women should take note of, regardless of whether it is due to shared genetic cause or previous exposure to maternal hyperglycemia.

Associations between birth weight and GDM are weaker when compared to other anthropometric risk factors, such as adulthood BMI or central adiposity. They are, however, independent of adulthood BMI, suggesting that low birth weight functions on a separate pathway. Innes et al. (2002) also found that the association with birth weight and GDM risk significantly differed (p-interaction = 0.007) when participants were stratified by BMI, such that women who were overweight/obese (BMI ≥25 kg/m^2) did not have increased risk of GDM due to low birth weight, whereas the inverse linear trend remained significant ($p < 0.001$) among leaner women

(BMI <25 kg/m^2). Nevertheless, this interaction remains to be replicated and it is widely accepted that low birth weight is a risk factor of GDM for all women.

The suggested mechanisms in explaining the association between low birth weight and risk of GDM are similar to those for height and leg length; that is, the increased risk arises from fetal programming or shared genetic risk (Innes et al. 2002). Individuals born during famine conditions have increased risk of cardiovascular disease and type 2 diabetes hypothesized to be due to fetal programming. Fetal programming involves metabolic adaptations made for the efficient use of energy in face of reduced caloric or protein intake. It is generally believed that these metabolic adaptations lead to dysfunction later in life, when, in childhood or in adulthood, the same individual faces caloric excess (Barker. 2005). The programming may occur by epigenetic changes (i.e., to DNA or histone proteins) modifying the expression of certain genes. Support for the change in caloric accessibility as being a putative cause has been found from studies of type 2 diabetes, which have shown that individuals, who are born at low birth weight and then undergo rapid catch-up growth as children, are at greatest risk of insulin resistance and metabolic dysfunction than their peers, due to being put on an early trajectory of increased weight gain (Eriksson et al. 2003).

126.2.9 Weight Cycling and Weight Gain Since Age 18 Years

Few studies have looked at weight cycling in the context of pregnancy outcomes. Here, we refer to weight cycling as the gaining and losing of weight prior to pregnancy. The Omega study, as previously discussed for height and GDM, also investigated weight cycling and found no association independent of pre-pregnancy BMI (Rudra et al. 2007). No other studies, to our knowledge, have been published on this association.

Conversely, longer-term changes in weight have been investigated (Solomon et al. 1997; Rudra et al. 2007). In a prospective study of 1,644 pregnant women, weight gain since adolescence (i.e., difference in weight at age 18 years and pre-pregnancy weight) was strongly associated with GDM risk even after adjusting for BMI with over twice the risk of GDM observed for women who gained 5–10 lbs (RR 2.19, 95%CI: 0.96–5.05) (Rudra et al. 2007). Weight gain of 10 or more lbs resulted in over three times the risk of GDM (Rudra et al. 2007). Similarly, among 14,613 women (722 GDM cases) in NHSII, a low weight gain of 5–10 lbs since age 18 was associated with a relative risk of GDM of 1.67 (95%CI: 1.37–2.05). Greater weight gain of 20 lbs or more increased the relative risk to 3.56 (95%CI: 2.70–4.69) (Solomon et al. 1997).

126.2.10 Gestational Weight Gain

Gestational weight gain (GWG) must optimize neonatal weight, while concurrently minimizing maternal overweight. Approximately 30–40% of weight gained during pregnancy is fat (Stevens-Simon et al. 1997; Gunderson et al. 2008), which leads it to be suspected as a contributor of GDM risk. Nevertheless, only a handful of studies have looked specifically at whether GWG or rates of weight gain are associated with increased risk of GDM and these investigations have not produced strong evidence (Ratner et al. 1991; Kieffer et al. 2001; Brennand et al. 2005; Saldana et al. 2006; Wolff et al. 2008; Herring et al. 2009; Tovar et al. 2009).

Table 126.7 IOM gestational weight gain and rate of weight gain recommendations by pre-pregnancy BMI

Pre-pregnancy BMI	BMI (kg/m^2) (WHO)	Total weight gain range (lbs)	Rates of weight gain second and third trimester (Mean range in lbs/wk)
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5–24.9	25–35	1 (0.8–1.0)
Overweight	25.0–29.9	15–25	0.6 (0.5–0.7)
Obese	≥30.0	11–20	0.5 (0.4–0.6)

This table consists of the IOM guidelines on gestational weight gain as reproduced with permission from The National Academies Press. Women who are overweight or obese prior to their pregnancy are recommended to gain less weight during pregnancy. Copyright 2009, National Academies of Sciences. Originally in IOM 2009s Weight Gain During Pregnancy: Reexamining the Guidelines Table 126.1. *New Recommendations for total and rate of weight gain during pregnancy, by prepregnancy BMI* (IOM (Institute of Medicine) 2009)
BMI body mass index, *IOM* Institute of Medicine, *WHO* World Health Organization

126.2.11 Guidelines on Gestational Weight Gain

In 2009, the Institute of Medicine (IOM) issued new gestational/pregnancy weight gain guidelines that were revised from guidelines previously issued in 1990 (Table 126.7). The guidelines were provided stratified on pre-pregnancy BMI, which remains the strongest predictor of GWG. The recommendations span a rather large range (~10 lbs). The guidelines draw from evidence among many studies based on maternal and neonatal outcomes. However, due to lack of evidence, GDM has been removed from the guidelines as a definitive complication of GWG. Studies of the adherence to the former IOM guidelines issued in 1990 have shown that many pregnant women do not adhere to the guidelines and frequently gain weight above the recommended levels (Saldana et al. 2006).

126.2.12 Gestational Weight Gain and GDM

Studies investigating GWG with the risk of GDM have made comparisons based on mean GWG, rates of GWG, and the ratio of GWG to the target weight participants should have gained according to the 1990 IOM guidelines. There are methodological difficulties in measuring the causal association between pregnancy weight gain and risk of GDM. Studies that calculated mean GWG as the difference between postpartum weight and pre-pregnancy weight may be affected by GDM treatment and so have found that women with GDM gain less or the same amount of weight as other women (Brennand et al. 2005; Nohr et al. 2008). It is most likely that this observation is due to reverse causality of women being told to restrict their dietary intake after the OGTT in the third trimester.

On the other hand, studies defining GWG by the difference between pre-pregnancy weight and weight prior to or at glucose testing in the third trimester does not capture maternal weight alone but also includes weight from the fetus, placenta, and water retained. Studies of the latter kind have argued that water retention is greatest during the third trimester and that weight prior to 28 weeks remains predominantly maternal weight (Herring et al. 2009). Despite this latter argument, the evidence remains mixed. Among those studies, two found no associations with glucose tolerance (Saldana et al. 2006; Tovar et al. 2009); one found a significant association of higher GWG with increasing risks of impaired glucose tolerance (IGT), a state of intermediate hyperglycemia prior to

overt GDM, but not with GDM itself (Herring et al. 2009); and only one study found a linear relationship with an increased odds ratio for GDM of 1.02 (95% CI: 1.004–1.042) per pound of weight gained (Kieffer et al. 2001). The evidence using rate of GWG and the ratio of GWG compared to target weight by IOM guidelines is equally as mixed, with some suggestion that a greater rate of GWG is more detrimental only among women with a pre-pregnancy BMI in the overweight or obese categories (Saldana et al. 2006; Herring et al. 2009; Tovar et al. 2009).

126.2.13 Weight Retention

Abrupt and dramatic decreases in skinfolds have been observed after delivery, with total measures decreasing by 6.5 mm in 2–3 days postpartum, indicating great anthropometric changes after pregnancy (Taggart et al. 1967). However, weight retention has been observed for many women. From the 1988 National Maternal and Infant Health Survey data, 44% white and 63% black women retain 4 or more lbs after pregnancy (Keppel and Taffel 1993). A more recent review of the data from five pregnancy cohort studies showed that 13–20% of women experienced postpartum weight retention of 5 lbs or more at 1 year after pregnancy (Gunderson 2009).

Pregravid body size, excessive GWG, race, higher parity, and not breastfeeding are some risk factors associated with greater postpartum weight retention (Gunderson 2009). Not many studies have investigated whether specific conditions during pregnancy may also affect weight retention. One study found that women with GDM or preeclampsia are more likely to retain more weight after pregnancy than women with normal births (Suntio et al. 2009). However, the direction of causality remains uncertain. Greater pre-pregnancy BMI and excessive pregnancy weight gain may have led to the development of these conditions and simultaneously to greater weight retention.

Weight retention may lead to risk of GDM in subsequent pregnancies. Childbearing has been shown to particularly increase visceral adiposity (Gunderson et al. 2008), which predisposes women to increased metabolic dysfunction. Parity has been shown to be associated with increased risk of GDM (Egeland et al. 2000). However, it is difficult to tease apart the effects of older maternal age with children born subsequently to the same mother. Parity has also been shown to be associated with increased risk of type 2 diabetes independent of weight, although only grand multiparity (having five or more children) was significantly associated with increased risk (Nicholson et al. 2006).

126.3 Applications to Other Areas of Health and Disease

As mentioned throughout the chapter, many of the findings reported for GDM were observed for type 2 diabetes, as they share some common features of pathology and women with a history of GDM are at substantially increased risk for type 2 diabetes later in life. Women who develop GDM are recommended to lose weight to lower their future risk for developing type 2 diabetes. A larger amount of evidence has been published for short stature, low birth weight, and central adiposity as being risk factors for T2D as well. The associations do not differ for T2D risk among men, suggesting that the etiology is not gender specific. It only remains that pregnancy is likely a stress test that unmasks a woman's risk of metabolic disorders earlier in life. Gestational weight gain may not be as relevant to T2D except as a marker for greater postpartum weight retention, which, in turn, may put a woman on the trajectory of greater BMI as she ages.

126.4 Conclusion

Pre-pregnancy BMI remains the strongest risk factor for GDM risk. Maternal birth weight, height, waist circumference, and gestational weight gain, all play minor roles in comparison to pregravid BMI. The high prevalence of overweight/obesity in women of reproductive age in USA and in some other countries foreshadows a continuing increase in GDM that requires many efforts to be made for weight loss both before and after pregnancy.

Summary Points

- Pre-pregnancy BMI is the strongest anthropometric predictor of GDM risk.
- There is some evidence that supports measurement of waist circumference or waist-to-hip ratio for discriminating risk of GDM in addition to BMI.
- Skinfold measurements remain difficult to perform, especially among pregnant women and there is scarce evidence suggestive that they would be helpful in discriminating who would be at increased risk of GDM.
- Birth weight, height, and leg length are weakly inversely associated with GDM risk and reflect underlying developmental challenges in the women.
- IOM guidelines recommend lower pregnancy weight gain among women of higher pre-pregnancy BMI, although the ranges for these recommendations remain wide. There is a lack of evidence demonstrating that gestational weight gain is associated with increased risk of GDM. It should also be noted that studies on such an association are limited.
- Postpartum weight retention is a concern, as it contributes to increasing BMI as women age, increasing their future risk of GDM in subsequent pregnancies and their future risk of T2D.

Key Terms Used in This Chapter on Maternal Anthropometry and Gestational Diabetes

Coefficient of variation	A statistical measurement of the reliability of a technique. The lower the number, the more reliable the test
Covariates	This term refers to risk factors that are adjusted for in statistical models to ensure that the association between exposure to disease is not due to these factors but rather the primary exposure of interest
Cross-sectional	A study that is conducted at one time point with estimates of risk made on prevalent (i.e., preexisting) conditions rather than incident (i.e., new) conditions
Epigenetic	Changes to the way that a gene functions due not to changes in the DNA sequence (i.e., mutations) but to changes that lead to genes not being expressed through blocking promoter binding or by stopping its translation. Some epigenetic mechanisms include DNA methylation, histone acetylation, and interfering RNA
Gestation	The state of being pregnant which includes time from conception to birth
Hyperglycemia	This medical term refers to when a person has blood glucose levels above normal
Insulin	A hormone the body makes in the pancreas that helps regulate the blood glucose (sugar) level in the body
Insulin resistance	The state in which a person's body no longer responds to insulin so that blood glucose levels are not lowered in response to insulin, leading to higher amounts of insulin being produced to compensate for the loss of effect
Insulin secretion	The ability of the pancreas to produce insulin

Meta-analysis	The process of collecting and quantitatively synthesizing findings from studies on the same topic
Neonatal	The newborn period that corresponds to 1–4 weeks after delivery
Obesity	This is medically defined as a BMI > 30 kg/m^2
Odds ratio	A measure of association which literally conveys the odds of disease in one group compared to the odds of disease in another group. An odds ratio approximates relative risk when the occurrence of the condition is small, which is true for GDM. Thus, it can be thought to be the same as a relative risk estimate
Oral glucose tolerance test	This test is used to diagnose GDM in the third trimester of pregnancy and involves measuring blood glucose levels after the ingestion of a certain dose of glucose (either 75 or 100 g)
Parity	Number of children a woman conceived and delivered
Pleiotropy	This genetic term refers to genes having multiple functions and related to multiple consequences or effects
Pregravid	This term refers to measures taken prior to pregnancy and is synonymous to pre-pregnancy
Perinatal	The duration of pregnancy and after pregnancy that spans approximately from the 20–28th week of gestation to 1–4 weeks after birth
Relative risk	The mathematical calculation of the probability that an event (i.e., GDM) will occur in one group compared to the probability that it occurs in another group. Usually the two groups differ by what they were exposed to (i.e., obese vs. non-obese)
Reliability	The repeatability of a measure; that the value of the first measurement is close to the value of the subsequent measurements
Screening	A medical test that is the first step in identifying who may have a certain condition. This is not the same as a diagnostic test which is necessary to confirm whether the person truly has the condition, in this case GDM
Subcutaneous adiposity	Adiposity that is located just beneath the skin
Type 2 diabetes	This term refers to the chronic medical condition of having persistent high blood glucose levels. The condition is associated with damage to nerves, kidneys, heart, and other organs, which together lead to increased risk of death
Visceral adiposity	Adiposity that is located near the organs and the inner parts of the body rather than near the skin
Weight retention	This refers to the amount of weight that a pregnant woman weighs after delivery that is above the amount they weighed prior to pregnancy

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Chapter 127
Body Size at Birth and Risk of Type 2 Diabetes in Adult Life

Yiqing Song, Lu Wang, Edwina Yeung, and Cuilin Zhang

Abstract A large body of evidence supports the hypothesis that the risk of developing chronic diseases including type 2 diabetes (T2D) in adulthood is related to body size at birth. Birth weight may reflect fetal adaptation to an adverse intrauterine environment due to both genetic and environmental factors. Epidemiologic studies, primarily from prospective cohorts, have consistently shown that birth weight in the 2,500–4,000 g range is inversely associated with T2D risk in adulthood, while increased risk has been found at both extremes of low (<2,500g) and high (>4,000g) birth weight. The association between birth weight and risk of T2D can be modified by postnatal growth. Recent evidence appears to support that low birth weight may be related to rapid postnatal weight gain, which has been associated with increased risk for central obesity and T2D in adult life. Several mechanisms have been proposed to explain the robust association between birth weight and T2D. The "fetal origins hypothesis" remains the most popular one and has been revised based on recent evidence. This review aims to summarize both epidemiological and experimental observations relating birth weight and rapid postnatal weight gain to T2D risk in adulthood. This article will also highlight recent evidence on the mechanisms of fetal programming of diabetes due to maternal and fetal genetic factors as well as fetal epigenetic changes.

Abbreviations

ACE	Angiotensin-converting enzyme
BMI	Body mass index
CDKAL1	Cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1
CDKN2A/CDKN2B	Cyclin-dependent kinase inhibitor 2A/2B
CI	Confidence interval
CVD	Cardiovascular disease
FTO	Fat mass and obesity-associated gene
GCK	Glucokinase gene

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_127,

GWAS	Genome-wide association studies
H19	Adult skeletal muscle gene
HFE	Human hemochromatosis gene
HHEX/IDE	Hematopoietically expressed homeobox/insulin-degrading enzyme
HPA	Hypothalamic-pituitary-adrenal axis
IGF	Insulin-like growth factor
IGF-I	Insulin-like growth factor-I
IGFR1	Insulin-like growth factor type 1 receptor
INS	Insulin gene
IUGR	Intrauterine growth restriction
JAZF1	Juxtaposed with another zinc finger gene 1
KCNJ11	Potassium inwardly-rectifying channel protein gene, subfamily 1, member 11
MC4R	Melanocortin 4 receptor
OR	Odds ratio
Pdx1	Pancreatic and duodenal homeobox 1
PPARG	Peroxisome proliferator-activated receptor gamma gene
RR	Relative risk
SGA	Small for gestational age
TCF7L2	Transcription factor 7-like 2 gene
T2D	Type 2 diabetes mellitus
UK	United Kingdom

127.1 Introduction

Type 2 diabetes (T2D) is considered "the epidemic of the twenty-first century," affecting more than 170 million individuals worldwide (Table 127.1). Overall, it is estimated that the prevalence of diabetes will increase by 42% among adults living in developed countries and by 170% among adults in developing countries by 2025 (Stumvoll et al. 2005). Given the rising global burden of T2D and its devastating complications, there is a great urgency to develop effective strategies to curb the epidemic by prevention and early treatment. In addition, the increasing prevalence of obesity in children has also become a growing threat to public health because it will also further fuel the increase in future prevalence of T2D.

Table 127.1 Key features of type 2 diabetes (T2D)

1. Diabetes mellitus is a group of metabolic diseases characterized by high blood glucose levels that result from impairments in insulin action and/or secretion
2. T2D is the most common form of diabetes. About 90–95% of all diabetes cases are T2D. Historically, it affects adults rather than children, but age of onset has become younger more recently
3. T2D is considered "the epidemic of the twenty-first century," affecting approximately 24 million individuals in USA alone and more than 170 million individuals worldwide. It is estimated that, by the year 2030, these numbers will double
4. It places patients at high risk for serious complications in the eyes, nerves, kidneys, and cardiovascular system
5. Diabetic angiopathy is a major cause of morbidity and mortality in diabetes mellitus. Cardiovascular complications are the leading cause of death in diabetes
6. T2D is a multifactorial disease that involves interactions between many genetic and environmental factors
7. There is an urgent need for early detection and prevention strategies to lessen the burden placed on individuals and society by T2D

This table lists some basic facts of T2D concerning its epidemiology and health effects

T2D is a multifactorial disease that involves interactions between many genetic and environmental factors. In addition to established diabetes risk factors, anthropometric measures at birth, especially birth weight, as surrogates of intrauterine malnutrition, have long been implicated as important predictors for risk of T2D. It has been hypothesized that fetal adaptation to an adverse intrauterine environment during critical periods may have lasting or lifelong effects on the development of metabolic syndrome and its associated chronic diseases, such as T2D, hypertension, and cardiovascular diseases, in adulthood (Hales et al. 1991; Hales and Barker 1992; Barker et al. 1993). Numerous studies have specifically tested this "fetal origins hypothesis" for the etiology of T2D in diverse populations. Majority of epidemiologic studies have focused on birth weight and shown consistent associations with subsequent risk of glucose intolerance and T2D in adult life (Harder et al. 2007; Whincup et al. 2008). Low birth weight is often followed by accelerated postnatal growth, which may be important for risk of T2D in adult life. Emerging evidence has shown that people who had low birth weight are more likely to have rapid weight gain in early life and thereby have higher risk for central obesity, T2D, and cardiovascular disease in later life (Colle et al. 1976; Eriksson et al. 2003; Singhal et al. 2003; Ekelund et al. 2007).

This chapter aims to summarize epidemiologic data on the relation between birth weight and T2D and interpret these data in the context of emerging biological evidence. Given the epidemic of obesity and T2D and trends for increasing birth weight in the general population, it becomes very important to address the public health issue of birth weight from the perspective of T2D prevention. Information regarding environmental and genetic determinants of birth weight and their roles in the development of T2D in adulthood will have major public health implications, from which specific intervention strategies can be better conceived and tailored for primary prevention of T2D in the general population.

127.2 Epidemiologic Evidence on Birth Weight and T2D

Over the last two decades, many observational studies have reported associations between birth weight and subsequent risk of T2D. In 1991, Hales and Barker and their colleagues first reported an inverse association between birth weight and T2D risk, with the highest risk at the lowest levels of birth weight (Hales et al. 1991; Hales and Barker 1992). Subsequently, numerous observational studies have tested the fetal origins hypothesis for T2D in diverse populations. The associations of both low birth weight (<2,500 g) and high birth weight (>4,000 g) with impaired glucose tolerance and increased risk of T2D appeared to be consistent and robust (Harder et al. 2007; Whincup et al. 2008).

127.2.1 The Strength of the Birth Weight–T2D Association

Differences in the study population and participants' basic characteristics may account for some discrepancies in the strength of the association found from the literature. Meta-analysis has been used to combine evidence across various studies and thus reduce sampling error and increase statistical power. A meta-analysis involving a total of 132,180 participants with 6,901 cases found that, as compared with a birth weight of ≥2,500 g, both low birth weight (<2,500 g) and high birth weight (>4,000 g) were associated with increased risk of T2D (odds ratio [OR] = 1.47, 95% confidence interval [CI] = 1.26–1.72 for low birth weight and OR = 1.36, 95% CI = 1.07–1.73 for high birth

weight) (Harder et al. 2007). This finding indicated a U-shaped relation between birth weight and later-life risk of T2D. Another recent meta-analysis, which included more studies (152,084 individuals and 6,090 diabetes cases), reported approximately 20–25% lower risk of T2D associated with each 1,000 g increase in birth weight, indicating a linear inverse relation between birth weight and T2D (Whincup et al. 2008). Because birth weight is closely correlated with many established risk factors for T2D, including parental socioeconomic status, it is very important to adjust for diabetes risk factors and socioeconomic indicators in observational studies including meta-analyses. Birth weight has been independently associated with T2D, even after adjusting for adulthood BMI, physical activity, smoking, dietary habits, and other lifestyle confounders, as well as socioeconomic status (Harder et al. 2007; Whincup et al. 2008). Overall, adjustment for adult socioeconomic status had no apparent effect on the strength of the birth weight–T2D association. It should be noted that approximately 58% of T2D globally could be attributable to overweight and obesity and 90% of T2D cases in Western countries is attributable to weight gain; however, birth weight appears to be associated with T2D independent of BMI at adulthood. In general, the inverse association tended to be slightly attenuated but remained significant after further controlling for adult BMI.

It is worth mentioning that both previous meta-analyses included retrospective studies (in which information was collected after the onset of disease) and therefore were limited by recall and selection bias. In observational studies, the prospective study design allows us to minimize bias due to recall or sample selection. Individual prospective studies with basic cohort characteristics are shown in Table 127.2. Discrepancies in the association between birth weight and T2D risk among these studies cannot clearly tell us the sufficiency or consistency of the evidence over time. To better track how the body of evidence has shifted over time, we performed a cumulative meta-analysis, which calculates the cumulated relative risk estimates over time of studies (Fig. 127.1). We first sorted the data by publication year and then ran a cumulative analysis to see how the combined effect shifted as each individual study was added one after the other. In the plot of the cumulative meta-analysis of 23 prospective cohort studies, we observed a consistent trend toward lower risk of T2D per 1,000 g increase in birth weight that became statistically significant and stabilized by 1999 (Fig. 127.1). With the increasing number of studies included, the influence of a single study on the final summary estimate tended to be minimal. Our summary estimate of RR of 0.78 (95% CI: 0.71–0.85) represents a reliable magnitude of the linear inverse relation between birth weight and T2D, particularly at birth weights of 4,000 g or less.

127.2.2 The Shape of the Birth Weight and T2D Association

Given significant heterogeneity in previous studies, epidemiologic evidence on the strength and shape of the association has been inconsistent. Of the two meta-analyses, one study has found a U-shaped association (Harder et al. 2007), whereas the other reported an inverse linear association (Whincup et al. 2008). Despite this discrepancy in the shape of the association, both studies consistently indicated an increased risk of T2D associated with both low birth weight (<2,500 g) and high birth weights (>4,000 g) (Harder et al. 2007; Whincup et al. 2008). Of note, there is strong evidence of heterogeneity among the published studies in both meta-analyses. For example, two large studies of native North Americans in Arizona and one study in young adults from the Saskatchewan population showed positive associations between birth weight and T2D (Whincup et al. 2008). For higher birth weight, maternal diabetes (including both prepregnancy T2D and gestational diabetes) may be an important factor. Maternal hyperglycemia due to prepregnancy T2D or gestational diabetes could result in fetal and neonatal macrosomia and thus explain most of the excess risk of T2D in individuals

Table 127.2 Prospective cohort studies quantifying the linear relation of birth weight with T2D risk

Author, (publication year)	Country	Year of birth	Mean age (years)	Total number of participants	Total number of T2D cases	RR per 1-kg increase in birth weight[a]
Hales et al. (1991) and Barker et al. (1993)	England	1920–1930 1935–1943	65	765	48	0.75 (0.53–1.06)
Phipps et al. (1993)	England	1935–1943	52	282	11	0.39 (0.13–1.17)
McCance et al. (1994)	United States	1940–1972	30	1,179	210	1.06 (0.84–1.35)
Curhan et al. (1996)	United States	1911–1946	62	22,312	424	0.78 (0.67–0.91)
Lithell et al. (1996)	Sweden	1920–1924	50	1,093	61	0.66 (0.41–1.06)
Fall et al. (1998)	South India	1934–1953	47	506	79	1.24 (0.69–2.25)
Hulman et al. (1998)	United States	1959–1965	29	137	2	2.41 (0.06–89.31)
Martyn et al. (1998)	England	1939–1940	52	337	18	2.03 (0.79–5.19)
Yarbrough et al. (1998)	United States	1907–1941	67	304	30	0.84 (0.56–1.25)
Rich-Edwards et al. (1999)	United States	1921–1946	59	68,396	1199	0.82 (0.77–0.89)
Vanhala et al. (1999)	Finland	1947–1957	48	374	44	0.51 (0.28–0.94)
Forsen et al. (2000)	Finland	1924–1933	70	7,086	513	0.72 (0.60–0.87)
Mi et al. (2000)	China	1948–1954	45	627	28	1.11 (0.48–2.59)
Shiell et al. (2000)	Scotland	1948–1954	43	89	2	0.14 (0.01–2.87)
Birgisdottir et al. (2002)	Iceland	1914–1935	50	4,537	100	0.75 (0.53–1.05)
Eriksson et al. (2003)	Finland	1934–1944	60	8,702	290	0.72 (0.57–0.92)
Hyppőnen et al. (2003)	UK	1958	41	10,683	88	0.71 (0.47–1.08)
Bhargava et al. (2004)	India	1969–1972	29	1,364	61	0.92 (0.49–1.76)
Huxley and Neil (2004)	England	1942–1944	55	129	7	1.36 (0.24–7.55)
Wadsworth et al. (2005)	UK	1946	53	2,715	78	0.66 (0.39–1.12)
De Rooij et al. (2006)	Netherlands	1943–1947	58	678	58	0.57 (0.26–1.23)
Jeffreys et al. (2006)	Scotland	1931–1944	64	2,237	207	0.84 (0.59–1.20)
Lawlor et al. (2006)	Scotland	1950–1956	49	6,845	377	0.48 (0.34–0.68)

T2D type 2 diabetes, *RR* relative risk, *UK* United Kingdom

[a]Multivariate-adjusted relative risk from each individual study; with the exception of three studies by Curhan, Lithell, and McCance et al., all other studies adjusted for age, sex, and BMI, excluding participants with birth weights of more than 4,000 g or maternal diabetes

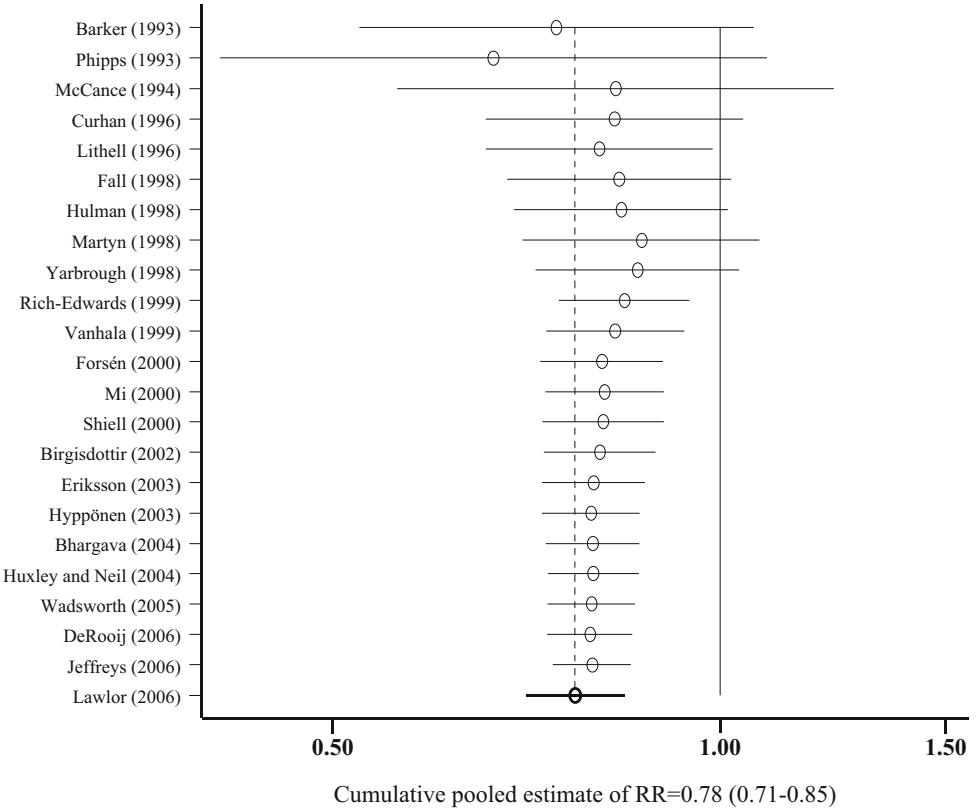

Fig. 127.1 Cumulative meta-analysis plot of relative risk (*RR*) and 95% confidence interval (*CI*) of T2D per 1-kg increase in birth weight based on prospective data (This plot of the cumulative meta-analysis of 23 prospective cohort studies showed a consistent trend toward lower risk of T2D per 1,000-g increase in birth weight that became statistically significant and stabilized after 1999. Source: unpublished meta-analysis results)

who had birth weights of 4,000 g or more. In fact, all three studies showed marked increase in T2D risk among participants with birth weights of more than 4,000 g and thereby showed strong U-shaped associations (Whincup et al. 2008). As a result, the ORs of T2D per 1,000-g increase in birth weight (assuming a linear relation) appeared to be positive, significantly deviating from the findings reported in other studies. Removal of these three studies greatly reduced the heterogeneity. Among 11 studies that had sufficient information, further exclusion of participants with macrosomia or maternal diabetes strengthened the inverse association between birth weight and T2D, lowering the pooled OR from 0.81 (95% CI, 0.77–0.86) to 0.67 (95% CI, 0.61–0.73). As shown in Fig. 127.2, a meta-analysis involving a total of 14 studies provided a suggestive evidence for a U-shaped curve for the relation between birth weight and T2D, with both low and high birth weights related to increased risk of T2D. Compared with the lowest birth weight category (≤ 2,000 g), birth weight within the range from 2,000 to 4,000 g was inversely related to T2D risk. In the birth weight categories of >4,000 g, there was an increasing trend, although the OR in the highest category (>4,500 g) was not statistically significant due to limited data. Taken together, it becomes evident that birth weight is related to T2D in adult life in a U-shaped manner. Both high birth weight (>4,000 g) and low birth weight (<2,500 g) were associated with increased risk of T2D.

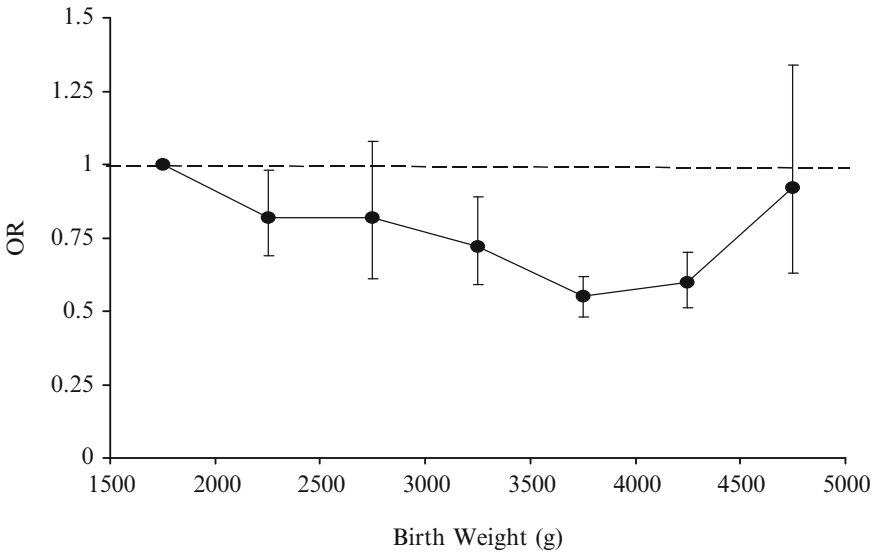

Fig. 127.2 Odds ratios for T2D risk stratified by category of birth weight in a meta-analysis of prospective studies (This figure was created based on the values from Table 3 published in the article by Harder et al. (2007). Based on a total of 14 studies, there was a suggestive evidence for a U-shaped curve for the relation between birth weight and T2D, with both low and high birth weights related to increased risk of T2D. The lowest category of birth weight was used as the reference category in each study. Source: unpublished figure)

127.3 Relations of Postnatal Weight Gain and T2D

Infants born with low birth weights are more likely to develop rapid growth during infancy and childhood. Such rapid postnatal weight gain may play an important role in the development of T2D associated with low birth weight. The largest variation in weight gain after birth occurs in the first 2 years of life, when infants born small for gestational age (SGA) show a rapid early weight gain (Holzhauer et al. 2009). Their fast growth rates are thought to be compensatory responses for the restraint on intrauterine fetal growth (Albertsson-Wikland and Karlberg 1994). A number of studies have shown that rapid postnatal weight gain, irrespective of birth weight, may have adverse effects on metabolic health in later childhood and adulthood (Colle et al. 1976; Eriksson et al. 2002a; Singhal et al. 2003; Ekelund et al. 2007).

127.3.1 Plausible Explanations for Adverse Effect of Rapid Postnatal Weight Gain

Proposed mechanisms for the harmful effect of rapid postnatal weight gain involve endocrine and metabolic changes in response to undernutrition in utero. It is hypothesized that the intrauterine exposure to insufficient nutrient supply during critical periods of fetal life affects the development of skeletal muscle, and results in a lower proportion of lean mass in SGA infants (Hediger et al. 1998). Because there is little muscle cell replication after birth (Widdowson. 1972), rapid postnatal weight

gain would lead to a disproportionately high fat mass relative to lean body mass (Hediger et al. 1998). The accumulation of fat mass in childhood would tend to induce an early onset of persistent obesity and the development of insulin resistance (Barker et al. 1993; Bavdekar et al. 1999; Eriksson et al. 2002a). This interpretation has been supported by several observational studies that linked rapid early weight gain to obesity in later life (Eid 1970; Stettler et al. 2002; Monteiro et al. 2003; Stettler et al. 2005). Another postulation that explains the adverse effect of rapid early weight gain is that when the tissues that are chronically depleted of insulin and insulin-like growth factor-I (IGF-I) during fetal life are exposed to increased concentrations of both hormones shortly after birth, insulin resistance develops as a metabolic defense mechanism to counteract the excessive insulin-like actions of the hormones and protect the organism from hypoglycemia (Cianfarani et al. 1999). Thus, the infants who experience slow fetal growth but early and quick postnatal recovery would have higher risk for insulin resistance and T2D compared to those with no fast postnatal weight gain (Cianfarani et al. 1999). Consistent with this hypothesis, a previous study of 15 full-term infants born with SGA have found a positive correlation between their glucose-induced insulin release and growth velocity during the first 6 months of life (Colle et al. 1976).

127.3.2 Timing Issue for Adverse Effects of Postnatal Growth

It remains unclear what time in the postnatal period with accelerated growth may be disadvantageous. Infants with intrauterine growth retardation usually show a rearrangement of the endocrine system after birth. Normalization of the endocrine parameters occurs during the first trimester of postnatal life (Leger et al. 1996; Cianfarani et al. 1998). Therefore, early infancy is considered a critical time for the development of long-term metabolic disorders (Karlberg and Albertsson-Wikland 1995). There have been several lines of evidence showing association of rapid weight gain in early postnatal period with the adverse metabolic profiles in later life. One intervention study randomized infants born preterm to receive a nutrient-enriched diet or a reference diet at birth and followed them to age 13–16 years (Singhal et al. 2003). The study found higher fasting proinsulin concentration in children given a nutrient-enriched diet than in those given the lower-nutrient diet and weight gain during the first 2 weeks of life was positively associated with insulin resistance in adolescence, irrespective of birth weight (Singhal et al. 2003). Another prospective cohort study reported that rapid weight gain during infancy (0–6 months) but not during early childhood (3–6 years) was positively associated with metabolic risk at age 17 years, independent of birth weight (Ekelund et al. 2007). One potential caveat in many previous studies is the correlation between rapid postnatal weight gain and low birth weight per se. The undernourishment state in SGA infants at the time of birth may facilitate a more efficient nutrient uptake and metabolism that results in a faster postnatal growth rate (Vaag 2009). Furthermore, the statistical "regression toward the mean" may explain the rapid weight gain in early life among SGA infants (Vaag 2009).

Although most infants born SGA show rapid weight gain in the first 2 years, some may have accelerated growth throughout childhood, adolescence, and into adulthood (Karlberg and Albertsson-Wikland 1995), which would further increase the risk of insulin resistance and T2D (Eriksson et al. 2003). Among young children, the degree of obesity as measured by BMI decreases after the age of 2 years, and achieves a minimum around 6 years before BMI increases again; the phenomenon is called adiposity rebound. Early age at adiposity rebound has been related to increased risk of obesity in childhood and adult life (Rolland-Cachera et al. 1987; Whitaker et al. 1998). A longitudinal study of 8,760 subjects born in Helsinki during 1934–1944 had found that the cumulative incidence of T2D decreased progressively from 8.6% in persons whose adiposity rebound occurred before the

age of 5 years to 1.8% in those where it occurred after 7 years (Eriksson et al.2003). Another prospective cohort study of 7,086 men and women in Finland found that the OR of developing T2D was 1.39 (95% CI: 1.21–1.61) for each standard deviation increase in weight between 7 and 15 years of age. The corresponding OR reached 1.83 (95% CI: 1.37–2.45) when the analysis was restricted to persons whose birth weights were below 3,000 g (Forsen et al. 2000).

127.4 Fetal Origins of Adult Onset of T2D

127.4.1 The Original "Thrifty Phenotype Hypothesis"

The development and growth of the fetus are likely determined by a complex interplay between environmental factors (e.g., maternal nutrition and metabolic state) and fetal genetic susceptibility. Several biological mechanisms have been proposed to explain the relation between altered programming in the uterus and birth weight. Hales and Barker first put forth the "thrifty phenotype hypothesis," also known as "the developmental origins of adult disease hypothesis" or the "fetal origins hypothesis" (Hales et al. 1991; Hales and Barker 1992; Barker et al. 1993). On the basis of this hypothesis, irreversible adaptations in tissue and organ growth and development in the fetus in response to prenatal malnutrition increase the predisposition to adult chronic diseases, including T2D and cardiovascular disease.

127.4.2 The "Fetal Insulin Hypothesis" Based on Genetic Evidence

Based on the growing evidence linking low birth weight and measures of insulin resistance, Hattersley and Tooke proposed an extension of the fetal origins hypothesis, called the "fetal insulin hypothesis," to explain the consistent association between low birth weight with diabetes and vascular disease (Hattersley and Tooke 1999). Insulin resistance and progressive pancreatic β-cell dysfunction are two fundamental features in the pathogenesis of T2D. Insulin is also a critical growth factor during fetal life. The central theme of the hypothesis focuses on the genetic basis for insulin-mediated fetal growth (shown in Fig. 127.3). It is hypothesized that fetal genetic factors affect both fetal insulin secretion and insulin sensitivity in peripheral tissues and thereby determine insulin-mediated fetal growth in utero, which may explain the development of insulin resistance in childhood and adulthood that is associated with birth weight.

This hypothesis is supported by the findings from familial genetic studies that have identified several mutations in the genes that affect fetal insulin secretion and insulin resistance, such as glucokinase, insulin receptor, sulfonylurea receptor, and insulin promoter factor 1 (Hattersley and Tooke 1999). The rare monogenic disorders caused by these mutations have significant effects on birth weight. In the general population, however, much remains unknown about the contribution of common genetic variation to birth weight and susceptibility to T2D. Some available genetic evidence is summarized in Table 127.3. Recently, this "fetal insulin hypothesis" is further supported by accumulating data from genome-wide association studies (GWAS) for T2D. In the past 3 years, GWAS has emerged as a comprehensive and powerful approach to identify genetic variants of complex chronic diseases without a priori hypothesis. Preponderance of evidence has led to the identification of more than 20 important genetic loci with robust associations with T2D (Groop and Lyssenko 2008).

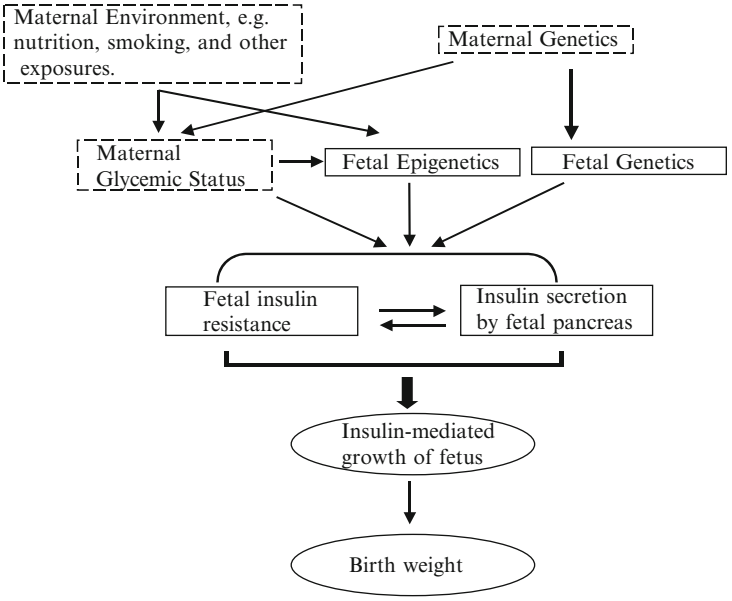

Fig. 127.3 Scheme showing the "fetal insulin hypothesis" for the pathogenesis of fetal growth (The central theme of the hypothesis focuses on the genetic basis for insulin-mediated fetal growth. It is hypothesized that fetal genetic factors affect both fetal insulin secretion and insulin sensitivity in peripheral tissues and thereby determine insulin-mediated fetal growth in utero. Source: unpublished figure)

Table 127.3 A list of potential candidate genes for both birth weight and T2D based on the available data

Source	Susceptibility genes	Main function
Maternal genotype	*TCF7L2*	Insulin secretion
	GCK	Insulin sensitivity
	INS	Insulin production
	H19; IGF1	Growth modulation
Fetal genotype	*HHEX/IDE; CDKAL1; CDKN2A/2B*	Insulin secretion
	FTO; MC4R	Postnatal growth and obesity
	ACE	Obesity and insulin sensitivity
	Leptin and leptin receptor	Appetite and energy balance
	IGF1; IGFR1	Growth modulation
	INS	Insulin production
	PPARG	Insulin sensitivity
	HFE	Iron metabolisms and T2D
	JAZF1	Unknown function

The evidence was summarized from the results from published genetic association studies up to August 2009

TF7L2 transcription factor 7-like 2 gene, *GCK* glucokinase gene, *INS* insulin gene, *H19* adult skeletal muscle gene, *IGF1* insulin-like growth factor 1, *HHEX/IDE* hematopoietically expressed homeobox/insulin-degrading enzyme, *CDKAL1* cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1, *CDKN2A/CDKN2B* cyclin-dependent kinase inhibitor 2A /2B, *KCNJ11* potassium inwardly rectifying channel, subfamily 1, member 11, *FTO* fat mass and obesity-associated, *MC4R* melanocortin 4 receptor, *ACE* angiotensin-converting enzyme gene, *IGFR1* insulin-like growth factor type 1 receptor, *PPARG* peroxisome proliferator-activated receptor gamma gene, *HFE* Human hemochromatosis gene, *JAZF1* juxtaposed with another zinc finger gene 1

Overall, there are several novel findings that may provide new insights into the "fetal insulin hypothesis." First, many genetic variants newly identified by GWAS appear to influence insulin secretion (Pulizzi et al. 2009) but, there is no strong evidence that any of these loci primarily alter insulin resistance. These findings have indicated the key role of genetically determined beta cell dysfunction

in the pathogenesis of T2D. Second, several genetic association studies in white Europeans have investigated the associations between birth weight and maternal or fetal genotype at several recently identified T2D susceptibility loci. Maternal inheritance of common risk alleles in some, but not in all T2D loci, appeared to be associated with higher offspring birth weight (Freathy et al. 2009). These results suggest that maternal risk alleles may determine maternal insulin secretion during pregnancy, which could in turn affect birth weight. Third, fetal inheritance of the risk alleles at *CDKAL1* (*cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1* gene) and *HHEX-IDE* (*hematopoietically expressed homeobox/insulin-degrading enzyme* gene) was also associated with reduced birth weight in four studies of 7,986 mothers and 19,200 offspring (Freathy et al. 2009). Finally, it remains to be defined whether obesity-susceptibility variants contribute to fetal programming, as no strong evidence to date has been shown. The common form of obesity-associated T2D in adults is polygenic and multifactorial in nature. GWAS has identified common variants in the FTO (*the fat mass and obesity associated*) (Freathy et al. 2009) and MC4R (*melanocortin 4 receptor*) genes (Zobel et al. 2009) that are reproducibly associated with T2D through their correlations with fat mass and obesity. However, *FTO* and *MC4R* risk variants appeared to contribute to weight gain during childhood, but not to birth weight (Lopez-Bermejo et al. 2008; Zobel et al. 2009). Taken together, the overall evidence from these findings, though limited, seems to support the "fetal insulin hypothesis" and further suggest that genetically determined beta-cell dysfunction, independent of insulin resistance, may congruently reduce birth weight and predispose individuals to the development of T2D.

127.4.3 Gene–Environment Interactions

It has become increasingly apparent that both birth weight and T2D are determined by a complex interplay between intrauterine environmental factors (e.g., diet and physical activity) and genetic susceptibility. The Helsinki Birth Cohort Study reported significant interactions between common risk variants of three T2D susceptibility genes (*HHEX, CDKN2A/2B*, and *JAZF1*) and birth weight on T2D risk among 2,003 participants with 311 T2D patients. The genetic association with T2D appeared to be more pronounced in individuals with a low birth weight (P for interaction = 0.03 for the most high-risk genotypes) (Pulizzi et al. 2009). Polymorphisms in *PPAR gamma* (*peroxisome proliferator-activated receptor-gamma*), a gene involved in the regulation of both adipogenesis and insulin sensitivity, have been associated with increased T2D risk only among those born with low birth weight (Eriksson et al. 2002b). It seems plausible that rapid weight gain during infancy also reflects a combination of genetically determined rapid weight gain in early life and postnatal environmental factors, but the data are scarce.

127.4.4 Epigenetic Mechanisms

Besides genetic effects, epigenetic modification of the fetal genome triggered by an adverse intrauterine environment has been proposed as part of fetal programming. Changes in intrauterine environment could act as epigenetic stimuli, but epigenetic changes of the genome seem more likely to reflect gene–environment interactions. In the past two decades, the role of epigenetics in human diseases involving regulation of gene expression has drawn widespread interest. Histone post-translational modifications and DNA methylation represent two major epigenetic mechanisms that modulate gene activities in response to environmental changes during development. So far, evidence for an important role of

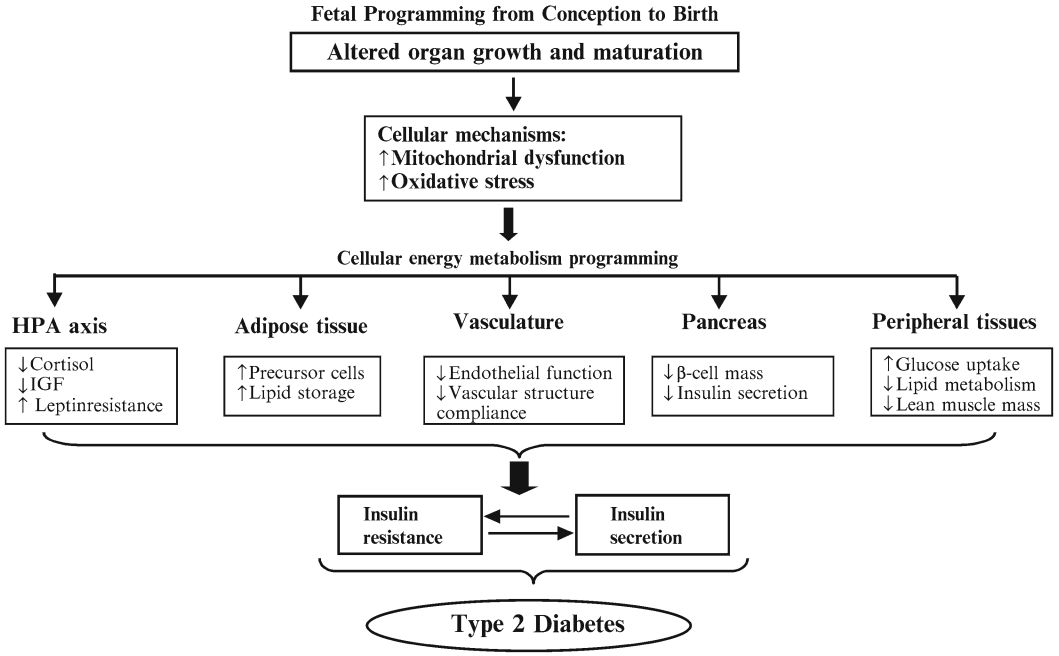

Fig. 127.4 Hypothetic pathways linking birth weight to the development of T2D (It is hypothesized that changes in neuroendocrine balance and cellular energy metabolism may be fundamental to the developmental programming response to intrauterine environments. Insulin resistance and progressive pancreatic β-cell dysfunction are two fundamental features in the pathogenesis of T2D. Abbreviations: HPA, hypothalamic–pituitary–adrenal axis; IGF, insulin-like growth factor. Source: unpublished figure)

epigenetics in the development of T2D predominantly comes from animal studies. For example, a gene (*pancreatic and duodenal homeobox 1*, *Pdx1*) critical for beta cell function and development was found to undergo distinct epigenetic changes in a rat model of intrauterine growth retardation, with its expression reduced by more than 50% (Park et al. 2008). Low levels of *Pdx1* expression persisted after birth and progressively deteriorated in response to dynamic epigenetic processes, finally leading to overt T2D in the IUGR animal. Such epigenetic adaptations in pancreatic gene silencing could induce beta-cell dysfunction in the human fetus, who underwent intrauterine growth retardation. Further investigation of the epigenetic basis of fetal programming holds the promise for unraveling the complex molecular events leading to T2D.

127.4.5 Molecular and Cellular Mechanisms

The development and growth of a fetus depends upon its genotype, intrauterine environments, and gene–environment interactions. The precise molecular and cellular mechanisms underlying the causal link between fetal development and later diseases have yet to be fully elucidated. There is growing evidence indicating that changes in neuroendocrine balance and cellular energy metabolism may be fundamental to the developmental programming response to maternal malnutrition. As shown in Fig. 127.4, proposed mechanisms include altered activation of the hypothalamic–pituitary–adrenal (HPA) axis,

increased tissue glucocorticoid and endocrine sensitivity, leptin resistance, impairment of tissue sensitivity to the insulin and the IGF systems, impaired mitochondrial function and reduced oxidative capacity, and increased number of adipocyte precursor cells. Consequently, these permanent developmental changes in cellular energy metabolism in response to suboptimal intrauterine environments have the potential to ensure short-term survival of the fetus during gestation but increase the risk of a variety of metabolic disorders in later life. It should be noted that fetal development in adipose tissue abundance and function might be critical for an individual's lifetime risk of obesity and T2D. A cohort of infants has been found born with reduced subcutaneous fat but with preserved visceral fat depots (Modi et al. 2006). An increased number of adipocytes may be one of the main determinants of postnatal growth and childhood obesity as well as T2D in later life.

127.5 Implications and Future Research

There is growing evidence supporting the "fetal origins hypothesis" for the development of diabetes in adult life. However, many important questions remain to be answered before we can incorporate measures of birth weight into diabetes risk prediction and treatment. First, fetal development is a multifaceted process, and anthropometric measurements, such as birth weight, may not fully reflect the extent to which body composition has been permanently altered by fetal malnutrition. For example, there is evidence suggesting that size proportions, abdominal circumference, head circumferences, and body length are associated with dyslipidemia in later life. Data for other anthropometric indices at birth in relation to subsequent risk of T2D are limited. Second, additional research is needed to elucidate the causal role of genetically determined insulin secretion in the development of diabetes mellitus during adult life. It is difficult to assess the interaction between maternal glycemia and fetal genetic factors on birth weight. Furthermore, the precise mechanisms that regulate fetal pancreas' development and glucose metabolism remain poorly defined and are likely to vary by different maternal nutrition status. It is also uncertain which period during gestation represents the key window linking fetal growth to risk of T2D in adulthood. Third, the epigenetic mechanisms for fetal programming remain largely uncharacterized. With advance of technology, global epigenetic profiling has recently emerged from basic laboratory exploration to practical applications in clinical research. Mapping and characterizing specific patterns of post-translational epigenetic modifications will transform our understanding of diabetes' pathogenesis and enhance our ability to diagnose and treat this disease. Fourth, most importantly, whether birth weight has a direct causal impact on the multifactorial etiology of T2D requires further evaluation. If birth weight is a genuine causal factor, the public health implication will be substantial. Finally, there is a notable lack of data from prospective studies regarding the clinical and public health significance of birth weight measurement in diabetes prevention, diagnosis, and treatment. Specifically, it is important to decide appropriate clinical cut points of birth weight for T2D risk prediction since its association with T2D is linear at birth weight <4,000 g. More research and careful consideration is needed to evaluate the predictive value of birth weight for risk of T2D.

127.6 Applications to Other Areas of Health and Disease

In addition to T2D, birth weight and postnatal rapid weight gain have been associated with hypertension, cardiovascular disease (CVD), and certain types of cancer, which may share common pathophysiological traits that also underlie T2D (such as insulin resistance and/or compensatory hyperinsulinemia).

Despite inconsistent findings in diverse populations, both birth weight and weight gain in children seemed to correlate significantly with all features of the metabolic syndrome (also known as insulin resistance syndrome) in adulthood including adiposity, hyperinsulinemia, insulin resistance, hypertriglyceridemia, low high-density lipoprotein cholesterol, and hypertension. There is growing recognition that, as a cluster of metabolic abnormalities, the metabolic syndrome is a common antecedent for the initiation of T2D, CVD, colorectal cancer, and prostate cancer. Birth weight measure could also influence the timing of puberty via a pathway related to intrauterine hormones. Low birth weight or rapid growth in infancy has been associated with early age at puberty onset, which may predispose an individual to many hormone-related cancers, including breast and testicular cancer (Michos et al. 2007; Xue and Michels 2007). The etiology of cancer is a multistage process that results from a complex interaction of multiple factors. Although biological mechanisms remain to be elucidated, intrauterine and early postnatal growth hormones may contribute to puberty onset and explain, at least in part, the associations between anthropometric measures at birth and hormone-related cancer risk. For example, high birth weight may result from high levels of growth factors in utero, especially insulin and IGFs, which have potential carcinogenic effects. Some studies have identified that high birth weight and preterm birth were associated with early age at menarche in girls (Terry et al. 2009), although the available evidence has been limited and inconsistent. Early age at menarche (less than 12 years of age) is a well-established risk factor for breast cancer through elevated cumulative exposure to endogenous sex-steroid hormones. There is need for further epidemiologic as well as mechanistic studies to elucidate the underlying biology of the fetal origins of certain types of cancer.

127.7 Conclusions

In summary, epidemiologic evidence from prospective studies for a relation between birth weight, postnatal weight gain, and T2D is accumulating, indicating that anthropometric measures at birth and in childhood may add significant value for clinical risk stratification and prognosis of T2D. Such findings, coupled with a large body of experimental work, advance our understanding of the pathophysiological role of fetal growth and development in the pathogenesis of adult diabetes mellitus. Further investigation is warranted to help decipher the mechanisms underlying the birth weight–T2D association, optimize anthropometric measures for infants and children, identify population at high risk for diabetes, and tailor prediction and intervention strategies in diabetes research.

Summary Points

- An infant's body weight at birth may reflect the degree of fetal growth as a result of maternal environment and fetal genetics.
- Accumulating evidence indicated an increased risk of T2D associated with both low birth weight (<2,500 g) and high birth weight (>4,000 g).
- Prospective data suggest that there is a linear and inverse association between birth weight and T2D in the range of 4,000 g or less and risk of T2D in adulthood.
- Infants with low birth weights are more likely to develop rapid growth during infancy and childhood, and this rapid early weight gain is significantly associated with obesity and T2D in adulthood.
- Genetic defects for insulin production from pancreas may play a critical role in fetal growth and determine future risk of T2D in adults.

- Body size at birth and rapid weight gain during infancy may result from a combination of genetic and environmental factors.
- The clinical utility of anthropometric assessment at birth and during postnatal growth for diabetes risk prediction deserves further investigation.

Terms Used in This Chapter on Body Size at Birth and T2D in Adulthood

Fetal growth	The process in which an embryo or fetus grows in mass during pregnancy, between conception and birth
Postnatal growth	The growth of an infant occurring after birth, especially during the period immediately after birth, with reference to the newborn
Intrauterine growth restriction (IUGR)	The growth of the fetus is abnormally slow. When born, the baby appears too small (fetal size is less than expected for gestational age). IUGR is often associated with increased risk of medical illness and death in the newborn
Birth weight	The measured heaviness of a baby when born, the average of which is about 3,500 g, or 7.5 lb. A baby weighing less than 2,500 g (5.5 lb) is consider small for gestational age and weighing more than 4,500 g (10 lb) is considered as large for gestational age
Macrosomia	The mass of a baby at its birth is above a defined limit at any gestational age
Small for gestational age (SGA)	Infants whose weight is below the 10th percentile at gestational age for all children born after the same number of weeks of pregnancy. A baby could have experienced some IUGR but not necessarily be SGA
Insulin resistance	A condition in which the body is unable to use available insulin effectively
Insulin secretion	The capability of the beta cells of the pancreas to regulate the production and release of mature insulin
Genome-wide association studies (GWAS)	Any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as birth weight or glycemia), or the presence or absence of a disease or condition
Prospective study	A study in which the subjects are identified and then followed forward in time
Cumulative meta-analysis	The repeated performance of conventional meta-analysis whenever a new study becomes available for inclusion. Such cumulative meta-analysis can retrospectively identify the point in time when an effect estimate first reached conventional levels of significance

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Chapter 128
Waist-Circumference Phenotype and Risk of Type 2 Diabetes

Ike S. Okosun and Tandeih A. Ghogomu

Abstract Waist phenotypes (waist circumference, waist-to-hip ratio and waist-to-height ratio) are associated with type 2 diabetes as demonstrated in many studies and confirmed in meta-analyses of prospective studies from various studies. Evidence for the association is stronger for waist circumference and waist-to hip ratio. A verdict is yet to be made with respect to the nature of the association of waist-to-height ratio with type 2 diabetes. The clinical and epidemiologic appeal for the use of waist phenotypes is irrefutable. Waist measurement is simple and requires only a measuring tape and a weighing scale. Effective translation of the use of waist phenotype into clinical practice to predict type 2 diabetes may help in reversing the increasing trend of type 2 diabetes.

Abbreviations

ARIC	Atherosclerosis risk in communities
AUC	Area under curve
BMI	Body mass index
IDF	International Diabetes Federation (IDF)
NCEP-ATPIII	National Cholesterol Education Program-Adult Treatment Panel III
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institute of Health

128.1 Introduction

Awareness of the association between upper-body adiposity and cardiovascular diseases was first recognized over 50 years ago (Vague 1956). Vague observed that upper-body obesity was a better correlate of cardiovascular diseases than excess body weight, as determined by body mass index. He used the terms "android adiposity" to describe the accumulation of fat around the abdomen

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_128,

and "gynoid adiposity" to depict the accumulation of fat found in the hips and thigh regions (Vague 1956). These adiposities were later described as upper- and lower-body fat accumulation (Kissebah et al. 1982). However, the term "abdominal or "central obesity" has replaced android and gynoid forms of obesity. In abdominal or central obesity (also called apple-shape body fat distribution), abdominal fat predominates (Rimm et al. 1988). This form of fat buildup is thought to pose greater health risks than fat accumulation in the hip area (also called pear-shape body fat accumulation). Epidemiologic evidence now suggests that abdominal obesity and not generalized obesity is the most potent form of adiposity that is associated with visceral adiposity. Visceral fat (deep abdominal fats) is the culprit for obesity-associated sequelae (Fox et al. 2007). This chapter will review data from prospective studies that indicated independent association of anthropometric surrogates of abdominal adiposity – waist phenotypes (waist circumference, waist-to-hip ratio, and waist-to-height ratio) with the risk of type 2 diabetes.

128.2 Determination of Abdominal Adiposity

There are various techniques for measuring abdominal obesity. These methods include magnetic resonance imaging, computed tomography, hydrodensitometry, and dual energy X-ray absorptiometry. However, these methods are difficult to use in large-scale epidemiologic settings. The cost, discomfort, and risk associated with these methods can be prohibitive. Also, some of the methods, including X-ray absorptiometry, magnetic resonance imaging, and computed tomography carry added risk of radiation. Hence, anthropometric indices, such as waist circumference, waist-to-hip ratio, and waist-to-height ratio are used as surrogates for abdominal obesity. The diagnostic performance or accuracy of waist circumference, waist-to-hip ratio, and waist-to-height ratio to discriminate cardiovascular risk factors, such as type-2 diabetes, is commonly evaluated using receiver operating characteristic curve analysis.

These anthropometric indices differ with respect to correlation with metabolic abnormalities and have markedly different values in different populations. Correlations between waist phenotypes and body mass index vary across populations. For example, in the Atherosclerosis Risk in Communities (ARIC) study, waist circumference was much highly correlated with body mass index as shown by a correlation coefficient value of 0.90 in African-American and white men and women (Harris et al. 2000). In the same study, the correction coefficient value for the waist-to-hip ratio with body mass index was ~0.60 for men and between 0.40 and 0.50 for women (Harris et al. 2000). The degree of correlation between waist circumference and waist-to-height ratio and between waist circumference and waist-to-hip ratio was high, with values of 0.90 and 0.70, respectively, in men and women (Harris et al. 2000). These differences in correlation may indicate that each waist phenotype measures different aspects of abdominal adiposity.

A meta-analysis of published work from 1966 to 2006 by Lee et al. (2008) indicates that measures of abdominal obesity tend to give a higher *Area under the curve* (AUC) value compared to body mass index, in both sexes, with the highest pooled AUC found for waist-to-height ratio, with values of 0.73 and 0.76, for males and females, respectively. The lowest pooled AUC values were for BMI with values of 0.67 and 0.69 for males and females, respectively (Lee et al. 2008). The tests for heterogeneity between each of the waist phenotypes with BMI showed statistically significant differences between BMI and waist-to-height ratio in males only (AUC for BMI was 0.67 vs AUC for waist-to-height ratio of 0.73) (Lee et al. 2008). The combinations of BMI and waist circumference, waist-to-hip ratio, or waist-to-height ratio did not significantly increase the discriminatory capability of BMI for type-2 diabetes (Lee et al. 2008).

128.3 Waist Variables of Abdominal Obesity

128.3.1 Waist Circumference

Waist circumference is an aggregate measure of the actual amount of total and abdominal fat accumulation (Kissebah et al. 1982). It is a crucial correlate of abnormal metabolic syndromes found among obese and overweight subjects. Waist measurement is simple, requires only a flexible tape, and, with appropriate training, measurement error is low due to the large circumference. Although waist circumference is a simple measure of abdominal obesity, it assumes that people with the same waist circumference would have the same cardiovascular risk, regardless of their height. This assumption is, however, invalid because the percentage body fat is higher for shorter subjects compared to taller individuals of the same body mass index. Waist circumference is highly linked to visceral adipose tissue accumulation (Molarius and Seidell 1998). Visceral adiposity is the component of body composition that is most highly associated with many metabolic abnormalities, such as type 2 diabetes, hypertension, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and high levels of low-density lipoprotein cholesterol (Lemieux et al. 1996; Haffner et al. 1992). Also, waist circumference has the best predictive value for visceral adipose tissue over many of the commonly used anthropometric indices of central body fatness, including triceps and subscapular skinfold thicknesses (Wei et al. 1997). In agreement with the increasing trends in body mass index often seen in many parts of the world, waist circumference is also increasing. An analysis (Okosun et al. 2004) of the US nationally representative sample of adults (20–79 years of age) using the 1960–1962, 1988–1994, and 1999–2000 National Health and Nutrition Examination Surveys showed that the distribution of waist circumference shifted to the right (higher values) in 1988–1994 and in 1999–2000 in both men and women (Fig. 128.1). The right shift suggests increasing prevalence of abdominal obesity.

128.3.2 Waist-to-Hip Ratio

Waist-to-hip measurement is a ratio and as a consequence suffers from statistical limitations in terms of analysis and interpretation (Kronmal 1993; Allison et al. 1995). As a ratio, waist-to-hip is fundamentally difficult to interpret in the public health context because lean and obese individuals can have equivalent values of waist-to-hip ratio. From a statistical viewpoint, ratio indices have shortcomings in modeling because their use can introduce spurious correlation with other ratio indices and variables (Kronmal 1993; Allison et al. 1995). Waist-to-hip ratio can remain unchanged even when there is a change in body size because waist circumference and hip circumference can increase or decrease proportionately. This ratio is associated with multiple disease outcomes as well as all-cause mortality (Zhang et al. 2008). Some investigators suggest that waist-to-hip ratio represents an aspect of body composition and distribution of fat which includes muscle that is not reflected in body mass index or waist circumference. The predictive value of waist-to-hip ratio for all-cause mortality and ischemic heart disease is greater than that of body mass index (Björntorp 1988).

128.3.3 Waist-to-Height Ratio

The waist-to-height ratio is less known compared to waist circumference, waist-to-hip ratio, and body mass index. Like waist-to-hip ratio, it has limitations in statistical analyses and interpretation (Kronmal 1993; Allison et al. 1995). The waist-to-height ratio will change only when there is a

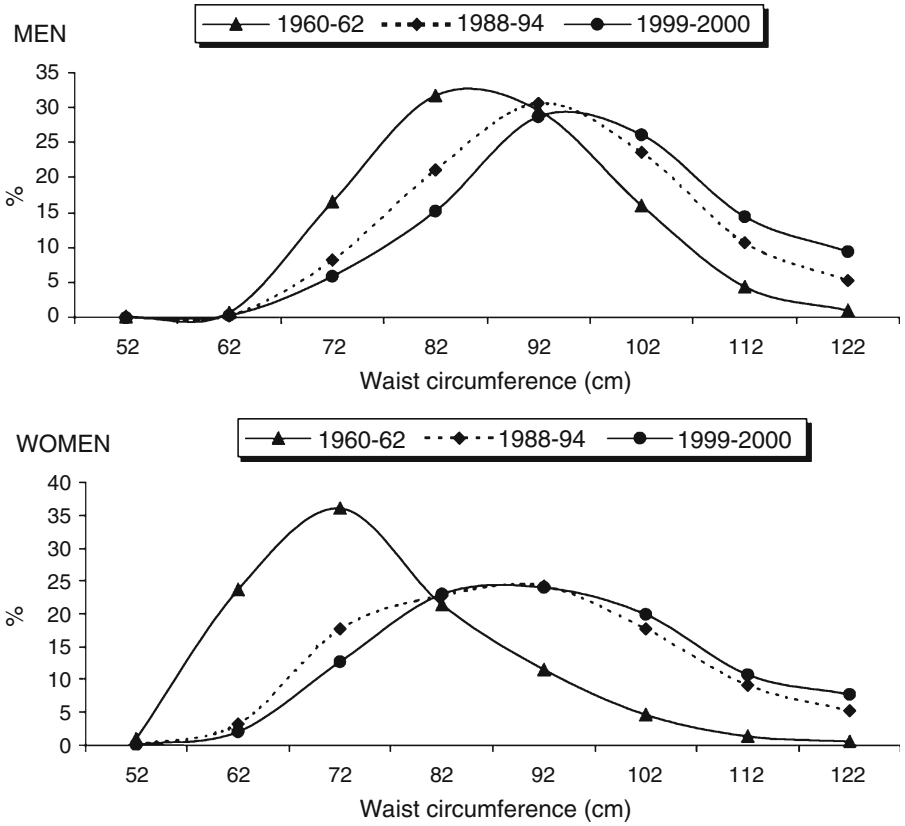

Fig. 128.1 Distribution of waist circumference in US adults from 1960 to 2000. In both men and women, the distribution of waist circumference shifted to the right (higher values) in 1988–1994 and 1999–2000 (Adapted from Okosun et al. 2004)

change in waist, given that height often remains constant in adults. Recent findings suggest that the waist-to-height ratio is more accurately descriptive of the distribution of body fat compared to body mass index, including abdominal fat distributions. Cohort studies have shown that the waist-to-height ratio is better than body mass index at predicting mortality from coronary heart disease and all-cause mortality (Lu et al. 2006; Chei et al. 2008). The waist-to-height ratio is, also to some extent, a better predictor of mortality than waist circumference (Ashwell 2009).

128.4 Cut-Points for Waist Circumference, Waist-to-Hip Ratio, and Waist-to-Height Ratio

The currently used waist phenotype cut-points are recommended by different agencies, including the United States National Heart, Lung, and Blood Institute (NHLBI), the International Diabetes Federation (IDF), and the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII). The NHLBI- and NCEP-ATPIII-recommended waist-circumference thresholds are based on studies in whites relating waist circumference to body mass index. A waist circumference value of ≥94 cm in men and ≥80 cm in women predicts overweight (BMI ≥ 25 kg/m²) (NIH/NHLBI

Table 128.1 Sex-specific waist circumference values that denote "increased risk" and "significantly increased risk" of cardiometabolic risks

	Risk of obesity-related cardiometabolic risks	
	Increased risk	Significantly increased risk
Men	≥94 cm (~37 in.)	≥102 cm (~40 in.)
Women	≥80 cm (~32 in.)	≥88 cm (~35 in.)

Waist cut-points differ by gender and risk of obesity-related cardiometabolic risks

1998), whereas a waist circumference of ≥102 cm in men and ≥88 cm in women predicts the presence of obesity (BMI ≥ 30 kg/m²) (NIH/NHLBI 1998) (Table 128.1). These waist circumference cut-points were proposed originally by Han et al. (1995), to assist professionals in managing subjects with obesity-related comorbidities. However, unlike the NCEP-ATPIII and NHLBI, the IDF advocates waist cut-points along national and racial/ethnic lines.

Waist-to-hip ratios have been arbitrarily recommended as 0.95 for men and 0.80 for women, and vary by race/ethnicity and national origin (Misra et al. 2005). A waist-to-height ratio of 0.5 has been proposed as the cut-point at which individuals should keep waist circumference to less than half their height, whereas the value of 0.6 has been suggested as the value for which adults should take action (Ashwell 2009). In agreement with the IDF and the NCEP-ATPIII, the United States National Institute of Health Clinical Guidelines recommends measurement of waist as a screening instrument for health-risk assessment.

A comparative analysis of studies of waist circumference and waist-to-hip ratio for assessing risk of type 2 diabetes was recently published (Qiao and Nyamdorj 2009). Both prospective and cross-sectional studies were reviewed. Tongans were found to have the highest waist circumference cut-points (103 cm for both men and women), followed by Americans and Europeans (Qiao and Nyamdorj 2009). The waist circumference cut-points were higher for all races in the USA and the UK studies compared to their counterparts in their original countries (Qiao and Nyamdorj 2009). The optimal waist-to-hip ratio cut-points were 0.95 for white men and 0.83–0.85 for white women living outside the USA and the UK, compared to 0.90 for Asian men and 0.79–0.85 for Asian women (Qiao and Nyamdorj 2009). The authors concluded that "there is no universal cutoff value that can be applied worldwide, and a country-specific value should be considered taking into account the purposes and resources."

128.5 Association of Waist Variables to Risk for Type 2 Diabetes

Studies linking waist variables to type 2 diabetes date back to 1956 when Schmidt et al. 1992, used a case-control study nested within a community-based survey. The aim of the study was to determine the relative importance of waist-to-hip ratio in type 2 diabetes. In that study, increased waist-to-hip ratios were 4.72 (95% CI: 2.39–9.34) and 2.17 (95% CI: 1.03–4.58) for women and men, respectively (Schmidt et al. 1992). Subsequently, many case-control and cross-sectional studies linking waist phenotypes to type 2 diabetes were published. The majority of these studies are based on waist circumference and waist-to-hip ratio, and not waist-to-height ratio.

This section provides an overview of the current evidence-based findings linking waist phenotypes with type 2 diabetes from prospective studies. Although numerous cross-sectional and case-control studies have associated waist phenotypes to increased risks for type 2 diabetes, they are excluded in this analysis because of their obvious inability to establish definite directionality between

waist phenotypes and type 2 diabetes. The public health significance of waist phenotypes for type 2 diabetes and the potential mechanism linking these variables to type 2 diabetes are also discussed.

Several prospective studies indicate that waist phenotypes, including waist circumference, waist-hip ratio, and waist-to-height ratio, are associated with the risk of type 2 diabetes. However, findings have been contradictory as to which of the phenotypes are most associated with type 2 diabetes. There is also ambiguity about how these measures perform across diverse ethnic/racial population groups. The majority of the evidence regarding the relationships between these obesity phenotypes and risks has been derived mainly from Caucasian populations. Hence, it remains unclear whether the relationships are consistent in non-Caucasian populations. The lack of consistencies across populations may be driven by varying methodology, sample size, type of study design, as well as cut-points for waist phenotype.

To the best of our knowledge, only a few meta-analyses of the association of waist circumference and waist-to-hip ratio with type 2 diabetes have been published. To compare the association of the incidence of type 2 diabetes with general and central obesity indicators, Vazquez et al. 2007, conducted a meta-analysis based on studies published from 1985 to 2004, retrieved from PubMed searches. The analysis was performed with 32 studies out of 432 publications that were identified (Vazquez et al.2007).

The result of the analysis, as summarized using forest plots, is shown in Fig. 128.2. The pooled relative rate estimate of waist circumference (SD: 11.6) was 1.87 (95% CI: 1.62–2.15), whereas that of waist-to-hip ratio (SD: 0.84) was 1.82 (95% CI: 1.55–2.13). Comparison of body mass index and waist circumference ($p = 0.50$) or body mass index and waist-to-hip ratio ($p = 0.73$) did not show any significant difference in the magnitude of association. The proportion of total variation ($I^2 > 0.90$) among study specific estimates was high, indicating that heterogeneity was present for all obesity indicators that were studied (Vazquez et al. 2007).

The pooled relative risks for waist circumference and waist-to-hip ratio stratified by study-level variables, as published by Vazquez et al. 2007, are shown in Fig. 128.3. Differences in relative risks for type 2 diabetes due to waist phenotypes are evident between groups based on the definition of type 2 diabetes, region, gender, and age. Studies that were restricted to a sample of subjects with a higher diabetes rate or with impaired glucose tolerance had lower relative risks for diabetes (Vazquez et al. 2007). When pooled relative risks between waist phenotypes were compared, some modest differences were also observed by region and age.

The pooled relative risks for waist circumference for Asia, USA, and Europe were 2.4 (95% CI: 1.5–4.0), 1.9 (95% CI: 1.4–2.5), and 2.1 (95% CI: 1.7–2.6), respectively. Pooled relative risks for waist-to-hip ratio were similar for the three regions, but was smaller in Asia at 1.4 (95% CI: 1.1–1.7) compared to Europe at 2.1 (95% CI: 1.7–2.6) and USA at 1.8 (95% CI: 1.4–2.2) (Vazquez et al. 2007). Where analysis was stratified by age, pooled relative risks for type 2 diabetes due to waist circumference was 2.0 (95% CI: 1.6–2.3) for those who were 50 years of age and older, and 1.6 (95% CI 1.4–1.9) for those who were <50 years of age. For studies where the mean age was ≥50 years, pooled risk for type 2 diabetes due to waist-to-hip ratio was 1.8 (95% CI: 1.5–2.2) and 2.1 (95% CI: 1.8–2.4), when mean age was <50 years (Vazquez et al. 2007).

We carried out a review through comprehensive PubMed searches of published prospective studies in English from 1985 to 2009 that investigated the relationship between waist phenotypes and incidence of type 2 diabetes in men and women. The waist phenotypes that were considered in the review were waist circumference, waist-to-hip ratio, and waist-to-height ratio. Table 128.2 summarizes the characteristics of the studies used for this review. All studies showed a positive association of waist circumference, waist-to-hip ratio, and waist-to-height ratio with incidence of type 2 diabetes.

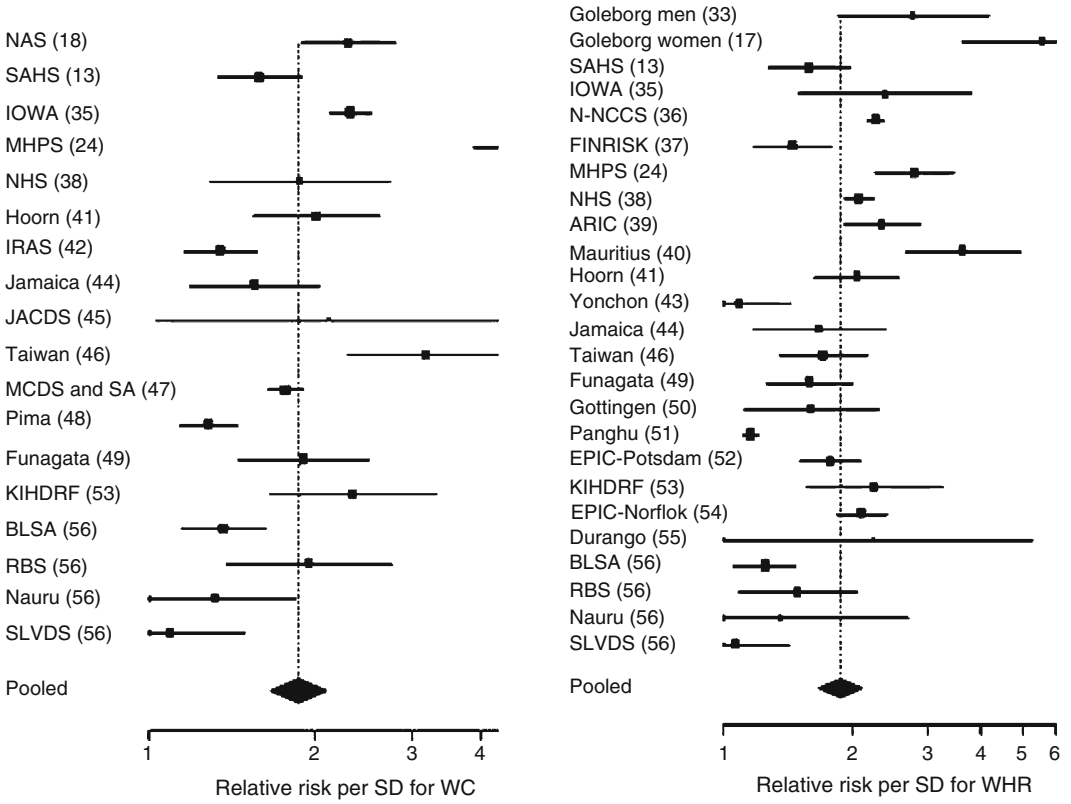

Fig. 128.2 Forest plot of the association of waist circumference and waist-to-hip ratio, with incident diabetes (95% confidence interval) for publications between 1985 and 2004) (*NAS* Normative Aging Study, *SAHS* San Antonio Heart Study, *IOWA* Iowa Women's Health Study, *MHPS* Male Health Professionals Study, *NHS* Nurses' Health Study, *IRAS* Insulin Resistance Atherosclerosis Study, *JACDS* Japanese-American Community Diabetes Study, *MCDS* Mexico City Diabetes Study, *SA* San Antonio, *KIHDRF* Kuopio Ischemic Heart Disease Risk Factor Study, *BLSA* Baltimore Longitudinal Study of Aging, *RBS* Rancho Bernardo Study, *SLVDS* San Luis Valley Diabetes Study, *N-NCCS* Northern Native Canadian Cohort Study, *MHPS* Male Health Professionals Study, *ARIC* Atherosclerosis Risk in Communities Study, *EPIC* European Prospective Investigation into Cancer and Nutrition). The pooled relative rate estimate of waist circumference (SD: 11.6) was 1.87 (95% CI: 1.62–2.15), whereas that of waist-to-hip ratio (SD: 0.84) was 1.82 (95% CI: 1.55–2.13). Comparison of body mass index and waist circumference ($p = 0.50$) or body mass index and waist-to-hip ratio ($p = 0.73$) did not show any significant difference in the magnitude of association. The proportion of total variation ($I^2 > 0.90$) among study specific estimates was high, indicating that heterogeneity was present for all obesity indicators that were studied (Adapted from Vazquez et al. 2007)

Kaye et al. (1991), Carey et al. (1997), and Meisinger et al. (2006) used participant self-report or medical record information to define diabetes. Kaye et al. (1991) examined a cohort of 41,837 women aged 55–69 years for an association between waist-to-hip ratio and 2 years' incidence of type 2 diabetes. After adjustment for body mass index, age, and education level using multivariate logistic regression, waist-to-hip ratio was a significant independent predictor of type 2 diabetes in a dose–response fashion. Subjects with diabetes were 4.6 times (95% CI = 3.8–5.6) more likely than those without diabetes to be in the upper tertile of waist-to-hip ratio and 2.2 times (95% CI = 1.8–2.7) more likely to be in the middle tertile. Women in the highest tertiles of waist-to-hip ratio had a 14.4-fold (95% CI = 9.5–21.9) higher risk of type 2 diabetes than women in the lowest tertiles (Kaye et al. 1991).

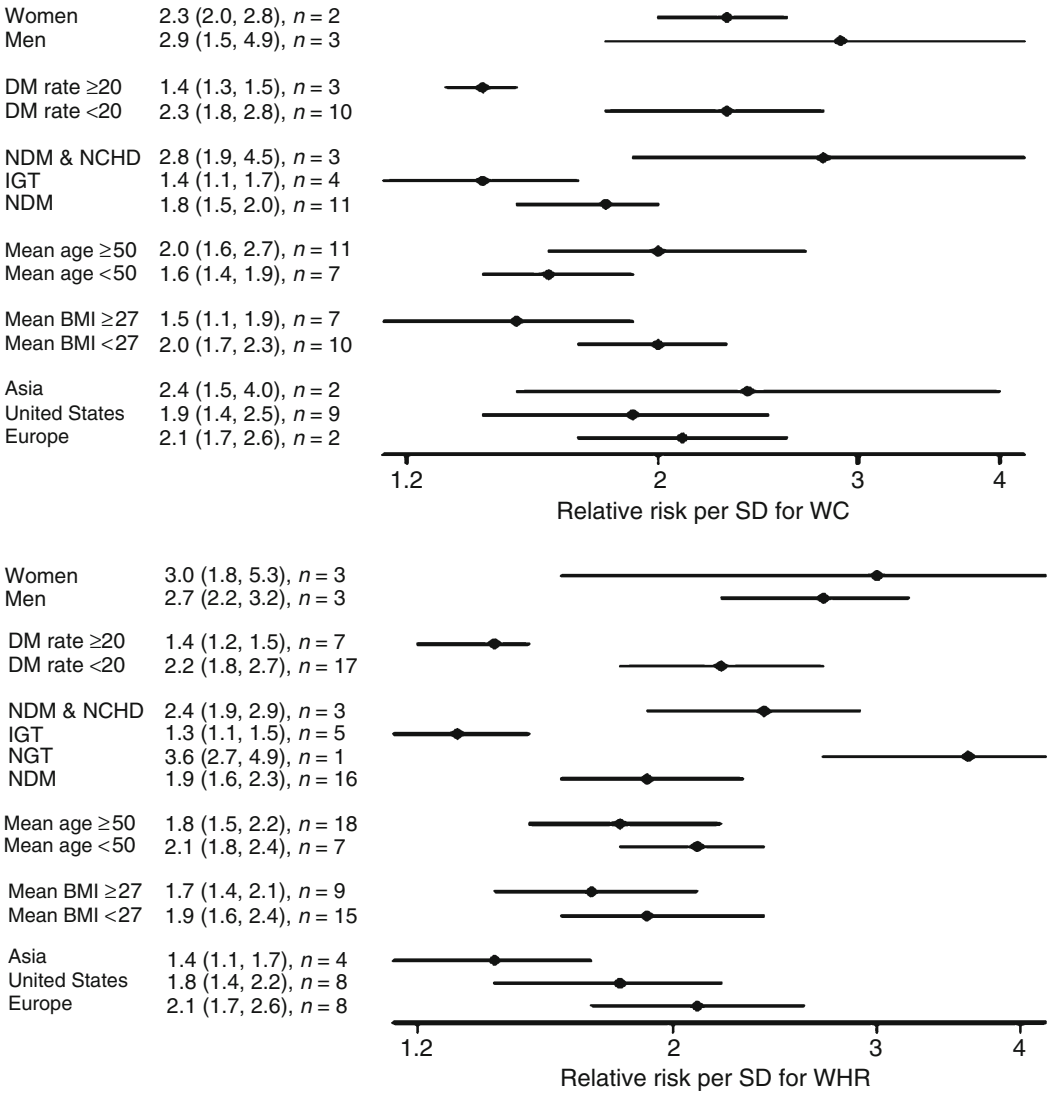

Fig. 128.3 Pooled relative risk (95% confidence interval) for waist circumference and waist-to-hip ratio with incident diabetes from the meta-analysis of studies published between 1985 and 2004, stratified by study-level population characteristics: gender, diabetes rate, inclusion criteria, age, general obesity, and region (*DM* diabetes mellitus, *NDM* non-diabetes mellitus, *NCHD* non-coronary heart disease, *IGT* impaired glucose tolerance, *BMI* body mass index, *SD* standard deviation). The pooled relative risks for waist circumference for Asia, USA, and Europe were 2.4 (95% CI: 1.5–4.0), 1.9 (95% CI: 1.4–2.5), and 2.1 (95% CI: 1.7–2.6), respectively. Pooled relative risks for waist-to-hip ratio were similar for the three regions, but was smaller in Asia at 1.4 (95% CI: 1.1–1.7) compared to Europe at 2.1 (95% CI: 1.7–2.6) and USA at 1.8 (95% CI: 1.4–2.2). Where analysis was stratified by age, pooled relative risk for type 2 diabetes due to waist circumference was 2.0 (95% CI: 1.6–2.3) for those who were 50 years of age and older, and 1.6 (95% CI 1.4–1.9) for those who were less than 50 years of age. For studies where the mean age was ≥50 years, pooled risk for type 2 diabetes due to waist-to-hip ratio was 1.8 (95% CI: 1.5–2.2) and was 2.1 (95% CI: 1.8–2.4) when mean age was less than 50 years (Adapted from Vazquez et al. 2007)

Table 128.2 Summary of studies linking waist phenotype to type 2 diabetes (*WC* waist circumference, *WHR* waist-to-hip ratio, *WthR* waist-to-height ratio)

Study	Waist variable	Sample size	Follow-up	Race/ethnicity	Gender	Age	Adjustment factors
Diabetes defined by self-report or medical record information							
Kaye et al. (1991)	WHR	41,837	2 years	USA	Female	55–69	Age, education, BMI
Carey et al. (1997)	WC, WHR	42,492	8 years	USA	Female	30–55	Age, family history, BMI, smoking, diet, exercise
Meisinger et al. (2005)	WC, WHR	6,012	9.2 years	Germany	Male/Female	35–74	Age, survey, education, Parental history of diabetes, hypertension, dyslipidemia, smoking, alcohol intake, and physical activity
Diabetes defined using fasting blood glucose and glucose tolerance tests							
Cassano et al. (1992)	WHR	1,972	18 years	Mainly Whites (98%)	Male	42	Age, smoking, BMI
Snijder et al. (2003)	WC, WHR	738	6 years	Whites	Female	60	Age, BMI, hip, thigh
Snijder et al. (2003)	WC, WHR	619	6 years	Whites	Male	60	Age, BMI, hip, thigh
Wang et al. (2005)	WC, WHR	22,270	13 years	USA	Male	40–75	Age, BMI, physical activity, smoking, alcohol, diet, fat intake
Wei et al. (1997)	WC, WHR	451	7.2 years	Mexican-American	Female	42	Age
Wei et al. (1997)	WC, WHR	270	7.2 years	Mexican-American	Male	42	Age
McNeely et al. (2001)	WC	466	5 years	Japanese American	Male/Female	52	Age, gender, family history, Smoking
Hadaegh et al. (2006)	WC, WHR	1,852	3.6 years	Iranian	Male	20+	Age, smoking, hypertension, family history
Diabetes defined using insulin and glucose concentration							
Wang et al. (1997)	WC, WHR	1,195	3.3 years	Chinese	Female	52	Age
Wang et al. (1997)	WC, WHR	995	3.3 years	Chinese	Male	54	Age
Sakurai et al. (2009)	WC	3,992	8 years	Japanese	Male/Female	35–55	Age, gender
Gruson et al. (2009)	WC, WHR, WthR	10,602	10 years	French and Irish	Male	50–59	Education, physical activity, Tobacco and alcohol

All the studies showed a positive association of waist phenotypes ((WC, waist circumference; WHR, waist-to-hip ratio; WthR, waist-to-height ratio) with the incidence of type 2 diabetes.

Using the US Nurses' Health Study, and after 8 years' follow-up, Carey et al. (1997), reported a positive association between waist-to-hip ratio and type 2 diabetes. After adjustment for BMI and other potential confounding factors, the relative risk for the 90th percentile of waist-to-hip ratio versus the 10th percentile was 3.1 (95% CI 2.3–4.1) and that for the 90th percentile of waist circumference versus the 10th percentile was 5.1 (95% CI 2.9–8.9) (Carey et al. 1997).

In a prospective population-based cohort study of 3,055 men and 2,957 women aged 35–74 years who participated in the MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases) study and followed up for about 9.2 years, Meisinger et al. (2006) found a positive association of waist circumference and waist-to-hip ratio with type 2 diabetes. In the study, multivariable-adjusted hazard ratios for type 2 diabetes estimated from Cox proportional hazards models across quartiles of waist circumference were 1.0, 1.15, 1.57, and 3.40 in men and 1.0, 3.21, 3.98, and 10.70 in women. Those for waist-to-hip ratio were 1.0, 1.14, 1.80, and 2.84 in men and 1.0, 0.82, 2.06, and 3.51 in women (Meisinger et al. 2006).

We found eight cohort studies that defined diabetes using fasting blood glucose and glucose-tolerance tests. All the studies observed positive independent associations of waist circumference or waist-to-hip ratio for diabetes risks. Cassano et al. (1992) used a proportional hazards model based on a prospective evaluation of male participants in the Department of Veterans Affairs Normative Aging Study cohort. Adjusting for age, body mass index, and cigarette smoking, men in the top tertile for waist-hip ratio had a 2.4-fold (95% CI 1.7–3.7) greater risk of diabetes than men in the lowest tertile (Cassano et al. 1992).

Snijder et al. (2003) reported data from the Hoorn study to prospectively determine the association of hip and thigh circumferences, independent of waist circumference, with the incidence of type 2 diabetes. Glucose tolerance was assessed by the use of a 75-g oral-glucose-tolerance test. When adjusted for hip circumference and BMI or thigh circumference and BMI, the ORs for WC were higher in both men and women, the highest being 2.66 per one SD larger waist for the latter adjustment in women (Snijder et al. 2003).

Wang et al. (2005) compared waist circumference and waist-to-hip ratio in predicting type 2 diabetes using a prospective cohort study (Health Professionals Follow-Up Study) of 27,270 men. During 13 years of follow-up, 884 incident type 2 diabetes cases were found. Age-adjusted relative risks across quintiles of waist circumference were 1.0, 2.0, 2.7, 5.0, and 12.0 and those of waist-to-hip ratio were 1.0, 2.1, 2.7, and 3.6 (p for trend < 0.0001 for all). Statistical adjustment for diabetes risk factors only slightly attenuated these relative risks (Wang et al. 2005).

In a study of 721 Mexican Americans aged 25–64 years who were followed for an average of 7.2 years, Wei et al. (1997) found that waist circumference was the best obesity-related predictor for type 2 diabetes. The risk for type 2 diabetes for those in the highest quartile of waist circumference was 11 (95% CI: 4.2–28.8) times greater than for those in the lowest quartile. The authors argue that abdominal fat localization was a more important determinant than the total amount of body fat in this population of mean age of 42 years and 43 years for men and women, respectively (Wei et al. 1997).

In a prospective, cohort study of Japanese Americans, McNeely et al. (2001) found that, in their younger subgroup aged 55 years or less (n = 240), waist circumference greater than or equal to the third tertile was associated (adjusted RR: 5.4; 95% CI: 1.7–17.0) with type 2 diabetes (McNeely et al. 2001).

To investigate whether central obesity variables are more important than general obesity variables in predicting the incidence of type 2 diabetes in Iranians, Hadaegh et al. (2006) investigated a representative sample of 1,852 males aged 20 years and older. After 3.6 years of follow-up, waist circumference was significantly associated with type 2 diabetes, adjusting for age, smoking, hypertension, and family history of diabetes.

Some studies, including those of Wang et al. (1997), Sakurai et al. (2009), and Gruson et al. (2009), also investigated the association of waist phenotype with type 2 diabetes by defining diabetes on the

Table 128.3 The association between waist phenotypes and the incidence of type 2 diabetes

Author	RR	95% CI	RR	95% CI
	Waist circumference			
Carey 1997	5.10	(2.90, 8.90)	–	–
Snijder 2003	1.98	(1.54, 2.55)	1.23	(0.95, 1.64)
Wang 1997	2.65	(1.90, 3.77)	2.20	(1.54, 3.16)
Wei 1997	1.80	(1.40, 2.33)	1.84	(1.13, 3.00)
Wang 2005	–	–	4.50	(3.00, 6.70)
	Waist-to-hip ratio			
	Females		Males	
Carey 1997	3.10	(2.30, 4.10)	–	–
Kaye 1991	4.60	(3.80, 5.60)	–	–
Cassano 1992	–	–	3.40	(1.90, 5.90)
Snijder 2003	2.15	(1.63, 2.83)	–	–
Wang 1997	1.76	(1.31, 2.38)	1.44	(1.11, 1.87)
Wei 1997	1.72	(1.28, 2.30)	1.80	(0.98, 3.31)
Wang 2005	–	–	2.80	(2.10, 3.80)

Point and interval estimates for type 2 diabetes due to waist circumference and waist-to-hip ratio from reviewed published articles are here summarized. In studies where waist circumference was used as a measure for abdominal obesity, relative risk for type 2 diabetes ranged from 1.8 to 5.1 for women and ranged from 1.23 to 4.50 for men. Using waist-to-hip ratio, relative risk ranged from 1.72 to 4.6 and 1.8 to 3.4 for women and men, respectively.

basis of insulin and glucose concentration. In Chinese men and women, Wang et al. (1997) found a stronger relationship between diabetes incidences in women than in men and indicated that waist circumference was a better predictor than waist-to-hip ratio. During an 8-year follow-up, Sakurai et al. (2009), calculated age- and sex-adjusted hazard ratios according to the sex-specific quintile of waist circumference at baseline. Age- and sex-adjusted hazard ratios across the quintiles of waist circumference were 1.78, 1.00, 1.59, 3.11, and 3.30, respectively (p for trend < 0.0001) (Wang et al. 1997).

Gruson et al. (2009) compared the associations of waist circumference, waist-to-hip ratio, and waist-to-height ratio with the incidence of coronary events, including type 2 diabetes in a prospective study of 10,602 men aged 50–59 years, recruited between 1991 and 1993 in three centers in France and one center in Northern Ireland. Waist circumference, waist-to-hip ratio, and waist-to-height ratios were positively associated with diabetes ($p < 0.0001$). The authors concluded that, in middle-aged European men, the waist-to-height ratio identifies coronary risk more strongly than waist circumference and waist-to-hip ratio (Gruson et al. 2009).

Table 128.3 summarizes point and interval estimates for type 2 diabetes due to waist circumference and waist-to-hip ratio from reviewed published articles. In studies where waist circumference was used as a measure for abdominal obesity, relative risk for type 2 diabetes ranged from 1.8 to 5.1 for women and from 1.23 to 4.50 for men. Using waist-to-hip ratio, relative risk ranged from 1.72 to 4.6 and 1.8 to 3.4 for women and men, respectively.

128.6 Mechanism of Waist Variables for Type 2 Diabetes

The mechanism linking waist phenotype to cardiometabolic risk factors including type 2 diabetes is not clear. Two likely mechanisms may be involved in the association of waist phenotypes with type 2 diabetes. One, through the preponderance of the highly sensitive lipolytic hypertrophied visceral

adipose tissues, elevated free fatty acids are suggested to incite insulin resistance (Bjorntorp 1990). Two, elevated free testosterone and reduced sex-hormone-binding globulin may be associated with the promotion of increased fat deposits in the waist region and reduced fractional hepatic extraction of insulin (Salans et al. 1968). Thus, the association of waist phenotypes with type 2 diabetes may be due to an enlarged visceral fat depot discharging free fatty acids into the portal and systemic circulation.

It has also been suggested that the connection between waist phenotype and cardiovascular diseases may be due to an overflow of chemical energy to intra-abdominal fat tissue and liver (Seppala-Lindroos et al. 2002). Intra-hepatic fat accumulation is associated with dyslipidemia and hepatic insulin resistance leading to type 2 diabetes (Seppala-Lindroos et al. 2002). Since intra-abdominal fat tissue is a marker for the degree of overflow of fatty acids from subcutaneous depots, waist phenotype may be a true marker of the overall impairment in energy storage regulation, in which an increase in intra-abdominal fat tissue signifies an altered capacity for energy storage in other adipose tissues (Seppala-Lindroos et al. 2002).

128.7 Public Health and Clinical Significance of Waist Phenotypes

As a correlate of type 2 diabetes, waist phenotype has both public health and clinical significance. From a public health perspective, waist circumference is a powerful indicator of body fat distribution, which can identify patients who are at increased risk of obesity-related cardiometabolic disease, above and beyond what is indicated by body mass index. Waist circumference is easy to measure, subject to little error, and requires an inexpensive apparatus. Given the increasing epidemics of obesity and the association between obesity and type 2 diabetes, advocating the use of waist phenotype for obesity surveillance could help in the early identification of those at risk for type 2 diabetes. Weight reduction programs or other interventions targeted specifically at abdominal regions may help to alleviate the risk of obesity-related sequelae. From a clinical point of view, measuring waist phenotypes could provide additional information above and beyond what is provided by body mass index. Prescribing abdominal obesity reduction in morbidly obese subjects may add to the clinical relevance of waist phenotypes in risk populations.

128.8 Applications to Other Areas of Health and Disease

The association of waist phenotypes with type 2 diabetes has been demonstrated in many studies and confirmed in our analysis of prospective studies and pooled estimates of the relative risks from various studies, including three studies that performed meta-analyses. Despite the largely unexplained heterogeneity of relative risk, studies have demonstrated consistent strong associations of increased waist circumference and waist-to-hip ratio with the risks for type 2 diabetes. The verdict is yet to be given with respect to the nature of the association of waist-to-height ratio with type 2 diabetes.

The clinical and epidemiologic appeal for the use of waist phenotypes is undeniable. Waist measurement is simple and requires only a measuring tape and a weighing scale. The statistical appeal is that waist circumference is highly correlated with adiposity measured with more precise techniques, including magnetic resonance imaging, computed tomography, hydrodensitometry (underwater weighing), and dual energy X-ray absorptiometry. Waist-hip ratio, despite lower correlation with body mass index, appears to have the same ability to predict diabetes as waist circumference.

However, the role of waist-to-height ratio in diabetes is poorly understood, and additional research is needed to define its predictive utility. The association of waist phenotypes with other diseases and components of metabolic syndrome needs to be investigated. Effective translation of the use of waist phenotypes into clinical practice to predict obesity-related diseases may help in reversing the increasing trend of components of the metabolic syndrome.

Summary Points

- The three most important waist phenotypes are waist circumference, waist-to-hip ratio, and waist-to-height ratio.
- Waist circumference, waist-to-hip ratio, and waist-to-height ratio are surrogate measures of abdominal obesity.
- Abdominal obesity is the most potent form of adiposity and is the culprit for obesity-associated diseases.
- Studies indicate that waist phenotypes of waist circumference, waist-hip ratio, and waist-to-height ratio are associated with the risk of type 2 diabetes.
- Routine assessment of waist phenotypes in clinical practice to predict obesity-related disorders may help in reversing the increasing trend of type 2 diabetes.

Key Features

Table 128.4 Key features of waist phenotypes

1. The three most widely used waist phenotypes for predicting obesity-related disorders are waist circumference, waist-to-hip, ratio and waist-to height ratio
2. Many studies showed a positive association of waist circumference, waist-to-hip ratio, and waist-to-height ratio with incidence of type 2 diabetes.
3. Waist phenotype cut-points for predicting type 2 diabetes vary by gender, race, and nationality.
4. Increased values of waist phenotypes are associated with increased risk for type 2 diabetes.
5. The connection between waist phenotype and cardiovascular diseases may be due to an overflow of chemical energy to intra-abdominal fat tissue and liver.
6. Weight-reduction programs or other interventions targeted specifically at abdominal regions may help to alleviate the risk of obesity-related sequelae, including type 2 diabetes.
7. Effective translation of waist phenotypes into clinical practice may be critical in reversing the increasing prevalence of obesity-related disorders.

This table lists the key facts of waist phenotypes, including potential mechanism and impact of its effective translation into medical practice

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Chapter 129
The Use of Skinfolds in Anthropometric Measures and Their Applications to Diabetes

Marie-Eve Mathieu and Louise Béliveau

Abstract Worldwide, the last few decades have been marked by a concomitant rise in adiposity and metabolic disorders. Based on current projections, it is expected that this situation will continue. To assess adiposity and not solely weight, various techniques have been used. The measurement of skinfold thickness has received a great deal of attention as early as the 1980s. In this chapter, we present the extent to which skinfold thickness is associated with metabolic impairments, in both cross-sectional and longitudinal studies. Gender, age-group and ethnicity specificities are brought forward when such information is known. Issues of gestational diabetes and familial diabetes history are also addressed. Moreover, the skinfolds, skinfold ratios or body fat percentage formulas based on skinfolds that have a better association with metabolic impairments are presented. Advantages, as well as limitations, versus other measurement techniques are discussed. As new technologies are now available to measure adiposity, it is important to understand the role of the simple technique that enables the measurement of subcutaneous adiposity. It was among the first to be used in large-scale studies, at a moment corresponding to the beginning of a drastic rise in obesity and diabetes. Revisiting the link between the skinfold technique and metabolic impairments will enable a good understanding of adiposity and diabetes studies that ground today's current state of knowledge.

Abbreviations

BMI Body mass index
T2D Type 2 diabetes

129.1 Introduction

Identified as early as circa 1500 BC, diabetes is a disease that can take many forms. Type 1 diabetes is characterized by the absence of insulin, whereas resistance to insulin is the primary characteristic of type 2 diabetes (T2D). During pregnancy, women can develop a transitory diabetes (i.e., gestational diabetes). Common features of these conditions are a rise in glycemia and the potential development

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_129,

of complications, such as metabolic, cardiovascular, and kidney diseases, as well as neurological complications. To work toward the prevention of this disease and to better treat individuals who have developed it, a better understanding of the characteristics of these individuals is important. The anthropometric profile is one parameter that has received a great deal of attention. Among all of the techniques used, skinfold thickness is one that stands out because of its use in large cohort studies for many years and in various populations.

Among the numerous studies that have addressed the issue of skinfolds in line with diabetes, the skinfolds selected have varied considerably, including abdomen, biceps, calf (lateral and medial), chest, midaxillary, subscapular, suprailiac, thigh, and triceps. The two most commonly measured skinfolds are the subscapular and the triceps. The subscapular-to-triceps ratio is also frequently used as an indicator of centralized adiposity, with a higher ratio indicating higher adiposity in the central portion of the body. Some authors have also used various combinations of skinfolds. For example, Chandalia et al. (1999) computed the sum of subscapular, midaxillary, chest, abdomen, and suprailiac skinfolds to reflect truncal adiposity and the sum of triceps, biceps, thigh, and calf skinfolds for peripheral adiposity. How do all of these adiposity indicators relate to glucose metabolism impairments? What is the adiposity profile of individuals who will develop the disease or who already have it? Do children with mothers who had gestational diabetes have a particular adiposity status? The present chapter aims at answering these questions and presents ethnic and gender specificities when such information is known. Although type 1 and gestational diabetes will be discussed when possible, most available data come from studies on T2D. Finally, the usefulness of skinfolds versus other anthropometric measurements in the assessment of the anthropometric characteristics of individuals at risk or with diabetes will be addressed.

129.2 Total Adiposity Assessed Using Skinfolds and Diabetes

129.2.1 Cross-Sectional Studies

Various groups of researchers have conducted cross-sectional studies aiming to better understand the relationship between glucose metabolism and total adiposity, as measured with skinfolds. Among them, Menke et al. (2007) reported, for a diverse ethnic sample (non-Hispanic black, Mexican-American, and non-Hispanic white individuals), that the age-adjusted prevalence of diabetes was higher for men and women having higher skinfold thicknesses (subscapular, suprailiac, thigh, and triceps). In men, the age-adjusted prevalence of T2D was 5.0 for individuals with a sum of skinfolds under 83.7 mm, versus 10.4 for those with values equal to or above 83.7 mm. In women, the age-adjusted prevalence was 3.4 if the sum of skinfolds was under 120.3 mm and 7.7 if equal to or above 120.3 mm. Globally, the prevalence was about double for individuals in the group with the highest adiposity. Similar findings have been reported with Algonquin individuals in Canada, in whom glucose tolerance abnormalities (impaired glucose tolerance and T2D) were significantly associated with the sum of triceps and subscapular skinfold thicknesses (Delisle and Ekoé 1993). Even in pregnant women, the presence of glucose metabolism impairments (gestational diabetes) is associated with a higher body fat percentage derived from skinfolds and higher skinfold thicknesses (subscapular, triceps, and biceps) (Yilmaz et al. 2009). Looking at the incidence of impaired glucose tolerance, impaired fasting glucose and T2D in women with gestational diabetes, Krishnaveni et al. (2007) measured the sum of skinfolds (biceps, subscapular, suprailiac, and triceps) and glucose metabolism for five years post pregnancy. As depicted in Fig. 129.1, women who had gestational diabetes tended

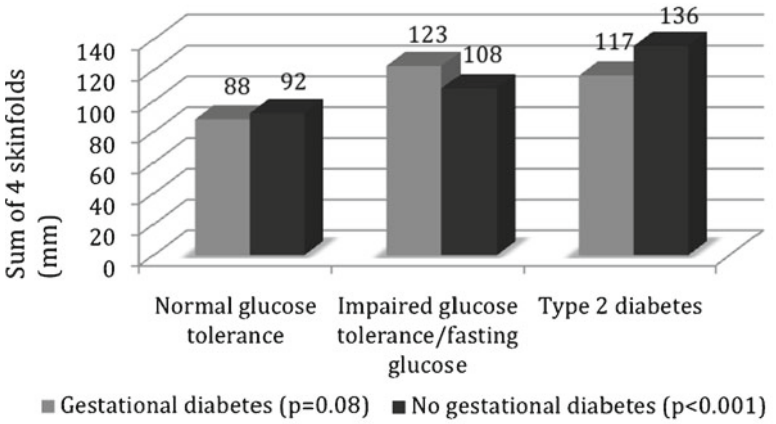

Fig. 129.1 Adiposity of women with and without gestational diabetes five years after giving birth, according to their metabolic status (Adapted from Krishaveni et al. 2007)

to have thicker skinfolds at follow-up if they developed glucose metabolism impairments. That trend was revealed to be significant in women who did not have glycemic impairments during gestation. Control of body fat thus appears to be important in order for both women who had or did not have gestational diabetes to remain free of diabetes and glycemic disorders post pregnancy.

In opposition to these studies, Misra et al. (2001) showed that fasting blood glucose was not associated with percent body fat calculated from skinfolds (subscapular, suprailiac, biceps, and triceps) in a sample of 424 Asian Indian individuals, of whom about 10% had T2D. This is in line with the study by Chandalia et al. (1999). In their study, the rate of glucose disposal was significantly correlated to total body fat, measured with underwater weighing, in Caucasian but not in Asian Indian individuals. However, the authors showed that, for a given amount of overall adipose tissue, Asian Indian individuals have lower insulin sensitivity, as assessed with the euglycemic hyperinsulinemic clamp technique. Therefore, concluding only on the basis of fasting blood glucose that there is no association between overall adiposity and glucose metabolism in Asian Indian individuals could be a mistake. In fact, insulin sensitivity is a key feature of T2D pathophysiology. Another study conducted with newborn babies also reinforces the link between adiposity and insulin defects among Asian Indians individuals. Insulin concentration at birth was directly related to subscapular thickness in Asian Indian, but not in Caucasian, individuals (Yajnik et al. 2002). Therefore, the available data from cross-sectional studies suggest that an association between high overall adiposity, as assessed with skinfolds, and glucose metabolism impairments could exist in non-Hispanic blacks, Mexican American, non-Hispanic whites, Algonquin, and Asian Indian individuals, as well as in women during and after pregnancy.

129.2.2 Longitudinal Studies

Cross-sectional studies are an interesting option for identifying associations. However, is the conclusion presented in the previous section supported by longitudinal studies? This appears to be the case for all but one study. In adult Mexican-American individuals who were T2D-free at baseline, Haffner et al. (1991) reported that those who developed the disease over the course of an eight-year period were the ones who had higher skinfold thicknesses at baseline (Table 129.1). A study by the same

Table 129.1 Eight-year incidence (%) of T2D by gender, according to anthropometric characteristics (Adapted from Haffner et al. 1991)

		Men	Women
Subscapular skinfold (mm)	Low (men: <17.5; women: <18.9)	2.4	0.8
	Moderate (men: 17.5–22.0; women: 18.9–27.0)	9.3	7.4
	High (men: >22.0; women: >27.0)	7.1	13.9
	p value	0.996	<0.001
Triceps skinfold (mm)	Low (men: <12.1; women: <20.5)	5.9	4.1
	Moderate (men: 12.1–17.8; women: 20.5–26.7)	6.0	5.7
	High (men: >27.0; women: >26.7)	>27.0	> 26.7
	p value	0.73	0.021
Body mass index (kg/m^2)	Low (men and women: <24.6)	2.4	2.5
	Medium (men and women: 24.6–28.2)	7.1	5.7
	High (men and women: >28.2)	9.5	13.9
	p value	0.21	<0.001
Centrality index (ratio of subscapular-to-triceps skinfolds)	Low (Men: <1.19; women: <0.85)	4.7	0.8
	Moderate (Men: 1.19–1.52; women: 0.85–1.11)	6.0	8.2
	High (men: >1.52; women: >1.11)	8.2	13.1
	p value	0.552	<0.001

group showed that age-adjusted odds ratios for developing T2D were 1.46 for women and 1.78 for men, for an increase of 0.98 mm in subscapular and 1.42 in triceps skinfold thicknesses in women and 1.82 and 0.87 mm, respectively, in men (Wei et al. 1997). A similar conclusion was reached in a representative sample of the Canadian population that was composed of more than 1,500 adult individuals. According to the authors, the incidence of diabetes over a 15.5-year period was associated with the sum of five skinfolds (biceps, triceps, subscapular, suprailiac, and calf) (Katzmarzyk et al. 2007). These findings are in line with results from Wang et al. (1997), who showed in a sample of 2,190 Chinese individuals that those who developed T2D over a 3.3-year period had, on average, a significantly higher subscapular skinfold thickness at baseline (men: 18.2 vs. 16.0 mm, $p = 0.016$; women: 26.4 vs. 18.9 mm, $p < 0.001$). In addition, the difference between those who developed the disease and those who did not was significant for triceps thicknesses in women (22.0 vs. 19.4 mm, $p = 0.020$).

As mentioned previously, only one study does not support the association between adiposity and the development of glucose metabolism impairment. In that study, which was conducted to investigate glucose metabolism in the first eight years of age, it was reported that insulin resistance at 8 years, as assessed with the homeostatic model, was neither associated with neonatal subscapular nor with triceps skinfold thicknesses (Ponsonby et al. 2008). However, skinfold thicknesses at age 8, as well as the gain in skinfold thicknesses from neonatal to childhood periods (adjusted for neonatal skinfold thicknesses), were associated with a higher insulin resistance. Consequently, it would not be the profile at birth, but the evolution thereafter that matters.

129.2.3 Gender Differences

Skinfold measurements, as well as T2D criteria, are the same in men and women, but the association between different parameters appears to vary. In their longitudinal study, Haffner et al. (1991) showed that the difference in subscapular and triceps skinfold thicknesses between individuals who developed T2D and those who did not was more marked in women than men (Table 129.1). For the

subscapular skinfold, the difference was 2.2 mm in men and 10.0 mm in women, whereas the difference was 0.8 mm in men and 4.0 mm in women for the triceps skinfolds. This gender difference was significant for the subscapular skinfold. The finding that suggests adiposity is more closely linked to T2D incidence in women is further supported by the interventional study of The Diabetes Prevention Program Research Group (2006). In their study, men and women were allocated to one of three groups: placebo, metformin (an anti-diabetic drug), and lifestyle (nutrition and physical activity). Subsequently, the incidence of T2D was followed over an average of 3.2 years. In men, they reported that only the calf skinfold thickness at baseline was a significant predictor of the development of the disease in the lifestyle group. In women, the subscapular skinfold and the sum of triceps and subscapular skinfolds were significant predictors of T2D development in the placebo and lifestyle groups. Furthermore, the suprailiac skinfold and sum of skinfolds (triceps, subscapular, suprailiac, and abdomen), including or excluding the calf skinfold, had a predictive value for women in the placebo group. It should also be noted that two skinfolds (subscapular and triceps) were higher in women that were developing T2D, whereas this was the case for only one skinfold type (subscapular) in men, as reported by Wang et al. (1997). Taken together, the available data from both cross-sectional and longitudinal studies suggest that the association between adiposity and T2D is stronger in women than in men.

129.3 Family History of Type 2 Diabetes and Adiposity Assessed with Skinfolds

If higher adiposity is associated with a higher prevalence and incidence of T2D and glucose metabolism impairments, then the adiposity status of individuals with a family history of T2D should be examined. In one large study ($n = 869$) conducted in Italy, it was reported that 10-year-old children had a larger sum of subscapular, bicep, triceps, and suprailiac skinfolds if they had a family history of diabetes (10.2 vs. 11.0 mm; $p < 0.05$) (Giampietro et al. 2002). Amini et al. (1997) also addressed the question of adiposity and family history of diabetes in 66 children with an average age of 9 in Papua New Guinea. While they reported that children having a family history of the disease were heavier, the difference in triceps skinfold thicknesses was not statistically different (7.7 vs. 6.6 mm; $p = 0.13$). In a longitudinal study by Srinivasan et al. (2003), a total of 1,439 children aged 4–17 years were evaluated at entry during childhood, adolescence, and adulthood to better understand the association between parental diabetes and adiposity, as assessed using subscapular skinfold measurements. A positive association between parental diabetes and adiposity was present in childhood and persisted through adolescence and adulthood. The authors also reported that the rate of increase in skinfold thickness was significantly higher in the offspring of parents with T2D (0.70 mm per year vs. 0.57 mm per year; $p = 0.02$). Based on these studies, it appears that children having diabetic parents tend to be fatter and that they also gain more fat every year.

The issue of ethnicity, adiposity, and familial history of diabetes has been addressed by two groups of researchers. Srinivasan et al. (1998) have identified that triceps and subscapular skinfold thicknesses were significantly higher in the offspring of diabetic parents, but this was only true for white individuals, not for black individuals. The difference between offspring of diabetic and non-diabetic parents was 5.9 mm in white individuals, compared to 3.5 mm in black individuals, for triceps skinfolds. The difference was 7.8 mm in white individuals, compared to –0.7 mm in black individuals, for subscapular skinfolds. Whereas this study was conducted in 53 individuals aged 7–25 years, a larger study ($n = 1,338$) in slightly older individuals (19–37 years of age) showed

different results (McClain et al. 2000). Body fat, also assessed with triceps and subscapular skinfolds, was higher in individuals with a parental history of diabetes, whether they were black or white. The authors also showed that the magnitude of differences in skinfold thicknesses between the offspring of diabetic and non-diabetic parents was greater among black individuals and that this ethnic difference was significant for the subscapular skinfold. More research will be needed to identify if the association is stronger in black or white individuals.

Another issue that should raise awareness is that the offspring of diabetic parents not only present more subcutaneous fat in most cases, but also have metabolic complications associated with a disadvantageous adiposity profile. In the study by McClain et al. (2000), the offspring of both black and white diabetic parents had, in addition to higher adiposity, higher cholesterol, triglycerides, very low density lipoprotein, glucose and insulin levels, insulin resistance, as well as lower high-density lipoprotein. Similarly, higher insulin, glucose, and insulin resistance was reported in adolescents and adults whose parents had diabetes, in the study by Srinivasan et al. (2003). Only during childhood was the metabolic profile similar between children whose parents had diabetes or not. Based on these studies, it can be concluded that adiposity is higher in individuals with parents having diabetes. A difference can be seen as early as childhood, and metabolic complications associated with an adverse adiposity profile and family history of the disease can appear in adolescence.

129.4 Gestational Diabetes and Adiposity Assessed with Skinfolds

In the previous sections, we addressed adiposity in individuals with diabetes or a family history of the disease. In the first case, the body has to deal with glucose metabolism impairments. In the second case, genetic susceptibility to the disease is present without impairments necessarily existing. Mid-way between these conditions is the case of individuals who are exposed to a milieu where glycemic control is not optimal but whose bodies are free of glucose metabolism impairments. This is the case of babies of women who had gestational diabetes.

How are the anthropometric characteristics of these babies? At birth, the group of Krishnaveni et al. (2005a, b) showed that a larger neonatal subscapular skinfold was positively associated with maternal glucose concentration. They also showed that babies of mothers with gestational diabetes had larger skinfold thicknesses than babies of mothers free from the disease. As illustrated in Fig 129.2, the authors reported small but significant differences. At 1 year of age, however, the difference was no longer significant (Krishnaveni et al. 2005a). This is similar to the findings of Wright et al. (2009), who showed that the children of mothers who had gestational diabetes or impaired glucose tolerance were not significantly fatter at 3 years of age. However, the authors found a significant 1.31-mm difference in the sum of subscapular and triceps skinfolds between the groups, when they took into account various factors including maternal age, education, race/ethnicity, smoking history, body mass index (BMI), pregnancy weight gain, parity, paternal BMI, and fetal growth. Differences between these studies could thus be attributable to different adjustment techniques, considering that Krishnaveni et al. (2005a) only adjusted for gestational age and sex.

Whereas no difference was noted at one year of age, Krishnaveni et al. (2005a) reported that, by the age of five, daughters of mothers who had gestational diabetes have significantly higher adiposity. They demonstrated 8.5 mm vs. 7.7 mm for triceps skinfolds ($p = 0.01$) and 6.6 mm vs. 5.9 mm for subscapular skinfolds ($p = 0.01$) (Fig. 129.2). This could indicate a larger adiposity rebound in children of mothers who had gestational diabetes, at least in girls. This is in line with findings from the same group, which showed that maternal insulin concentrations, along with neonatal skinfold thicknesses, were significant predictors of skinfold thickness at four years of age. However, it should

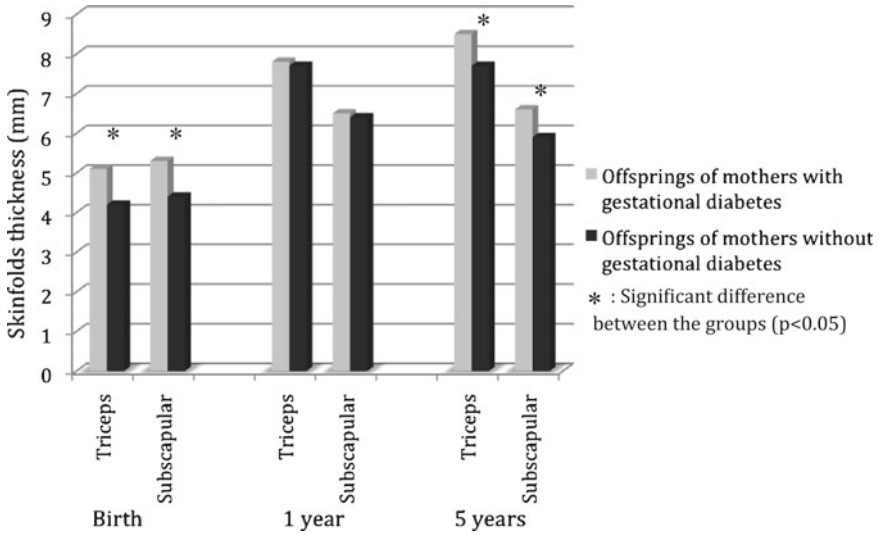

Fig. 129.2 Skinfold thicknesses of the offspring of mothers with gestational diabetes and control children (Adapted from Krishnaveni et al. 2005a)

be noted that differences between the groups are always quite small (less than 1 mm per skinfold), when they are present. In fact, factors such as maternal insulin levels and neonatal skinfold thicknesses explained less than 1% of the variability in skinfold thickness at four years of age, according to Krishnaveni et al. (2005b). Thus, it appears that gestational diabetes could, in some cases, be detrimental to the adiposity status of a child, but only to a very small extent.

129.5 Adiposity Localization as Assessed with Skinfolds and Diabetes

Skinfolds are a useful tool to document overall adiposity based on the amount of fat present under the skin. Most authors use the absolute thickness of each skinfold or the sum of various skinfold thicknesses, whereas others compute the percent body fat according to formulas. Potentially even more interesting is the comparison between various skinfolds, to better appreciate fat localization. The case of fat localization documented with skinfolds and diabetes deserves special attention considering that a growing body of research tends to indicate that fat present in the central portion of the body is associated with metabolic abnormalities.

129.5.1 Comparison of Various Skinfolds and T2D

Where fat is localized in relation to T2D presence and incidence has been addressed by several research groups for various ethnic groups. In a large cohort of 1,155 Mexican-American individuals aged 10 years and over, Mueller et al. (1984) showed that diabetic individuals have more fat in the upper portion of the body (subscapular skinfold) than age- and sex-matched non-diabetic individuals. On the other hand, diabetic individuals had less fat in the lower portion of the body, as assessed by calf skinfolds. This appears to suggest a preferential deposition of fat in the central portion of the

Table 129.2 Standardized relative risk of type 2 diabetes incidence for skinfolds – adjusted for age (Adapted from Wang et al. 1997)

	Men		Women	
	Standardized relative risk	95% confidence interval	Standardized relative risk	95% confidence interval
Subscapular	1.62	1.12–2.32	3.07	2.12–4.55
Triceps	1.37	0.97–1.87	1.57	1.11–2.20

body in T2D individuals. These cross-sectional findings were further supported by longitudinal studies. For example, Wang et al. (1997) reported that the incidence of T2D was more associated to indices of trunk adiposity (i.e., subscapular skinfold) than indices of fat in the extremities (i.e., triceps skinfolds) in Chinese individuals. In men, the standardized relative risk of developing the disease was 1.62 for the subscapular and 1.37 for the triceps skinfolds. In women, the difference in the standardized relative risk was about two times higher for the subscapular skinfold than for the triceps skinfolds (3.07 vs. 1.57, respectively). These findings are in line with those of Haffner et al. (1991), who showed that the incidence of the disease was more strongly linked to subscapular skinfolds, compared to triceps skinfolds, in Mexican-American women (Table 129.1). As in the study by Wang et al. (1997), it was also reported that, in men, the subscapular skinfold was better than the triceps skinfolds at predicting disease incidence. However, this was only the case to a smaller extent in women (Table 129.2). Therefore, cross-sectional, as well as longitudinal, studies indicate that, among various ethnic groups, the subscapular skinfold was more closely linked to the disease than peripheral skinfolds, such as the triceps and calf. Researchers who addressed the question of gender differences indicated that this association was even stronger in women.

129.5.2 Centrality Index and T2D

Apart from documenting the association of the disease with various skinfolds distributed throughout the body, the link between glucose metabolism impairments and the centrality index has been addressed. This index, which refers to the ratio of subscapular-to-triceps skinfolds, is a good indicator of fat localization. The higher the ratio, the more fat is present in the central portion of the body. For First Nation individuals in Canada, the centrality index was not associated with glucose intolerance abnormalities (Delisle and Ekoé 1993). On the other hand, the sum of skinfolds was associated with glucose metabolism impairments in this population, suggesting that, for First Nation individuals, the adiposity per se, but not its distribution, is associated with the disease. In Mexican-American individuals, Wei et al. (1997) also reported that the risk of T2D was associated with skinfold thicknesses (subscapular and triceps), but not with the centrality index. These findings are in opposition to what was reported for Asian Indian individuals, in whom the centrality index was significantly associated with the presence of T2D (Menon et al. 2006). Moreover, Marshall et al. (1993) identified a positive association between the risk of T2D and centrality index, for both non-Hispanic white and Hispanic individuals. However, they identified that, for each increase of 0.2 units in the centrality index, the odds ratios associated with the risk of T2D were higher in non-Hispanic whites than in Hispanic individuals (1.4 vs. 1.2, respectively). The association between central adiposity and T2D was also stronger among women, in whom an increase in 0.2 units corresponded to an odds ratio of 1.5, versus an odds ratio of 1.2 in men. Based on available cross-sectional studies, it is thus difficult to determine if the centrality index is linked to T2D. If so, it could be linked to a larger extent in non-Hispanic whites and Asian Indian individuals, compared with Mexican-American and First Nation individuals.

It could also be more detrimental for glucose metabolism in women. These conclusions, which were based on cross-sectional studies, are partly confirmed by the longitudinal study of Haffner et al. (1991), as they showed that the incidence of T2D was more closely linked to the centrality index in women than in men (Table 129.1). Considering also that this study was conducted in Mexican-American individuals, the conclusion indicating that the centrality index was not linked to the presence of T2D in Mexican-American individuals could be questioned. Based on the current state of knowledge, we can only affirm that the centrality index could potentially allow for the identification of non-diabetic individuals who are at a higher risk of developing the disease.

129.5.3 Type 1 Versus Type 2 Diabetes

Whereas the pathophysiology of the two main types of diabetes (type 1 and type 2) differs, very little information is available regarding the morphologic profile of individuals having type 1 diabetes. In fact, the only study that has addressed this is the one by Lev-Ran and Hill (1987). In a comparative study between anthropometric characteristics of individuals with type 1 and type 2 diabetes, they showed that, for similar BMI, men with T2D have a higher centrality index than men with type 1 diabetes (2.48 vs. 1.95, $p = 0.049$). On the other hand, women with either types of diabetes have a similar centrality index (1.18 for T2D and 1.09 for type 1 diabetes, $p = 0.284$). This is despite a larger BMI in T2D women. The limited data do not however allow for a firm conclusion.

129.6 Comparison of Skinfolds with Other Anthropometric Measures

In large cohort studies addressing the topic of the anthropometric characteristics of individuals presenting or at risk of developing diabetes, various measurement techniques other than skinfolds are used. The present section aims to compare the usefulness of skinfold thickness versus other anthropometric measures, such as BMI, waist circumference, hip circumference, and waist-to-hip ratio. Unfortunately, more recent techniques, such as electrical bioimpedance and dual energy X-ray absorptiometry, have not been compared to skinfold measurements in the assessment of the anthropometric characteristics of individuals with or at risk of developing diabetes. Therefore, the next sections will focus on the comparison of skinfolds to BMI and various body circumferences.

129.6.1 Skinfolds Versus Weight and Body Mass Index

In the only study on anthropometric differences between type 1 and type 2 diabetic individuals, no distinction was made based on their BMI or centrality index (subscapular-to-triceps ratio) (Lev-Ran and Hill 1987). This is similar to the study conducted with Mexican-American individuals who were free of diabetes at baseline, in whom the odds of developing the disease were similar for individuals based on their BMI, subscapular skinfold, triceps skinfolds, and the sum of seven skinfolds. In fact, sex- and age-adjusted odds ratios were 1.51, 1.55, 1.49, and 1.52, respectively (Wei et al. 1997). These studies suggest that there is no advantage in using the absolute skinfold value over BMI. The latter even appears to have a better predictive capacity than the centrality index, which has an odds ratio of only 1.26 in the study by Wei et al. (1997). Other groups have also indicated that weight or

BMI could be better than skinfolds at predicting the presence and incidence of T2D. Misra et al. (2001) reported that, in Asian Indian individuals, BMI was a predictor of fasting blood glucose in both men and women, whereas the sum of four skinfolds (biceps, triceps, subscapular, and suprailiac) was not. In the lifestyle group of The Diabetes Prevention Program, the incidence of T2D was predicted by the weight, but not by the adiposity per se, as assessed by skinfolds (The Diabetes Prevention Program Research Group 2006). On the other hand, Haffner et al. (1991) reported that the effect of BMI on T2D incidence was present, although less important than the effect of the centrality index (Table 129.1). Also supporting the use of skinfolds, the study of Katzmarzyk et al. (2007) showed that the odds of developing the disease were slightly higher for individuals presenting high adiposity (sum of five skinfolds) versus high BMI (odds ratios of 2.09 vs. 1.99, respectively).

What emerges from these studies is that discrepancies exist when trying to determine if skinfolds are more closely linked to the prevalence and incidence of diabetes than body weight and BMI. These differences could be partly explained by the choice of skinfolds. Indeed, Wang et al. (1997) identified that indices measured at the trunk, such as the subscapular skinfold, and measurements representing overall adiposity, such as BMI, are more closely linked to T2D incidence than indices from the extremities, such as the triceps skinfolds. Pooling indices from the center and extremities of the body could thus reduce the usefulness of skinfolds. Also, Yilmez et al. (2009) documented no relation between BMI, sum of skinfolds, and insulin resistance. However, skinfolds were linked to insulin resistance when the percent of body fat based on skinfolds was computed. In all other studies that compared anthropometric measurements, skinfolds were always summed and the percent body fat was not calculated. Based on these findings, we recommend that further studies make a distinction between central and peripheral skinfolds, as well as make use of percent body fat in addition to the sum of skinfold thicknesses. Until then, the choice between skinfolds, body weight, and BMI in the assessment of anthropometric characteristics of individuals presenting or at risk of developing the disease remains to be established.

129.6.2 Skinfolds Versus Waist Circumference, Hip Circumference, Waist-to-Hip Ratio, and Waist-to-Thigh Ratio

The study by Lev-Ran and Hill (1987), which was conducted with type 1 and type 2 diabetic individuals, used different anthropometric measures to try to differentiate both types of the disease. The BMI, waist-to-hip, waist-to-thigh, arms-to-thigh, and subscapular-to-triceps ratios were assessed in both men and women. Of all these parameters, only the waist-to-thigh ratio was independently correlated with diabetes type. Individuals having T2D presented higher waist-to-thigh ratio, suggesting more fat in the trunk than in the extremities.

Compared to the waist-to-thigh ratio, the waist-to-hip ratio is more commonly used. In a recent study, it was identified as the anthropometric parameter more closely linked to the incidence of T2D. The odds ratios for the incidence of the disease were 2.94 for the waist-to-hip ratio, 2.53 for waist circumference, and 2.09 for the sum of five skinfolds (Katzmarzyk et al. 2007). Furthermore, this ratio was identified as the best predictor of T2D development in men for the lifestyle group of The Diabetes Prevention Program, when compared to a wide spectrum of skinfold measures (triceps, abdomen, subscapular, and suprailiac skinfolds, the sum of these skinfolds, and the sum of abdomen and suprailiac skinfolds) (The Diabetes Prevention Program Research Group 2006). Waist circumference was also a good predictor in this study. For women in the placebo group, waist circumference was in fact the best predictor of disease development. The importance of waist circumference over skinfold thicknesses also applies to women who had glucose metabolism impairments during pregnancy (impaired glucose tolerance, impaired fasting glucose, or gestational diabetes). In this

population, waist circumference stands as a better predictor of the development of subsequent glucose metabolism impairments, superseding skinfold thicknesses and BMI (Krishnaveni et al. 2007). Whereas some studies indicate that waist circumference is linked to T2D in both men and women (Menke et al. 2007; The Diabetes Prevention Program Research Group 2006; Katzmarzyk et al. 2007), Wang et al. (1997) suggest that the association would be even stronger in women.

Overall, it appears that other parameters, such as the waist-to-thigh ratio, waist-to-hip ratio, and waist circumference, could present more interest. This is despite the utility of skinfold measurements at discriminating the anthropometric characteristics of individuals presenting or being at risk of developing diabetes. Compared to weight and BMI, the conclusion is somehow less clear, given contradictory findings among studies that compared methods. In the future, it would be important to rely on studies that compared these anthropometric techniques to new ones, such as electrical bioimpedance and dual energy X-ray absorptiometry, in the assessment of morphologic characteristics of individuals having or at risk of developing the disease.

129.7 Applications to Other Areas of Health and Disease

Skinfold thickness assessment is a technique that has been used in many health areas where adiposity is part of the pathophysiology. Metabolic impairments, such as impaired glucose tolerance, impaired fasting glucose, type 1 and type 2 diabetes, gestational diabetes, and familial history of type 2 diabetes have been discussed thoroughly in this chapter. However, cardiovascular health is another area in which skinfolds have been used to better understand the association between anthropometric characteristics and diseases. In the case of coronary heart diseases, for example, it is interesting to note that the association with the condition is similar to that reported for metabolic diseases: (i) BMI and skinfolds appear to be similar in their association with coronary heart diseases; (ii) skinfolds in the trunk are linked to a greater extent to coronary heart diseases than those in the periphery; and (iii) the waist-to-hip ratio is more associated to these diseases than skinfold thicknesses (Williams et al. 1997). Cancer is another pathology that was studied in relation to adiposity. In agreement with what was presented for the other diseases, a higher adiposity was associated with the presence of endometrial cancer, as assessed with subscapular skinfold thickness and a higher deposition of fat in the central portion of the body, which was measured with the subscapular-to-thigh ratio (Pischon et al. 2008). However, in opposition to what was reported for metabolic and cardiovascular diseases, subscapular skinfold thickness could better predict the risk of having this type of cancer than the waist-to-hip ratio. Consequently, each disease appears to have a specific association with skinfold thicknesses, supporting the importance of not generalizing findings from one condition to the other.

129.8 Conclusion

Skinfold thickness assessment is among the first techniques that have been used to document the adiposity of healthy individuals and those presenting health impairments. The association of skinfold thicknesses with metabolic impairments has been reported in various ethnic groups, from birth to adulthood and in both men and women, with a better association in the latter group when gender differences exist. Specifically, skinfolds in the central portion of the body, which are indicative of abdominal adiposity, appear to have a better association with the disease in most cases. This is probably why other measurements of abdominal adiposity (i.e., waist-to-hip ratio and waist circumference) that are not restricted to subcutaneous fat, but are estimates of the overall amount of fat present in the abdomen (subcutaneous and visceral), have a better association with metabolic impairments.

With the introduction of other techniques, such as dual energy X-ray absorptiometry and bioimpedance, which allow for overall adiposity measurements and not only those located subcutaneously, it is important to compare their association with metabolic impairments to those obtained with skinfold thicknesses. Presently, no study has compared the adiposity status obtained using skinfold assessment with more recent techniques. This would enable the documentation of whether skinfolds are still useful and would facilitate links with studies conducted before the end of the last century, when skinfold thickness assessment was largely used. Also, for studies where more advanced techniques cannot be used, skinfold thickness assessment could be an alternative, along with body weight and circumference measurements. Recently, we published changes in BMI, waist circumference, and skinfold thicknesses for individuals with or at-risk of T2D who were taking part in the DiabetAction program (Mathieu et al. 2008, 2009). The choice of skinfold measurements was supported by the fact that the implementation study was taking place in clinical settings, where other measurements of adiposity were not possible. Skinfold thickness assessments are also widely used in clinical settings for physical evaluation prior to and following lifestyle interventions. Therefore, it would be important to not create a gap between research, where skinfolds appear to be less used, and the clinic, where they are an important tool for adiposity assessment of individuals who, in a large proportion, have cardiometabolic conditions or are at risk of developing them.

Summary Points

- The higher the skinfold thickness, the higher the prevalence and incidence of metabolic impairments.
- In some cases, the association between skinfolds and metabolism appears to be stronger in women.
- Skinfolds in the central portion of the body are more associated to metabolic impairments than those at the periphery, in most cases.
- Measuring skinfolds does not appear to yield better results than body mass index.
- Circumferences appear to be more useful than skinfolds to document the association and development of metabolic impairments, such as type 2 diabetes.

Key Features

Table 129.3 Key facts on skinfold thickness and glucose and/or insulin metabolism

Metabolic impairments	Based on cross-sectional studies, a positive association between adiposity assessed with skinfolds and metabolic impairments has been shown in – Diverse ethnic groups (non-Hispanic black, non-Hispanic white, Mexican-American, Asian, and First Nation individuals); – Men, women, and pregnant women; – Individuals from birth to adulthood. Based on longitudinal studies, a positive association between baseline adiposity assessed with skinfolds and the incidence of type 2 diabetes is – Reported in Mexican-American, Canadian, and Chinese individuals; – Applicable for periods of three to 15.5 years; – Stronger in women, when gender differences in the association exist; – Not shown in children, although a gain in adiposity is associated with the incidence of metabolic impairments.

Adiposity localization	The association with metabolic impairments – Is stronger for skinfolds in the central portion of the body than at the periphery, according to cross-sectional and longitudinal studies, and in women, when a gender difference is present; – Is positive with the centrality index in non-Hispanic white and Hispanic individuals; – Is better for skinfold thicknesses than the centrality index in First Nation and Mexican-American individuals in cross-sectional studies, but not in longitudinal studies with Mexican Americans; – Is stronger for the centrality index in type 2 than in type 1 diabetic individuals for men, whereas no difference is present in women.
Skinfolds vs. other measurements	The advantage of skinfold measurements over body mass index is not clearly supported. – Waist-to-hip ratio and/or waist circumference are more linked to metabolic impairments (e.g., the incidence of type 2 diabetes and impaired glucose metabolism during pregnancy) than skinfold thicknesses in both men and women, with a stronger association in women when a gender difference exists.

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Part XX
Anthropometry in Cardiovascular Disease

Chapter 130
Altered Bone Geometry of the Radius and Tibia Among Stroke Survivors

Marco Y.C. Pang and Ricky W.K. Lau

Abstract Stroke is a major cause of disability, with muscle weakness, balance deficits, spasticity, and sensory loss being some of the most common physical impairments observed in stroke survivors. The skeleton also undergoes considerable change after stroke, which includes secondary bone loss. This not only leads to changes in bone mineral density but also causes substantial alterations in long bone cross-sectional geometry. Bone geometry is an important determinant of bone strength and fracture risk. It is thus highly relevant to study bone geometry among individuals living with stroke, as this population has a much higher risk of fragility fractures than age-matched reference populations. Peripheral quantitative computed tomography (pQCT), a relatively new bone imaging technology, enables researchers to evaluate bone geometric properties at different skeletal sites. Recent pQCT studies of chronic stroke patients revealed that both the radius and tibia on the hemiparetic side had significantly altered geometric properties, which resulted in lower estimated bone strength than on the unaffected side. These studies also showed that muscle strength, degree of functional recovery, and severity of spasticity were closely associated with long bone geometry. Further research is required to determine the temporal changes in geometric properties at different skeletal sites and their determinants among stroke survivors. Such information is essential for developing effective intervention strategies that enhance bone geometry, and hence reduce fracture risk in this vulnerable population.

Abbreviations

BMD	Bone mineral density
BSIc	Bone strength index for compression
C of G	Center of gravity
DXA	Dual energy X-ray absorptiometry
pQCT	Peripheral quantitative computed tomography
SSI	Stress-strain index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_130,

130.1 Introduction

Stroke is one of the most common chronic conditions among older adults (Feigin et al. 2003). The prevalence of stroke in USA currently stands at approximately 5.5 million cases, with a reported incidence of 700,000 cases per annum (American Heart Association Statistics Committee and Stroke Statistics Committee 2006). Stroke is a major cause of disability. It is well documented that stroke often causes physical impairments, such as hemiparesis, balance problems, spasticity, and deficits in sensory functioning. Less well known, however, is that the skeletal system also undergoes significant change following a stroke event. Mounting evidence demonstrates that secondary bone loss is prevalent after stroke, particularly on the side of the body affected (Ramnemark et al. 1999; Jorgensen and Jacobsen 2001). Loss of bone material not only has a detrimental impact on bone mineral density (BMD), but also causes unfavorable changes in the geometric properties of bone (Ashe et al. 2006; Pang et al. 2007, 2008, 2009). Bone geometry is an important determinant of bone strength (Burr and Turner 2003; Bouxsein and Karasik 2006). It has been shown that the geometric properties of bone are closely related to fracture risk (Ahlborg et al. 2003 and Peacock et al. 1995). Given the high rate of fragility fractures among stroke survivors (Kanis et al. 2001; Dennis et al. 2002), studying bone geometry among stroke patients is highly clinically relevant. Research into bone geometry post stroke has only recently started to emerge. In this chapter, the relevant research findings in this important area are reviewed and discussed.

130.2 Why Study Bone Geometry?

As mentioned, bone geometry has strong clinical relevance, as it influences bone strength. Bone strength is strongly dependent on BMD and the distribution of bone mass. Resistance to bending and torsional loading requires bone material to be distributed far from the neutral axis of bending or torsion, which is typically close to the center of the bone (Burr and Turner 2003; Bouxsein and Karasik 2006). This distribution of bone mass about the bending or torsional axis is referred to as the area moment of inertia and is directly proportional to the resistance to bending and torsional forces (Bouxsein and Karasik 2006). An example is illustrated in Fig. 130.1. Both bones shown in the figure have exactly the same BMD as measured by dual-energy X-ray absorptiometry (DXA). However, if the bone mass is distributed further away from the neutral bending or torsional axis, then the area moment of inertia increases, leading to greater bending or torsional strength. Moreover, this bone mass distribution also increases the total cross-sectional area of the bone, which is directly proportional to the resistance of the bone to compressive forces. Both bending and compressive strength are thus highly influenced by bone geometry (Bouxsein and Karasik 2006). Indeed, a reduced cross-sectional area of the radius is associated with increased wrist fracture risk in postmenopausal women (Ahlborg et al. 2003).

The importance of bone geometry has been illustrated in several studies of changes in bone geometry associated with the aging process (Riggs et al. 2004; Lauretani et al. 2008). In a cross-sectional population-based study using peripheral computed quantitative tomography (pQCT), Riggs et al. (2004) reported that, at the distal radial site, older adults had a significantly greater total bone cross-sectional area and total marrow area than had younger adults (Riggs et al. 2004). They suggested that periosteal apposition (the addition of bone to the periosteal surface) may explain the expansion of the total cross-sectional area, whereas endosteal resorption (bone resorption on the endosteal surface) may account for the expansion of the marrow area. As the addition of bone to the periosteal surface increases the area moment of inertia, they postulated that periosteal apposition is a compensatory

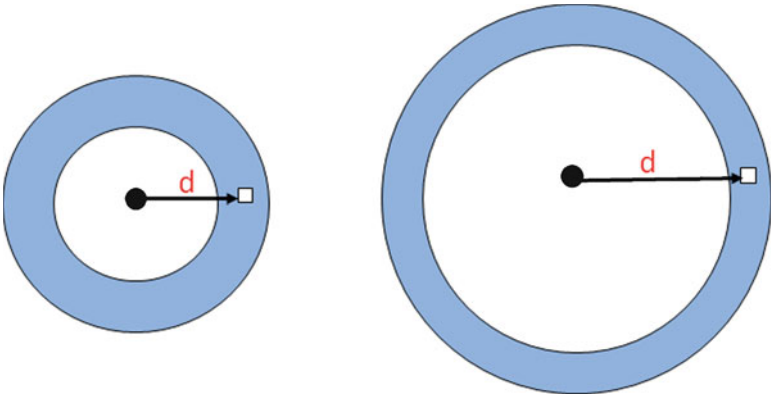

Fig. 130.1 Effect of bone geometry on bone strength. The *shaded areas* represent the cross-sectional view of the cortical shell of a long bone. Both bones have identical bone mineral density as measured by dual energy X-ray absorptiometry (DXA). However, the bone mass is distributed further away from the center of the neutral torsional axis in the bone on the right (distance *d*, illustrated by the *arrow*). This increases the total cross-sectional area and the area moment of inertia, which increases the compressive and bending or torsional bone strength

adaptation to maintain bone strength in response to age-related decline in bone mass (Riggs et al. 2004). A recent longitudinal study found that the rate of age-related medullary expansion due to endosteal resorption was significantly higher among women than among men (Lauretani et al. 2008). This indicates that accelerated endosteal resorption is insufficiently offset by periosteal apposition in elderly women, leading to cortical thinning and a reduction in the area moment of inertia. These differential changes in bone geometry between men and women may partly explain why fragility fractures are more prevalent among elderly women than among elderly men (Riggs et al. 2004; Lauretani et al. 2008).

As bone geometry is a major contributor to bone strength, it is clinically important to study bone geometry among stroke survivors, as these individuals are highly susceptible to fragility fractures. For example, within the first year of hospitalization for stroke, the relative risk of fractures is more than seven times greater among survivors than among age-and gender-matched reference populations (Kanis et al. 2001). Fractures in the stroke population are associated with adverse consequences including increased mortality and morbidity (Ramnemark et al. 2000). The medical cost associated with the treatment of fractures also imposes a financial strain on the healthcare sector. Although it is well documented that stroke survivors sustain a decline in BMD at various skeletal sites (Ramnemark et al. 1999), it is essential to gain a better understanding of the changes in bone geometry that occur after stroke and the factors associated with these changes so that proper therapeutic strategies can be devised to enhance bone geometry and reduce the fracture risk of this compromised population.

130.3 Measuring Bone Geometry

The method most commonly used to diagnose osteoporosis is dual-energy X-ray absorptiometry (DXA). However, because of its planar nature, DXA provides only a two-dimensional BMD measurement (areal BMD in g/cm^2) of a three-dimensional bone structure. Thus, bone-geometry parameters must be estimated indirectly using equations derived from areal BMD measurements and projections of the area of the region of interest (Szulc et al. 2004). For example, the endocortical

Fig. 130.2 A peripheral quantitative computed tomography (pQCT) device. A pQCT device can be used to measure bone geometry

diameter can be estimated from the bone mineral content and external diameter of the bone (Szulc et al. 2006). Cortical thickness can then be calculated based on the external and estimated endocortical diameters (Szulc et al. 2006). However, this technique has many limitations, not the least of which is that the estimation of the endocortical diameter is indirect. This technique also assumes a perfectly circular bone shape and constant cortical porosity (Boivin et al. 2002; Beck et al. 2003). Nevertheless, for certain skeletal regions, such as the diaphyseal sites of long bones (e.g., the radius), this technique may provide a reasonable estimate of bone geometric properties, as the bone at such sites is nearly circular in shape and the bone material is almost entirely cortical (Boivin et al. 2002; Szulc et al. 2006).

Peripheral quantitative computed tomography (pQCT), by contrast, is a relatively new technique that is capable of providing a volumetric bone density measure (in mg/cm^3; see Fig. 130.2). In addition, pQCT analyzes the cortical and trabecular compartments separately, and provides valuable information on bone geometry, including parameters, such as the total cross-sectional area, total cortical bone area, and cortical thickness. Figures 130.3 and 130.4 show the pQCT images of the tibia and radius, respectively. The effective radiation dose is also very small (<0.5 μV per slice) compared with that of DXA (1–10 μV), making pQCT a very safe imaging technique.

The precision of pQCT measurements of bone structure is comparable to that of peripheral DXA, with a precision error of just 1–2% and trueness error of 2–8% (Genant et al. 1996; Boutroy et al. 2005). Various estimates of bone strength can be computed using the densitometric and geometric parameters generated by pQCT. Several bone strength indices derived in this way have been validated in human cadaver studies, indicating that pQCT is a useful and noninvasive means of estimating bone strength. For example, the stress–strain index (SSI), which is the product of section modulus

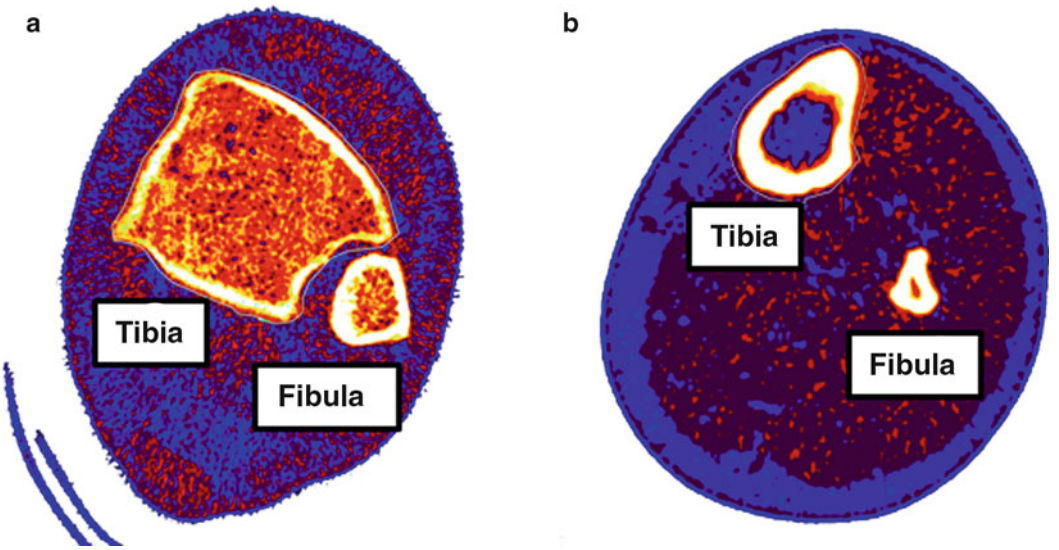

Fig. 130.3 A peripheral quantitative computed tomography (pQCT) image of the tibia. (**a**) A pQCT image of the epiphyseal site of the tibia (mostly trabecular bone). The white area represents the cortical bone shell. (**b**) A pQCT image of the diaphyseal site of the tibia (mostly cortical bone)

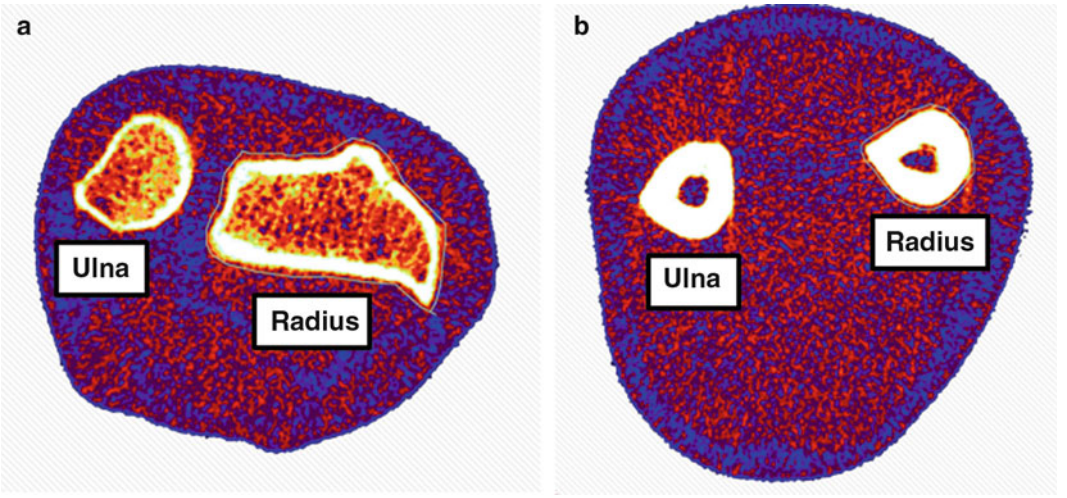

Fig. 130.4 A peripheral quantitative computed tomography (pQCT) image of the radius. (**a**) A pQCT image of the epiphyseal site of the radius (mostly trabecular bone). (**b**) A pQCT image of the diaphyseal site of the radius (mostly cortical bone)

measurements (i.e., the maximum distance from the periosteal surface to a particular bending or torsional axis) and the ratio of measured cortical BMD to physiological BMD (1,200 mg/cm^3) (Fig. 130.5), has been shown to be strongly associated with the bending failure load at the epiphyseal and diaphyseal sites of the radius and tibia (Lochmuller et al. 2002; Kontulainen et al. 2008). Another bone strength index, the bone strength index for compression (BSIc), which is the product of the

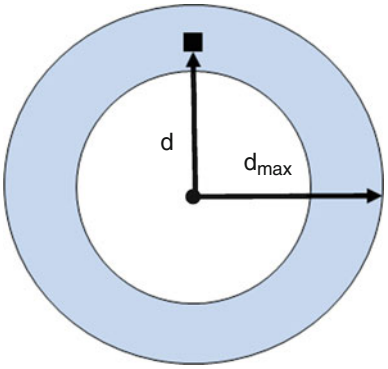

Fig. 130.5 Stress–strain index (SSI). SSI is computed from densitometric and geometric parameters derived from peripheral quantitative computed tomography (pQCT). It reflects the resistance of the bone to bending and torsional loads. The filled square represents the area of one voxel and the filled circle represents the center of gravity (C of G). [a = area of one voxel (mm^2); d = distance of one voxel to the C of G (mm); d_{max} = maximum distance to the C of G (mm); CD = volumetric cortical bone mineral density in one voxel (mg/cm^3); ND = normal physiological bone mineral density (1,200 mg/cm^3)]

Table 130.1 Key features of the stress–strain index (SSI)

1. Data generated by peripheral quantitative computed tomography (pQCT) can be used to compute a bone strength index called the stress–strain index (SSI).
2. The calculation of the SSI takes into account both the geometric and densitometric properties of the bone.
3. The SSI reflects the ability of the bone to withstand bending or torsional forces.
4. It is usually used for the cortical sites of long bones, where bending and torsional loading predominate.
5. The calculation of the SSI requires the accurate measurement of cortical parameters. Therefore, this index may not be appropriate for the epiphyseal sites of long bones, where the cortical shell can be very thin, and pQCT may not have adequate resolution to assess the cortical compartments at these sites.

This table lists the key features of the stress–strain index, including its properties and potential use

Table 130.2 Key features of the bone strength index for compression (BSIc)

Data generated by peripheral quantitative computed tomography (pQCT) can be used to compute the bone strength index for compression (BSIc).
BSIc = (total cross-sectional area) × (total bone mineral density)^2.
The calculation of the BSIc takes into account both the geometric and densitometric properties of the bone.
The BSIc reflects the ability of the bone to withstand compressive forces.
It is usually used for the distal end of long bones, which is subjected primarily to axial compression.

This table lists the key features of the bone strength index for compression (BSIc), including its computation, properties, and potential use.

measurements of the total bone cross-sectional area and the square of the total BMD, has been shown to account for 85% of the compressive failure load and 57% of the stiffness at epiphyseal sites of the tibia (Kontulainen et al. 2008). Tables 130.1 and 130.2 summarize the key features of the SSI and BSIc, respectively.

130.4 Practical Guidelines

Stroke patients often demonstrate impaired motor control. Therefore, it is important that the scanned limb segment be stabilized when performing pQCT measurements among these patients, as any movement will cause image artifacts. The subject should sit comfortably on a chair in front of the device (Fig. 130.6). Ideally, the limb segment to be scanned should be supported by a holder of a suitable size.

The length of the limb segment concerned should be measured before scanning. Next, a scout view of the radius/tibia should be obtained to ensure correct positioning of the limb segment, and to determine the reference line. For a radial scan, the cortical end plate of the radius should be used as an anatomical landmark. For a tibial scan, the middle of the distal end of the tibia is where the reference line should be placed (XCT 3000 Manual, Stratec 2007).

After the reference line has been determined, the measurement line can be defined. The distance between the reference line and measurement line is usually expressed as a percentage of the total length of the limb segment. For example, scanning the tibia at the 4% site means that the measurement line is 4% of the lower leg length proximal to the reference line (XCT 3000 Manual, Stratec 2007).

The voxel size needs to be specified. For more accurate measurements, a smaller voxel size should be chosen (i.e., better resolution). However, the achievement of better resolution necessitates a slower scanning speed. As mentioned previously, stroke patients may demonstrate spasticity or tremor, which may induce movement artifacts. In addition, they may not tolerate staying in a static position for an extended period of time because of fatigue or balance problems. There needs to be a balance between the resolution of images and scanning speed when performing pQCT scans on these individuals. In previous studies of stroke, a scan speed of 25 mm/s and voxel sizes ranging from 300 to 500 μm were used (Ashe et al. 2006; Pang et al. 2007, 2008, 2010).

To assess the trabecular bone compartments of the tibia and radius, the most common measurement site is the 4% one (Russo et al. 2003; Lauretani et al. 2008; Pang et al. 2010). To assess the cortical bone sites of the radius, the 30% site is commonly used (Uusi-Rasi et al. 2002; Pang et al. 2007).

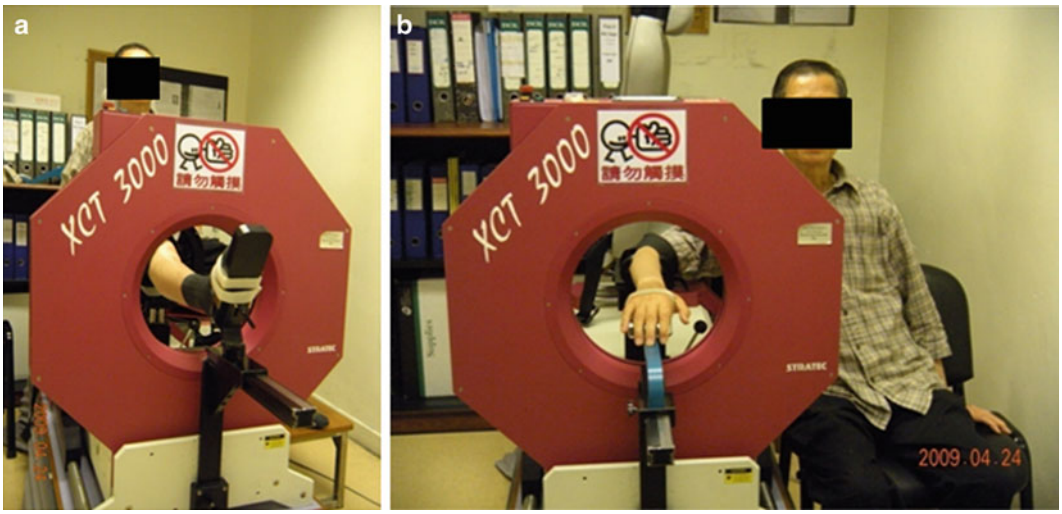

Fig. 130.6 Bone scanning using peripheral quantitative computed tomography (pQCT). (**a**) A stroke patient is undergoing pQCT scanning of the tibia. (**b**) The same individual is undergoing scanning of the radius

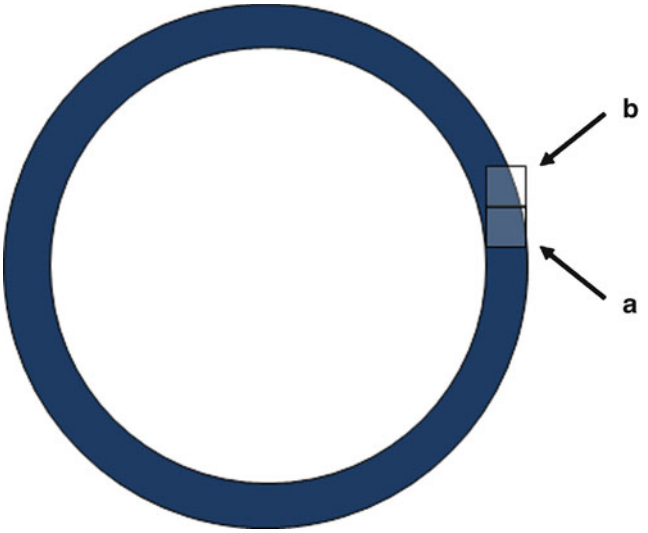

Fig. 130.7 Illustration of the partial volume effect. When a low resolution is used and the cortical shell is thin (<2 mm), the partial volume effect may occur. Voxel (**a**) contains mostly bone material, and the computed bone mineral density value is thus an accurate reflection of the true density of the bone material contained within the voxel. However, a substantial proportion of the area covered by voxel (**b**) contains non-bone material. Thus, the calculated bone mineral density value will be much lower than the true density of the bone material contained within the voxel. If a large number of voxels behave similarly to voxel (**b**), then the bone mineral density may be grossly underestimated

For the tibia, the 30%, 38%, and 50% sites have been used in previous studies (Uusi-Rasi et al. 2002; Lauretani et al. 2008; Pang et al. 2008).

As mentioned, a relatively fast scanning speed (e.g., 25 mm/s) may be used to keep the scanning time short to avoid movement artifacts, particularly among patients who are susceptible to involuntary movements or tremors, such as those with stroke (Ashe et al. 2006). However, this means that a lower-resolution/larger voxel size (e.g., 800 μm) has to be used to improve the signal-to-noise ratio (XCT 3000 Manual, Stratec 2007). With a lower image resolution, the accurate measurement of the cortical thickness at the distal sites of long bones can be difficult, particularly for bones with a thin cortical shell (<2 mm), as observed among patients with osteoporosis (Hangartner et al. 1996). The combination of a lower resolution and thin cortical bone shell may also lead to the "partial volume effect," which occurs when there is heterogeneous material within a single voxel. In areas where cortical bone is thin, the voxels are only partially filled by bone material. These partially filled voxels will yield falsely lower densities because of the surrounding soft tissues, which have significantly lower densities (Hangartner et al. 1996; Leonard and Shore 2003) (Fig. 130.7). Recently, a high-resolution pQCT system has become available that is capable of measuring bone parameters at high resolutions of up to 80 μm (Boutroy et al. 2006).

130.5 Geometric Changes in the Tibia After Stroke

As yet, no prospective studies have been conducted to examine the specific changes in bone geometry that occur after stroke. Alterations in the geometric properties of bone post stroke are generally inferred by comparing the differences between the paretic and non-paretic sides among stroke survivors. However, these comparisons do not reveal temporal changes in bone geometry as recovery progresses.

Table 130.3 Peripheral quantitative computed tomography (pQCT) parameters at the 30% tibial site (Reproduced from J. Bone. Miner. Res. 2008; 23; 1023–1030 with the permission of the American Society for Bone and Mineral Research)

pQCT parameter		Paretic side	Non-paretic side	*P**	% difference†
Total bone area (ToA, mm^2)	Men	419.9 ± 50.9	423.3 ± 51.4	0.252	0.7 ± 3.7
	Women	311.1 ± 47.6	320.1 ± 49.2	0.003*	2.8 ± 4.2
Cortical bone area (CoA, mm^2)	Men	290.7 ± 32.9	299.5 ± 33.9	0.007*	1.5 ± 6.0
	Women	194.3 ± 36.6	206.2 ± 41.2	<0.001*	4.5 ± 6.8
Marrow cavity area (CavA, mm^2)	Men	129.2 ± 38.5	123.8 ± 35.3	0.011*	–4.6 ± 8.6
	Women	116.8 ± 44.5	113.9 ± 42.9	0.367	–3.0 ± 16.7
Cortical bone mineral content (BMC_{cort}, mg/mm)	Men	338.4 ± 39.0	349.4 ± 40.0	0.003*	1.9 ± 5.8
	Women	226.2 ± 46.4	239.5 ± 50.3	0.001*	4.5 ± 7.0
Cortical bone mineral density (BMD_{cort}, mg/cm^3)	Men	1164.2 ± 30.9	1166.8 ± 35.3	0.394	0.2 ± 1.4
	Women	1159.3 ± 48.7	1158.4 ± 42.1	0.799	–0.1 ± 1.5
Cortical thickness (mm)	Men	5.6 ± 0.7	5.8 ± 0.8	0.001*	2.6 ± 6.3
	Women	4.2 ± 0.8	4.5 ± 0.9	0.012*	3.6 ± 8.4
Bone strength index (BSI, mm^3)	Men	1788.0 ± 277.1	1836.8 ± 299.0	0.016*	2.4 ± 5.3
	Women	1077.7 ± 246.4	1156.2 ± 268.8	<0.001*	6.5 ± 6.7‡

A negative % difference denotes a lower value on the non-paretic than the paretic side
*indicates a significant difference between the paretic and non-paretic sides ($P < 0.05$)
†A positive % difference denotes a higher value on the non-paretic than the paretic side
‡Indicates a significant difference between men and women ($p < 0.05$)

Further, it is possible that the affected and unaffected extremities may undergo different changes in bone geometry after the onset of stroke.

The tibia, a major weight-bearing bone in the lower extremity, may undergo substantial geometric changes after stroke. In a study of Pang et al (2008), 55 individuals with chronic stroke underwent pQCT scans of the diaphyseal site (30% site, mostly cortical bone) of the tibia. Both male and female stroke subjects had a significantly lower cortical bone mineral content and smaller cortical area on the paretic than the non-paretic side, indicating a loss of bone mineral (Table 130.3). Other geometric changes seemed to be gender specific. In men, the marrow cavity area was significantly larger on the paretic side, with no significant difference between sides in the total cross-sectional area (Fig. 130.8a). By contrast, in women, the total area on the paretic side was significantly smaller than that on the non-paretic side, but no significant difference in the marrow cavity area was identified between sides (Fig. 130.8b). These findings indicate that, in male stroke survivors, endosteal resorption may occur, whereas in women, periosteal resorption may predominate. Losing bone from the periosteal surface compromises bone strength more than does endosteal resorption, as it reduces the total cross-sectional area and area moment of inertia. The reasons for such gender-specific differences in bone geometry after stroke are currently unknown. It is possible that lifestyle factors, genetics, and endogenous sex hormones may play a role (Pang et al. 2008).

At the tibia epiphysis (4% site, mostly trabecular bone), the bone changes are different. Based on a sample of 45 individuals with chronic stroke, Pang et al. (2010) found that although there was a significantly lower trabecular BMD on the paretic side, there was no significant difference in the total cross-sectional area. However, despite the apparent preservation of the total cross-sectional area, the lower trabecular BMD on the paretic side contributed to a lower compressive bone strength index (BSIc) than that on the non-paretic side.

Researchers have also attempted to identify the correlates of the bone geometry of the tibia. It has been demonstrated that cardiovascular function and muscle atrophy/weakness are independently associated with the estimated bone strength of the tibia measured at both the epiphyseal and diaphyseal sites in stroke patients (Pang et al. 2008, 2010). These findings indicate the possibility that tibial

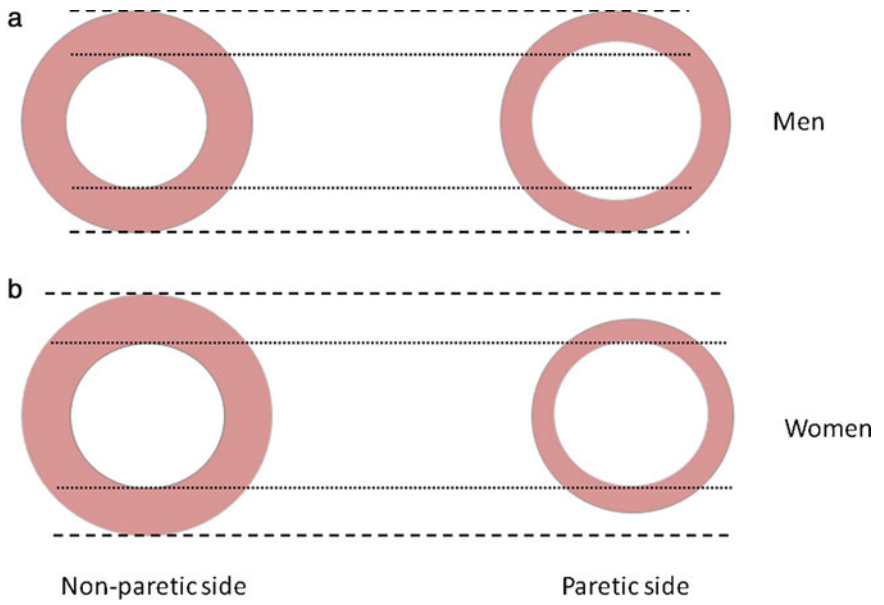

Fig. 130.8 Geometric properties of the tibia measured at the 30% (cortical) site in chronic stroke patients. (**a**) In men, the cortical shell is significantly thinner on the paretic than the non-paretic side. However, there is no significant difference in the total cross-sectional area between the two sides. This suggests that endosteal resorption may have occurred in the tibia on the paretic side (Pang et al. 2008). (**b**) In women, the cortical shell is significantly thinner on the paretic than the non-paretic side. However, the total cross-sectional area is also significantly smaller on the paretic side. This suggests that periosteal resorption may have occurred in the tibia on the paretic side (Pang et al. 2008) (Illustration adapted from Pang 2010)

bone geometry could be enhanced by improvement in cardiovascular fitness, muscle strength, mobility, and spasticity levels, but further investigation is required.

130.6 Geometric Changes in the Radius After Stroke

Only two studies have examined the geometric properties of the radius among stroke patients. Ashe et al. (2006) conducted a small study of 15 chronic stroke patients, all of whom had substantial muscle weakness in the affected upper extremity. Using pQCT, it was found that, at the diaphyseal site of the radius (30% of bone length as measured from the distal end of the radius; mostly cortical bone), the paretic side had a significantly lower cortical bone mineral content and cortical BMD than the non-paretic side by 8% and 3%, respectively, indicating possible secondary bone loss on the paretic side post-stroke. Interestingly, there was no difference in the total bone cross-sectional area between sides, indicating that bone material on the periosteal surface of the hemiparetic radius may be spared (Ashe et al. 2006).

Pang et al. (2007) conducted a larger study of 47 individuals with chronic stroke, all of whom underwent pQCT scanning of the same 30% site of the radius (Pang et al. 2007). Similar to the findings of Ashe et al. (2006), significantly lower cortical bone mineral content (8%) and cortical BMD (2%) were found on the paretic side compared with the non-paretic side. A more interesting finding is that there was no significant difference in the total cross-sectional area between the paretic and non-paretic sides, whereas the cortical bone area and cortical thickness values were significantly lower on the paretic side (Table 130.4). This indicates that bone loss occurred primarily on

Table 130.4 Peripheral quantitative computed tomography (pQCT) parameters at the 30% radial site (Reproduced from Pang et al. 2007. With the permission of Springer)

pQCT parameter		Paretic side	Non-paretic side	P[a]	Percent difference
Total area ($Area_{total}$, mm^2)	Male	116.6 ± 18.3	116.9 ± 18.7	0.877	–0.2 ± 8.3
	Female	76.1 ± 12.9	76.1 ± 12.9	0.963	–0.1 ± 5.8
	All	**100.2 ± 25.8**	**100.4 ± 26.1**	**0.871**	**–0.2 ± 7.3**
Cortical area ($Area_{cort}$, mm^2)	Male	94.2 ± 15.7	100.4 ± 13.3	<0.001	6.3 ± 7.7
	Female	59.0 ± 11.4	63.1 ± 11.0	0.025	6.0 ± 11.5
	All	**1182.4 ± 42.4**	**85.3 ± 22.2**	**<0.001**	**6.2 ± 9.3**
Cortical bone mineral content (BMC_{cort}, mg/mm)	Male	111.3 ± 20.0	121.0 ± 17.2	<0.001	8.2 ± 8.1
	Female	70.2 ± 15.1	76.0 ± 15.6	0.020	6.7 ± 13.0
	All	**84.7 ± 27.2**	**102.8 ± 27.7**	**<0.001**	**7.6 ± 10.2**
Cortical bone mineral density (BMD_{cort}, mg/cm^3)	Male	1179.8 ± 40.4	1204.2 ± 33.2	0.003	2.0 ± 3.3
	Female	1186.2 ± 46.0	1198.5 ± 59.9	0.192	0.9 ± 3.4
	All	**1182.4 ± 42.4**	**1201.9 ± 45.4**	**0.001**	**1.6 ± 3.3**
Cortical thickness (mm)	Male	3.6 ± 0.8	4.0 ± 0.7	<0.001	10.1 ± 12.2
	Female	2.9 ± 1.0	3.2 ± 0.9	0.018	9.2 ± 16.5
	All	**3.3 ± 0.9**	**3.7 ± 0.9**	**<0.001**	**9.8 ± 14.0**
Polar Stress–strain Index (p-SSI, mm^3)	Male	313.1 ± 62.5	331.1 ± 64.6	0.005	5.1 ± 8.9
	Female	165.9 ± 29.5	175.8 ± 35.8	0.073	4.5 ± 11.7
	All	**253.6 ± 89.2**	**268.3 ± 94.2**	**0.001**	**4.8 ± 10.0**

[a] Paired *t*-test to compare the paretic and non-paretic sides

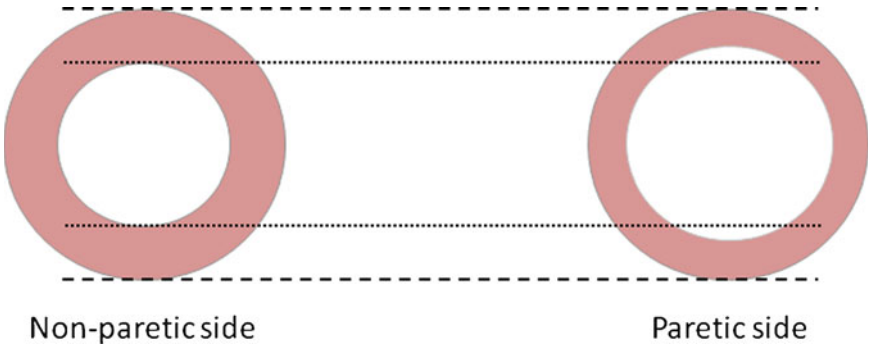

Fig. 130.9 Geometric properties of the radius measured at the 30% (cortical) site in chronic stroke patients. This diagram shows a cross-sectional view of the midshaft site (30% site) on both sides of the radius. The shaded area represents the cortical bone shell. The cortical bone area and cortical thickness are significantly reduced on the paretic side as compared with the non-paretic side, but there is no difference in the total cross-sectional area between the two sides. This suggests that endosteal resorption may have occurred in the radius on the paretic side (Pang et al. 2007) (Illustration adapted from Pang 2010)

the endosteal surface (i.e., there was endosteal resorption) of the hemiparetic radius (Fig. 130.9). Despite the relative preservation of bone on the periosteal surface, the overall decrease in cortical thickness due to endosteal resorption contributed to the significantly lower SSI on the paretic side (Pang et al. 2007).

Studying the bone geometry of the distal epiphysis of the radius is particularly relevant, as this is a common site of wrist fracture and the second most common site of fracture among stroke patients (Dennis et al. 2002). Ashe et al. (2006) found a trend toward a lower trabecular BMD on the paretic side at the epiphyseal site of the radius (at 4% of the total bone length as measured from the distal end), suggesting possible loss of trabecular elements. Similar to the findings for the cortical bone

Table 130.5 Key differences in the bone geometry of the tibia and radius at the cortical sites

Mid-shaft of the tibia on the paretic side (compared with the non-paretic side)	
Men	Women
Smaller cortical bone area	Smaller cortical bone area
Larger marrow cavity area	Similar marrow cavity area
Thinner cortical shell	Thinner cortical shell
Similar total cross-sectional area	Smaller total cross-sectional area
Lower estimated compressive bone strength	Lower estimated compressive bone strength
Mid-shaft of the radius on the paretic side (compared with the non-paretic side)	
Smaller cortical bone area	
Thinner cortical shell	
Similar total cross-sectional area	
Lower estimated torsional bone strength	

This table summarizes the main differences in bone geometry at the cortical sites of the tibia and radius between the paretic and non-paretic sides in chronic stroke survivors. The findings are based on the studies of Ashe et al. (2006), Pang et al. (2007), and Pang et al. (2008)

site, no difference was found in the total cross-sectional area between the paretic and non-paretic sides. However, further study is required to fully determine the changes in the geometric properties at the epiphyseal site of the radius after stroke (Table 130.5).

There is also evidence that the geometric properties of the radius are associated with the severity of stroke impairment. Pang et al. (2007) showed that a greater difference in cortical thickness at the 30% radial site between the affected and unaffected sides was correlated with poorer functional recovery of the upper extremity, more severe spasticity, greater disuse, and greater deficits in muscle strength (Pang et al. 2007). It would be interesting to determine whether modifying these factors through various means (e.g., upper extremity muscle strengthening or functional training, anti-spastic agents) could improve the bone geometry of the radius and thus reduce the risk of wrist fracture among the stroke population.

130.7 Applications to Other Health Areas and Disease Groups

As mentioned, alterations to bone geometry can affect fracture risk. Thus, measuring bone geometry is an important aspect in the study of bone health. pQCT provides a safe way to evaluate the geometric properties of bone, and has been used among healthy subjects of various age groups, including children (McDonald et al. 2006) and the elderly (Riggs et al. 2004; Lauretani et al. 2008). The evaluation of bone geometry is particularly applicable among certain disease groups in which bone health and fracture risk are of major concern. For example, patients living with chronic conditions may benefit from the measurement of bone geometry, as these individuals are often subject to an elevated risk of falls or fractures because of factors, such as secondary bone loss, muscle atrophy, cardiovascular deconditioning, visual impairment, and depression. In addition to stroke, bone geometry has been studied among patients with other chronic conditions, such as spinal cord injury (Eser et al. 2004) and arthritis (Burnham et al. 2008). Using pQCT to evaluate bone geometry may also be of value for those with chronic diseases, such as Parkinson's disease, which is known to be associated with compromised BMD and an elevated fracture risk (Di Monaco et al. 2006). It may also be worth evaluating the bone geometry of individuals at risk of glucocorticoid-induced osteoporosis, as observed among some patients with chronic obstructive pulmonary disease (Nuti et al. 2009).

130.8 Conclusion

In summary, among chronic stroke survivors, the radius and tibia have significantly different geometric properties on the affected side as compared with the unaffected side, leading to reduced bone strength and hence increased fracture risk. The stroke-related alterations in radial and tibial bone geometry are drastically different from those observed to result from general aging (i.e., endosteal resorption with concomitant periosteal apposition) (Riggs et al. 2004; Lauretani et al. 2008). There is therefore a need for longitudinal studies that examine the temporal changes in bone geometry after the onset of stroke and their determinants. Such information could be instrumental in the development of effective interventions to improve bone geometry and reduce fracture risk in this vulnerable population.

Summary Points

- Bone geometry plays an important role in bone strength.
- Peripheral quantitative computed tomography (pQCT) can be used to measure cross-sectional long-bone geometry.
- There is a significant difference in radial and tibial geometry between the affected and non-affected sides in stroke survivors.
- Endosteal resorption may predominate in the radial diaphysis on the hemiparetic side.
- In men, endosteal resorption may predominate in the tibial diaphysis on the hemiparetic side.
- In women, periosteal resorption may predominate in the tibial diaphysis on the hemiparetic side.
- Both the radius and tibia on the affected side demonstrate a lower estimated bone strength than on the unaffected side in stroke survivors.

Acknowledgments The authors thank Dr. Janice J. Eng for her mentorship and support.

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Chapter 131
Waist Circumference and Cardiovascular Risk

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Abstract The epidemic of obesity poses a global concern because of its related health problems. The related risk appears to be directly linked to the increased deposition of fat in the body. While most adipose tissue is located under the skin, intra-abdominal fat is more closely associated with the risk of several chronic diseases. A simple measurement of such visceral fat is waist circumference, which is strongly correlated with the risk for diabetes mellitus and cardiovascular disease. The relative contribution of intra-abdominal fat to total body fat is influenced by sex, age, race/ethnicity, physical activity and total adiposity. Excess visceral adiposity/ectopic fat affects the incidence of the metabolic syndrome. Given the long-term health implications of this syndrome it was suggested to add the combination of elevated waist circumference and triglycerides to the list of variables considered in global risk algorithm, which thereby transforms it into a global cardiometabolic risk assessment algorithm. There is an urgent need to increase the awareness among both health professionals and the general public about the health hazards of central or abdominal obesity. Although maintaining a healthy weight should continue to be a cornerstone in the prevention of chronic diseases and premature death, maintaining a healthy waist size should also be an important goal.

Abbreviations

ADA	American Diabetes Association
AHEAD	Action for Health in Diabetes
AMI	Acute myocardial infarction
ARIC	The Atherosclerosis Risk in Communities
ATP	Adult Treatment Panel
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_131,

ESC	European Society of Cardiology
GEMCAS	German Metabolic and Cardiovascular Risk Project
HDL	High-density lipoprotein
MetS	Metabolic syndrome
NHANES	The National Health and Nutrition Examination Survey
PAD	Peripheral arterial disease
PRR	Prevalence rate ratio
SCORE	Risk Score System of the European Society of Cardiology
T2DM	Type 2 diabetes mellitus
WC	Waist circumference
WHR	Waist-hip ratio
WHtR	Waist-height ratio

131.1 Introduction

Obesity is a complex metabolic disorder characterized by a positive balance between energy intake and expenditure that increases the risk for diabetes mellitus (DM), hypertension, coronary heart disease, dyslipidemia, certain cancers, and obstructive sleep apnea, among other comorbidities (Baskin et al. 2005; Ness-Abramof and Apovian 2008). The precise mechanisms underlying these associations are still poorly understood.

Although overweight and obesity by themselves are associated with an increased risk, the pattern of fat distribution is also important in risk stratification. Most adipose tissue (about 85% of total adipose tissue mass) is located under the skin (subcutaneous fat), and a smaller amount (about 15%) is located within the abdomen (intra-abdominal fat) in lean and obese persons. (Klein et al. 2007) Excess abdominal fat (also known as central or upper-body fat) is associated with an increased risk of cardiometabolic disease. However, precise measurement of abdominal fat content requires the use of expensive radiological imaging techniques. Therefore, waist circumference (WC) is often used as a surrogate marker of abdominal fat mass because it correlates with abdominal fat mass (subcutaneous and intra-abdominal) (Pouliot et al. 1994) and is associated with cardiometabolic disease risk (Kissebah et al. 1982). However, measurement of WC has not been widely adopted in clinical practice, and the anatomical, metabolic, and clinical implications of WC data can be confusing.

Intra-abdominal (visceral) fat is more closely associated with the risk of several chronic diseases than a more peripheral (subcutaneous) fat distribution and large studies have suggested that waist circumference or the waist–hip ratio, as indicators of abdominal obesity, may be better predictors of the risk of disease than the BMI, an indicator of general adiposity (Yusuf et al. 2005; Hu 2007). Besides that, even when body weight is kept constant or decreases during the aging process, total and regional adiposity may increase due to predominant decreases in lean body mass. For instance, data from our research group (Markus et al. 2010) revealed that hypertensive individuals who normalized their blood pressure values after 10 years of follow-up due to changes in their dietary habits had, on average, a decrease in total body weight, fat-free mass and fat mass. Nevertheless, the aging process resulted, at the same time, in an increase in waist circumference and waist–hip ratio due to a redistribution of their fat deposits from subcutaneous to intra-abdominal. One may even question if the benefit in the blood pressure control due to weight loss can supplant the detrimental increase in waist circumference, as fat distribution has substantive effects on morbidity and mortality risk (Huang et al. 2005). Moreover, some studies have shown that abdominal adiposity is an important predictor of the risk of death (Simpson et al. 2007; Zhang et al. 2007). In a large European cohort study,

the associations of BMI with the risk of death were J-shaped, with higher risks of death observed in the very low and upper BMI categories than in the middle categories (Pischon et al. 2008). By contrast, abdominal fat distribution was positively associated with the risk of death when this risk was adjusted for BMI. These associations tended to be stronger among participants with a lower BMI than among those with a higher BMI. Thus, measurement of both general and abdominal adiposity provides a better assessment of the risk of death, particularly among people with a lower BMI. These results underscore the importance of assessing the distribution of body fat even among persons of normal weight and challenge the use of cutoff points to define abdominal obesity, at least when they are used to predict the risk of death (Pischon et al. 2008; Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults 1998b; Obesity: preventing and managing the global epidemic. Report of a WHO consultation 2000).

131.2 Waist Circumference and Related Risk

131.2.1 Waist Circumference and CV Risk

Identification of patients with high cardiovascular risk, an immanent task of primary care physicians, is laborious, cost intensive, and, thus, difficult to perform. Conversely, waist circumference (WC), given its association with multiple risk factors, is an easy-to-use tool for initial assessment of cardiovascular risk. Data from the German Metabolic and Cardiovascular Risk Project (GEMCAS) were used to predict the validity of measuring waist circumference in primary care and its correlation with the prevalence of risk factors and the risk score assessment (SCORE) of the European Society of Cardiology (ESC) (Schunkert et al. 2008). The SCORE risk assessment is derived from a large data set of prospective European studies and predicts fatal atherosclerotic CVD events over a ten-year period. This risk estimation is based on the following risk factors: gender, age, smoking, systolic blood pressure, and total cholesterol. The threshold for high risk based on fatal cardiovascular events is defined as "higher than 5%," using a composite coronary endpoint. The global cardiovascular risk, using the SCORE, was assessed in 10,323 men (aged 35–65) and 18,852 women (aged 45–65). Logistic regressions and Spearman correlations were used to evaluate the interdependence of WC and cardiovascular risk factors, as well as the estimated cardiovascular risk. Of these unselected individuals, 21.9% had an increased WC (women >80–88, men >94–102 cm) and a further 36.5% had a high WC (women >88, men >102 cm). The proportion of patients with a low HDL-cholesterol was higher in high WC compared to normal WC (prevalence rate ratio (Schunkert et al.) 1.88 [95%CI: 1.74–2.02] in men and 2.97 [2.75–3.21] in women). The same applied to elevated triglycerides (PRR 1.72 [1.62–1.84] and 2.57 [2.36–2.80], respectively), impaired fasting glucose (PRR 2.30 [2.13–2.49] and 3.66 [3.29–4.06]), and elevated blood pressure (PRR 1.27 [1.23–1.30] and 1.57 [1.52–1.62]), respectively (Table 131.1). A SCORE score result necessitating action (>5% risk) was observed in 24.12% of men (age-adjusted PRR of 1.27, 95%CI: 1.12–1.44) and 3.19% of women (age-adjusted PRR of 1.77, 95%CI: 1.26–2.49) with a high WC as compared to 10.88% of men and 0.95% of women with a normal WC (Fig. 131.1).

Furthermore, there are various studies showing associations between waist circumference and risk of diseases. The INTERHEART study reported the effect of various measures of adiposity on rates of acute myocardial infarction (AMI) by comparing acute myocardial infarct cases and standardized controls of varying ethnicity from 52 countries (Yusuf et al. 2004). BMI showed a modest association with AMI, but this association was lost after adjustment for other risk factors.

Table 131.1 Risk factor prevalence in patients with an increased waist circumference (Data presented are reprinted by permission of the publisher of reference (Schunkert et al. 2008))

	Total sample		Normal WC[a]		Increased Wc[b]				High WC[c]			
	N	%	*N*	%	*N*	%	PRR[e]	95%CI	*N*	%	PRR[e]	95%CI
Men												
HDL cholesterol < 1.0 mmol/l												
A1 (HDL-C < threshold)	1,667	12.2	391	7.7	417	11.6	1.76	[1.54; 2.02]	859	17.3	2.71	[2.41; 3.06]
A2 (lipid therapy[d])	2,515	18.2	516	10.0	721	19.9	1.31	[1.19; 1.46]	1,278	25.4	1.55	[1.41; 1.70]
A (total (A1 and/or A2))	3,816	27.5	853	16.5	1,045	28.8	1.48	[1.36; 1.60]	1,918	38.0	1.88	[1.74; 2.02]
Triglycerides > 1.7 mmol/l												
B1 (Triglycerides > threshold)	2,673	24.0	612	13.9	759	26.1	1.88	[1.71; 2.08]	1,302	34.6	2.52	[2.30; 2.76]
B2 (lipid lowering therapy[d])	2,515	18.2	516	10.0	721	19.9	1.31	[1.19; 1.46]	1,278	25.4	1.55	[1.41; 1.70]
B (total (B1 and/or B2))	4,569	33.0	1,042	20.1	1,302	35.9	1.45	[1.35; 1.56]	2,225	44.1	1.72	[1.62; 1.84]
Fasting glucose > 5.6 mmol/l												
C1 (DM or Gluc. > threshold)	3,775	29.6	662	13.9	950	28.3	1.50	[1.37; 1.64]	2,163	46.7	2.28	[2.11; 2.47]
C2 (Antidiabetic therapy)	1,669	12.0	231	4.5	385	10.6	1.66	[1.42; 1.94]	1,053	20.9	3.00	[2.62; 3.45]
C (total (C1 and/or C2))	3,775	27.2	662	12.8	950	26.2	1.52	[1.39; 1.66]	2,163	42.9	2.30	[2.13; 2.49]
BP > 130/>85 mmHg												
D1 (BP > threshold)	9,207	66.6	2,663	51.5	2,568	70.9	1.25	[1.20; 1.29]	3,976	79.1	1.35	[1.31; 1.39]
D2 (antihypertensive therapy)	5,699	41.1	1,109	21.4	1,557	42.9	1.33	[1.25; 1.41]	3,033	60.2	1.64	[1.56; 1.73]
D (total (D1 and/or D2))	10,433	75.3	2,985	57.6	2,928	80.7	1.20	[1.17; 1.24]	4,520	89.7	1.27	[1.23; 1.30]
Women												
HDL Cholesterol < 1.3 mmol/l												
A1 (HDL-C < threshold)	2,978	13.9	524	6.4	491	11.1	1.95	[1.73; 2.20]	1,963	22.0	4.06	[3.69; 4.47]
A2 (lipid therapy[d])	2,289	10.5	303	3.7	501	11.2	1.66	[1.45; 1.90]	1,485	16.4	2.00	[1.78; 2.25]
A (total (A1 and/or A2))	4,792	22.0	798	9.7	924	20.6	1.93	[1.76; 2.11]	3,070	34.0	2.97	[2.75; 3.21]
Triglycerides > 1.7 mmol/l												
B1 (triglycerides > threshold)	2,458	12.9	355	4.6	440	11.1	2.09	[1.82; 2.39]	1,663	22.5	4.00	[3.56; 4.49]
B2 (lipid lowering therapy[d])	2,289	10.5	303	3.7	501	11.2	1.66	[1.45; 1.90]	1,485	16.4	2.00	[1.78; 2.25]
B (total (B1 and/or B2))	4,248	19.5	622	7.5	859	19.1	1.84	[1.67; 2.03]	2,767	30.6	2.57	[2.36; 2.80]
Fasting Glucose > 5.6 mmol/l												
C1 (DM or Gluc. > threshold)	3,561	17.6	382	4.9	529	12.6	1.71	[1.51; 1.94]	2,650	31.8	3.65	[3.29; 4.06]
C2 (antidiabetic therapy)	1,552	7.1	115	1.4	181	4.0	1.80	[1.43; 2.27]	1,226	13.6	5.05	[4.17; 6.13]
C (total (C1 and/or C2))	3,561	16.3	382	4.6	529	11.8	1.72	[1.52; 1.96]	2,650	29.3	3.66	[3.29; 4.06]

BP > 130/>85 mmHg												
D1 (BP > threshold)	11,507	52.9	2,605	31.6	2,395	53.4	1.36	[1.31; 1.42]	6,507	72.1	1.65	[1.59; 1.71]
D2 (antihypertensive therapy)	7,263	33.4	1,151	13.9	1,397	31.1	1.39	[1.30; 1.48]	4,715	52.2	1.88	[1.78; 1.99]
D (total (D1 and/or D2))	13,163	60.5	2,973	36.0	2,779	61.9	1.36	[1.31; 1.41]	7,411	82.0	1.57	[1.52; 1.62]

Crude (bivariate) and age adjusted rho for the correlation of waist circumference with cardiovascular risk factors

[a]Normal WC: male ≤ 94, female ≤ 80 cm

[b]Increased WC: male > 94 and ≤102 cm, Female > 80 and ≤88 cm

[c]High WC: male > 102 cm. Female > 88 cm; *N* and % based on available case analysis (missing values excluded from row)

[d]Lipid lowering agents

[e]*PRR* Prevalence ratio relative to reference group "normal WC". Adjusted for age

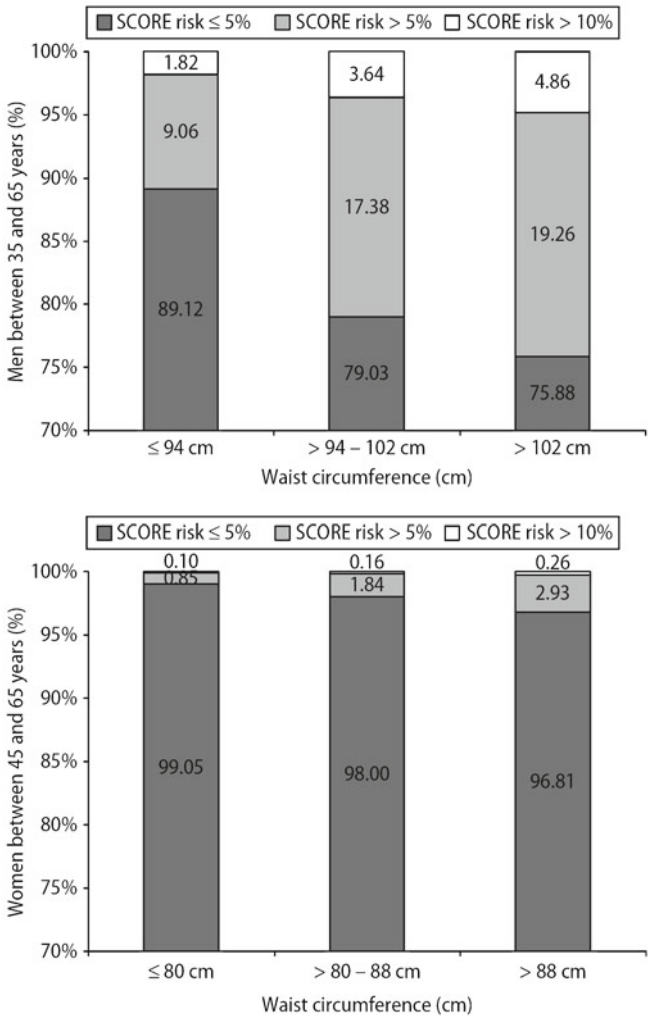

Fig. 131.1 Proportion of individuals exceeding a SCORE score of 10% (*white*), between 5% and 10% (*light grey*), or below 5% (*dark grey*). Panel A: men, panel B: women (Data presented are reprinted by permission of the publisher of reference (Schunkert et al. 2008))

Otherwise, the waist–hip ratio and the waist and hip circumferences were highly associated with the risk of AMI, even after adjustment for other risk factors. Moreover, the EPIC-Norfolk study reported that waist circumference, but not BMI, was a significant estimate for all CHD events during 9.1 years and that hip circumference appeared to protect against CHD (Canoy et al. 2007). Taken together, a redefinition of obesity based on waist circumference, instead of BMI, is a better estimate of CHD in most ethnic groups and the notion can be supported that abdominal adiposity, not subcutaneous adiposity, is closely linked to the onset of CHD (Shimabukuro 2009).

The Atherosclerosis Risk in Communities (ARIC) study determined the contribution of risk factors on ischemic stroke subtypes.(Ohira et al. 2006) In addition to the traditional risk factors, such as hypertension, current smoking, and T2DM, the waist–hip ratio was associated with increased risk for non-lacunar and cardioembolic stroke, but not with lacunar stroke.

A meta-regression analysis (de Koning et al. 2007) consisting of 15 studies (12 with primary outcome of coronary heart disease, three with primary outcome of stroke), comprising 258,114 participants (35.7% men) with a mean age of 57 years, and over 1,520,864 person-years with a mean follow-up of 5.9 years, where 4,355 cardiovascular disease events were recorded, was performed by Koning et al. (Table 131.2). The analyses demonstrated that the risk of incident CVD increases in men and women with elevations in waist circumference or waist–hip ratio. Specifically, a 1-cm increase in waist circumference is associated with a 2% increase and a 0.01 increase in the waist–hip ratio is associated with a 5% increase in risk of future cardiovascular disease after adjusting for age and cohort characteristics (Table 131.3).

Finally, more recently, the analyses of two German cohort studies (DETECT and SHIP) by Schneider et al. (2010), concluded that waist–height ratio (WHtR) represents the best predictor of cardiovascular risk and mortality, followed by waist circumference (WC) and waist–hip ratio (WHR) and their results discouraged the use of the body mass index (BMI). The analyses showed a positive association of the composite endpoint (incident stroke, myocardial infarction, or cardiovascular death) with WHtR, WC, and WHR, but not with BMI. There was no heterogeneity among studies. The relative risks in the highest versus the lowest sex- and age-specific quartiles of WHtR, WC, WHR, and BMI, after adjustment for multiple confounders, were 2.16 (1.39–3.35), 1.59 (1.04–2.44), 1.49 (1.07–2.07), and 0.57 (0.37–0.89), respectively. Separate analyses of sex and age groups yielded comparable results.

131.2.2 Waist Circumference and Metabolic Risk

In the Paris Prospective Study I, which investigated the mortality of 6,678 middle-aged men who were free of T2DM and CHD at baseline, sagittal abdominal diameter, a substitute for waist circumference, and the presence of MetS were associated with an increase in sudden death, as with non-sudden death from AMI (Empana et al. 2007). Sudden death could be related to arrhythmic events, including lethal ventricular fibrillation, because patients with MetS had significantly higher values of corrected QT interval and QT dispersion on ECG, which reflects myocardial refractoriness and electrical instability (Pietrasik et al. 2007).

131.2.3 Waist Circumference and Vascular Risk

A recent prospective cohort study revealed a positive relationship between waist–hip ratio, not BMI, and PAD prevalence (Planas et al. 2001). Mechanisms (if any) by which obesity may cause PAD could be different from those for CHD, as they do have different risk profiles (e.g., cigarette smoking is more strongly associated with the development of PAD than CHD) (Leng et al. 1995).

Numerous studies have shown a clear relationship between obesity and the risk of idiopathic venous thrombo-embolism (deep vein thrombosis and pulmonary embolism), independent of other traditional risk factors (Darvall et al. 2007; Samama 2000). For instance, in a study from Sweden, men with a waist circumference ≥100 cm had a fourfold higher risk of venous thrombo-embolism than with those with a waist <100 cm.(Darvall et al. 2007) More recently, a Danish prospective study (Diet, Cancer, and Health) with 27,178 men and 29,876 women, from 50 to 64 years of age with 10 years of follow-up, showed that hip circumference was positively associated with venous thrombo-embolism in women, but not in men, whereas waist circumference was positively associated with

Table 131.2 Features of included studies (Data presented are adapted by permission of the publisher of reference (de Koning et al. 2007))

Author	Sample size (*n*)	Men (%)	Mean age (years)	Mean follow-up (years)	Measures reported	Outcome	Events
(Bengtsson et al. 1993)	1,450	0	49	20	WHR	CHD (fatal)	26
(Dey et al. 2002)	2,287	46	70	15	WC	Stroke (fatal + non-fatal)	453
(Dey and Lissner 2003)	1,597	46	70	15	WC	CHD (fatal + non-fatal)	684
(Folsom et al. 1998)	14,040	44	55	6.2	WHR	CHD (fatal + non-fatal)	398
(Folsom et al. 2000)	31,702	0	62	11.5	WC and WHR	CHD (fatal)	438
(Lakka et al. 2002)	2,682	100	51	10.6	WC and WHR	CHD (fatal + non-fatal)	123
(Lawlor et al. 2006)	3,589	0	70	4.4	WC and WHR	CHD (fatal + non-fatal)	194
(Nicklas et al. 2004)	2,503	51	75	4.6	WC	CHD (fatal + non-fatal)	116
(Rexrode et al. 1998)	44,702	0	53	8	WC and WHR	CHD (fatal + non-fatal)	320
(Rexrode et al. 2001)	16,164	100	62	3.9	WC and WHR	CHD (fatal + non-fatal)	552
(Rimm et al. 1995)	29,122	100	58	3	WC and WHR	CHD (fatal + non-fatal)	420
(Silventoinen et al. 2003)	11,510	47	45	8	WC and WHR	CHD (fatal + non-fatal)	386
(Walker et al. 1996)	28,643	100	58	5	WHR	Stroke (fatal + non-fatal)	118
(Welin et al. 1987)	789	100	54	18.5	WHR	Stroke (fatal + non-fatal)	57
(Zhang et al. 2004)	67,334	0	55	2.5	WC and WHR	CHD (fatal + non-fatal)	70

WC waist circumference, *WHR* waist–hip ratio, *CHD* coronary heart disease

Table 131.3 Changes in waist circumference and waist–hip ratio and an equivalent increase in risk of future cardiovascular disease after adjusting for age and cohort characteristics. Data presented are adapted by permission of the publisher of reference (de Koning et al. 2007)

WC (cm)			WHR (U)			
Men	Women	Men and women	Men	Women	Men and women	% Increase in risk
Minimally adjusted						
4.71	5.08	5.04	0.02	0.02	0.02	10
9.02	9.72	9.65	0.03	0.04	0.03	20
12.98	13.99	13.88	0.05	0.05	0.05	30
16.64	17.95	17.80	0.06	0.07	0.06	40
20.06	21.63	21.46	0.08	0.08	0.08	50
Moderately adjusted						
5.00	2.13	3.20	0.01	0.01	0.01	10
9.56	4.07	6.12	0.03	0.02	0.02	20
13.76	5.86	8.81	0.04	0.03	0.03	30
17.64	7.52	11.30	0.05	0.03	0.04	40
21.26	9.06	13.62	0.06	0.04	0.05	50
Maximally adjusted						
8.46	2.99	4.26	0.02	0.02	0.02	10
16.18	5.72	8.15	0.04	0.05	0.05	20
23.28	8.23	11.73	0.06	0.07	0.07	30
29.86	10.55	15.05	0.08	0.08	0.09	40
35.98	12.72	18.13	0.09	0.10	0.10	50

venous thrombo-embolism in men, but not in women (Severinsen et al. 2009). Obese patients have chronically raised intra-abdominal pressure and decreased blood velocity in the common femoral vein. Inactivity and poor gait, as well as other comorbidities, may collectively impair venous return from the lower limbs. Alternatively, obesity, in particular visceral obesity, may have a prothrombotic propensity via mechanisms including actions of adipocytokines, increased activity of the coagulation cascade and decreased activity of the fibrinolytic cascade, inflammation, oxidative stress, endothelial dysfunction, and disturbances in lipids and glucose homeostasis (Shimabukuro 2009).

131.3 Waist Circumference and Risk Assessment

Traditional risk factors, such as hypertension, elevated low-density lipoprotein-cholesterol, smoking, and diabetes mellitus, have long been linked to CVD. One key criticism is that associations between CVD and the metabolic syndrome, which are also linked to these risk factors, cannot account for all potentially confounding variables, which make such comparisons rather difficult (Gami et al. 2007). On the other hand, although remarkable progress has been made in the management of the classical risk factors, abdominal obesity/MetS and T2DM have reached such epidemic proportions that CVD remains a major cause of morbidity and mortality worldwide (Shimabukuro 2009). Moreover, as already discussed, abdominal obesity is the most prevalent form of the clustering of proatherogenic and pro-inflammatory abnormalities associated with insulin resistance.

The extent by which the specific clustering of visceral obesity abnormalities increases the overall CVD risk remains to be elucidated. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), as well as the International Chair on Cardiometabolic Risk, have emphasized the critical importance of first using global risk calculators, such as the Framingham risk score, the PROCAM algorithm, or the European SCORE (Kahn et al. 2005).

However, there is evidence to suggest that the risk assessment algorithms may not accurately estimate the global CVD risk in patients with visceral obesity/MetS. Besides that, it is also claimed that the Framingham risk score does not properly assess lifetime risk, particularly among young adults or adolescents with abdominal obesity (Grundy 2007), who are not considered at risk of CVD by current algorithms because of their youth. On the other hand, a clinical diagnosis of visceral obesity, insulin resistance, or of the metabolic syndrome is not sufficient to assess global risk of cardiovascular disease. To achieve this goal, physicians should first pay attention to the classical risk factors while also taking into account the additional risk resulting from the presence of abdominal obesity and the metabolic syndrome, which should be considered to be another modifiable CVD risk factor.

Thus, it is essential to develop a risk assessment model of global CVD in the presence of traditional risk factors and the emerging markers found in individuals with visceral obesity. Després et al. defined this model as global cardiometabolic risk (Despres et al. 2008). Under this model, cardiometabolic risk is the global risk of CVD resulting from the presence of traditional risk factors combined with the possible additional contribution of the MetS. It is important to highlight that the global CVD risk algorithms already consider three (HDL-cholesterol, blood pressure, and glucose) of the five metabolic syndrome features. Moreover, as the most prevalent form of the MetS is observed among patients with excess visceral adiposity/ectopic fat, Després proposed that the combination of elevated waist circumference and triglycerides was enough to screen for patients with an excess of visceral/ectopic fat and insulin resistance (Lemieux et al. 2000). Therefore, further attention should be given to add "hypertriglyceridemic waist" to the list of variables considered in global risk algorithms (Lemieux et al. 2000; Lemieux et al. 2007), which will ultimately lead to the global cardiometabolic risk assessment algorithms (Fig. 131.2).

131.4 Practical Methods and Techniques

Waist circumference is actually a perimeter, which provides an estimate of body girth at the level of the abdomen. Different studies used different anatomic landmarks to determine the exact location for measuring WC, including 1) midpoint between the lowest rib and the iliac crest; 2) the umbilicus; 3) narrowest (minimum) or widest (maximum) WC; 4) just below the lowest rib; and 5) just above the iliac crest. The specific site used to measure WC influences the absolute WC value that is obtained (Wang et al. 2003). The most commonly used sites reported in studies that evaluated the relation between morbidity or mortality rate and WC were the midpoint between the lowest rib and the iliac crest (29%), the umbilicus (28%), and the narrowest WC (22%). Although sites that use an easily identifiable and reproducible landmark (e.g., just above the bony landmark of the lilac crest) might be more precise and easier to use than other sites, we are not aware of data from any studies that demonstrate an advantage of one measurement site over others. WC measurements should be made around a patient's bare midriff, after the patient exhales while standing without shoes and with both feet touching the floor and arms hanging freely. The measuring tape should be made of a material that is not easily stretched, such as fiberglass. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface. In a research setting, WC measurements are typically taken thrice and recorded to the nearest 0.1 cm. Although specific techniques have been recommended for measuring WC in the clinical setting (Douketis et al. 2005; Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults–The Evidence Report. National Institutes of Health 1998a), there is no approach uniformly accepted. Training technicians and even patients to use an appropriate technique for measuring WC is essential to obtain reliable data; special tape measures,

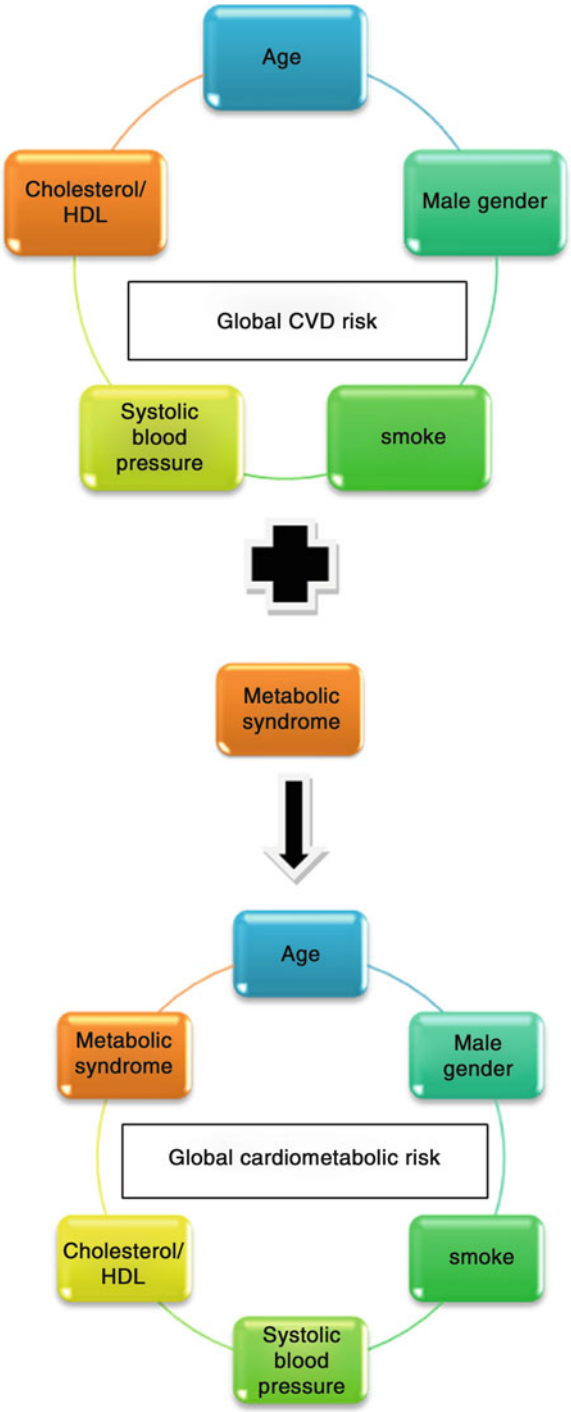

Fig. 131.2 Global cardiometabolic risk. The global cardiometabolic risk is the result of the traditional global CVD risk, which includes age, male gender, smoke, systolic blood pressure and total cholesterol and HDL cholesterol plus metabolic syndrome

instructional manuals, and videotapes are available for this purpose (2008). The reproducibility of WC measurements at all sites is high for both men and women (e.g., at the iliac crest site, intraclass correlation coefficient, r = 0.998 and r = 0.999, respectively) (Wang et al. 2003). The correlation between technician- and self-measured WC after proper training can also be high for men (r = 0.95)

Table 131.4 Ethnic specific values for waist circumference (Data presented are reprinted by permission of the publisher of reference (The IDF consensus worldwide definition of the Metabolic Syndrome 2006))

	Waist circumference	
Country/ethnic group	Men	Women
Europids[a]	≥94 cm	≥80 cm
In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes		
South Asians	≥90 cm	≥80 cm
Based on a Chinese, Malay, and Asian-Indian population		
Chinese	≥90 cm	≥80 cm
Japanese[b]	≥90 cm	≥80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

[a]In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut points to allow better comparisons

[b]Originally, different values were proposed for Japanese people but new data support the use of the values shown above

and women (r = 0.89), respectively (Rimm et al. 1990). However, self-reported measurements are prone to a systematic bias, and there is a nontrivial underestimate of self-measured WC at all anatomic sites (Klein et al. 2007).

The American recommendation for waist circumference thresholds for increased cardiometabolic risk in men (>102 cm) and women (>88 cm) were derived from WC values that correlated with a BMI ≥ 30 (1998a). The National Health and Nutrition Examination Survey III (NHANES III) found that about 14% of women and about 1% of men had a "high" WC but a normal BMI (18.5–24.9) (Meisinger et al. 2006). In addition, about 70% of women who were overweight (BMI 25.0– 29.9) had a WC > 88 cm and about 25% of men who were overweight had a WC > 102 cm. An estimate based on data available from the World Health Organization's MONICA Project, conducted in > 32,000 men and women from Europe, Australia, and New Zealand, suggests that about 10% of participants, who had a BMI < 30, had a WC above the recommended cut points for increased risk (Meisinger et al. 2006). It is not known what portion of subjects who had a large WC would have been identified as having increased cardiometabolic risk, based on findings from a standard medical evaluation. Therefore, the optimal WC criteria needed to identify patients at increased risk of metabolic disease, who would otherwise not be identified by evaluating BMI and/or other standard cardiometabolic risk factors, is not known and will likely require adjustments based on BMI, sex, age, and race/ethnicity (Klein et al. 2007).

Central obesity is most easily measured by waist circumference in persons with a BMI between 25.0 and 34.9, resulting in gender- and race/ethnic-group-specific cut points as defined by the guidelines (Table 131.4). Although a higher cut point is currently used for all ethnic groups in the USA for clinical diagnosis, it is strongly recommended that, for epidemiological studies and, wherever possible, for case detection, ethnic-group-specific cut points should be used for people of the same ethnic group, wherever they are found. Thus, the criteria recommended for Japan would also be used in expatriate Japanese communities, as would be those for South Asian males and females, regardless of place and country of residence (Tan et al. 2004; The IDF consensus worldwide definition of the Metabolic Syndrome 2006).

It is a consensus that these pragmatic cut points are taken from various data sources and that better data will be needed to link these to risk (2006).

131.5 Visceral Fat Management

Obesity management goals should encompass a reduction in total cardiovascular morbidity and mortality. Losing 5–10% of body weight reduces the traditional CV risk factors in obese subjects (Klein et al. 2007). Increasing physical activity, in combination with a diet that emphasizes fresh fruits and vegetables, whole grains, and low-fat dairy products, can help patients to reduce their weight and obesity comorbidity. Less is known about the long-term effect of weight loss on the development of T2DM and CVD outcomes in the form of death, myocardial infarction, and stroke. Currently, ongoing clinical trials use health-promoting lifestyle interventions, new drugs, and even surgery, all of which are aimed at weight loss, reduction in disease manifestations, and improved outcomes (Pi-Sunyer et al. 2007). A trial to answer the most important question whether the improvements in cardiovascular risk factors by managed weight loss will be associated with reduction in long-term cardiovascular events is under investigation (The Look AHEAD (Action for Health in Diabetes) trial) (Pi-Sunyer et al. 2007) and the expected data are essential for the future development of effective CVD prevention strategies.

131.6 Applications to Other Areas of Health and Disease

131.6.1 To Measure or Not to Measure? That Is the Question

The crucial answer to this question, even in individuals not related to the Prince of Denmark (Shakespeare 1601), should not only be based on statistical predictivity of fat distribution measures, but also on practical considerations, such as added burden to already busy clinical practices and the acceptability of the measures to patients and clinicians. Although determination of waist circumference looks simple and requires only a tape measure, there is no standardized protocol in research or clinical practice setting, and studies have used various locations of waist circumferences. In addition, there is no standard cut point for defining central obesity. The International Diabetes Federation proposed sex- and ethnicity-specific cut points for central obesity as measured by waist circumference (2006). However, these cut points are controversial and are complicated to use in clinical practice. Finally, it is unclear whether waist circumference should be recommended to all patients or only to subgroups of patients. Fat distribution may have greater added value beyond BMI in predicting morbidity and mortality among patients who are of normal weight or moderate overweight than among those who are overtly obese, as assessed by BMI. Obviously, a waist circumference measurement is unnecessary for morbidly obese patients (BMI $\geq$ 35).

Taken together, it seems that, among various measurements of fat distribution, waist circumference is the most practical and the simplest to interpret. Despite several unresolved questions regarding the use of fat distribution measures in clinical practice, mounting evidence indicates the importance of monitoring changes in waist size. There is an urgent need to increase the awareness among both health professionals and the general public about the health hazards of central or abdominal obesity. Although maintaining a healthy weight should continue to be a cornerstone in the prevention of chronic diseases and premature death, maintaining a healthy waist size should also be an important goal (Hu 2007).

Summary Points

- The obesity epidemic poses a global concern because of its related health problems.
- The most appropriate adiposity markers for assessing the risk of disease and death are debated.
- Most adipose tissue is located under the skin (about 85%) and a smaller amount (about 15%) is located within the abdomen (intra-abdominal or visceral fat).
- The relative contribution of intra-abdominal fat to total body fat is influenced by sex, age, race/ethnicity, physical activity, and total adiposity.
- Intra-abdominal fat is more closely associated with the risk of several chronic diseases than a more peripheral (subcutaneous) fat distribution.
- Waist circumference or the waist–hip ratio, as indicators of abdominal obesity, may be better predictors of the risk of disease than the body mass index, an indicator of general adiposity.
- A simple measurement of waist circumference is strongly correlated with risk for diabetes mellitus and cardiovascular disease.
- Insulin resistance is a key factor associated with a typical atherogenic dyslipidemic state, a prothrombotic profile, a state of inflammation, an elevated blood pressure, and dysglycemia.
- The waist–hip ratio and the waist and hip circumferences were highly associated with the risk of acute myocardial infarction. The waist–hip ratio was associated with increased risk for non-lacunar and cardioembolic stroke and peripheral arterial disease. The waist circumference was associated with a higher risk of venous thrombo-embolism.
- Després defined a global cardiometabolic risk model, which results from the presence of traditional risk factors combined with the possible additional contribution of elevated waist circumference and triglycerides to the list of variables considered in global risk algorithms, which will ultimately lead to the global cardiometabolic risk assessment algorithms.
- Increasing physical activity, in combination with a diet that emphasizes fresh fruits and vegetables, whole grains, and low-fat dairy products, can help patients to reduce their weight and obesity comorbidity.
- Taken together, it seems that among various measurements of fat distribution, waist circumference is the most practical and the simplest to interpret.
- Despite several unresolved questions regarding the use of fat distribution measures in clinical practice, mounting evidence indicates the importance of monitoring changes in waist size.
- There is an urgent need to increase the awareness among both health professionals and the general public about the health hazards of central or abdominal obesity.
- Although maintaining a healthy weight should continue to be a cornerstone in the prevention of chronic diseases and premature death, maintaining a healthy waist size should also be an important goal.

Key Features

Table 131.5 Key points

1.	The obesity epidemic poses a global concern because of its related health problems.
2.	Intra-abdominal fat is more closely associated with the risk of several chronic diseases than a more peripheral (subcutaneous) fat distribution.
3.	A simple measurement of waist circumference is strongly correlated with risk for diabetes mellitus and cardiovascular disease.

Acknowledgment The authors wish to acknowledge Renate Domeier for her assistance with preparation of the chapter.

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Chapter 132
Anthropometry, Body Surface Area and Cardiopulmonary Bypass: Determining the Pump Flow Rate of the Heart–Lung Machine Using Body Size

R. Peter Alston

Abstract Cardiopulmonary bypass (CPB) is the keystone that enables heart surgery to be safely performed on hundreds of thousands of patients around the world each year. During CPB, two crucial factors, the oxygen content of arterial blood and the pump flow rate, determine whether sufficient oxygen is supplied to the body to match its metabolic demands. With modern oxygenators, full oxygenation of the arterial blood is easily achieved. However, the pump flow rate remains important as both too low and too high flow rates may be harmful.

Traditionally, pump flow rate has been based on body surface area (BSA), estimated from height and weight, commonly using the formula of du Bois and du Bois. This formula was developed nearly a century ago from an original sample of only nine subjects. Although it may have been of acceptable accuracy for the population at that time, it might no longer be appropriate for the increasing number of obese patients now presenting for heart surgery. Recent research findings, using the saturation of haemoglobin with oxygen in the mixed-venous blood [$\bar{S}vO_2$] as a measure of the adequacy of the perfusion of the body, would suggest that lean body mass (LBM) might be a better basis for determining pump flow rate during CPB than BSA.

Alternatively, guiding pump flow rate during CPB via inline, real-time $\bar{S}vO_2$ could overcome the important limitations of any determination based on an anthropometric estimate of body size. However, the introduction of either LBM or $\bar{S}vO_2$ to determine pump flow rate would require further research, including a randomised control trial in a very large number of patients undergoing heart surgery with CPB. Therefore, regardless of the limitations associated with the use of BSA to determine pump flow rate, it would appear that this will remain the standard method for the foreseeable future.

Abbreviations

BSA	Body surface area
BMI	Body mass index
CPB	Cardiopulmonary bypass
LBM	Lean body mass

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_132,

$\bar{S}vO_2$ Saturation of mixed-venous haemoglobin with oxygen
VO_2 Systemic oxygen uptake.

132.1 Introduction

Cardiopulmonary bypass (CPB) is the technique of mechanically replacing the functions of the heart and lungs to supply oxygen for all the metabolic requirements of the body. John Gibbon pioneered CPB in clinical practice more than 55 years ago and, subsequently, this technique became the keystone that has enabled millions of patients around the world to safely undergo heart surgery.

CPB has two essential functions, the mechanical pumping of blood throughout the body and gas exchange to remove carbon dioxide from and add oxygen to the blood. As the pump flow rate controls the volume of blood that is pumped around the body per unit time, usually expressed in units of litres per minute (l min^{-1}), it is the equivalent of cardiac output in the intact cardiovascular circulation. Determining the correct pump flow rate is critical; rates that are too low will result in systemic hypoperfusion and, as a consequence, potential organ damage, and rates that are too high may also be deleterious by causing hypertension and excessive bleeding.

Whilst techniques may vary from institution to institution, pump flow rate has historically been based upon body surface area (BSA). The aim of this chapter is to explore why pump flow rate became based on this particular anthropometric measure and why it may no longer be appropriate today. Alternative methods of determining pump flow rate will be considered and their relative merits and potential for replacing BSA will be assessed. Before doing so, a brief overview of the technique of CPB will be given and the methods by which the efficiency of CPB is assessed will be considered.

132.2 Cardiopulmonary Bypass

132.2.1 Technique of Cardiopulmonary Bypass

A full description of CPB is beyond the scope of this chapter and readers wishing further detail are referred to a textbook dedicated to the theory and clinical practice of CPB (Gravlee et al. 2008). However, the basic principles are as follows. Venous blood is drained from the body, usually directly from a cannula inserted into the inferior vena cava and indirectly from the superior vena cava via a cannula placed in the right atrium, into a reservoir (Fig. 132.1). Blood from the inferior and superior vena cavae have different oxygen contents and their combination in the common venous line is termed mixed-venous blood. The mixed-venous blood is partially deoxygenated and, normally, the haemoglobin in this blood is nearly 75% saturated with oxygen. The blood is then pumped through an oxygenator that removes carbon dioxide and adds oxygen to the blood. From the oxygenator, the decarboxylated and oxygenated blood flows back into the arterial vascular system, usually via a cannula inserted into the ascending aorta, to supply oxygen for the metabolic needs of the body (Table 132.1).

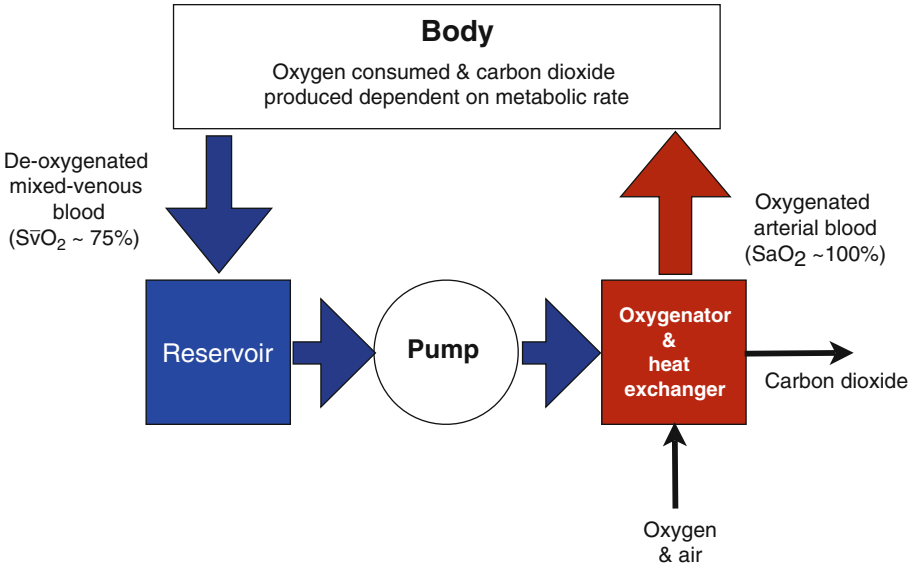

Fig. 132.1 Schematic diagram of a cardiopulmonary bypass circuit. Schematic diagram of a cardiopulmonary bypass (CPB) circuit. The body consumes oxygen (systemic oxygen uptake) in a quantity required to match its metabolic rate and produces carbon dioxide (systemic carbon dioxide output). Venous blood is drained from the body, usually directly from a cannula inserted into the inferior vena cava and indirectly from the superior vena cava via a cannula placed in the right atrium, into a reservoir. Blood from the inferior and superior vena cavae have different oxygen contents and their combination in the common venous line is termed mixed-venous blood. The mixed-venous blood is partially deoxygenated and, normally, the haemoglobin in this blood is nearly 75% saturated with oxygen. The blood is then pumped from the reservoir into an oxygenator through which passes a mixture of oxygen and air that removes carbon dioxide from and adds oxygen to, the blood. The flow rate of the pump is the volume of blood pumped through the body per unit time (l min^{-1}) and is equivalent to the cardiac output in the intact cardiovascular system. Blood can also be cooled to induce hypothermia or heated to rewarm the patient back to normothermia (37°C) at the end of CPB. Oxygenated blood, with haemoglobin that is nearly 100% saturated with oxygen, then flows back into the body's arterial system, usually via a cannula placed in the ascending aorta

Table 132.1 Key facts about cardiopulmonary bypass

- The primary functions of the heart and lungs are to supply oxygen to and remove carbon dioxide from the body.
- Cardiopulmonary bypass (CPB) mechanically replaces the functions of the heart and lungs.
- The mechanical device used for CPB is commonly called a heart–lung machine.
- The first successful use of CPB to perform heart surgery was in 1953.
- CPB now enables heart surgery to be safely performed on hundreds of thousands of patients every year around the world.
- Hypothermia is often used with CPB because it increases the margin of safety as it reduces the metabolic rate and therefore the body's oxygen requirement.
- The flow rate of the pump during CPB is the volume of blood circulating through the body per unit time and is equivalent to the cardiac output in the intact cardiovascular system.
- Along with the oxygen content of arterial blood, the pump flow rate determines how much oxygen is delivered to the body.
- Pump flow rates that are too high or too low may be harmful.
- For about 50 years, the pump flow rate for individual patients has been based on a multiple, commonly 2.4, of body surface area.

Key facts about cardiopulmonary bypass including its function of replacing the heart and lungs, supplying oxygen and removing carbon dioxide from the body, its history and the importance of the pump flow rate.

132.2.2 Hypothermia

A heat exchanger is incorporated with the oxygenator and this allows the body to be cooled to induce hypothermia. Hypothermia has traditionally been used to increase the margin of safety during CPB. The degree of hypothermia depends on the surgical requirement, for example, heart valve surgery is generally performed at lower temperatures than coronary artery bypass grafting surgery. The body's temperature may be reduced from normothermia of 37°C by a few degrees, to induce mild hypothermia, all the way down to 15°C, for profound hypothermia, or somewhere in between. By reducing metabolic rate, hypothermia makes it easier to ensure that the oxygen supply during CPB is an adequate match to the oxygen demands of the body, especially when using low rates of pump flow. This was particularly important during the early years of CPB, as the oxygenators of this time often had only a limited capacity to oxygenate the blood and this may have been insufficient for patients with a large body size. The heat exchanger is also used towards the end of CPB to add heat energy to the blood and thus re-warm the body back to normothermia.

132.3 Assessing the Adequacy of Cardiopulmonary Bypass

132.3.1 Blood Oxygenation and Carbon-Dioxide Removal

The first essential function of CPB is gas exchange, removing carbon dioxide and adding oxygen to the blood. Early oxygenators were not efficient at this process and, originally, the only way that their effectiveness could be assessed was by intermittent arterial blood sampling and remote analysis on a bench blood-gas analyser. Inevitably, there was a time delay before the results were available for interpretation by the perfusionist operating the CPB machine, during which period there may have been important changes in the clinical condition of the patient. Therefore, the standard practice was to make the blood hyperoxic to maintain a margin of safety. Today, modern oxygenators achieve gas exchange with a high degree of efficiency. Moreover, in-line blood gas monitors, available for over two decades, allow real-time display of oxygen and carbon dioxide tensions, thus providing continuous assessment of the efficiency of gas exchange. Therefore, in current practice, this function of CPB is reliable and safe.

132.3.2 Pump Flow Rate

Ensuring systemic oxygen delivery and carbon-dioxide removal is the other essential function of CPB and this is achieved by mechanically pumping the blood around the body. In the intact circulation, this is the function of the heart and, unless there is heart failure, systemic oxygen delivery is matched to the metabolic requirements of body. This function is measured by the cardiac output and, during CPB, the pump flow rate is its equivalent. During the early years of CPB, low pump flow rates were favoured, as less efficient heart–lung machines could be used, there was less blood loss and a lower volume of blood was required to prime the circuit (Andersen 1958). However, others argued for the use of a pump flow rate during CPB that equated with a normal cardiac output (Kirklin et al. 1956).

Although carbon-dioxide output can also be used (Alston et al. 2003), the adequacy of pump flow rate has traditionally been assessed by systemic oxygen uptake (VO_2) (Paneth et al. 1957; Andersen and Senning. 1958; Clark 1958; Clowes et al. 1958; Vetto et al. 1958; Cheng et al. 1959; Starr 1959; Galletti and Brecher 1962) Table 132.2. With these methodologies, the terms carbon dioxide output and VO_2 are used because the fluxes in body temperature that occur during CPB cause important changes in the solubility of these gases, making it impossible to determine the actual rates of carbon-dioxide production or oxygen consumption by the body. As, under normal conditions the metabolism of the body is aerobic, these measures are indirect calorimetric estimates of the body's metabolism. The ratio between carbon dioxide output and VO_2 depends on the relative proportions of carbohydrate, fat and protein that are being metabolised. As a result, the carbon dioxide output will be slightly less than VO_2 and the relative difference in volume per unit time represents the respiratory quotient.

132.3.3 Fick's Principle

Traditionally, VO_2 has been calculated using Fick's principle. Samples of mixed-venous and arterial blood are simultaneously aspirated from the CPB circuit and the pump flow rate noted. The saturations of haemoglobin with oxygen, partial pressures of oxygen and haemoglobin concentrations in the arterial and mixed-venous blood samples are measured using a blood-gas analyser. The oxygen content in the arterial and mixed-venous blood samples are then calculated using the formula in Table 132.3. Finally, using the formula in Table 132.4 the difference in oxygen content between arterial and mixed-venous blood is then multiplied with the pump flow rate, moderated by surface area, to obtain VO_2.

Table 132.2 Key facts of systemic oxygen uptake

- The systemic oxygen uptake (VO_2) is the total amount of oxygen consumed to metabolise substrates so as to produce the energy that runs the normal functions of the body.
- The rate of VO_2 depends on the metabolic rate of the body: the VO_2 is low at rest and is high during exercise.
- Temperature has a marked effect on metabolic rate and hence, VO_2. For example, fever increases VO_2 and hypothermia decreases VO_2.
- VO_2 is commonly calculated using Fick's principle, which requires measurement of the oxygen content of arterial and mixed-venous blood and the cardiac output, or pump flow rate during cardiopulmonary bypass (see Table 132.3).
- The rate of carbon dioxide output is always less than the rate of VO_2.
- The ratio of carbon dioxide output to VO_2 is called the respiratory quotient and depends on the substrates that the body is metabolising.

Key facts about systemic oxygen uptake (VO_2) and its relationship to the metabolism and temperature of the body; also, how VO_2 is calculated and its relationship to systemic carbon dioxide output

Table 132.3 Formula for calculating the oxygen content of blood

$$CO_2 = Hb * 1.34\ SO_2 + 0.003 * PO_2$$

The formula for calculating the oxygen content of blood from measurements of haemoglobin concentration, the saturation of haemoglobin with oxygen and the oxygen partial pressure, where: CO_2 = oxygen content of blood (ml^{-1} l), Hb = concentration of haemoglobin in blood (g^{-1} l), SO_2 = saturation of haemoglobin with oxygen (%), 1.34 = Hufner's factor, 0.003 = solubility factor of oxygen in blood at 37°C and PO_2 = partial pressure of oxygen in blood (kPa)

Table 132.4 Formula for calculating systemic oxygen uptake using Fick's principle

$$VO_2 = (CaO_2 - C\bar{v}O_2) * Q/BSA$$

Systemic oxygen uptake during cardiopulmonary bypass may be calculated using Fick's principle with the above formula, if the oxygen contents of arterial and mixed-venous blood and the pump flow rate are known, where: VO_2 = systemic oxygen uptake (ml min^{-1} m^{-2}), CaO_2 = oxygen content of arterial blood (ml l^{-1}), $C\bar{v}O_2$ = oxygen content of mixed-venous blood (ml l^{-1}), Q = pump flow rate (l m^{-2}) and BSA (body surface area)

132.3.4 Limitations of Fick's Principle

Unfortunately, this technique is error prone, as it requires measuring seven different variables, each having its own measurement error and these errors are then compounded by the arithmetical combination (Alston et al. 2003). In addition, VO_2 calculated in this way is directly related to several important predictor variables, limiting its use in statistical analyses.

132.3.5 Measuring Systemic Oxygen Uptake in the Gas Phase

Rather than using Fick's principle, a more statistically independent and less error-prone approach to determine VO_2, is to measure the concentrations of oxygen in the oxygenator's gas supply and exhaust (High et al. 2000). VO_2 can then be calculated by compounding the difference between oxygen concentrations of gas entering and exhausting the oxygenator with the gas flow rate. However, as the volume of carbon dioxide produced by the body is less than the oxygen consumed, the exhaust gas flow rate is less than the measured inflow rate. Whilst it is possible to correct for this difference using a dilutional gas (High et al. 2000), this would be complex in clinical practice. In addition, because the solubility of oxygen and, particularly, carbon dioxide, is influenced by temperature, this technique would be prone to error during induction of hypothermia and re-warming (Alston et al. 2006). Therefore, like the previous technique based on Fick's principle, calculating VO_2 based on measurements of the oxygenator's gas inflow rate and the difference between input and exhaust oxygen concentrations also has important limitations.

132.3.6 $S\bar{v}O_2$ as an Estimate of the Adequacy of Pump Flow Rate

Mixed-venous haemoglobin saturation with oxygen $S\bar{v}O_2$ requires measurement of a single variable and offers a statically independent estimate of the adequacy of pump flow rate (Alston et al. 2006). As this is the average of all the tissues supplied, it can estimate the efficacy of the pump flow rate in supplying the body with oxygen. Moreover, it is now possible to do this with in-line, real-time measurement of $S\bar{v}O_2$ (Table 132.5)

132.4 Why Base Pump Flow Rate on Body Surface Area?

One of the challenges facing the pioneers of CPB was the variance in the size of patients requiring heart surgery, ranging from tiny infants to large adults. For this reason, one focus of early research was the determination of adequate pump flow rates for patients of different sizes. Initially, pump flow

Table 132.5 Key facts of oxygen carriage in the blood and the importance of $S\bar{v}O_2$

- Oxygen is carried in the blood: a very small amount is in solution in the plasma and the vast majority is carried by haemoglobin.
- The amount of oxygen attached to haemoglobin is described as the percentage of the maximum that can possibly be carried and is referred to as saturation.
- The haemoglobin in arterial blood during CPB is nearly always close to 100% saturated with oxygen.
- Oxygen is extracted from the haemoglobin by the body as it passes through the tissues.
- The amount of oxygen extracted from haemoglobin varies, depending on the metabolic activity of the tissues through which it is passing, producing blood that has different saturations with oxygen.
- On returning to the heart, blood from the inferior and superior venae, that are of differing saturations with oxygen, are mixed and this is termed the mixed-venous haemoglobin oxygen saturation ($S\bar{v}O_2$).
- $S\bar{v}O_2$ is an estimate of the adequacy of pump flow rate to supply oxygen in amounts that match the metabolic demands of the body during CPB.
- The normal level of $S\bar{v}O_2$ is nearly 75%. Commonly, low levels of $S\bar{v}O_2$ indicate hypoperfusion and high levels of hyperperfusion.

Key facts about oxygen transport in the blood and extraction of oxygen by the tissues; also, the importance of mixed-venous haemoglobin saturation with oxygen $S\bar{v}O_2$ as an estimate of the adequacy of pump flow rate during CPB

rates were based on body weight, but body surface area (BSA) soon became the international standard. To this day, with some minor variation between institutions, pump flow rates are still predetermined using BSA. However, as will be discussed, these predetermined pump flow rates may no longer be appropriate for today's patients.

From the late nineteenth century onwards, there was a widespread belief that the metabolic rate of a homogeneous animal, regardless of species, was related to its BSA. This idea was crystallised by the work of Max Rubner who created the 'law of surface area', stating that the heat value of the metabolism of a resting individual is proportional to their body surface area (Rubner 1883; Chambers 1952). Given the difficulties inherent in the measurement of BSA, this law was difficult to disprove.

As measurement by direct calorimetry was too complex for the clinical setting, BSA seemed an acceptable alternative estimate of metabolic rate. For this reason, efforts at the beginning of the twentieth century concentrated on the calculation of BSA from simple mathematical formulae of body dimensions and during the rest of the century there were many attempts to simplify the equations (Gibson and Numa 2003). Despite an uncertain relationship with metabolic rate and the questionable accuracy of many of the derived formulae, indexing a variety of physiological functions to BSA became standard in medicine at this time. Glomerular function and, notably for this chapter, cardiac output are examples of this practice.

Much of the original work to determine what was an adequate pump flow rate during CPB was undertaken in animals, commonly canine, and pump flow rates were usually based on body weight. Indeed, body weight was also used in the first series of heart surgery in humans to determine the pump flow rate during CPB (Clark 1958; Kirklin et al. 1958). Adequate flow rates were believed to be those which equated with the cardiac output that supplied the metabolic needs of a human under light general anaesthesia (Clark 1958; Kirklin et al. 1958; Galletti and Brecher. 1962). This was because of the mistaken belief that 'somnolent metabolic rate' was lower than basal metabolic rate (Galletti and Brecher 1962). On this basis, Kirklin's group at the Mayo Clinic originally used a flow rate of 75 ml min^{-1} kg^{-1} (Kirklin et al. 1958).

The use of BSA to determine pump flow rate is attributed to Emerson Moffitt whose study of these early patients and his expression of pump flow rate as litres per minute per square metre (l min^{-1} m^{-2}) led to the realisation that 75 ml min^{-1} kg^{-1} did not approximate to the cardiac output of the lightly anaesthetised patient (Kirklin et al. 1958). As a result, the Mayo Clinic changed to pump

flow rates, based upon BSA, of 2.3 l min^{-1} m^{-2} (Kirklin et al. 1958). This revised flow rate was also determined by their observation that the VO_2 of humans on CPB was 110–120 ml min^{-1} m^{-2} and that, if $\bar{S}vO_2$ was to be maintained at 75%, the normal level in the intact circulation, the oxygenator would have to add 110–120 ml min^{-1} m^{-2} and, therefore, the pump flow rate would have to be in the range of 2.2–2.5 l min^{-1} m^{-2} (Kirklin et al. 1957).

132.5 Body Surface Area May Be an Inappropriate Predictor of Oxygen Uptake

The formula of du Bois and du Bois that is commonly used to determine BSA for CPB was based upon measurements undertaken in only nine patients nearly 100 years ago (du Bois and du Bois 1916). Although this may have provided an acceptable accuracy for the population at that time, obesity is now far more prevalent than in 1953 when CPB was first introduced into clinical practice. In patients who are obese, a far greater proportion of fat, relative to lean tissue, contributes to BSA. Lean tissue, such as muscle, is the major determinant of basal metabolic rate and, therefore, should be an important predictor of how much oxygen the body requires during CPB (Bogardus et al. 1986). Consequently, when based upon BSA, pump flow rates may be higher than required to provide an adequate VO_2 in obese patients, with the potential of causing hypertension and excessive bleeding.

132.6 Other Body Size Estimates That May Predict Systemic Oxygen Uptake During Cardiopulmonary Bypass

132.6.1 Body Mass Index

For heart surgery with CPB in the obese patient, an estimate of body fat might be a better predictor of oxygen uptake. Although abdominal girth has recently been introduced as a measure of obesity, body mass index (BMI) has traditionally been the anthropomorphic measure most widely used to determine the relative amount of body fat. Therefore, BMI might be a useful estimate for VO_2 in today's increasingly obese patients undergoing CPB. However, as with any surrogate measure, because BMI is only an estimate of the proportion of body fat, there are limitations related to its accuracy and ability to discriminate (Prentice and Jebb. 2001).

132.6.2 Lean Body Mass

If an estimate of body fat is not necessarily the answer, then an estimate of the amount of lean tissue might be a better approach. Lean tissue is far more metabolically active than fat and therefore consumes the majority of oxygen in the body. Lean body mass (LBM) provides an estimate of how much of the body's mass is composed of lean tissue and, consequently, could provide a better estimate of systemic oxygen consumption during CPB than BSA.

A number of ways of actually measuring or estimating LBM are discussed earlier in this book in the chapters of Sect. 1: Tools and techniques in anthropometry: techniques and general methods.

Table 132.6 Estimation of lean body mass using skinfold thicknesses

Density = (*c* – *m*) * log (biceps + triceps + suprailiac + subscapularis skinfold thicknesses),
where *c* and *m* are regression coefficients, obtained from a table, which relate to gender and various age groups.
Total fat (%) = (4:95/density – 4:5) * 100
Lean body mass (%) = 100 – % fat
Lean body mass (kg) = (100 – % fat) * weight (kg)

Lean body mass may be estimated by measuring the skinfold thicknesses at four sites and using the above formulae (Durnin and Womersley 1974)

However, measurements of skinfold thicknesses provide a simple estimate of LBM that can be easily made in the clinical environment with minimal training and simple equipment (Table 132.6).

132.7 Predictors of $\bar{S}v0_2$ During Cardiopulmonary Bypass

With the aim of determining which estimate of body size best predicted systemic metabolism, and hence VO_2, during CPB, the author and colleagues undertook a study of $\bar{S}vO_2$ during CPB (Alston et al. 2006). A total of 48 patients undergoing elective cardiac surgery with CPB were enrolled and, prior to surgery, height, weight and skinfold thicknesses were measured. Following induction of general anaesthesia, CPB was established using a standardised technique. The body was cooled to induce systemic hypothermia and, except for brief reductions for surgical interventions, the pump flow rate was maintained at a constant value of 2.4 l min^{-1} m^{-2} throughout CPB.

During CPB, arterial and mixed-venous blood samples were taken at three time points, cooling (10 min after commencing CPB), stable hypothermia and rewarming (a nasopharyngeal temperature of approximately 36°C). The sampling periods were chosen to cover the range of thermal conditions that patients experience during CPB and nasopharyngeal temperatures, as an estimate of metabolic rate, were recorded at each time point. Blood samples were then subjected to blood-gas analysis and measurement of $\bar{S}vO_2$ using standardised techniques.

132.7.1 Correlates of $\bar{S}v0_2$

For the initial exploration of the data, the mean $\bar{S}vO_2$ from the three sampling times was correlated with BSA, BMI, LBM and nasopharyngeal temperature. Significant univariate correlations with $\bar{S}vO_2$ were only found for BMI, LBM and nasopharyngeal temperature. These predictor variables were then entered into a stepwise multiple regression model with $\bar{S}vO_2$ as the dependant variable. The final regression model included only the inverse of nasopharyngeal temperature ($\beta = 0.615$, $p < 0.001$) and LBM ($\beta = 0.256$, $p < 0.028$) (Figs. 132.2 and 132.3).

132.7.2 Body Temperature and $\bar{S}v0_2$

The strong inverse association found between $\bar{S}vO_2$ and nasopharyngeal temperature is clearly explained by the fundamental effect of temperature on the body's metabolism. Hypothermia reduces metabolic rate and hence oxygen consumption by the body. As the pump flow rate was constant,

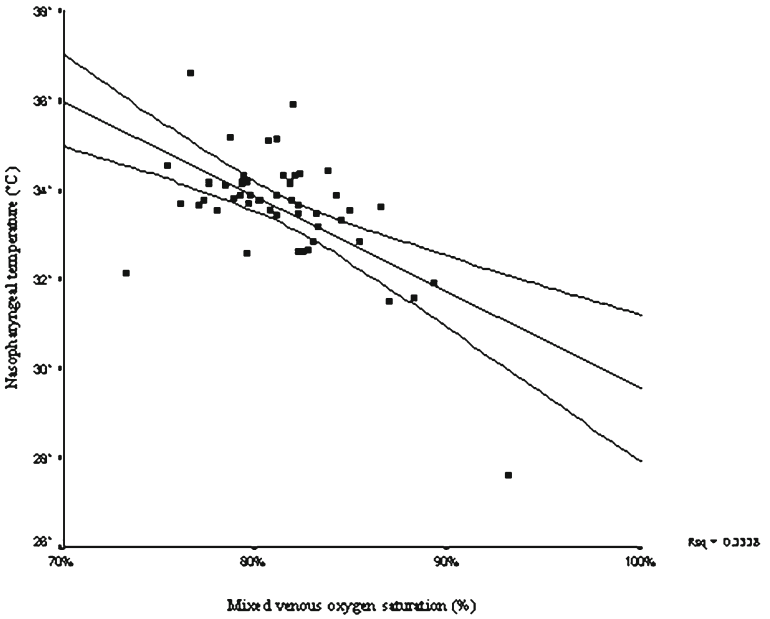

Fig. 132.2 Scatter plot of the saturation of mixed-venous haemoglobin with oxygen against nasopharyngeal temperature. Scatter plot of the saturation of mixed-venous haemoglobin with oxygen $S\bar{v}O_2$ against the nasopharyngeal temperature during cardiopulmonary bypass, showing a negative correlation. As the temperature of the body decreases, the metabolic rate decreases and, therefore, less oxygen is extracted. Assuming that the arterial blood is fully oxygenated and pump flow rate is maintained constant, then, according to Fick's principle, the oxygen content of venous blood must increase, resulting in a higher $S\bar{v}O_2$ (Reprinted from Alston et al. 2006. With permission)

systemic oxygen delivery was also constant and, according to Fick's principle, $S\bar{v}O_2$ must rise, resulting in an inverse relationship with body temperature. Conversely, $S\bar{v}O_2$ must be lower at higher body temperatures, if the pump flow rate is not altered.

132.7.3 $S\bar{v}0_2$ and Body Surface Area

Although BSA did not predict $S\bar{v}O_2$, there were a number of limitations that may explain the lack of a significant association in this study. Most importantly, pump flow rates were not randomly assigned and were determined by BSA, which may have reduced any variance in $S\bar{v}O_2$ between patients. Nevertheless, as indicated by their BMI, these patients were obese and BSA may not have been an accurate estimate of the mass of metabolically active tissue.

132.7.4 $S\bar{v}0_2$ and Body Mass Index

Although BMI was found to be a significant univariate correlate of $S\bar{v}O_2$, the subsequent regression analysis did not find BMI to be a significant predictor of $S\bar{v}O_2$. Based on age, sex and race, BMI is

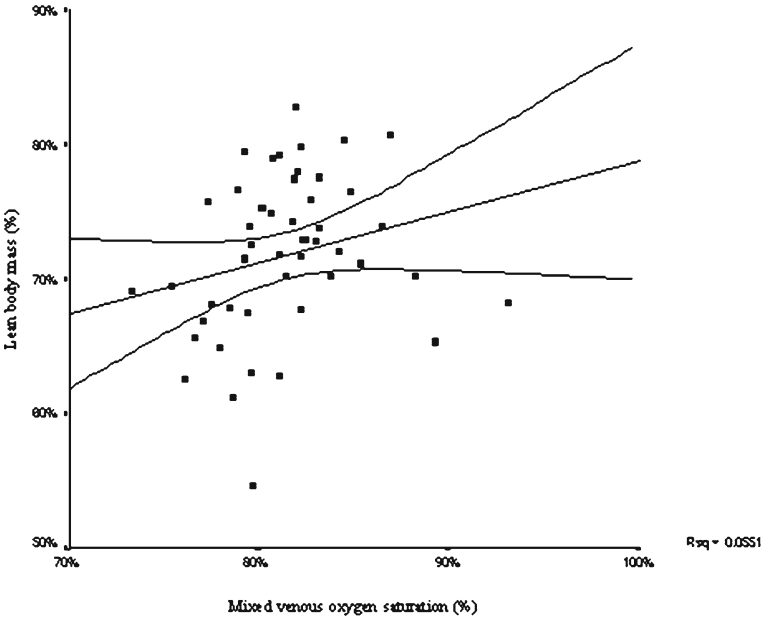

Fig. 132.3 Scatter plot of the saturation of mixed-venous haemoglobin with oxygen against lean body mass. Scatter plot of the saturation of mixed-venous haemoglobin with oxygen $S\bar{v}O_2$ versus lean body mass (LBM) during cardiopulmonary bypass showing a positive correlation. Fick's principle would indicate that patients with a higher LBM would have a higher systemic oxygen uptake, hence a lower $S\bar{v}O_2$. However, this study's findings suggest that using BSA underestimates the mass of metabolically active tissue patients with a low percentage of fat and overestimates it in patients who are obese. This inaccuracy will result in variance in $S\bar{v}O_2$ that produces a positive correlation with LBM as a more accurate estimate of the mass of metabolically active tissue in the body (Reprinted from Alston et al. 2006. With permission)

a good estimate of the percentage of body fat and, therefore, it should be an acceptable inverse estimate of lean tissue. In this study, as the population size was insufficient to detect associations of a small or moderate effect size, a true association between BMI and $S\bar{v}O_2$ may not have been identified.

132.7.5 $S\bar{v}0_2$ and Lean Body Mass

Alston and colleagues also found a significant association between LBM and $S\bar{v}O_2$, suggesting that the conventional calculation of 2.4 times BSA to determine pump flow rate does not completely estimate the VO_2 during CPB. According to Fick's principle, patients with a higher LBM would have a higher VO_2 and thus a lower $S\bar{v}O_2$. Nevertheless, the authors found a positive correlation between LBM and $S\bar{v}O_2$. Although interpretation is difficult, because BSA was used to calculate the pump flow rate, the explanation for this counter-intuitive finding could simply be that using BSA underestimates the mass of metabolically active tissue in patients with a high LBM and overestimates it in patients with a low LBM. Therefore, at pump flow rates of 2.4 l min^{-1} m^{-2}, patients with a high LBM are relatively overperfused and those with a higher mass of fat are relatively underperfused.

132.8 Using Lean Body Mass to Determine Pump Flow Rates During Cardiopulmonary Bypass

If, as the study by Alston and colleagues would suggest, LBM is a more accurate predictor of VO_2 than BSA, could LBM be used clinically to determine pump flow rates during CPB? Although, with appropriate training, it is relatively simple to calculate LBM by measurement of weight and skinfold thickness, the difficulty lies in determining and validating an appropriate formula to allow the calculation of pump flow rates from LBM.

Such an undertaking would require at least two further studies. First, it is needed to using a range of pump flow rates in order to devise a formula using LBM to calculate flow rates and then to compare the pump flow rates, based on that formula, with those calculated conventionally using BSA. Second, to determine the efficacy and safety of the new technique, a randomised controlled trial with a very large population would be required to compare the effects on important clinical outcomes, such as mortality, stroke, myocardial infarction and renal failure. For example, the current ATACAS trial, examining the effects of the antifibrinolytic, tranexamic acid, and aspirin on major ischaemic events after coronary artery bypass surgery requires a population size of 4,600 (Myles et al. 2008). Given the long history and perceived safety of CPB using pump flow rates based on BSA and the study size and complexity required to introduce LBM into clinical practice, it seems unlikely that this will occur.

132.9 Using Real-Time Measurement of Mixed-Venous Oxygen Saturation as an Alternative to Anthropomorphic Estimation of an Adequate Pump Flow Rate

The findings of the study undertaken by the author and colleagues would suggest that using a fixed, standardised pump flow rate is an insensitive approach, as it does not take into account individual variations in LBM and temperature (Alston et al. 2006). Reducing pump flow during induced hypothermia to a fixed level, such a 1.6 l min^{-1} m^{-2}, is one common approach. However, this is a relatively crude tactic and may only be appropriate for stable periods of hypothermia, but not for the thermally unstable periods that are required to induce hypothermia and rewarm the patient to normothermia.

Controlling the pump flow rate to maintain $S\bar{v}O_2$ at a safe fixed level would be sensitive to the important factors, including LBM and temperature, which determine metabolism and, therefore, VO_2. When Golan proposed this approach, some 50 years ago, it was impractical, as measurement of $S\bar{v}O_2$ was by intermittent blood sampling and remote bench oximetry (Gollan 1959). This involved an inevitable delay before the results could be interpreted, during which time there may have been many changes to the patient's systemic oxygen delivery and uptake. In-line monitors that measure $S\bar{v}O_2$ in real-time are now in routine clinical use. Determining pump flow rates by such in-line $S\bar{v}O_2$ monitors should allow the safe use of lower flow rates, especially during hypothermia, whilst ensuring the adequacy of systemic perfusion.

Whilst using $S\bar{v}O_2$ appears to be a physiologically satisfying approach to controlling pump flow rates during CPB, one has to be cautious before introducing such a technique. During low pump flow, tissue hypoperfusion may occur as a result of shunting in the capillary beds. Such shunting might result in apparently normal levels of $S\bar{v}O_2$, whilst organ damage was occurring. As discussed previously, when considering LBM, demonstration that any new technique is effective and safe would require a randomised controlled study, in a very large number of patients undergoing heart

surgery with CPB. Although evaluation of $\bar{S}vO_2$ to control pump flow rate during CPD, would, potentially, be less complex than the LBM study, it would still require a very large population to compare important clinical outcomes, such as mortality, myocardial infarction and renal failure between patients having pump flow rates controlled with $\bar{S}vO_2$ with those having rates controlled according to BSA. Therefore, until such a study is undertaken, it is most likely that pump flow rates during CPB will continue to be determined by the anthropometric measure of BSA, regardless of the associated limitations.

132.10 Applications to Other Areas of Health and Disease

132.10.1 Using BSA to Index Cardiac Output

Cardiac output is the volume of blood ejected from the left ventricle of the heart per unit time, usually expressed as litres per minute. Commonly, cardiac output is assessed in patients of different sizes by indexing it to 1 m^2 of BSA. If BSA is not an accurate means of matching pump flow to metabolic rate in humans undergoing cardiopulmonary bypass, then the logic of indexing cardiac output by BSA may also be flawed.

This potential flaw could therefore be relevant when using a cardiac index of 1.6–1.8 l min^{-1} m^{-2} as a definition of low cardiac output. Patients with a cardiac index below these thresholds are defined as having cardiac failure and are treated with positive inotropic agents, such as adrenaline. If indexing to BSA is flawed, then some patients may be being overtreated and others undertreated with positive inotropic agents in order to obtain a potentially flawed threshold of cardiac index.

132.10.2 Using Systemic Oxygen Uptake to Guide Treatment of Critically Ill Patients

Some goal-directed treatments of critically ill patients are based on achieving a threshold of VO_2, usually by increasing cardiac output with positive inotropic agents, such as adrenaline. As with cardiac output, if indexing to BSA is not appropriate, some patients may not receive treatment when they should and, vice versa, other patients may be treated when they should not be treated.

132.11 Practical Methods and Techniques

The anthropometric measures used in this chapter require accurate measurement of weight and some, also weight.

132.11.1 Body Surface Area

As discussed in detail earlier in this book in the chapter entitled ‘Analysis and comparison of the methods to measure body surface area and of the estimated values’, there are several different ways of measuring and estimating BSA. For clinical practice, it is calculated from the height and weight

of the patient. Whilst there are a number of formulae for estimating BSA from height and weight, that of du Bois and du Bois has traditionally been used to calculate pump flow rate during CPB (du Bois and du Bois 1916):

$$\mathrm{BSA}(\mathrm{m}^2) = \mathrm{weight}\left(\mathrm{kg}\right)^{0:425} * \mathrm{height}\left(\mathrm{m}\right)^{0:725} * 0:007184$$

132.11.2 Body Mass Index

$$\mathrm{BMI}\ (\mathrm{kg\ m}^{-2}) = \mathrm{weight}\left(\mathrm{kg}\right) * \mathrm{height}\ (\mathrm{m})^{-2}$$

132.11.3 Lean Body Mass

There are a number of different ways of measuring LBM, including electrical bioimpedence, air displacement, dual energy X-ray absorptiometry, magnetic resonance imaging and computed tomography and these methods are described in detail in the chapters of Section 1: Tools and techniques in anthropometry. However, they are expensive and less readily available in the clinical setting. An appropriately trained person can perform an alternative technique simply and inexpensively using skinfold thicknesses. In addition to accurately weighing the patient, estimation of LBM by this technique requires measurement of skinfold thicknesses at four sites on the body (biceps, triceps, subscapular and suprailiac) using the guidelines of the International Society for the Advancement of Kinanthropometry (Marfell-Jones et al. 2006). Linear regression equations, which take into account age and sex, are then applied to estimate body density and, from this, the percentage of fat is determined and, thus, LBM can be calculated (Table 132.6) (Durnin and Womersley 1974).

Summary Points

- Cardiopulmonary bypass (CPB) is the keystone allowing cardiac surgery to be safely performed on hundreds of thousands of patients each year around the world.
- CPB is used to replace the functions of the heart and lungs to enable surgery to be performed on the heart.
- CPB has two essential functions, the mechanical pumping of blood around the body and gas exchange to remove carbon dioxide and oxygenate the blood.
- Pump flow rate during CPB is one of two crucial factors that determine whether there is an adequate supply of oxygen to and removal of carbon dioxide from the body.
- Too low or too high a pump flow rate may cause adverse effects.
- Accurate determination of the correct pump flow rate is essential for the safe use of CPB.
- Heart surgery is performed on humans with a wide variety of body sizes, from small infants to obese adults.
- Pump flow rate has to supply sufficient oxygen to match the body's metabolic rate.
- Hypothermia is commonly used during CPB as this reduces metabolic rate and so increases the margin of safety.
- Body surface area (BSA) has been used to calculate pump flow rate during cardiopulmonary bypass for nearly 50 years.
- BSA is not measured directly, but is calculated from height and weight using a formula devised nearly 100 years ago from only nine human subjects.

- Obesity is far more common now than when the formula for BSA was devised and, therefore, this formula may no longer be appropriate for patients presenting for heart surgery today.
- Research indicates that BSA may not be the most accurate means of determining pump flow rate during CPB.
- Lean body mass LBM) may be a more sensitive measure of metabolic rate and could be used to determine pump flow rates during CPB.
- Using in-line, real-time measurement of the saturation of mixed-venous blood with oxygen $\bar{S}vO_2$ to control pump flow rate during CPB would overcome variations in metabolic rate resulting from different body sizes and changes in body temperature.
- The introduction of LBM or $\bar{S}vO_2$ in the determination of pump flow rates would require a randomised controlled trial in a very large number of patients undergoing heart surgery with CPB.
- For the foreseeable future, it is therefore most likely that pump flow rate during CPB will continue to be determined by the anthropometric measure of BSA, regardless of its limitations.

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Chapter 133
Anthropometric Measurements, Adipokines and Abdominal Aortic Calcification

Adam Franklin Parr and Jonathan Golledge

Abstract Obesity and arterial calcification are associated with increased cardiovascular morbidity and mortality. The relationship between obesity and abdominal aortic calcification has been under investigated. The majority of research has focused on the relationship between clinical anthropometric measures and aortic calcification, with mixed results. Numerous calcification measurement protocols have hindered appropriate analysis of the literature. However, recently a reproducible computed tomography method for aortic calcification quantification has been published. Similarly, many methods are available for anthropometric assessment. Clinical measures include body mass index, waist circumference, waist to hip ratio, skin fold and percent body fat. Alternatively, computed tomography can be reproducibly utilized to measure abdominal adipose diameters, area and volume.

Recently, the relationship between calcification and anthropometric measurements has been investigated by computed tomography. It was found that a measure of visceral adiposity was associated with abdominal aortic calcification. In addition, visceral adiposity was positively and negatively correlated to circulating concentrations of osteoprotegerin and leptin, respectively. This has provided a possible pathogenic mechanism for the accumulation of abdominal aortic calcification.

The aims of this chapter are two fold:

1. To outline the various anthropometric and calcification protocols currently employed for vascular research.
2. To review the current literature regarding the relationship between anthropometric measures and abdominal aortic calcification.

Abbreviations

AAA	Abdominal Aortic Aneurysm
AP1	Anterior-posterior diameter – skin to skin
AP2	Anterior-posterior diameter – muscle to muscle
APR	Anterior-posterior ratio (AP2/AP1)
BMI	Body mass index
CT	Computed tomography
CH	Center hounsfield unit

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_133,

EBCT	External beam computed tomography
HU	Hounsfield unit
IDF	International diabetes federation
SC	Subcutaneous fat
T1	Transverse diameter – skin to skin
T2	Transverse diameter – muscle to muscle
TR	Transverse ratio
US	Ultrasound
WH	Window width hounsfield unit
WHR	Waist hip ratio
WHO	World Health Organisation

133.1 Introduction

Obesity and arterial calcification have independently been linked to increased cardiovascular events, such as stroke and myocardial infarction (Wilson et al. 2001). The mechanisms underlying the negative effects of obesity appear to be complex, with a variety of cytokines and metabolic effects implicated (Van Gaal et al. 2006). Many anthropometric measurements have been employed to study fat distribution patterns and their role in cardiovascular disease (Janssen et al. 2004): for example, waist-to-hip ratio (WHR), body mass index (BMI) and more recent imaging-based assessments (Golledge et al. 2008) (Table 133.1). Using these techniques, central adipose deposition has been independently correlated to the presence of occlusive coronary and peripheral arterial disease (Golledge et al. 2007b).

Arterial calcification has been measured by a variety of techniques, such as plain X-ray and computed tomography (CT) throughout the arterial system (Jayalath et al. 2005). The association of coronary artery calcification with cardiovascular morbidity and mortality has been extensively investigated (O'Malley et al. 2000), with much less attention given to aortic mineralisation. Whereas combined aortic and coronary atherosclerosis is not uncommon, many of the characteristics of coronary and aortic pathology are different. For example, the aorta is more prone to aneurysm formation than the coronary arteries and there appear to be some differences in risk factor profiles of patients with pathology centred at different artery sites (Michel 2001).

The association of obesity and coronary artery calcification appears well established (Allison and Wright 2004; Kim et al. 2008). The link between abdominal aortic calcification and obesity is less well established. Recently, visceral adiposity has been implicated as a causative factor in abdominal aortic calcification (Golledge et al. 2008). The mechanisms driving this process are largely unknown. Insulin resistance is believed to be a major mechanism by which central obesity accelerates atherosclerosis (Van Gaal et al. 2006). However, other factors, such as adipokines, and other cytokines, such as osteoprotegerin, may play a role (Golledge et al. 2008). This article will review the literature surrounding the association between fat distribution and abdominal aortic calcification.

133.2 Literature Review

The literature was searched through MEDLINE and Cochrane databases, limited to publications in English. The titles and abstracts of studies identified were reviewed for their appropriateness and a manual search of reference lists was also performed. The search terms were 'abdominal aorta' AND

Table 133.1 Commonly employed anthropometric measurements in vascular research

Measurement	Units	Interpretation	Advantages	Disadvantages
Clinical				
Body mass index	kg/m^2	Normal level: 18.5–24.9 Overweight: 25.0–29.9 Obese: 30.0–39.9 Morbidly obese: ≥40.0	Easy to perform	Does not distinguish between muscular physique and fat
Waist circumference	cm	Normal IDF levels – European: $F < 80$ cm; $M < 94$ cm South Asians and Chinese: $F < 80$ cm; $M < 90$ cm	Surrogate marker of visceral adipose	Many different definitions are in use
Waist-to-hip ratio	0–1	Normal IDF level: F < 0.85; M < 0.90	Easy to perform	Does not directly measure visceral compared to subcutaneous adiposity
Computed tomography				
Fat diameters	SC or ratio	Closer to 1 = increased visceral compartment	Good reproducibility Easy to perform	No current definition of obesity
Fat area	cm^2 or ratio	Area of visceral or subcutaneous fat on one CT slice	Easy to perform	May not be representative of whole abdomen
Fat volume	cm^3 or ratio	Total abdominal fat Total visceral fat Visceral/subcutaneous ratio	Takes into account all abdominal fat	Time consuming Varying CT protocols and reproducibility data

This table describes common clinical and computed tomography anthropometric measurements in vascular surgery
kg kilograms, *m* meters, *cm* centimetres, *SC* subcutaneous, *CT* computed tomography, *M* male, *F* female, *IDF* International Diabetes Federation

'calcification'. A total of 298 publications were initially identified prior to further selection. These papers were examined for relevance related to anthropometric measurements. The search terms 'abdominal aorta' AND 'calcification' AND 'obesity' yielded three articles.

133.3 Practical Methods

133.3.1 Anthropometric Measurements

Anthropometry is the measurement of variation in body dimensions in humans. Whereas this encompasses measurements of most body regions, its use in vascular surgery is often synonymous with defining body fat composition.

133.3.2 Clinical Measurements

Clinical data are the primary method for defining anthropometric measurements. For physical examination, patients should wear thin, loose-fitting clothing and remove their footwear. Examination should begin with height (to the nearest 1.0 cm) and weight (to the nearest 0.1 kg) measurements. From these measurements, BMI can be computed [(weight in kg)/(height in meters)^2]. The BMI can be categorised into World Health Organization (WHO) classifications: underweight (<18.5); normal (20–24.9); overweight (25–29.9); obese (30–39.9); and morbidly obese (≥40). Waist circumference, measured at the midpoint between the 12th rib and the iliac crest at the end of gentle expiration, and hip circumference, measured at the level of the greater trochanter, should also be assessed. WHR [waist circumference (cm)/hip circumference (cm)] can then be determined. The WHO guidelines recommend ratios <0.85 for females and <0.90 for males. Additional measurements could include body fat percentage, midhumeral circumference (to nearest 1 mm) and triceps skinfolds (to nearest 0.2–0.5 mm, depending on the calliper).

133.3.3 Computed Tomography

Recently, CT fat distribution and quantification has been utilised in patients undergoing assessment for abdominal aortic pathology (Golledge et al. 2008). There are two major methods currently being employed for CT assessment of abdominal adiposity: adipose diameter and volume measurements.

133.3.3.1 Diameter Measurements

Axial CT slices can be used to determine anthropometric diameter measurements for assessment of visceral adiposity (Fig. 133.1). Measurements are made with electronic callipers (to the nearest millimetre) on the most cephalad CT slice in which the iliac crest appears. Two anterior-posterior diameters are measured by creating a vertical line from the anterior abdominal skin through the middle of the vertebral body to the skin of the posterior surface. AP1 represents the entire length of

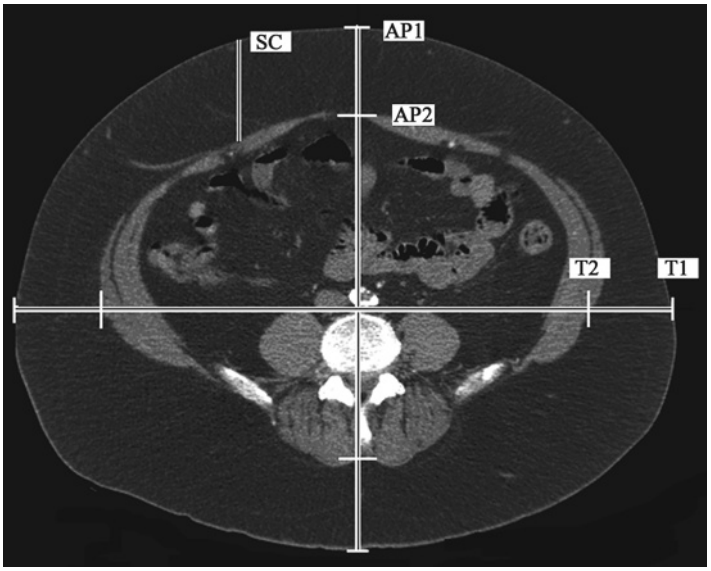

Fig. 133.1 Illustration of anthropometric measurements made from computed tomography images. The anterior-posterior line is drawn and measured as total line (*AP1*) and linea alba to posterior aspect of the spinous process (*AP2*). The anterior-posterior ratio (*APR*) is calculated by dividing AP2/AP1. The transverse line is drawn and measured as total line (*T1*) and anterior aspect of external obliques (*T2*). The transverse ratio (*TR*) was calculated by dividing the T2/T1. The subcutaneous fat depth (*SC*) was measured as shown (Reprinted from Golledge et al. 2008, with permission)

Table 133.2 Relationship of computed tomography anthropometric diameters to clinical anthropometric measurements (Reprinted from Golledge et al. 2008. With permission)

Measurement	AP1	AP2	T1	T2
Waist circumference	$r = 0.73$, $p < 0.0001$	$R = 0.66$, $p < 0.0001$	$r = 0.62$, $p < 0.0001$	$r = 0.66$, $p < 0.0001$
Waist-to-hip ratio	$r = 0.43$, $p = 0.01$	$R = 0.51$, $p = 0.002$	$r = 0.32$, $p = 0.04$	$r = 0.37$, $p = 0.03$
Body mass index	$r = 0.43$, $p = 0.01$	$R = 0.19$, $p = 0.25$	$r = 0.60$, $p < 0.0001$	$r = 0.48$, $p = 0.003$

This table depicts correlations and significance of waist circumference, waist-to-hip ratio and body mass index in relation to diameter measurements

Fat diameters are most closely correlated to waist circumference.

AP1 Anterior-posterior diameter – skin to skin, *AP2* Anterior-posterior diameter – muscle to muscle, *T1* Transverse diameter – skin to skin, *T2* = Transverse diameter – muscle to muscle

this line, whereas AP2 is the distance from the linea alba to the posterior aspect of the spinous process. The anterior–posterior ratio (APR) was calculated as AP2/AP1. Two similar transverse diameters were made by creating a horizontal line passing through the most anterior aspect of the vertebral body. T1 represented the entire length of this line, whereas T2 was the distance from the anterior surface of the right external oblique to that of the left. The transverse ratio (TR) was calculated as T2/T1. Interpretation of the anthropometric diameters is often subject to confusion. A larger visceral compared to subcutaneous compartment would lead to an increase in both ratios. In a study of 148 patients, AP and T diameters were associated with waist circumference, waist-to-hip ratio and BMI (see Table 133.2) (Golledge et al. 2008). A further estimate of the subcutaneous fat is made by creating a vertical line from the anterior aspect of the skin to that of the external oblique at a point 50 mm

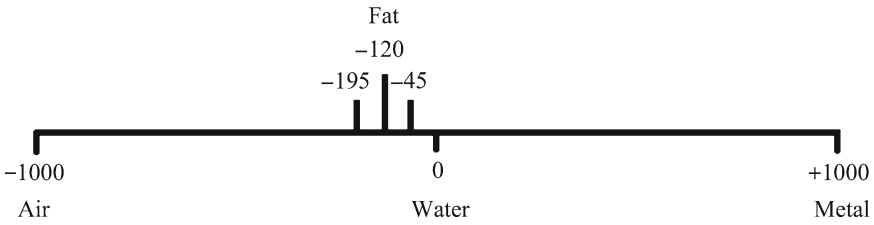

Fig. 133.2 A representation of the computed tomography radiographic grey scale with illustration of adipose densities. Numbers are presented in Hounsfield Units (*HU*). Radiographic density spectrum is from air (−1,000 HU) to metal (+1,000 HU). Adipose density has a Center HU (*CH*) of −120 HU and a Window-width HU (*WH*) of 75 HU. As a result, the upper and lower limit of WH is −195 to −45 HU

right of the umbilicus (SC). A reproducibility study of 15 patients measured repeat diameters with multiple observers (Golledge et al. 2008). The intra-observer coefficient of variation was 0.9%, 0.7% and 4.0% for APR, TR and SC, respectively. The inter-observer coefficient of variation was 2.6%, 3.2% and 10% for APR, TR and SC, respectively.

133.3.3.2 Adipose Thresholds

Recently, techniques have been developed to estimate adiposity using threshold density levels on CT (Maurovich-Horvat et al. 2006). CT workstations can be used to identify tissues based on density profiles, known as thresholding. Parameters are defined by Hounsfield units (HU), setting the Center Hounsfield Unit (CH) level and a Window-width Hounsfield Unit (WH) for the tissue of interest. Past studies have used various thresholds to define adipose tissue (Jensen et al. 1995; Yoshizumi et al. 1999; Maurovich-Horvat et al. 2006). Commonly, a CH of -120 HU and a WH of 75 HU (−195 to −45 HU) are used (Maurovich-Horvat et al. 2006) (see Fig. 133.2). The abdominal fat area or volume can then be estimated over a selected region of interest. The slice(s) chosen for area and volume measurements vary between protocols (Yoshizumi et al. 1999; Maurovich-Horvat et al. 2006). One volumetric protocol assesses from the most superior level of the first sacral vertebral body to 125-mm cephalad (Maurovich-Horvat et al. 2006). Manual separation of the visceral and subcutaneous compartment then occurs by semi-automated tracing of the abdominal muscular wall separating the two compartments (see Fig. 133.3). This allows absolute evaluation of visceral and subcutaneous compartments in addition to ratio generation. Reproducibility of these methods is often unreported (Nicklas et al. 2004). However, a subcohort of 100 patients from the Framingham Heart Study was assessed for intra- and inter-observer reproducibility of abdominal fat measurements (Maurovich-Horvat et al. 2006). Reproducibility was high, with both assessments displaying intraclass correlation coefficient of 0.99.

133.4 Arterial Calcification

Initially, theories regarding vascular calcification suggested that minerals deposited passively in vessel walls (Jayalath et al. 2005). Increasing evidence suggests that vascular calcification is an active and regulated process. In this active model, a process analogous to bone formation occurs.

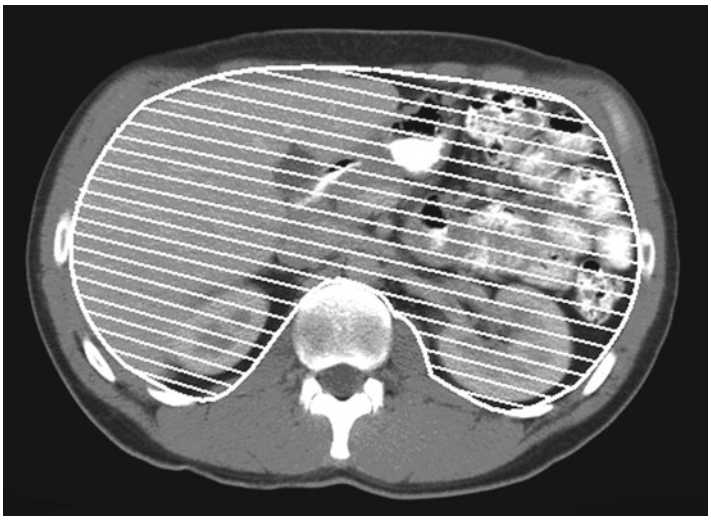

Fig. 133.3 Intra-abdominal fat quantification on computed tomography. The *white line* represents the region of interest, with the threshold area (*white hash*) set for adipose density (as displayed in Fig. 133.2)

133.4.1 Classification

Anatomically, vascular calcification is classified into intimal and medial deposition (Jayalath et al. 2005). This variation is increasingly being recognised as a dichotomous process. Intimal calcification is generally associated with the development of atherosclerosis. Conversely, medial calcification occurs independently of atherosclerosis and shares an association with metabolic disturbances, such as diabetes mellitus and renal failure. Unfortunately, differentiation between types rarely occurs in the literature and can be difficult to do in many imaging assessments, such as plain X-ray.

133.4.2 Abdominal Aortic Calcification

Currently, there is no agreed measurement method or grading scale for abdominal aortic calcification. Table 133.3 displays various methods which have been used to assess abdominal aortic calcification. Table 133.4 displays the key facts of this phenomenon. The relationship between abdominal aortic calcification and both local pathological and overall patient outcomes is of significant interest.

133.4.2.1 Relationship to Abdominal Aortic Aneurysm

The association of abdominal aortic calcification and abdominal aortic aneurysm (AAA) is controversial. AAA is a weakening of the aorta usually affecting the infrarenal segment and is commonly defined by an aortic diameter ≥30 mm (Golledge et al. 2006). It represents an important cause of mortality in the older population. Intimal calcification has been associated with increased aortic diameters in patients who do not have AAAs (Allison et al. 2008). Most studies have shown no association between CT-detected aortic calcification and AAA growth (Vega de Ceniga et al. 2006; Parr et al. 2009).

Table 133.3 Description of various methods for abdominal aortic calcification assessment

Modality	Calcification score	Description
Plain lateral lumbar x-rays	Aortic calcification score	Calcification scores 0–3 across four segments making an overall score of 0–24
	Length involved	Calcification lengths ≤1 cm, 2–5 cm, 6–10 cm, and >10 cm
Ultrasound	High or low	Calcification greater or less than 50% of the intimal maximal AAA circumference
	Present or absent	High echogenic plaques considered calcification
Computed tomography	Calcification appearance	Thin, discontinuous; thin, continuous; thick, discontinuous; thick, continuous; and abrupt break in thin or thick continuous pattern
	Aortic calcification index 1	A total of 15 CT slices (1cm intervals) above iliac bifurcation, with each slice subdivided into 16 sectors. Each sector scores positive, if calcification is present. The score is from 0 to 240
	Aortic calcification index 2	Proportion of aortic circumference covered by calcification. Patients were then grouped into I 0–10%, II 11–30%, III 31–50%, and IV 51–100%
	Aortic calcification index 3	Two slices (at bifurcation and 1 cm superior) were analysed and calcification expressed as an average percentage
	Aortic calcification index 4	Calcification score from 0 to 4 at the area of maximal dilation
	Aortic calcification index 5	Minimal (<10% of aortic circumference), moderate (10–15%) and severe (>50%) at the aortic neck, area of maximal diameter and aortic bifurcation
	Aortic calcification volume	Infra-renal aortic calcification volume (cm^3) as determined by density on post-analysis software; CH = 1,400; WH= 2,000
EBCT	Agatston scores	Intimal calcification mostly detected

This table describes the currently used methods to measure calcification. No consensus "gold standard" is recognised. However, aortic calcification volume is highly reproducible

CT Computed tomography, *CH* Center Hounsfield unit, *WH* Window width Hounsfield unit, *AAA* Abdominal aortic aneurysm, *CH* Center Hounsfield unit, *WH* Window width Hounsfield unit, *EBCT* External beam computed tomography

Table 133.4 Key facts of aortic calcification

1. Aortic calcification occurs by a complex process of biomineralisation
2. This is thought to occur by an active process
3. Two types of aortic calcification are anatomically recognised; medial or intimal depending on the vascular layer of deposition
4. Medial calcification is associated with metabolic derangements, such as diabetes mellitus and renal failure, and is often seen in the aorta
5. Intimal calcification is primarily associated with atherosclerosis
6. Coronary calcification is associated with vessel occlusion, and, hence, coronary events
7. The role of aortic calcification is less clear, as aortic occlusive disease is relatively rare
8. Aortic calcifications' positive relationship to cardiovascular events is becoming increasingly evident; however, this may reflect an overall vascular state
9. Aortic calcification may be associated with reduced abdominal aortic aneurysm growth rates

This table outlines key features pertaining to abdominal aortic calcification. The significance of abdominal aortic calcification is still unclear.

By contrast, a recent ultrasound study reported that patients with ≥50% aortic wall calcification had significantly slower AAA progression than their less-calcified counterparts (Lindholt 2008). Rupture rates have not been reported to be associated with aortic calcification quantity. However, a focal gap of otherwise circumferential wall calcification has been associated with AAA rupture (Siegel et al. 1994). Thus, currently, the importance of calcification in AAA pathology is unclear.

133.4.2.2 Relationship to Cardiovascular Events

Coronary artery calcification has repeatedly been associated with cardiovascular events, such as myocardial infarction (O'Malley et al. 2000). Whereas aortic calcification is associated with coronary calcification (Kuller et al. 1999), its independent significance has been relatively under investigated. Aortic atherosclerosis has a number of differences from atherosclerosis at other sites. For example, aortic atherosclerosis appears to have less potential to lead to arterial occlusion since aortic occlusion is less common than coronary artery occlusion (Jayalath et al. 2005). In some studies, the presence of aortic calcification has been associated with coronary artery disease, peripheral vascular disease, cardiovascular disease mortality and future coronary heart disease (Wilson et al. 2001). Large studies employing reproducible imaging techniques are required to confirm the association of aortic calcification with cardiovascular events (Jayalath et al. 2005).

133.4.3 Relationship Between Clinical Anthropometric Measurements and Abdominal Aortic Calcification

Waist circumference has been associated with increased cardiovascular events (Bigaard et al. 2005). However, the relationship between clinical anthropometric measurements and abdominal aortic calcification is unclear (see Table 133.5). Studies have related increased BMI to both low (Shinagawa et al. 1992; Reaven et al. 2005) *and* high (Allison et al. 2007) calcification. However, most studies concluded BMI was not associated with aortic calcification presence (Jie et al. 1995; Kuller et al. 1999; Blancher et al. 2001; O'Donnell et al. 2002; Arai et al. 2002; Allison et al. 2004) or progression (Hak et al. 2000). Conversely, BMI and WHR appear to be positively correlated to coronary calcification (Kuller et al. 1999; Allison et al. 2004, 2007). WHR has been correlated to aortic calcification when using CT (Kuller et al. 1999), but not lateral X-rays (Jie et al. 1995), in postmenopausal women. Total body fat percentage and body weight appear to be correlated with increased aortic calcification (Alexanderson et al. 2006; Allison et al. 2007). No significant association was found between suprailiac or triceps skinfold measurements and aortic calcification (Kuller et al. 1999).

The inconsistency of clinical anthropometric results could be accounted for by the variation in calcification measurement techniques and protocols that have been used, many without clear reproducibility (Lindholt 2008). In addition, confounding factors, such as diabetes, hypertension and smoking, are known to be strongly associated with arterial calcification and obesity, and therefore may affect associations in different cohorts (Jayalath et al. 2005). Alternatively, the inherent deficiencies of clinical measurements may be responsible for the lack of consistency between results. For example, WHR may not be a reliable index of visceral/subcutaneous fat distribution in obese individuals.

Table 133.5 Methods and results of major studies relating clinical fat measurements to abdominal aortic calcification

Study	Patients	Method	Region assessed	Results
O'Donnell et al. (2002)	2,151	Lateral lumbar X-ray calcification score	Abdominal aorta	Calcification was not correlated with BMI ($r = -0.03$)
Allison et al. (2007)	1,078	EBCT	Abdominal aorta	Patients with calcification ($n = 593$) had similar BMI (26.9 vs 26.6) and percent body fat (29.5 vs 29.5)
Shinagawa et al. (1992)	845	CT – ACI 3	Abdominal aorta	Calcification was highest in men with low BMI
Hak et al. (2000)	720	US – High or low	Abdominal aorta	BMI was not associated with calcification progression at 9 years reassessment
Allison et al. (2004)	650	EBCT	Diaphragm to iliac bifurcation	No association between aortic calcification and BMI Total body fat (5%) (OR 0.6–0.9, 95% CI 0.4–1.7) was not correlated with aortic calcification
Reaven et al. (2005)	309	EBCT	Upper pole of right kidney to iliac bifurcation	BMI was increased in subjects with low calcification scores (mean 32.9) compared to those with high scores (mean 31.2), $p < 0.05$
Kuller et al. (1999)	169	EBCT	Aortic arch to the iliac bifurcation	BMI was related to increased coronary calcification ($p = 0.03$) but not aortic calcification ($p = 0.43$) WHR was correlated to coronary ($p = 0.004$) and aortic calcification ($p = 0.07$)
Alexanderson et al. (2006)	168	Lateral lumbar X-ray calcification score	Abdominal aorta	Aortic calcification was inversely associated with peripheral lean mass even after adjusting for age and BMI ($p < 0.05$)
Jie et al. (1995)	113	Lateral lumbar X-ray length	Abdominal aorta	BMI (mean 26.5 vs 25.4, $p = 0.07$) and WHR (mean 0.84 vs 0.84, $p = 0.81$) were not associated with aortic calcification
Blancher et al. (2001)	110	US – present or absent	Arterial calcification	No association of BMI with arterial calcification, as determined by presence or absence of calcification of the carotids, aorta, iliofemoral axis and legs
Arai et al. (2002)	29	CT – ACI 3	1 cm above and including iliac bifurcation	BMI was similar between the groups with high and low calcification (22.7 vs. 23.2 kg/m^2)

This table describes the 11 major studies examining fat measurements and abdominal aortic calcification. Studies utilised various regions of the abdominal aorta, calcification protocols and patients

EBCT external beam computed tomography, *BMI* Body mass index, *WHR* Waist-to-hip ratio, *CT* Computed tomography, *US* Ultrasound, *CVD* Cardiovascular disease, *ACI 3* Aortic calcification score 3, *OR* Odds ratio

133.4.4 Relationship Between CT Anthropometric Measurements and Abdominal Aortic Calcification

In a small number of studies, CT-measured visceral adipose volume was found to be a stronger predictor of cardiovascular events than other measures of obesity (Nicklas et al. 2004). The relationship between fat distribution and abdominal aortic calcification has been relatively little studied. One study (Shinagawa et al. 1992) examined 845 patients for abdominal adiposity and calcification using CT. They found that males with low subcutaneous fat had increased aortic calcification.

Table 133.6 Table outlining key facts in anthropometric measurements and abdominal aortic calcification

1. Computed tomography methods can reliably be employed to measure anthropometric parameters
2. Increased calcification of the abdominal aorta predicts increased cardiovascular morbidity and mortality
3. Leptin is negatively associated with visceral adiposity
4. Osteoprotegerin is associated with increased visceral adiposity and vascular calcification
5. Aortic calcification is associated with increased visceral adiposity, as estimated by computed tomography

This table displays the key facts relating to anthropometric measurements and abdominal aortic calcification

Table 133.7 Association of anterior-posterior ratio (APR) tertiles with calcification, lipids and cytokine concentrations (Reprinted from Golledge et al. 2008. With permission)

	APR tertile 1	APR tertile 2	APR tertile 3	*P* value
Number	50	49	49	
APR	0.73 ± 0.05	0.84 ± 0.02	0.91 ± 0.02	<0.0001
TPR	0.86 ± 0.07	0.91 ± 0.04	0.94 ± 0.03	<0.0001
SC (mm)	34.9 ± 10.9	23.9 ± 6.1	16.0 ± 6.6	<0.0001
Aortic calcification volume (mm^3)	1,256 ± 1,184	1,871 ± 1,762	2,266 ± 1,820	0.01
Adiponectin (μg/ml)	8.33 ± 4.36	9.49 ± 4.48	10.26 ± 5.09	0.25
Leptin (ng/ml)	36.22 ± 28.79	21.00 ± 25.56	12.04 ± 13.62	<0.0001
Resistin (ng/ml)	25.69 ± 19.97	24.69 ± 13.20	25.45 ± 10.74	0.45
OPG (pM)	6.37 ± 2.37	6.53 ± 2.37	7.82 ± 3.26	0.01
OPN (ng/ml)	26.0 ± 19.1	24.5 ± 18.5	24.6 ± 18.2	0.89
MGP (nM)	24.9 ± 18.6	25.7 ± 14.6	29.8 ± 18.7	0.20

This table examines the association of anterior-posterior ratio (APR) tertiles with calcification, lipids and cytokines. Increasing intra-abdominal compartment compared to subcutaneous compartment (APR) is correlated positively with calcification volume and osteoprotegerin and negatively with leptin concentration. Numbers are mean ± standard deviation
APR Anterior-posterior ratio, *TPR* Transverse ratio, *SC* Subcutaneous adipose depth, *OPG* Osteoprotegerin, *OPN* Osteopontin, *MGP* Matrix Gla protein

This was only the case in middle-aged men and not women. In 85 patients, they further analysed the visceral/subcutaneous ratio in relation to calcification. An increasing ratio, hence, increased visceral adiposity, was associated with decreased calcification. However, this paper was not published in English and only the abstract was available.

Recently, a prospective study involving 148 vascular patients assessed the relationship between abdominal aortic calcification and CT anthropometric diameters (Golledge et al. 2008). Table 133.6 outlines key facts related to this study. Inclusion criteria into the study were (1) diagnosis of symptomatic peripheral vascular disease (55%) or AAA (45%); and (2) CT angiogram required to further assess diagnosis. The exclusion criteria were (1) previous surgical repair of AAA; and (2) patient deemed not suitable for a CT angiogram. Abdominal aortic calcification was quantified by validated techniques (CH 1,400 HU; WH 2,000 HU) with excellent reproducibility (intra- and inter-observer coefficient of variation approximately 1%). Anthropometric measurements were measured as outlined above.

Traditional risk factors among the patients included male gender (72%), diabetes (26%), hypertension (66%), current smoking (39%) and ex-smoker (35%). Mean age, cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein and creatinine concentrations were 67.7 ± 9.4 years, 4.89 ± 1.71 mM, 1.96 ± 1.21 mM, 1.27 ± 0.34 mM, 2.80 ± 1.64 mM and 97.8 ± 39.5 μM, respectively.

The study identified an association between a surrogate measure of visceral adipose and aortic calcification. Specifically, abdominal aortic calcification was positively correlated with APR ($r = 0.27$, $p = 0.001$) and TR ($r = 0.26$, $p = 0.001$), but negatively correlated with SC ($r = -0.28$, $p = 0.001$). Tertiles of APR and TR were associated with aortic calcification volume (Table 133.7). Taking into account traditional risk factors (age, gender, smoking history, diabetes, hypertension and lipids), APR ($\beta = 0.26$, $p = 0.006$) and TR ($\beta = 0.23$, $p = 0.01$) were independently associated with aortic calcification volume.

Table 133.8 Key facts of adipokines

1. Adipose tissue is highly metabolically active
2. It manufactures and secretes many important proteins
3. These products are known as adipokines
4. Adipokines include leptin, adiponectin, resistin and various cytokines
5. Adipokines have various cardiovascular roles under investigation, such as regulation of insulin resistance

This table outlines the basic facts pertaining to adipokines

133.4.5 Mechanism of Calcification

The mechanisms underlying the more detrimental effects of visceral compared to peripheral and subcutaneous adipose are presently not defined. It has been postulated that visceral adipose tissue releases different quantities of adipokines (Diamant et al. 2005). More precisely termed adipose-derived hormones, these include leptin, adiponectin and resistin, which are released from adipocytes and act on peripheral tissues. Table 133.8 displays the key facts regarding adipokines.

133.4.5.1 Leptin

In animal models, leptin plays an important role in inhibiting appetite and has also been shown to inhibit visceral deposition of fat (Friedman and Halaas 1998). In humans, leptin gene expression in subcutaneous adipocytes has also been previously negatively correlated to visceral fat volume (Diamant et al. 2005). The concentration of leptin has been demonstrated to be higher in subcutaneous compared to visceral adipose biopsies (Lihn et al. 2004). Serum leptin strongly negatively correlated with increasing size of the visceral compartment, as determined by CT fat diameters (see Table 133.7). (Golledge et al. 2008). In patients with high visceral to subcutaneous compartment ratio, the relatively smaller volume of superficial adipocytes may account for the lower concentration of circulating leptin. Whether the visceral compartment directly produces factors inhibiting leptin production remains to be defined (Golledge et al. 2007a). The negative association of leptin with visceral adipose deposition does not explain the link between visceral obesity and aortic calcification.

133.4.5.2 Osteoprotegerin

Osteoprotegerin, also known as osteoclastogenesis inhibitory factor, is a bone cytokine. Osteoprotegerin-deficient mice develop severe osteoporosis and medial calcification (Min et al. 2000). Human osteoprotegerin has been independently associated with cardiovascular events and general arterial and abdominal aortic calcification (Clancy et al. 2006). Furthermore, one study (Golledge et al. 2008) found an association between serum osteoprotegerin and visceral compartment size as determined by CT fat diameters (see Table 133.7). It has been demonstrated that adipose tissue contains stem cells capable of differentiating into osteoblasts in vitro and that similar control pathways modulate bone and adipocyte differentiation (Iribarren et al. 2007). Thus, it is possible that the components of visceral adipose are able to produce osteoprotegerin or other cytokines, which can control the development of vascular calcification and atherosclerosis. This hypothesis requires further investigation.

133.4.6 Applications to Other Areas of Health and Disease

Intimal vascular calcification is a general marker of atherosclerosis load. Whether abdominal aortic calcification, as a pathological process, is detrimental remains unclear. It may simply be a marker of atherosclerosis load.

Summary Points

- Abdominal obesity, as determined by waist circumference, has been associated with increased cardiovascular events.
- Visceral adipose volume on CT has been found to be the stronger predictor of cardiovascular event.
- On CT, there appears to be an association between the size of the visceral compartment and the severity of abdominal aortic calcification.
- There appears to be a correlation between the visceral compartment size and circulating osteoprotegerin concentrations, which is a proposed mechanism that may contribute to the poor prognosis associated with visceral adipose deposition.

Financial Disclosure and Conflict of Interest JG is supported by grants from the NHMRC, Australia (project grants 540403, 540404, 540405) and NIH, USA (RO1 HL080010), and a Practitioner Fellowship from the NHMRC, Australia (431503).

Acknowledgements We would like to thank Ms Moira McCann, Ms Barbara Bradshaw, Mr Keith Rich and The Townsville Hospital radiology and vascular surgery departments.

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Part XXI
Anthropometry in Organ Disease

Chapter 134
Body Composition in Liver Cirrhosis

Lindsay D. Plank and John L. McCall

Abstract Patients with liver injury resulting in cirrhosis exhibit marked derangements in body composition. This is not surprising given the central role played by the liver in substrate metabolism. Progressive loss of muscle mass accompanies worsening liver disease and in end-stage disease patients typically appear wasted in the extremities with a distended abdomen due to ascites and peripheral edema. The ascites and edema in cirrhotic patients masks the profound weight loss that would otherwise occur. For this reason, malnutrition in these patients is often underdiagnosed and the widely used 2-compartment model which partitions the body into a fat compartment and a fat-free compartment is inadequate for characterizing the important features of their body composition.

Measurements of body protein stores using neutron activation analysis in a large group of cirrhotics of diverse etiology highlighted the extent of malnutrition in these patients. Significant malnutrition was evident even in patients with well compensated cirrhosis and malnutrition worsened with the severity of liver disease. Protein depletion was more severe in males compared to females irrespective of disease severity. Measurement of cellular mass of the body based on assessment of total body potassium confirmed the marked depletion of muscle mass in cirrhotic patients. Fat mass depletion was shown to increase with severity of disease and to be more marked in females than males. Total body water, expressed as a fraction of the fat-free mass, was significantly elevated, with 45% of Child's A and 80% of Child's C patients falling outside the normal reference range. Overhydration of the fat-free mass was often present in patients with no clinical evidence of fluid retention. Cirrhosis was associated with loss of bone mineral and reduced bone mineral density. There is some evidence suggesting that malnutrition may underlie the pathophysiology of bone loss in these patients.

Body composition assessment which provides detailed information on body compartments that is not confounded by fluid retention is essential to understanding the extent of compositional derangement that occurs in the cirrhotic patient.

Abbreviations

BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BMC	Bone mineral content

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_134,

BMD	Body mineral density
DXA	Dual-energy X-ray absorptiometry
ECW	Extracellular water
FFM	Fat free mass
IVNAA	In vivo neutron activation analysis
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
PI	Protein index
TBK	Total body potassium
TBP	Total body protein
TBW	Total body water
TSF	Triceps skinfold thickness

134.1 Introduction

The liver is the central organ of intermediary metabolism and has a major role in the metabolism of protein, carbohydrate, and fat. Nutrients absorbed from the digestive tract are transported directly to the liver via the portal circulation. Nutrient blood levels are maintained within narrow limits by the liver despite wide variation in substrate availability. Not surprisingly, injury to the liver may lead to profound derangements in macro- and micronutrient metabolism with subsequent effects on body composition.

Liver cirrhosis is characterized by a progressive reduction in liver cell mass and function, as well as distortion of normal architecture that interferes with normal portal blood flow. Loss of synthetic and metabolic function leads to derangements in blood clotting, depletion of essential proteins, such as albumin, and a wide range of metabolic abnormalities. Portal hypertension contributes to ascites and the portal-systemic shunting results in variceal formation and predisposes to hepatic encephalopathy. The hemodynamic changes that accompany cirrhosis include increased splanchnic blood flow, reduced peripheral vascular resistance, and reduced renal blood flow. These changes, together with reduced plasma oncotic pressure due to hypoalbuminemia, result in impaired water excretion and sodium retention, and contribute to ascites and peripheral edema. Cirrhosis of all causes predisposes to the development of hepatocellular carcinoma, which is the fifth leading cause of cancer death worldwide and responsible for nearly half of all deaths related to cirrhosis. Key features of cirrhosis are summarized in Table 134.1.

The most common causes of liver cirrhosis in USA and Europe are related to alcohol and infection with hepatitis C. Hepatitis B is the predominant cause of cirrhosis in the Asia-Pacific and sub-Saharan Africa. Non-alcoholic steatohepatitis is becoming increasingly important in affluent societies. There are a wide variety of other causes of cirrhosis, including inherited diseases (e.g., alpha-1 antitrypsin deficiency, hemochromatosis, and Wilson's disease), autoimmune hepatitis, and cholestatic liver diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis.

The Child-Pugh scoring system, based on serum bilirubin, serum albumin, prothrombin activity, and presence and severity of ascites and encephalopathy, is the most commonly used classification for severity of liver disease. Based on an aggregate score, patients are categorized as grades A, B, or C (Pugh et al. 1973). The probability of 5-year survival without transplantation for a Child A patient is approximately 80–90% compared with 20–30% for Child C cirrhosis.

The patient with advanced cirrhosis typically has a large distended abdomen due to ascites, muscle wasting of the extremities, and dependent edema. Tissue wasting is obvious and multiple factors may

Table 134.1 Key features of cirrhosis

1.	Liver cirrhosis is scarring of the liver with distortion of the normal architecture and progressive loss of function as the disease advances.
2.	There are many causes of cirrhosis, but the most common are chronic viral infections, alcohol, and conditions that prevent normal excretion of bile (cholestatic liver disease).
3.	Depending on the underlying cause, further deterioration can sometimes be prevented by appropriate treatment.
4.	Cirrhosis can be diagnosed by a combination of blood tests and radiological findings, or a liver biopsy.
5.	Cirrhosis is often asymptomatic in the early stages.
6.	Cirrhosis results in portal hypertension and formation of abnormal vessels (varices), which can rupture and bleed into the gut.
7.	Loss of protein synthetic function results in impaired blood clotting and low levels of albumin in the blood.
8.	Loss of metabolic function causes jaundice and other metabolic derangements.
9.	In the later stages, fluid accumulates in the abdomen (ascites) and legs (edema).
10.	Secondary effects on the kidney (hepatorenal syndrome) and brain (hepatic encephalopathy) commonly occur in end-stage cirrhosis.
11.	Cirrhosis is associated with a very high incidence of primary liver cancer.
12.	Liver transplantation is the only effective treatment for end-stage cirrhosis.

This table lists key facts relating to cirrhosis, including the effects on other organ systems and the symptoms that may be evident

contribute to the malnutrition, including anorexia with reduced calorie and nutrient intake, maldigestion, and malabsorption. Weight loss, often used to identify the malnourished patient, may be masked by water retention. Similarly, a simple two-compartment body composition model comprising fat and fat-free mass (FFM) does not provide information on muscle or lean tissue wasting in these patients and more detailed body compartmentalization is required (Morgan et al. 2006).

134.2 Body Protein

Protein is a vital structural and functional component of the body, and loss of body protein is associated with loss of function (Windsor and Hill 1988a, b). The 'gold standard' for measurement of this component is in vivo neutron activation analysis. In this technique, the subject is irradiated in a neutron field and characteristic gamma rays are emitted as a result of neutron interactions with nitrogen nuclei. By counting these gamma emissions and with appropriate calibration of the machine, total body nitrogen is determined, which is then converted to protein given that nitrogen is almost exclusively confined to protein in the body at a mean level of 16%. Total body protein (TBP) has been measured using this technique in patients with alcohol-related cirrhosis (Prijatmoko et al. 1993) and in patients with cirrhosis due to a wide range of causes (Peng et al. 2007). In the latter study, 268 patients with cirrhosis due to hepatitis B (n = 77), hepatitis C (n = 71), hepatitis B and C (n = 2), alcohol (n = 43), cholestatic liver disease (n = 28) and a variety of other causes (n = 47) were measured and the distribution of TBP is shown in Fig. 134.1 for the men and women, separately. These distributions are shifted downward in comparison to those for healthy volunteers.

TBP may be expressed as a protein index (PI) equal to the ratio of measured TBP to that predicted from regression equations developed from the healthy volunteers based on sex, age, height and weight (Peng et al. 2007). In these equations, a patient-recalled pre-illness weight was used. As shown in Fig. 134.2, PI for the patients was distributed around a mean of 0.82 (SD 0.11), suggesting an average depletion of protein stores of 18%. This mean is close to the 5th percentile of the distribution of PI for the volunteers (centered at 1.00 with SD 0.09) and patients with a PI < 0.82 can be regarded as being significantly malnourished. Of the 268 patients, significant protein depletion was

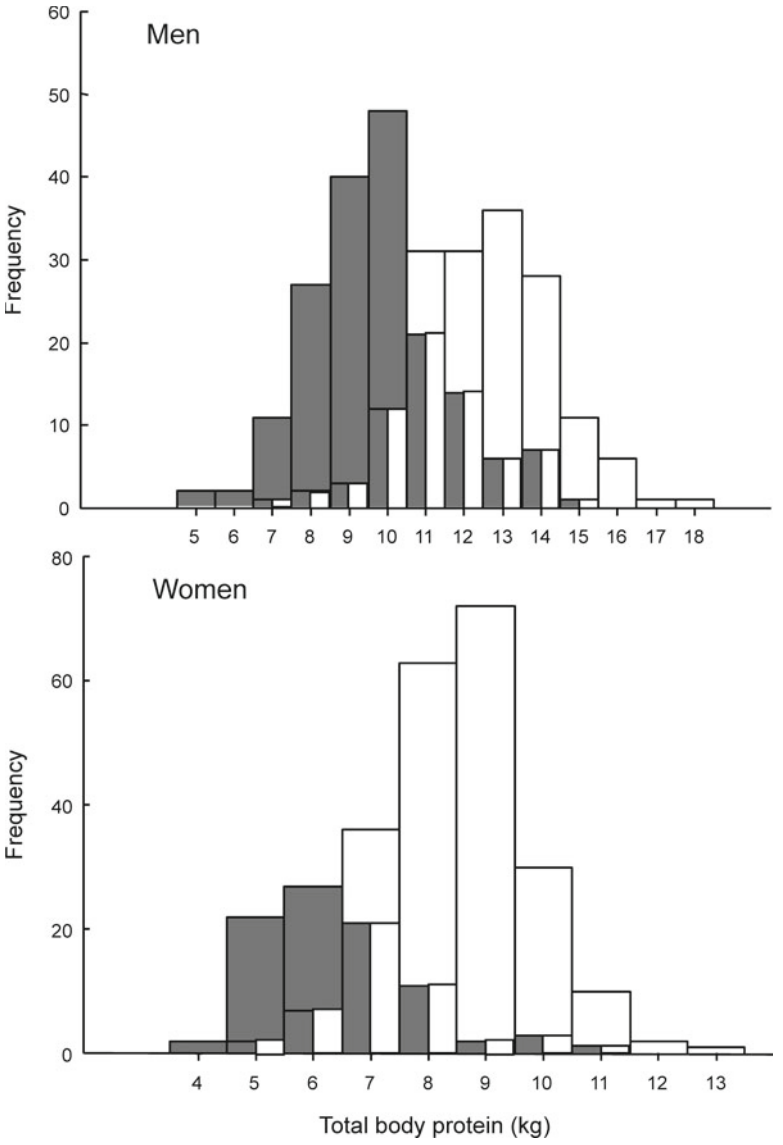

Fig. 134.1 Distributions of total body protein for men and women with liver cirrhosis compared to those for healthy volunteers. Distributions of total body protein for 179 men and 89 women with liver cirrhosis (*shaded bars*) are shifted downward in comparison with those for 163 male and 223 female healthy volunteers (*open bars*) (From Peng et al. (2007). The American Society for Nutrition)

seen in 138 (51%) patients and these were predominantly men, with 113 (63%) men being protein depleted compared to 25 (28%) women ($P < 0.0001$).

Patients with alcoholic liver disease were significantly more protein depleted than patients with viral cirrhosis, cholestatic disease, and others ($P < 0.0001$, Fig. 134.3). The prevalence of protein depletion increased with disease severity, as defined by Child-Pugh grade (Fig. 134.4). Protein depletion was observed in just over 40% of patients with Child A cirrhosis compared with 72% of patients with Child C cirrhosis. Irrespective of disease severity or etiology, protein stores in women were better conserved than in men.

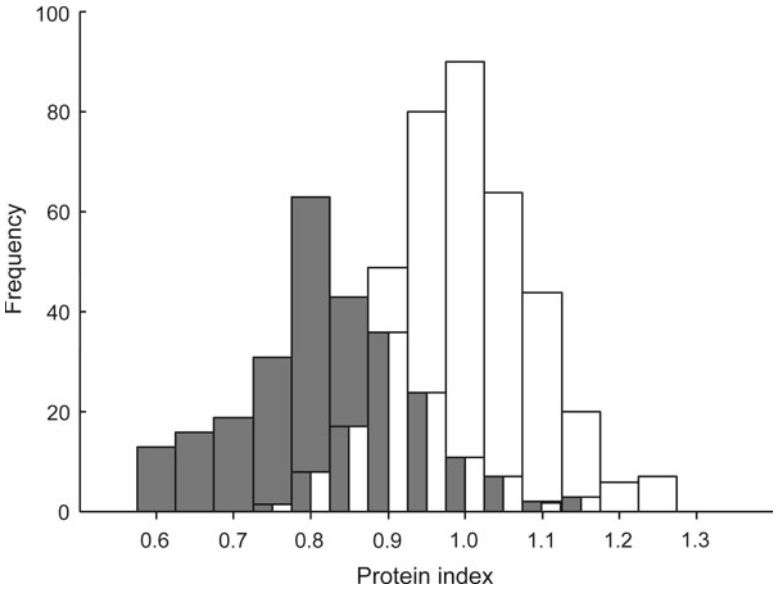

Fig. 134.2 Distributions of the ratio of measured to estimated pre-illness total body protein (protein index) in cirrhosis patients and healthy volunteers. Comparison of the distribution of protein index for 268 patients with liver cirrhosis (*shaded bars*) to that for 386 healthy volunteers (*open bars*) shows the marked depletion of body protein in the cirrhotic patients, which is close to 20% on average (From Peng et al. (2007). The American Society for Nutrition)

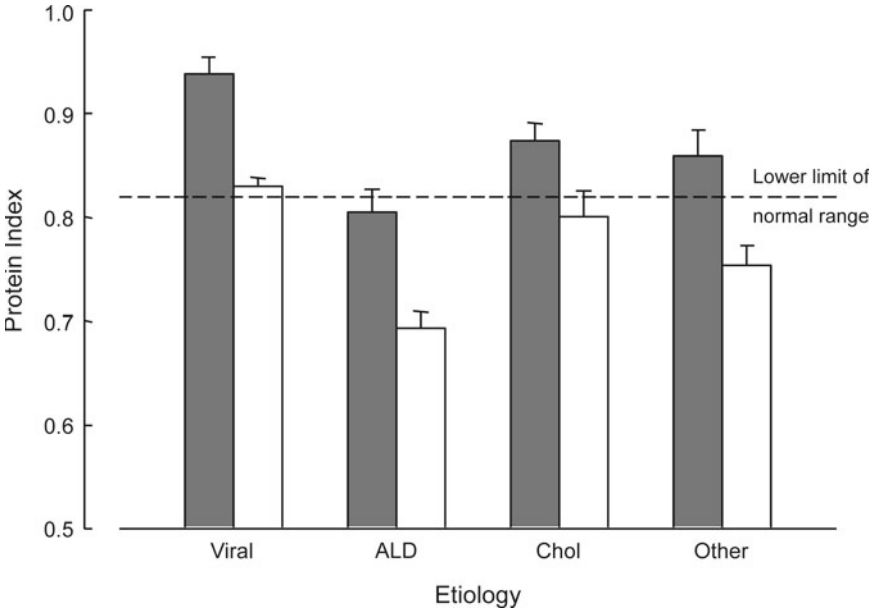

Fig. 134.3 Protein index in men and women with liver cirrhosis grouped according to etiology. Protein depletion, as assessed by protein index (ratio of measured to estimated pre-illness total body protein), for 179 men (*open bars*) and 89 women (*shaded bars*) with liver cirrhosis varies with etiology (*ALD* alcoholic liver disease, *Chol* cholestatic liver disease). By two-factor ANOVA: $P = 0.87$ for etiology × sex interaction, $P < 0.0001$ for etiology effect, and $P < 0.0001$ for sex effect. The dashed line shows the lower 2SD limit of protein index for healthy controls. Results are expressed as mean (± SEM) (From Peng et al. (2007). The American Society for Nutrition)

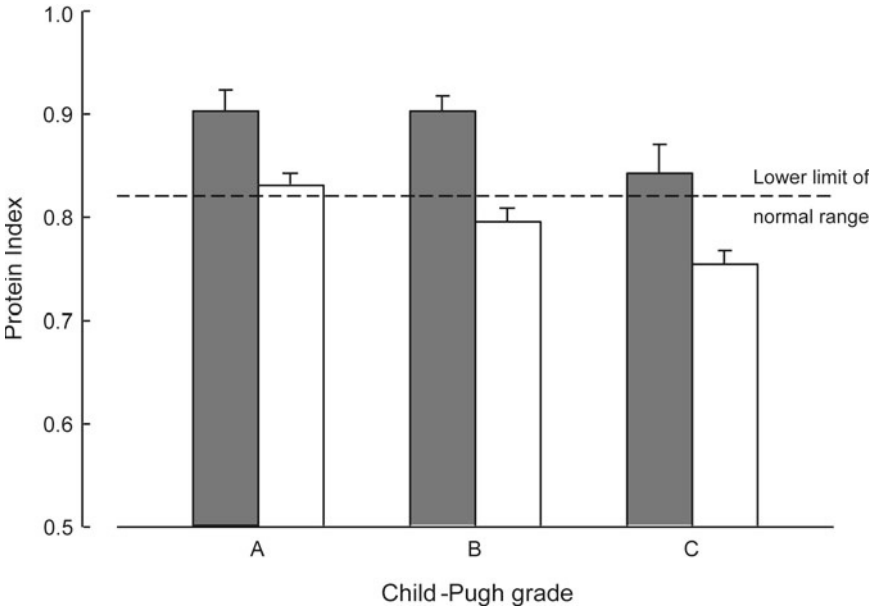

Fig. 134.4 Protein index in men and women with liver cirrhosis grouped according to severity of liver disease. Protein depletion, as assessed by protein index (ratio of measured to estimated pre-illness total body protein), for 179 men (*open bars*) and 89 women (*shaded bars*) with liver cirrhosis increases with worsening severity of liver disease, as assessed by Child-Pugh grade. By two-factor ANOVA: $P = 0.49$ for grade × sex interaction, $P = 0.003$ for grade effect, $P < 0.0001$ for sex effect. The dashed line shows the lower 2SD limit of protein index for healthy controls. Results are expressed as mean (± SEM) (From Peng et al. (2007). The American Society for Nutrition)

A widely used approach for assessing protein depletion and malnutrition in cirrhosis uses measurements of mid-arm circumference (MAC) and triceps skinfold thickness (TSF) to derive estimates of mid-arm muscle circumference (MAMC) using the relation TSF – πMAC. Severe muscle mass depletion is defined as MAMC below the 5th percentile of reference normal data based on age and sex (e.g., Frisancho 1981) and moderate depletion as MAMC below the 10th percentile. This anthropometric technique requires experienced operators and relies on the assumption that the upper arm is relatively unaffected by the water retention that often accompanies cirrhosis (Italian Multicentre Cooperative Project 1994). Alberino et al. (2001) showed in consecutive hospitalized cirrhotic patients (143 male, 69 female) that severe muscle depletion worsened with disease severity and that the prevalence of muscle mass depletion was higher in males than females (Fig. 134.5). Patients with upper-extremity edema were excluded from this study. Others have also found that muscle-mass depletion, identified by reduction in mid-arm muscle area, was more evident in males than females (Italian Multicentre Cooperative Project 1994).

Progressive loss of muscle stores with worsening disease may be due, at least in part, to abnormal fuel metabolism in the cirrhotic patient. After overnight fasting, cirrhotic patients exhibit increased rates of fat oxidation and gluconeogenesis and reduced rates of glucose utilization and glycogenolysis compared to normal controls (Owen et al. 1981). This metabolic profile, similar to that seen in healthy volunteers after 2–3 days' starvation, is consistent with reduced glycogen storage capacity of the cirrhotic liver. A longitudinal 12-month study showed that TBP status of cirrhotic patients could be significantly improved by nighttime nutritional supplementation (Plank et al. 2008). Protein stores were maintained in those patients randomized to daytime supplementation (Fig. 134.6).

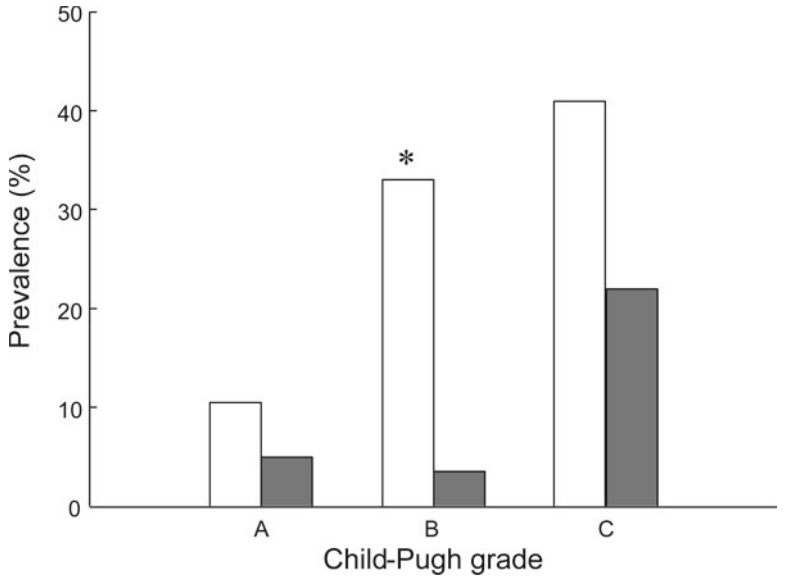

Fig. 134.5 Prevalence of severe muscle depletion assessed by mid-arm muscle circumference in male and female cirrhotics grouped according to severity of liver disease as assessed by Child-Pugh grade. Severe muscle depletion (mid-arm muscle circumference < 5th percentile) tended to be more prevalent in male (*open bars*, $n = 143$) patients with cirrhosis than female (*shaded bars*, $n = 69$) patients, irrespective of disease severity. *$P < 0.001$ versus females (Adapted from Alberino et al. (2001). By permission of Elsevier Science)

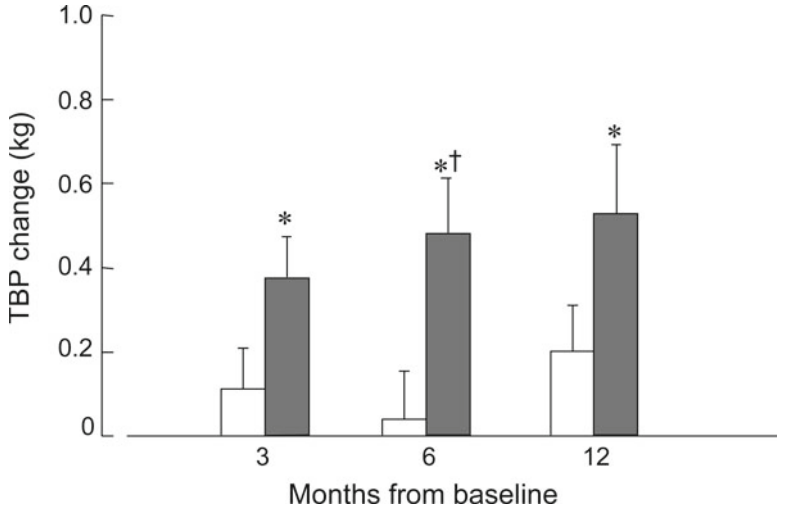

Fig. 134.6 Total body protein changes in patients having daytime or night-time nutritional supplementation over a 1-year period. Significant gains in total body protein (TBP) were seen after three ($n = 42$), six ($n = 40$) and 12 ($n = 39$) months of nighttime nutritional supplementation in cirrhotic patients (*shaded bars*). Patients randomized to daytime nutritional supplementation (*open bars*) showed no change in TBP stores at three ($n = 40$), six ($n = 35$) and 12 ($n = 30$) months. *$P < 0.003$ versus zero change. †$P = 0.02$ for comparison of groups. Results are expressed as mean (± SEM) (From Plank et al. (2008). By permission of John Wiley & Sons)

134.3 Body Fat

Depletion of body fat stores accompanies the malnutrition characteristic of cirrhotic patients and may be caused by the increased reliance on lipids as a fuel source, coupled with poor nutritional intake and intestinal fat malabsorption (Matos et al. 2002). The traditional approach to body-fat estimation is underwater weighing. This technique is impractical in patient populations and an alternative approach, air-displacement plethysmography using the Bod Pod® (Life Measurement Instruments, Inc., Concord, CA), may find application in cirrhosis in the future. Many body-composition centers now have access to whole-body dual-energy X-ray absorptiometry (DXA) to partition body tissue into fat, non-fat soft tissue and bone mineral compartments. For accurate partitioning, a fundamental assumption of this approach is that the soft tissue is normally hydrated. However, in practice, any differences in measured composition that can be ascribed to fluid changes are likely to be relatively minor (Pietrobelli et al. 1998). Total fat mass measurements by DXA before and after paracentesis of ascites in cirrhotic patients were not different (Haderslev et al. 1999). Good agreement between body fat measured by DXA and a multicompartment model was shown by Strauss et al. (2000) in 198 adult cirrhotic patients. In this four-compartment model, body fat was derived as the difference between body weight and the sum of total body protein measured by IVNAA, total body water (TBW) measured by deuterium dilution and bone mineral content (BMC) measured by DXA. Such multicompartment models can be considered the gold standard for fat-mass estimation.

Fat-mass depletion has most commonly been assessed in cirrhosis using triceps skinfold thickness or upper-arm fat area and comparing these measurements with established normal data (e.g., Frisancho 1981). Alberino et al. (2001) found that the prevalence of severe fat depletion, defined as TSF below the 5th percentile of the reference norms, tended to increase with severity of the liver disease and was markedly lower in males than in females (Fig. 134.7). A similar sex difference was seen by Riggio et al. (1997), where DXA measurements of percent body fat in age-, sex-, and BMI-matched controls were compared to those from cirrhotic patients with no ascites or detectable edema.

Bioelectrical impedance analysis (BIA) is an easily applied, non-invasive and inexpensive technique that is widely used in studies of healthy individuals. In the study by Strauss et al. (2000), both single-frequency impedance analysis and multifrequency impedance spectroscopy estimates of fat mass, based on equations developed in healthy populations, were compared to measurements using DXA. Both impedance techniques substantially overestimated fat mass and the 2SD limits of agreement were wide. Such discrepancy is not surprising, given that BIA measurements most closely reflect body water and, in patients with abnormal and widely varying fluid status, estimation of fat-free mass or fat mass is problematic. No equations relating BIA resistance and reactance values to fat mass have been developed in a cirrhotic population.

134.4 Body Water

Measurements of TBW in healthy adults are widely used to estimate FFM, based on the constancy of the ratio of TBW to FFM observed not only in human adults but also across a wide range of mammalian species (Schoeller 2005). The generally accepted value for this ratio is 0.73 (Pace and Rathbun 1945). An increase in this ratio accompanies most illnesses. In these conditions, TBW does not provide an accurate estimate of FFM and the ratio itself provides an important indicator of the extent of overhydration. The dilution principle that the amount of a tracer injected into an unknown volume is

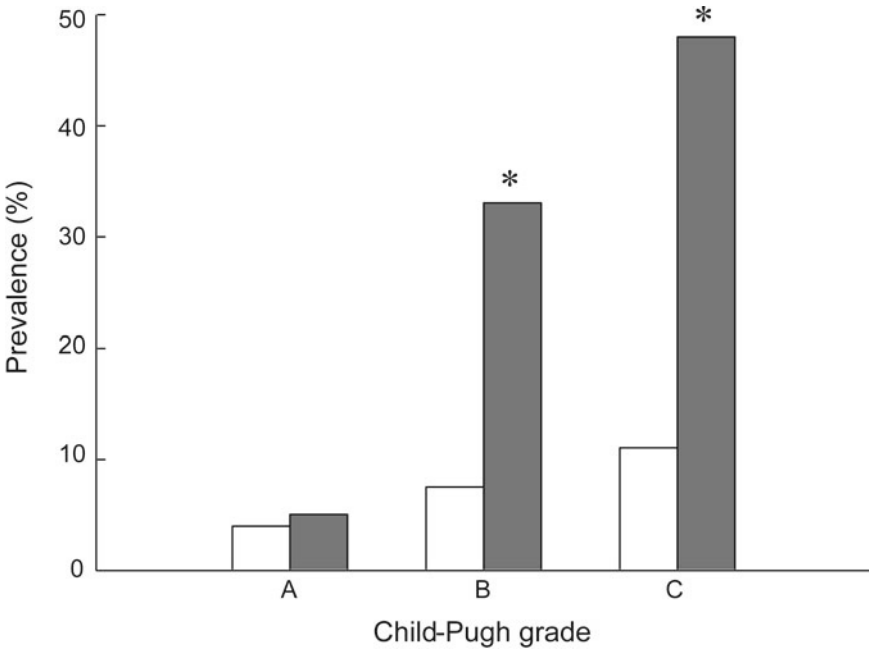

Fig. 134.7 Prevalence of severe fat depletion assessed by triceps skinfold thickness in male and female cirrhotics grouped according to severity of liver disease as assessed by Child-Pugh grade. Severe fat depletion (triceps skinfold thickness < 5th percentile) was more prevalent in female (*shaded bars*, $n = 69$) patients with Child's B and C cirrhosis than in their male counterparts (*open bars*, $n = 143$). *$P < 0.001$ versus males (Adapted from Alberino et al. (2001). By permission of Elsevier Science)

the same both before and after thorough mixing in that volume underlies the classical approach to estimating TBW. Deuterium or tritium, as deuterated or tritiated water, is commonly used as a tracer. Tracer equilibration is generally complete within 2.5–3 h in healthy individuals. In cirrhotic patients where water retention often manifests as ascites, there is some lack of agreement in the literature regarding the required equilibration time with at least 4–5 h suggested by the oxygen-18 data of McCullough et al. (1991), whereas Zillikens et al. (1992a) found 2.5 h was adequate using deuterated water.

Peng et al. (2007) derived TBW based on a six-compartment model for the body. In this approach, TBW equals the difference between body weight and the sum of TBP, measured by IVNAA, total body fat and BMC, measured by DXA, non-bone minerals, and glycogen. The small non-bone mineral and glycogen compartments (typically summing to less than 1 kg) are estimated from TBP and total minerals, respectively, based on the sizes of these compartments in the Reference Man (Snyder et al. 1975). Significant over-hydration was defined as a TBW to FFM ratio >0.76, which represented two standard deviations above the mean (0.73) for the distribution of this variable in a large group of healthy volunteers. Peng et al. (2007) showed that the prevalence of overhydration increased with severity of disease. In compensated cirrhosis, 45% and 73% of Child's A and B patients, respectively, were overhydrated, compared with 80% of Child's C patients. The percent hydration of the FFM is shown in Fig. 134.8, as a function of disease severity. A similar pattern was seen in men with alcohol-related cirrhosis, where TBW was estimated by deuterium dilution and FFM by a multicompartment model (Prijatmoko et al. 1993). In that study, hydration of the FFM was 77.7% in the 17 Child's A patients and 82.6% in the six Child's C patients. It is noteworthy that overhydration, as determined by the TBW:FFM ratio, was seen in patients who show no clinical evidence of fluid retention (Morgan et al. 2006).

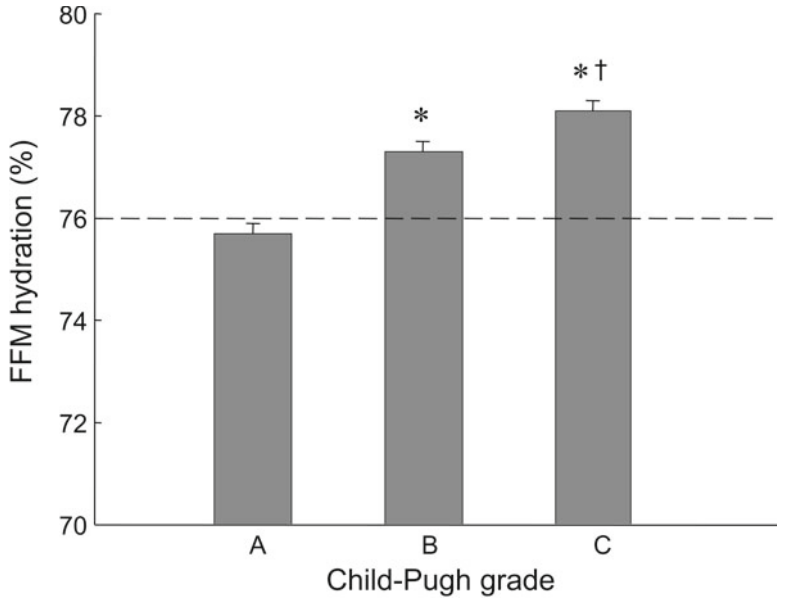

Fig. 134.8 Fat-free mass hydration in patients grouped according to severity of liver disease. Percent hydration of the fat-free mass (FFM) measured in 268 patients with liver cirrhosis increased with severity of liver disease, as assessed by Child-Pugh grade. The *dashed line* shows the upper 2SD limit of hydration for healthy controls. *$P < 0.0001$ versus Child's A; †$P < 0.017$ versus Child's B. Results are expressed as mean (± SEM) (Data from Peng et al. 2007)

The BIA technique, by virtue of its portability and ability to provide immediate results, offers potential for routine clinical use. McCullough et al. (1991) compared single-frequency BIA estimates of TBW with those from dilution of oxygen-18 labeled water in cirrhotic patients with and without ascites. Although a small study, it was clear that, in the latter group, the BIA results were unsatisfactory, with a poor correlation between the two methods (r = 0.17). In patients without ascites, an excellent correlation was seen (r = 0.98). In addition, the BIA technique measured a mean change of only 2.1 L in TBW before and after paracentesis, averaging 6.9 L in the patients with ascites. This inability to detect fluid changes in the trunk area, found also by others (Guglielmi et al. 1991; Zillikens et al. 1992b), is a reflection of the very small contribution to the overall body resistance contributed by truncal tissue. In healthy individuals, application of multifrequency BIA allows the partitioning of TBW into extra- and intracellular compartments. In cirrhotic patients without ascites, impedance measurements at three frequencies were shown to provide reliable estimates of TBW and extracellular water, as determined by deuterium and bromide dilution, respectively (Borghi et al. 1996). Bioimpedance spectroscopy applied to a group of cirrhotics, some with ascites, yielded wide limits of agreement for TBW and extracellular water when compared with the deuterium and bromide estimates, especially when ascitic patients were included, such that routine use for individual patients is questionable (Lehnert et al. 2001).

134.5 Body Cell Mass

The body cell mass (BCM), the cellular compartment of the fat-free mass, was originally conceptualized by Moore et al. (1963) as "the working, energy-metabolizing portion of the human body in relationship to its supporting structures" and is generally assessed most directly by measurement of

total body potassium (TBK). Given that TBK is almost wholly (>98%) intracellular (Forbes et al. 1962), changes in this quantity will reflect changes in cellular mass unless intracellular potassium concentration is reduced. A number of studies in cirrhotic patients indicate that TBK loss is due to depletion of BCM and not to changes in intracellular concentration (Mas et al. 1981; Vitale et al. 1985). Although not widely available, whole-body counters designed to measure the natural radioactivity of the body from ^{40}K are most commonly used to estimate TBK. Selberg et al. (1999) showed, in 225 cirrhotics covering a wide range of etiologies and severity of disease, a profound loss of TBK when compared with healthy controls and with normal predicted values, based on age and height. This observation is consistent with loss of muscle tissue and, therefore, body protein, in these patients. Although not statistically significant, TBK trended downward with Child-Pugh grade. Diuretic therapy had no noticeable effect on TBK loss.

134.6 Bone Mineral

DXA provides a non-invasive measurement of BMC, the inorganic calcified content of bone, and bone mineral density (BMD), an areal density calculated by dividing BMC by the projected area of the skeleton. Riggio et al. (1997) showed in both male and female cirrhotics of mixed etiology, a significant reduction in these measures in comparison with age-, sex-, and BMI-matched controls. In the much larger study from Peng et al. (2007), BMD divided by height, which provides a measure of volumetric density that is independent of frame size, was similarly significantly lower than that in healthy controls, for both males and females. In that study, BMD or BMD/height did not differ significantly between Child-Pugh or between etiological groups. BMD/height tended to be lower, however, in patients with significant protein depletion than in those without ($P = 0.05$). In patients with alcoholic cirrhosis, reduction in BMC and BMD was shown also to be more closely related to malnutrition than the liver disease per se (Santolaria et al. 2000).

Sex-adjusted values of BMD measured at sites, such as the lumbar spine or femoral neck that have been referenced to peak bone mass in the normal population (so-called T-scores), indicate high prevalences of osteopenia (*T*-scores between -1 and -2.5) and osteoporosis (*T*-scores < -2.5) in cirrhotic patients. In a group of cirrhotics of diverse etiology, osteopenia was present in almost 40%, and osteoporosis in 20% of women and 30% of men (Crawford et al. 2003). Not dissimilar results were seen in patients with cirrhosis due to hepatitis C or alcohol measured before liver transplantation (Carey et al. 2003).

134.7 Applications to Other Areas of Health and Disease

Detailed body composition analysis that involves assessment of the principal compartments of the body is essential to understanding the type and magnitude of the derangements that occur in a number of disease states. Most particularly, these include conditions where large shifts in fluid and fluid distribution may occur. Patients who are critically ill due to serious sepsis or major traumatic injury fall into this category. Other patient groups where abnormal fluid status is present include those with end-stage renal disease, heart failure, and those in the early postoperative phase after a major surgical operation. In all these patient groups, depletion of muscle, and hence protein, stores occurs to a greater or lesser extent.

Compartmental analysis that provides measures, such as total body protein or total body potassium, has application in investigations of energy metabolism. For example, such analysis provides

an appropriate means of assessing hypermetabolism in patients where fluid excess may be present. Accurate compartmental analysis may also provide measures with application for prediction of survival, particularly in chronic catabolic conditions, where, for instance, disease progression is associated with increasing muscle loss.

Summary Points

- Body composition of patients with cirrhosis is markedly deranged.
- Full understanding of these derangements requires compartmental assessment of the body that is not confounded by fluid retention.
- Malnutrition, recognized by significant reduction in protein stores, is highly prevalent in cirrhotic patients.
- Regardless of etiology, body protein depletion, and, hence, malnutrition, increases in prevalence with the severity of underlying liver disease.
- Males are more protein depleted than females, whereas the reverse is true for fat depletion.
- An expanded total body water space is a characteristic of the cirrhotic patient.
- Higher than normal total body water as a fraction of the fat-free mass occurs even in patients with no clinical evidence of fluid retention.
- Depletion of the cellular mass of the body, as assessed by total body potassium measurement, seen in these patients provides further evidence of muscle loss.
- Loss of bone mineral and bone mineral density is seen in a significant proportion of cirrhotic patients and these losses appear to be associated with malnutrition.

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Chapter 135
Liver Damage Severity Evaluated by Liver Function Tests and the Nutritional Status Estimated by Anthropometric Indicators

Alfredo Larrosa-Haro, Erika F. Hurtado-López, Rocío Macías-Rosales, and Edgar M. Vásquez-Garibay

Abstract Pediatric patients with chronic liver disease (CLD) may present impaired growth and acute malnutrition. In most pediatric series the prevalence of these nutritional-related conditions is high. Secondary malnutrition mechanisms include low caloric intake, malabsorption of lipids and fat soluble vitamins and increased energy expenditure. In children younger than 5 years, the degree of liver damage is closely related to growth impairment and their current nutritional status; both may be predicted by liver function tests such as direct bilirubin, albumin and gamma-glutamyl transpeptidase.

Anthropometry has been widely used to evaluate the nutritional status of children with CLD. In infants and toddlers, growth can be properly assessed by measuring head circumference and length; in older children growth may be evaluated by height. When ascitis and/or hepatosplenomegaly are present, weight for height might underestimate the current nutritional status. Arm anthropometrics could become an alternative tool in identifying malnutrition since it estimates muscle mass or fat stores; recent observations of DXA in infants with CLD have shown a good correlation between body compartments and arm anthropometric indicators.

In addition to its prognostic value, the crucial reason for anthropometrically evaluating a patient with CLD is to recommend nutritional intervention which will improve growth and current nutritional status or at least avoid its deterioration.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_135,

Abbreviations

CLD	Chronic liver disease
DRI	Daily recommended intake
DXA	Double X-ray absorptiometry
MUAC	Medium upper arm circumference
OR	Odds ratio
PELD	Pediatric end-stage liver disease
SD	Standard deviation

135.1 Introduction

Infants and children with chronic liver disease (CLD) may present impaired growth, protein–energy malnutrition, fat-soluble vitamin deficiencies, and diminished bone mineralization (Ramaccioni et al. 2000; Stephenson et al. 2001; Heubi et al. 2002). These nutritional-associated disorders are thought to be secondary to the interaction of factors, such as reduced caloric intake, lipid- and fat-soluble vitamin malabsorption, increased energy expenditure, altered intermediate metabolism, hormonal dysregulation, and chronic anemia related to hypersplenism and portal hypertension (Shepherd et al. 1991; Madden and Morgan 1999; Roggero et al. 1997).

Anthropometrics has been used as a tool to assess the nutritional status of children with CLD (Sokol and Stall 1990; Wasserman et al. 1999; McDiarmid et al. 2002). Although the anthropometrical indicators based on weight (weight for height, weight for age, and body mass index) have been extensively used in pediatric patients with liver disease, they may not accurately assess the current nutritional status due to liver and spleen enlargement and particularly to ascitis and peripheral fluid retention (Hurtado-López et al. 2007). Arm anthropometrical indicators could well become an alternative tool in the nutritional evaluation of children with CLD. Arm composition is not altered as much as weight when fluid retention occurs (Hurtado-López et al. 2007; de Onis and Habicht 1996; Macías-Rosales et al. 2004), and is probably not modified at all by ascitis and liver and/or spleen enlargement.

The association between the degree of liver damage and the nutritional status in pediatric patients with end-stage liver disease has been reported in multivariate analysis studies (McDiarmid et al. 2002; Hurtado-López et al. 2007). Hurtado et al. demonstrated that liver damage severity evaluated by liver function tests could predict the nutritional status measured by anthropometrical indicators (Hurtado-López et al. 2007).

The aims of this chapter are: (a) to discuss the value of nutritional status assessment by anthropometric indicators in pediatric patients with CLD; (b) to present some novel data describing liver function tests that indicate liver damage severity and its correlation with anthropometrical nutritional status indicators; and (c) to underline the clinical implications of an accurate nutritional diagnosis in infants and children with CLD.

135.2 Prevalence of Growth Impairment and Malnutrition in Children with CLD

The association between growth impairment and malnutrition in children with CLD has been described over the last two decades. Cywes et al. reported diminished speed growth velocity and vitamin and other micronutrient deficiencies in infants and children with biliary atresia (Cywes and

Table 135.1 Frequencies and percentages of height for age, weight for height, and medium upper-arm circumference (MUAC) for age < −2SD in 79 pediatric patients with chronic liver disease. The patients were distributed by pediatric age groups. Percentages were calculated from total sample

	1–23 months		24–71 months		72–143 months		144–172 months		Total	
Anthropometrical indicators	*n*	(%)	*n*	%	*n*	%	*n*	%	*n*	%
Height for age < −2SD	13	(16.4)	13	(16.4)	4	(5.1)	5	(6.3)	35	(44.3)
Weight for height < −2SD	5	(6.3)	3	(3.8)	1	(1.3)	0	–	9	(11.4)
MUAC for age < −2SD	15	(19.0)	15	(19.9)	0	–	4		34	(43.0)
MUAC for height < −2SD	8	(10.1)	5	(6.3)	0	–	2	(2.5)	15	(19.0)

Millar 1990). Shepherd et al. demonstrated progressive nutritional deterioration in a group of 37 pediatric patients waiting for liver transplants; the nutritional indicators were low-speed growth velocity and loss of cell mass measured by total body potassium (Shepherd et al. 1991).

The nutritional status of pediatric patients with CLD has been anthropometrically evaluated by several authors. The anthropometrical indicators used in most studies have been height for age and weight for height; however, some authors have also reported their experience with arm indicators (Sokol and Stall 1990; Wasserman et al. 1999; Chin et al. 1992; Charlton et al. 1992; Vegnente et al. 1992). The general consensus of these studies is that the proportion of growth impairment and malnutrition in infants and children with CLD is undoubtedly high.

In a study by Hurtado et al. at a pediatric referral hospital's Liver Clinic, growth impairment (height for age < −2SD) was identified in 44.3% out of 79 pediatric patients with CLD (Hurtado-López et al. 2007). In the same sample, acute malnutrition (weight for height < −2SD) was identified in 11.4% of the cases. In identifying cases with *z*-score < −2SD, medium upper arm circumference (MUAC) for age increased 32 percentage points compared to weight for height; however, when MUAC was adjusted for height, this difference persisted by almost 8 percentage points (Hurtado-López et al. 2007). This disparity between the proportion of malnutrition identified by MUAC and weight for height – the most used acute malnutrition indicator – was associated with the ascitis incidence present in 20% of the cases studied. In the ascitis subgroup ($n = 19$), cases identified with < −2SD when MUAC was 75%, whereas weight for height demonstrated acute malnutrition in 25% ($p < 0.003$). In this study, in children 5-year-old or younger, growth impairment distribution and malnutrition by age groups showed a higher proportion of cases (Table 135.1). Risk analyses by age groups (infants plus preschoolers vs school age children plus adolescents) showed significant odds ratios with height for age (OR 3.8, CI.3–11.2), MUAC for age (OR 15, CI 3.9–61.8), and MUAC for height (OR 8.3, CI 1.4–64.3). These results clearly showed that children younger than 6 years of age with CLD had an increased risk of acute and chronic malnutrition.

In a cross-sectional study by Larrosa et al. 256 pediatric patients demonstrated that children with CLD had the highest rate of chronic malnutrition (height for age < −2SD, 38.9%) and the second highest rate of protein–energy malnutrition when evaluated with MUAC for age (Larrosa-Haro et al. 2006). Frequencies and percentages of growth impairment and malnutrition distributed by diagnoses are presented in Table 135.2.

135.3 Correlation of Growth and Body Composition Anthropometric Indicators

If height is considered to be the anthropometric axis of growth, then, in normal subjects, it might predict the effect of other growth anthropometric indicators, such as head circumference. However, in CLD pathology, these variables and their interactions are less well known. In a study of 79 pediatric

Table 135.2 Frequencies and percentages of grouped *z*-scores < −2SD of height for age, weight for height and medium upper-arm circumference (MUAC) for age in 256 outpatients or hospitalized pediatric patients seen in the Department of Gastroenterology and Nutrition in a pediatric referral hospital. The data are related to the five more frequent diagnoses. Percentages were calculated from total sample (Hurtado 2005)

	Chronic liver disease		Gastro-esophageal reflux		Persistent diarrhea		Chronic functional constipation		Acute pancreatitis	
Anthropometrical indicators	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Height for age < −2SD	21	(8.2)	7	(2.7)	7	(2.7)	1	(0.4)	0	–
Weight for height < −2SD	9	(3.5)	9	(3.5)	8	(3.1)	2	(0.78)	2	(0.78)
MUAC for age < −2SD	12	(4.7)	11	(4.3)	14	(5.5)	1	(0.4)	3	(1.2)

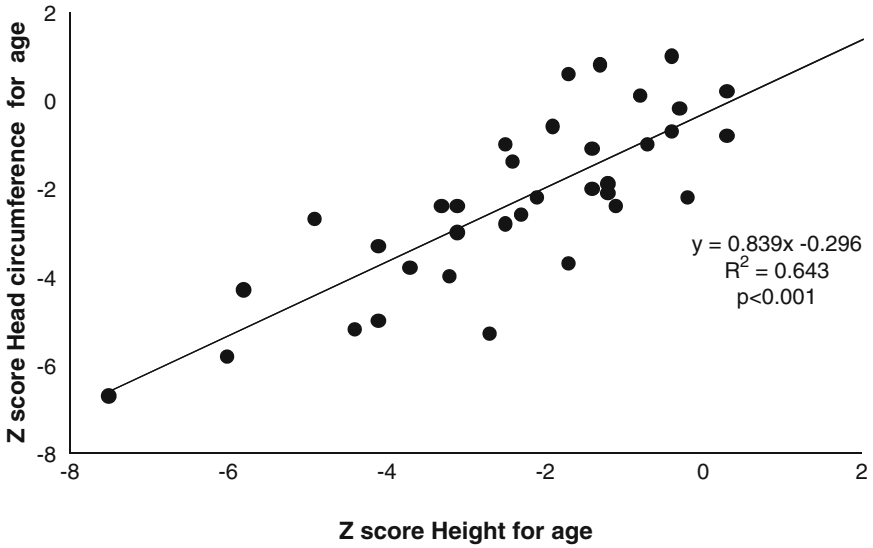

Fig. 135.1 *z*-Scores linear regression of height for age (independent variable) and head circumference for age (dependent variable) in 79 children with chronic liver disease

patients with CLD (Hurtado 2005), height for age *z*-scores showed a strong and highly significant correlation with head circumference *z*-scores (Fig. 135.1); children with lower height for age *z*-scores had lower head circumference *z*-scores. The statistical association involving these two variables in our children with CLD suggests that height and head circumference impairment are closely related. Similar to the implications of early growth retardation in final adult height, the impairment of head circumference size could be related to neurodevelopment delays or other unknown conditions.

The bivariate correlations of height for age *z*-scores with weight for height and arm anthropometrical *z*-scores in a group of children with CLD are presented in Table 135.3. Correlations with weight for height were not statistically significant. However, all arm indicators showed significant correlations with height. It is interesting to point out that the highest R^2 values were for indirect arm indicators, particularly, arm muscle area and total arm area. These anthropometric findings seem to underline the close interaction between growth and body composition, when framed by the complex biological events that take place in children with diseased livers.

Table 135.3 *z*-Scores correlation of height for age and the anthropometric body composition indicators in 79 pediatric patients with chronic liver disease. Triceps skinfold and arm areas were calculated for age (United Network for Organ Sharing)

Anthropometric indicators	*r*	R^2	*p*
Weight for age	0.22	0.05	0.05
MUAC for age	0.046	0.21	0.02
MUAC for height	0.39	0.11	0.02
Triceps skinfold	0.39	0.15	<0.001
Total arm area	0.43	0.19	<0.001
Arm muscle area	0.47	0.22	<0.001
Arm fat area	0.29	0.14	0.009

MUAC Medium upper-arm circumference

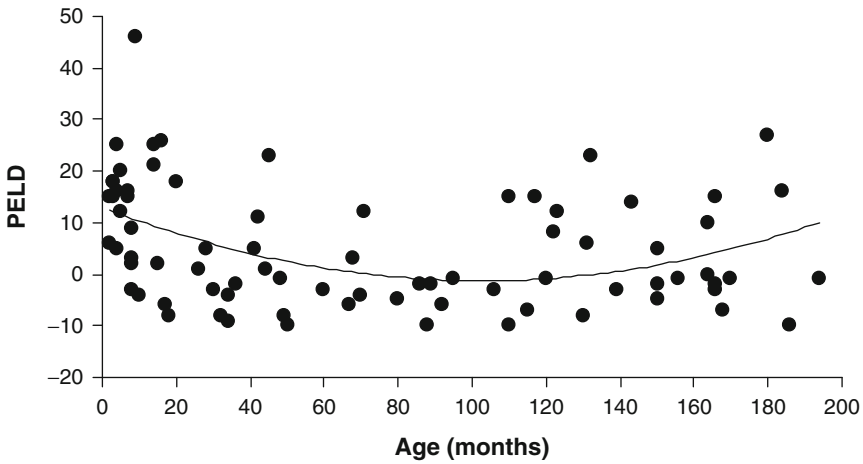

Fig. 135.2 PELD scores correlation age in months in 79 pediatric patients with chronic liver disease (Larrosa-Haro et al. 2006)

135.4 Liver Damage Severity and Nutritional Status

The pediatric end-stage liver disease (PELD) score is a quantitative classification of liver damage (United Network for Organ Sharing); it is currently used in North America to select pediatric patients for liver transplant. This evaluation tool includes three liver function tests (conjugated bilirubin, albumin, and INR), two anthropometric indicators (weight for height and height for age), age, and gender. With higher PELD scores, the probability of gastrointestinal bleeding, liver encephalopathy, admission to a pediatric intensive care unit, and death, is increased. Infants and adolescents are the pediatric CLD age groups with the severest liver damage. Biliary atresia and most metabolic disorders are present early in life and are associated with severe liver damage. In all pediatric age groups with CLD (Fig. 135.2), these disorders account for the highest proportion and severity of acute and chronic malnutrition. Table 135.4 shows the mean values of PELD scores distributed by pediatric age groups in a series of infants and children with CLD. Bivariate correlations of PELD scores with anthropometrical *z*-score indicators are presented in Table 135.5; the highest "*r*" values were observed with direct and indirect arm indicators (Hurtado 2005).

In a recent study by Hurtado et al. several multivariate regression models performed with liver function tests as independent variables and anthropometrical indicators as dependent variables showed that

Table 135.4 PELD scores of 79 pediatric patients with chronic liver disease. Results are reported in means and SD. The patients are distributed by pediatric age groups (Larrosa-Haro et al. 2006)

Age groups	*n*	PEDL score	
		Mean	SD
Infants (1–23 months)	21	15.3	9.7
Preschoolers (24–71 months)	24	4.3	10.6
School-age children (71–143 months)	13	–2.9	5.3
Adolescents (143–198 months)	21	0.24	9.4

Table 135.5 Pediatric End-Stage Liver Disease, bivariate correlation classification with anthropometrical indicators in 79 pediatric patients with chronic liver disease

Anthropometrical indicator	*r*	*p*
Triceps skinfold	–0.602	<0.001
Arm fat area	–0.552	<0.001
Total arm area	–0.503	<0.001
Muscular arm area	–0.497	<0.001
Medium upper-arm circumference	–0.492	<0.001
Weight for age	–0.482	<0.001
Arm fat index	–0.470	<0.001
Height for age	–0.467	<0.001
Weight for height	–0.302	<0.001
Body mass index	–0.271	0.035
Head circumference	–0.291	0.089

Table 135.6 Regression models with liver function tests as independent variables and anthropometrical growth and body composition indicators as dependent variables in 79 pediatric patients with chronic liver disease

Dependent variable Anthropometrical indicator	Independent variable Liver function test	*b*	*β*	*r*	r^2	*p*
Height for age	Conjugated bilirubin	–0.22	–0.65	0.63	0.39	<0.001
		0.08	0.26			
	Prothrombin time	–0.01	–0.21			
	Alanine aminotransferase					
Weight for height	Conjugated bilirubin	–0.10	–0.52	0.46	0.22	<0.001
	Unconjugated bilirubin	–0.17	–0.24			
Mid upper-arm circumference	Conjugated bilirubin	–0.14	–0.39	0.57	0.33	<0.001
	Gamma glutamyltransferase	0.01	–0.35			
Triceps skinfold	Conjugated bilirubin	–0.07	–0.32	0.67	0.45	<0.001
		0.47	0.19			
	Albumin	–0.01	–0.26			
	Gamma glutamyltransferase					
Total arm area	Conjugated bilirubin	–0.13	–0.43	0.57	0.33	<0.001
	Gamma glutamyltransferase	–0.01	–0.33			
Fat arm area	Conjugated bilirubin	–0.09	–0.42	0.61	0.37	<0.001
	Gamma glutamyltransferase	–0.01	–0.25			
Muscle arm area	Conjugated bilirubin	–0.07	0.34	0.59	0.35	<0.001

b Anthropometrical indicators increased value for each added unit of every liver function test. *β Z* score of *b*. *r* correlation coefficient. r^2 determination coefficient

nutritional status may be predicted by biochemical liver damage severity indicators (Hurtado-López et al. 2007). The liver function tests with higher correlations were conjugated bilirubin and albumin; the anthropometrical indicators with the highest R^2 were height and arm indicators (Table 135.6). These interesting findings underline the correlation between liver damage severity and nutritional status and reflect the close relationship of liver function to growth and current nutritional status.

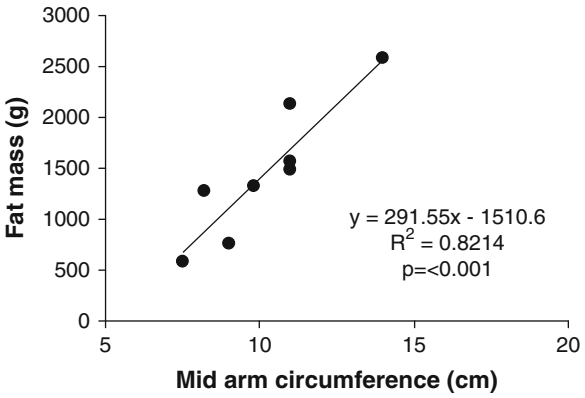

Fig. 135.3 Mid arm circumference (cm) bivariate correlation with fat mass (g) by dual X-ray absorptiometry in eight infants with chronic liver disease ($r = 0$, $R^2 = 0.67$, $p = 0.044$)

135.5 Validation of Arm Anthropometrics

Double X-ray absorptiometry, one of the current gold standard techniques to measure body composition with plausible correlations, has been used to measure fat stores and muscle mass in children in order to validate the anthropometric accuracy (Brambila et al. 2006). However, to our knowledge, there are no corroborating arm anthropometrics studies in infants with CLD. Preliminary results in an ongoing study by the authors of this chapter have shown statistical bivariate correlations of most arm anthropometrical indicators with body composition compartments evaluated by double X-ray absorptiometry (unpublished data, Fig. 135.3).

135.6 Clinical Implications of Secondary Malnutrition

Pediatric patients younger than six year with CLD, particularly those with end-stage liver disease, should be evaluated periodically and frequently. The clinical rationale for this protocol is the overall identification of complications, such as liver encephalopathy, acute or chronic anemia secondary to gastrointestinal bleeding and systemic infections, as well as specific conditions related to the primary disease. Although anthropometric measurements are routinely performed at these evaluations, many times, they are not converted into anthropometrical indicators and, as a result, an adequate nutritional diagnosis is not attained. As already shown in this chapter, anthropometrical indicators might become an accurate way of identifying liver-function deterioration and could become valuable in the global assessment of particular cases.

Clinical trials published in the last two decades have shown the value of nutritional intervention in pediatric patients with CLD (Table 135.7). These studies have demonstrated two facts: (a) in children with CLD, the energy requirements, proteins, and other nutrients are higher than the daily recommended intake; and (b) nutritional intervention with specific nutrients, such as medium-chain triglycerides or branched-chain amino acids, increasing energy and nutrient intake by formula fortification, and/or enteral nutrition with continuous infusion, may improve or at least avoid nutritional status deterioration for weeks or months (Shepherd et al. 1991; Macías-Rosales et al. 2004; Charlton et al. 1992; Moreno 1991; Chin et al. 1990). The final nutritional outcome depends on the evolution of the primary liver disease. On the other hand, nutritional intervention may offer energy stores and specific nutrients that deal with medical complications and special situations, such as a liver transplant. This could modify the final height and the growth of the central nervous system growth along the first 36 months of life.

Table 135.7 Clinical trials related to nutritional intervention in pediatric patients with chronic liver disease

	Reference	Setting	*n*	Design	Intervention	Results
[AU2]	Charlton et al. (1992)	Institute of Child Health, University of Birmingham.	10 Advanced cirrhosis	Open clinical trial	Enteral nutrition	Improvement in weight, height, and arm indicators. No
[AU3]	Chin et al. (1992): 158–63	Royal Children's Hospital, Brisbane, Australia.	19 Liver transplant waiting list	Clinical trial	Enteral nutrition Branch-chain amino acid formula versus standard formula	Weight, height, MUAC, TSF, and body total potassium improvement Less requirements of albumin infusion
	Moreno (1991)	Service de Pédiatrie, Hôpital Huriez, CHU de Lille, France	6	Open clinical trial	Ad libitum PO versus enteral feeding with 180–200% of DRI	Improvement of weight and arm indicator with enteral nutrition
	Shepherd et al. (1991)	Royal Children's Hospital, Brisbane, Queensland, Australia.	37 Liver transplant waiting list	Clinical trial	Liver transplant	Improvement of anthropometrical indices and ad libitum energy intake
	Chin et al. (1990)	Royal Children's Hospital, Brisbane, Australia.	28 Liver transplant waiting list	Clinical trial	Ad libitum PO versus enteral nutrition	Weight and height maintained increase rates in children with enteral nutrition

135.7 Applications to Other Areas of Health and Disease

Anthropometrics is a valuable tool to measure growth and estimate body composition. This technique is sensitive to gender phenotype and changes in body compositions that occur throughout pediatric age groups. In this chapter, we underlined its pros and cons in evaluating growth and nutritional status in pediatric patients with liver disease. Given the specific growth and body composition characteristics of the different kinds of pediatric pathology, anthropometrics should be tested and analyzed in each one of these fields. The new 2006 WHO reference patterns constitute an important advance that permit comparisons of anthropometric data from children measured in different geographic areas. Specific parameters are still needed as reference patterns for arm areas in children younger than 6 years of age.

135.8 Practical Methods and Techniques

135.8.1 Anthropometrical Standardization

Before data are collected, an anthropometrical standardization should be done. Consistency (intra-group individual measurements) and validity (inter-group comparison with a gold standard) may be evaluated with Pearson bivariate correlations; when the value of "*r*" is equal to or below 0.8, the anthropometrical technique should be reviewed and corrected until the desired intra- and inter-group correlations, ideally around 0.9, are obtained (Villasis-Keever et al. 2001).

135.8.2 Weight

Babies are weighed without diapers on a leveled pan scale with a beam and a movable weight, making sure the weight is distributed equally on each side of the pan's center. Weight is recorded to the nearest 5 grams. Children older than 2 years will be weighed with a movable weight platform-beam scale; subjects are measured without shoes and minimum clothing. Weight is recorded to the nearest 100 g (Frisancho 1990).

135.8.3 Length or Height

In children less than 2 years of age, the length is measured and recorded to the nearest 0.1 cm in a recumbent position using an infantometer. An assistant holds the infant's head while the examiner straightens its legs holding the feet with toes pointed up moving the footboard against the feet. In children older than 2 years, height is measured and recorded to the nearest 0.1 cm using a standiometer with a movable block. The subjects are measured while standing, without shoes, heels together, back as straight as possible, and arms hanging freely; the head is positioned in the Frankfort horizontal plane and the movable block is brought down until it touches the head (Frisancho 1990).

135.8.4 Mid-Upper-Arm Circumference (MUAC)

With the right or left arm bent at the elbow at a 90° angle while the upper arm is held parallel to the side of the body, the distance between the acromion and the olecranon is measured with a fiberglass tape and the midpoint between these two spots is marked; the side of the body to be measured may be selected in accordance with the side measured in the selected reference pattern. The baby's arm must hang loosely down the side of its body while relaxed. A fiberglass metric tape is positioned at the marked midpoint and the circumference is recorded to the nearest 0.1 cm (Frisancho 1990). Babies should sit on their mother's laps. Children are measured standing up.

135.8.5 Triceps Skinfold (TSF)

TSF should be measured with a skinfold caliper at the previously marked midpoint of the posterior right upper arm, with the arm extended in the same relaxed position used for MUAC. The examiner grasps a vertical pinch of skin and subcutaneous fat between thumb and forefinger about 1 cm above the previously marked midpoint pulling away gently from the underlying muscle. The skinfold caliper is placed at the marked midpoint while maintaining the skinfold grasp. Readings are taken in millimeter as soon as the caliper comes in contact with the skin and the dial reading has stabilized. Babies should sit on their mother's laps and children are measured standing up (Frisancho 1990).

135.8.6 Total, Muscular, and Arm Fat Areas

Arm areas may be calculated with MUAC and TSF measurements, according to the formulas described by Frishancho (Frisancho 1990); results are expressed in square millimeters.

135.8.7 Reference Patterns, Indices, and Nutritional Status Indicators

For infants, children and adolescents, anthropometrical indicators obtained from height, weight, MUAC, and triceps skinfold may be calculated with the 2006 WHO parameter. However, arm areas reference patterns are lacking the 2006 WHO documents; hence, these may be calculated with other parameters (Frisancho 1990; Sann et al. 1988; WHO Child Growth Standards 2006).

Summary Points

- In infants and children with chronic liver disease, the prevalence of growth impairment and malnutrition is high.
- Head circumference *z*-score for age may be used as an anthropometrical indicator of growth in children with CLD.
- The significant bivariate correlations of height with arm anthropometrical indicators underline the close interactions between growth and body composition.

- Biochemical liver damage indicators predict the severity of growth impairment and malnutrition in children with CLD.
- Children with CLD need more than the recommended daily intake of energy, proteins, and other nutrients.
- Nutritional intervention with particular nutrients, such as medium-chain triglycerides or branched-chain amino acids, increasing the energy and nutrient intake by formula fortification, and enteral nutrition with continuous infusion may improve or at least avoid nutritional deterioration for weeks or months.

Key Features

Table 135.8 Key points of liver damage severity evaluated by liver function tests and the nutritional status estimated by anthropometric indicators in children with chronic liver disease

1. CLD associates with growth impairment and malnutrition.
2. Head circumference predicts height in the first 3 months of life.
3. Growth indicators have strong correlations with body composition anthropometrical indicators.
4. Biochemical indicators of liver damage predict growth impairment and acute malnutrition.
5. Nutriment requirements of children with CLD are higher than the DRIs.
6. Nutritional intervention in children with CLD may improve or at least avoid deterioration of their nutritional status.

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Chapter 136
Waist Circumference Correlates and Hepatic Fat Accumulation

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Abstract Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease and is a major public health problem worldwide. It has been suggested that simple fatty liver, the most common type of NAFLD, is a reversible condition in which large vacuoles containing triglycerides accumulate in hepatocytes. Simple fatty liver is often a precursor to non-alcoholic steatohepatitis, which can progress to liver cirrhosis and hepatocellular carcinoma. NAFLD is considered one of the phenotypes of metabolic syndrome, which is characterized by obesity, type 2 diabetes mellitus, hyperlipidemia and hypertension. Obesity, particularly abdominal obesity, is a major risk factor for NAFLD. Several recent studies have revealed a relationship between excessive visceral fat accumulation and the severity of hepatic fat accumulation. On the other hand, in the current definitions of metabolic syndrome, waist circumference measurement has been proposed as a simple and useful estimate of abdominal obesity, taking into account sex differences in waist circumference. Recent studies have also reported that waist circumference could be a marker for hepatic fat accumulation. In this chapter, we first discuss the relationship between waist circumference, hepatic fat accumulation and liver function. Finally, we discuss the sex and age-group differences in these relationships, based on recent findings.

Abbreviations

ALT	Alanine aminotransferase
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
HOMA-IR	Homeostasis model assessment-insulin resistance
JSG-NAFLD	Japan Study Group for NAFLD
L/S ratio	Liver/spleen attenuation ratio
MRS	Magnetic resonance spectroscopy
NAFLD	Nonalcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_136,

OR Odds ratio
SD Standard deviation
WC Waist circumference

136.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and a major public health problem. It has been recognized that simple fatty liver (non-alcoholic fatty liver), the most common type of NAFLD, is a reversible condition in which large vacuoles containing triglycerides accumulate in hepatocytes. Simple fatty liver is often a precursor to non-alcoholic steatohepatitis (NASH), which can progress to liver cirrhosis and hepatocellular carcinoma. Recent surveys indicate that NAFLD may account for approximately 80% of cases with liver dysfunction in many countries. NAFLD is considered to be one of the phenotypes of metabolic syndrome, which is characterized by abdominal obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension. It is also well recognized that visceral fat accumulation is a more important risk factor than subcutaneous fat for NAFLD and metabolic syndrome (Marchesini et al. 2003; Stranges et al. 2005; Kogiso et al. 2007; Jakobsen et al. 2007; Sung et al. 2007; Leite et al. 2009). Furthermore, recent studies have reported that hepatic fat accumulation, but not visceral fat accumulation, is associated with the metabolic complications of obesity (Kotronen et al. 2007; Wasada et al. 2008, Fabbrini et al. 2009).

Waist circumference is widely used as an indirect measurement of abdominal obesity in many epidemiologic studies and is included as a criterion in the NCEP-ATP III and IDF consensus definition of the metabolic syndrome. We previously reported that the degree of hepatic fat accumulation, as estimated by ultrasonography and CT, is correlated with visceral fat area estimated by abdominal CT in patients with NAFLD (Eguchi et al. 2006). However, in clinical practice, it is not always possible to evaluate visceral fat accumulation by abdominal CT. Several studies revealed that visceral fat accumulation estimated by waist circumference was closely related to NAFLD (Sabir et al. 2001; Eguchi et al. 2006; Jakobsen et al. 2007). Measuring waist circumference is an essential part of clinical practice for the management of NAFLD, in addition to measuring body weight and body mass index (BMI); indeed, waist circumference should be measured in most research studies. Hu et al. reported that the validity of BMI as a marker of body fatness in older adults decreased as a result of changes in body composition associated with aging. However, waist circumference has been shown to be a good predictor of adiposity, particularly abdominal obesity (Hu 2008).

In this chapter, we review the clinical and epidemiologic studies that report waist circumference, an essential anthropometric measurement for the evaluation of visceral obesity and hepatic fat accumulation. We also report results from the joint multicenter NAFLD research database in Japan.

136.2 NAFLD and Its Progression to Non-alcoholic Steatohepatitis and Liver Cirrhosis

NAFLD is the most common cause of chronic liver disease in adults in USA, European countries, and Asia in parallel with the increase of obesity in developed countries. NAFLD is recognized as the hepatic manifestation of insulin resistance and metabolic syndrome (Table 136.1). The incidence and prevalence of NAFLD are thought to be rising, as the prevalence of obesity and type 2 diabetes has dramatically increased in two decades. The estimated prevalence of NAFLD is 20–30%, whereas that of NASH is estimated to be 3–5%. NAFLD occurs in patients of both sexes, all ethnicities and

Table 136.1 Key facts of nonalcoholic fatty liver disease

1. Non-alcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis characterized by lipid droplets' accumulation within hepatocytes without intake of ethanol
2. Insulin resistance and metabolic syndrome are associated with the pathogenesis and progression of NAFLD
3. NAFLD is a clinical pathological term for a spectrum of structural findings ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with progressive hepatic fibrosis, liver cirrhosis, and hepatocellular carcinoma
4. The "two-hits" model of NASH pathogenesis has been proposed Day et al., whereby a "first hit" (hepatic steatosis) increases the sensitivity of the liver to the secondary hepatic injury and oxidative stress, lipid peroxidation, mitochondrial dysfunction, and inflammatory adipocytokines provide the "second hit" that triggers NASH
5. NAFLD is clinically suspected in subjects with asymptomatic elevation of serum aminotransferase levels, radiological findings of fatty liver, and hepatomegaly
6. Only histological examination of the liver can confirm the diagnosis of NAFLD and its clinical severity (i.e. steatosis alone or advanced stages of NASH)
7. Therapies for NAFLD are limited. Moderate and gradual weight reduction can result biochemical and histological improvement
8. Pharmacological treatments have been demonstrated with antioxidants, insulin sensitizers, hepatoprotectants, and lipid-lowering agents. However, without larger randomized studies, no pharmacological treatments can be recommended at this time

This table lists the key facts of nonalcoholic fatty liver disease including the pathogenesis, diagnosis and therapies

in all age groups. NAFLD has few symptoms and is clinically characterized by a slight elevation of the serum aminotransferase levels, hyperglycemia, and insulin resistance in combination with obesity. It has been suggested that NAFLD subtypes differ in their potential for progression. Most patients with simple fatty liver do not progress to overt liver disease. By contrast, non-alcoholic steatohepatitis (NASH) can progress to liver cirrhosis and hepatocellular carcinoma. NASH, which was first described by Ludwig (Ludwig et al. 1980), is characterized by histopathologically macrovesicular steatosis, hepatocellular ballooning and lobular inflammation with scatterd leukocytes and monocytes. Hepatocyte ballooning degeneration, Mallory's hyaline (hyaline cytoplasmic inclusions of cyto keratin within hepatocyte), and pericellular and perisinusoidal fibrosis are discriminating findings suggestive of progressive NASH. The transition of simple fatty liver to NASH is not clearly demarcated and each clinical symptom is similar. According to Day and James (1998), the pathogenesis of NASH comprises two steps. The first step is characterized by the accumulation of triglyceride droplets in the hepatocyte cytoplasm as simple fatty liver. This is mainly a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from excessive visceral fat to the liver is increased. The second step is induced by oxidative stress and inflammatory cytokines from an excessive visceral fat tissue, such as tissue necrosis factor-alpha (TNF-alpha), tumor growth factor-beta (TGF-beta), and IL-6. This leads to exacerbation of insulin resistance, further oxidative stress, and organelle dysfunction within liver cells, resulting in an inflammatory process, hepatocellular degeneration, and fibrosis. Hepatic fibrosis can progress to liver cirrhosis, which initially occurs in a micronodular pattern, but macronodular regeneration may develop.

The diagnosis can be made by liver biopsy and/or by imaging, such as abdominal computed tomography (CT), magnetic resonance imaging, magnetic resonance spectroscopy, and ultrasonography. Liver biopsy is the gold standard, particularly for NASH, for evaluation of steatosis, inflammation, and fibrosis. However, liver biopsy is invasive and is sometimes associated with incidental peritoneal bleeding. Noninvasive evaluation of liver fat accumulation is mainly performed based on ultrasonographic findings and abdominal CT, using the liver/spleen attenuation ratio (L/S ratio) (Fig. 136.1 and Table 136.2). The CT numbers (in Hounsfield units) of region of interest (ROI) of 60 mm^2 in the periphery of the liver and the spleen, away from major vessels, are measured at five points in each organ, and the mean numbers are used to determine L/S ratio as an index of fat accumulation in the liver.

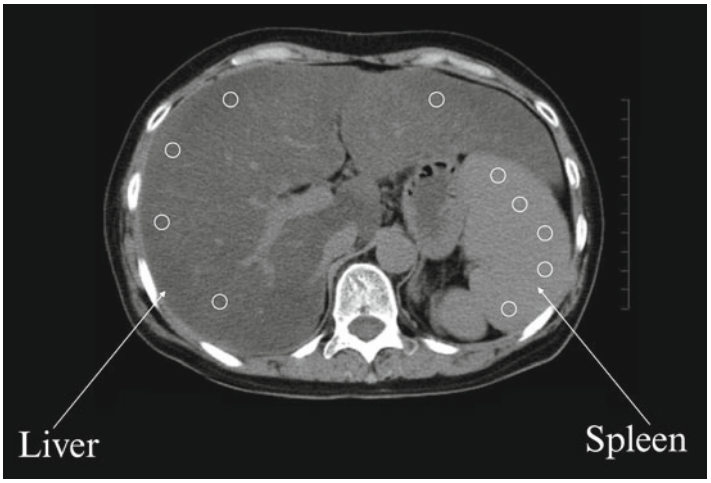

Fig. 136.1 Hepatic fat accumulation and the measurement of the liver/spleen attenuation ratio (L/S ratio). This CT image of a case with severe fatty liver shows very low CT attenuation. The CT values (in Hounsfield units) were determined for five 60-mm^2 regions of interest (*ROI*) placed in the periphery of the liver and the spleen, away from major vessels. The mean values were used to determine the L/S ratio as an index of fat accumulation in the liver

Table 136.2 Key facts of liver/spleen attenuation ratio

1. Hepatic steatosis can be non-invasively diagnosed with ultrasonography (US), computed tomography (CT), and magnetic resonance (MRI). These radiologic modalities have several advantages and disadvantages when compared with gold standard liver biopsy
2. Non-contrast-CT has been widely used for detecting fatty infiltration in the liver
3. Hepatic steatosis produces a low-density hepatic parenchyma on CT scanning, with an inverse correlation with the degree of fatty infiltration
4. CT has a low attenuation of hepatic parenchyma in steatosis, with the liver appearing darker than the spleen rather than brighter. The severity of the steatosis correlates not only with the liver density, but also for the liver to spleen attenuation ratio.
5. All measurements were manually obtained by four or five circular region-of-interest (ROI) cursors in the liver parenchyma and four in the spleen, with care being taken to avoid vessels, artifacts, and other areas that might have spuriously increased or decreased measurements. The measurements in each segment of the liver and spleen were averaged as follows:

   Liver/spleen attenuation ratio = Average attenuation value of liver/Average attenuation value of spleen

6. Although CT scanning is widely available, it is particularly limited in serial assessments of hepatic steatosis due to significant radiation exposure

This table lists the key of liver/spleen attenuation ratio including the principle and methods

136.3 Waist Circumference and Hepatic Fat Accumulation

It has been hypothesized that visceral fat releases free fatty acids and various adipokines and thereby stimulates fat accumulation in the liver. Free fatty acids released from visceral fat are transported via the portal vein to the liver, as demonstrated in a study by Nielsen et al. (2004). Using tracer methods, they found a direct association between the amount of visceral fat and the delivery of free fatty acids to the liver.

Visceral fat accumulation is significantly correlated with waist circumference, indicating that waist circumference is a good marker for visceral obesity (Hu 2008). Between 2001 and 2009, 19 studies involving at least 100 subjects reported an association between waist circumference and fatty liver. As shown in Table 136.3, some studies reported associations between waist circumference and hepatic fat accumulation. Among the studies that used waist circumference as a marker for visceral fat accumulation, two studies (Sabir et al. 2001; Eguchi et al. 2006) found a significant correlation

Table 136.3 Summary of clinical studies that evaluated the association between waist circumference and non-alcoholic fatty liver disease among 100 subjects or more

First author and year of publication (ref.) ethnicity or country of residence	No. of subjects (% female)	Mean age (years)	Results description
Sabir, 2001 (14) Turkey	68 obese females 40 non-obese female controls	44 (SD, 9) 34 (SD, 9)	Significant correlation between WC and liver fat content (obese persons: $r = 0.45$, $p < 0.0001$; non-obese individuals: $r = 0.58$, $p < 0.0001$)
Marchesini, 2003 Italy	304 individuals with NAFLD (17% female)	42 (SD, 12)	Individuals with NASH had significantly higher WC than those with fatty liver ($p < 0.024$)
Shen et al., 2003 (16) China	4,009 individuals (36% female)	46 (SE/SD not given)	WC was significantly associated with NAFLD ($p = 0.0000$)
Hsiao, 2004 (17) Taiwan	210 obese individuals (78% female)	36 (SD, 10)	In multivariate logistic regression analysis (including sex, age, BMI, serum ferritin level, and HOMA-IR), WC was significantly associated with fatty liver (per 1-cm increase in WC: OR = 1.10, 95% CI = 1.04–1.16)
Bugianesi et al., 2005 (20) Italy	174 individuals with NAFLD (10% female) 42 controls matched for BMI (20% female)	41 (SD, 11) 43 (SD, 11)	Individuals with NAFLD had significantly higher WC than controls ($p < 0.0001$)
Stranges, 2005 United States	195 individuals with hypertension (59.0% female) 702 controls without hypertension (67.3% female)	58 (SD, 11)	Individuals with a gamma-glutamyl transpeptidase concentration had a graded increase associated with the increase of WC ($p < 0.001$)
Targher, 2005 (22) Italy	65 males without fatty liver 35 males with fatty liver	43 (SD, 4) 41 (SD, 4)	Men with fatty liver had significantly higher WC than men without fatty liver ($p < 0.01$)
Church, 2006 (24) Non-Hispanic Caucasian	194 males without NAFLD 24 males with NAFLD	52 (SD, 7) 51 (SD, 5)	In multivariate logistic regression analysis (including age and alcohol consumption), WC was significantly directly associated with NAFLD (per 1-cm increase in WC: OR = 1.11, 95% CI = 1.06–1.17). Additional adjustment for visceral fat area attenuated the association (OR = 1.05, 95% CI = 0.97–1.10), whereas additional adjustment for subcutaneous abdominal fat area did not affect the association (OR = 1.10, 95% CI = 1.02–1.17)
Eguchi, 2006 (25) Japan	129 individuals with NAFLD (49% female)	59 (SD, 12)	WC was associated with the severity of fatty liver (mild, moderate, or severe) ($p < 0.0001$)
Oh et al., 2006 (28) South Korea	3,091 individuals with NAFLD (33% female)	48 (SD, 11)	Individuals with an elevated ALT concentration had significantly higher WC than individuals with a normal ALT concentration ($p < 0.001$)
Zelber, 2006 (30) Israel	326 individuals (53% female)	51 (SD, 10)	In multivariate logistic regression analysis (including sex, age, BMI, HOMA, and triglycerides), WC was significantly associated with NAFLD (for WC >102 cm in males and WC >88 cm in females: OR = 2.9, 95% CI = 1.3–6.4)

(continued)

Table 136.3 (continued)

First author and year of publication (ref.) ethnicity or country of residence	No. of subjects (% female)	Mean age (years)	Results description
Park, 2007 South Korea	117 overweight men with NAFLD 117 controls	43 (SE, 1)	In multivariate logistic regression analysis (including age, BMI, percentage body fat, iron, triglycerides, Apo B, and HOMA), WC was significantly associated with NAFLD (per 4.6-cm increase in WC: OR = 1.67, 95% CI = 1.10–2.62)
Kogiso, 2007 Japan	348 individuals with NAFLD (17.2% females) 906 controls (55.1% female)	52–59 (SD, 14)	In multivariate logistic regression analysis (including body weight, BMI, fasting blood glucose, and triglycerides), WC was significantly associated with NAFLD (for WC <85 cm in males and <95 cm in females: OR = 5.02, 95% CI = 1.74–14.52)
Kotronen, 2007 United States	271 non-diabetic individuals (59.8% females)	38 (SD, 12)	Liver fat determined by MRS was significantly associated with WC (females: $r = 0.59$, $p < 0.0001$; males: $r = 0.56$; $p < 0.0001$)
Sung, 2007 South Korea	36654 non-diabetic individuals (37.2 5 female)	41 (SD, 9)	In multivariate logistic regression analysis (including age and BMI), WC was significantly associated with sonographically assessed fatty liver and elevated ALT (per 1-cm increase in WC; males with normal ALT: OR = 1.03, 95% CI = 1.01–1.04; females with normal ALT: OR = 1.06, 95% CI = 1.03–1.08; males with elevated ALT: OR = 1.11, 95% CI = 1.09–1.12; females with elevated ALT: OR = 1.06, 95% CI = 1.04–1.09)
Wasada, 2008 Japan	142 individuals with NAFLD (25% female)	53 (SD, 9)	High-molecular-weight adiponectin concentration, insulin-like growth factor binding protein 1, and HOMA were significantly associated with WC ($r = -0.414$, $r = -0.345$ and $r = 0.396$, respectively, all $p < 0.001$)
Ishibashi, 2008 Japan	221 individuals with NAFLD (46.6% female)	55.2 (SD, 11.9)	Hepatic fat accumulation determined by CT scan was associated with WC in males, but not in females (males, $r = -0.356$, $p < 0.01$; females, NS), and hepatic fat accumulation was associated with visceral fat accumulation in both sexes (males, $r = -0.269$, $p < 0.01$; females, $r = -0.319$, $p < 0.01$)
Kogiso et al., 2009 Japan	57 individuals with NAFLD (42.1% female) 173 controls (65.3% female)	55.8–62.8 (SD, 6.1–14.8)	WC increased with the severity of NAFLD (normal, NAFLD with normal ALT, and NAFLD with elevated ALT) ($p < 0.01$)
Leite, 2009 Brazil	125 individuals with NAFLD (70.4% female) 55 controls (69.2% female)	54.3 (SD, 8) 55.6 (SD, 7)	WC increased with the severity of hepatic steatosis (normal, mild, moderate, or severe) ($p < 0.01$)

All of 19 studies showed the association between waist circumference and the severity of fatty liver disease

SD standard deviation, *WC* waist circumference, *NASH* non-alcoholic steatohepatitis, *NAFLD* non-alcoholic fatty liver disease, *BMI* body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *OR* odds ratio, *CI* confidence interval, *ALT* alanine aminotransferase, *MRS* magnetic resonance spectroscopy, *CT* computed tomography

between waist circumference and the severity of hepatic fat accumulation. Sabir et al. reported that the severity of hepatic fat accumulation estimated by ultrasonography was significantly correlated with BMI, waist–hip ratio, waist circumference, and visceral fat thickness estimated by ultrasonography in 68 obese and 40 non-obese subjects. Our study of 126 patients with NAFLD demonstrated that the liver–spleen ratio calculated by CT and the severity of hepatic steatosis estimated by ultrasonography are closely correlated with visceral fat accumulation estimated by abdominal CT. Previous studies have indicated that visceral fat accumulation evaluated by CT at the umbilical level is correlated with visceral fat volume, and that the accumulation of risk factors for metabolic syndrome is related to an increase in visceral fat area.

In six studies that reported multivariate logistic regression analyses, the analyses included adjustment for metabolic factors associated with hepatic fat accumulation (Hsiao et al. 2004; Church et al. 2006; Zelber-Sagi et al. 2006; Park et al. 2007; Kogiso et al. 2007; Sung et al. 2007). In the multivariate logistic regression analysis performed by Hsiao et al., waist circumference was significantly associated with the existence of fatty liver in Taiwanese subjects. Similarly, Church et al. reported that waist circumference was significantly associated with NAFLD in non-Hispanic Caucasian subjects. In that study, additional adjustment for visceral fat area attenuated the association, whereas additional adjustment for subcutaneous abdominal fat area did not affect the association. Zelber et al. reported that waist circumference was significantly associated with NAFLD in Israelis and Park et al. reported a similar association in South Korean individuals. Kogiso et al. reported that waist circumference significantly associated with NAFLD in Japanese subjects. Sung et al. reported that waist circumference was significantly associated with sonographic findings of fatty liver and elevated ALT in South Koreans.

Fifteen studies were carried out in men and women, three studies were carried out in men only, and one was carried out in women only. Our study investigated differences between sexes in terms of the association between waist circumference and hepatic fat accumulation in Japanese patients with NAFLD. The results indicated that the differences in associations between waist circumference and hepatic fat accumulation were at least partly related to differences in the distribution of visceral fat and subcutaneous fat at the umbilical level (Ishibashi et al. 2008).

136.4 Relationship Between Waist Circumference and the Severity of Hepatic Fat Accumulation in a Multicenter Study

This article introduces evidence for sex and age differences in the correlation between waist circumference/visceral fat accumulation and hepatic fat accumulation, based on analyses of the Japan Study Group for NAFLD (JSG-NAFLD) database. This database was established for multicenter clinical research in Japanese subjects with NAFLD in 2009. Clinical cases registered in the JSG-NAFLD database (499 cases: 276 males and 223 females; age 20–84 years, mean 51.7 years) were included in this analysis. All subjects were diagnosed as NAFLD based on clinical findings and ultrasonography, and underwent liver biopsy and abdominal CT scans. Waist circumference was measured at the umbilical level in an upright position during a light breath exhalation, as described in other chapters in this Handbook.

As shown in Figs. 136.1–136.4, which represent analyses of the JSG-NAFLD database, there is a significant relationship between waist circumference and visceral fat accumulation evaluated by CT. The analyses also show a relationship between visceral fat accumulation and hepatic fat accumulation estimated by the L/S ratio. In the total study population and in both sexes, there was a significant relationship between waist circumference and hepatic fat accumulation (Figs. 136.2 and 136.3), and between hepatic fat accumulation and aminotransferase levels. It should be noted that there was a

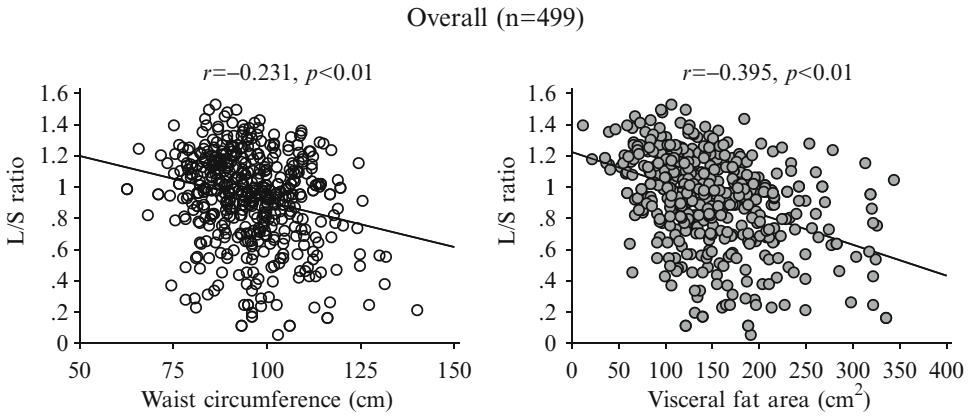

Fig. 136.2 Relationship between liver/spleen attenuation ratio (L/S ratio) and waist circumference/visceral fat area. Significant negative correlations were found between waist circumference (*left*) and visceral fat area determined by abdominal plain CT (*right*) in 499 subjects with NAFLD (liver/spleen ratio and waist circumference: $r = –0.231$, $p < 0.01$; L/S ratio and visceral fat area: $r = –0.395$, $p < 0.01$)

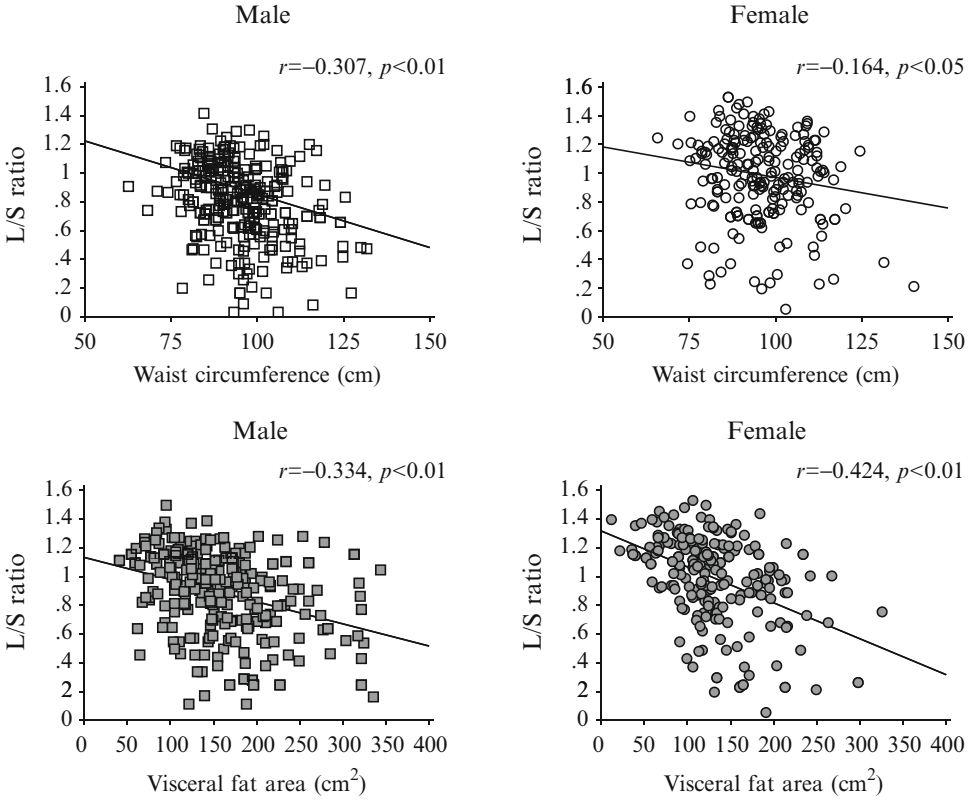

Fig. 136.3 Relationship between liver/spleen ratio (L/S ratio) and waist circumference/visceral fat area in males and females. In males ($n = 276$), there is a significant negative correlation between L/S ratio and waist circumference (*upper left*) and between L/S ratio and visceral fat area determined by abdominal plain CT (*lower left*) (L/S ratio and waist circumference: $r = –0.307$, $p < 0.01$; L/S ratio and visceral fat area: $r = –0.334$, $p < 0.01$). In females ($n = 223$), there is a weak negative correlation between L/S ratio and waist circumference ($r = –0.164$, $p < 0.05$) (*upper right*) and a stronger negative correlation between L/S ratio and visceral fat area ($r = –0.424$, $p < 0.01$) (*lower right*)

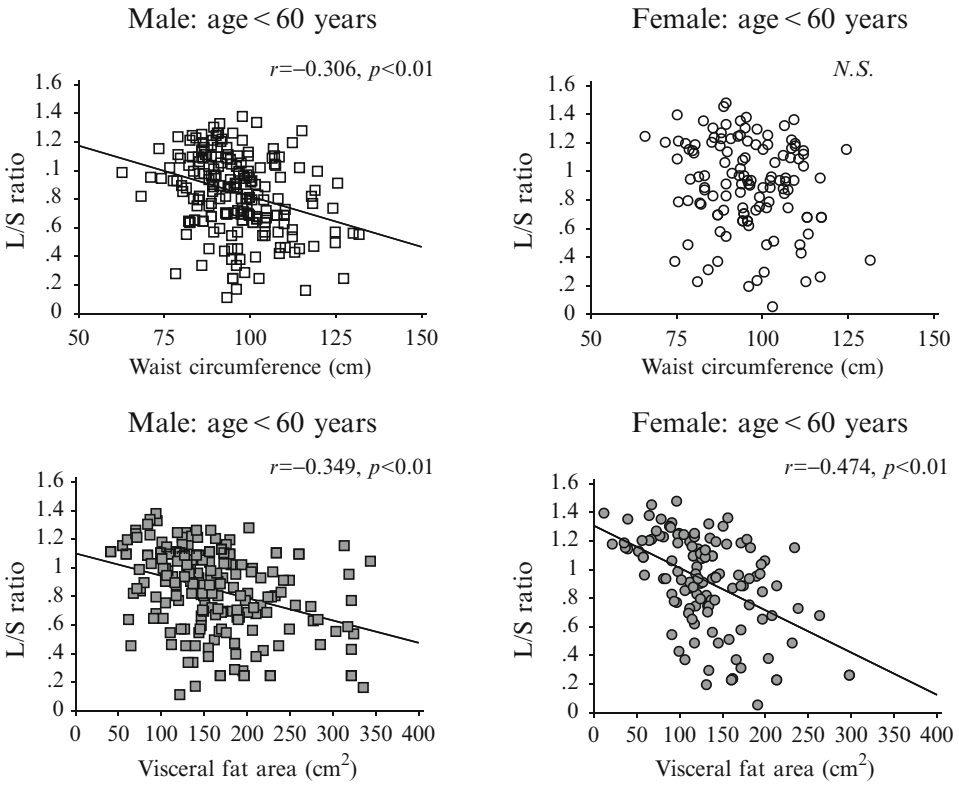

Fig. 136.4 Relationship between liver/spleen ratio (L/S ratio) and waist circumference/visceral fat area in males and females aged <60 years. In males (n = 198), there is a significant negative correlation between L/S ratio and waist circumference (*upper left*) and between L/S ratio and visceral fat area determined by abdominal plain CT (*lower left*) (L/S ratio and waist circumference: r = –0.306, p < 0.01; L/S ratio and visceral fat area: r = –0.349, p < 0.01). In females (n = 130), there is no correlation between L/S ratio and waist circumference (*upper right*), but there is a significant negative correlation between L/S ratio and visceral fat area (r = –0.474, p < 0.01) (*lower right*)

weaker correlation between waist circumference and hepatic fat accumulation in females than in males (Fig, 136.3, upper panel). By contrast, the significant correlations between visceral fat area and hepatic fat accumulation were comparable in both sexes (Fig. 136.3, lower panel).

136.5 Age and Sex Differences in the Relationship Between Waist Circumference and Hepatic Fat Accumulation

Analyses of the JSG-NAFLD database revealed that there is an age difference in the relationship between waist circumference and the degree of hepatic fat accumulation in NAFLD patients. In particular, the relationship between waist circumference/visceral fat accumulation and hepatic fat accumulation has been assessed for males and females aged <60 or ≥60 years. In individuals aged <60 years, the relationship between waist circumference and hepatic fat accumulation showed a significant negative correlation in males, but not in females aged <60 years (Fig. 136.4). Meanwhile, there was a significant positive correlation between visceral fat accumulation and hepatic fat

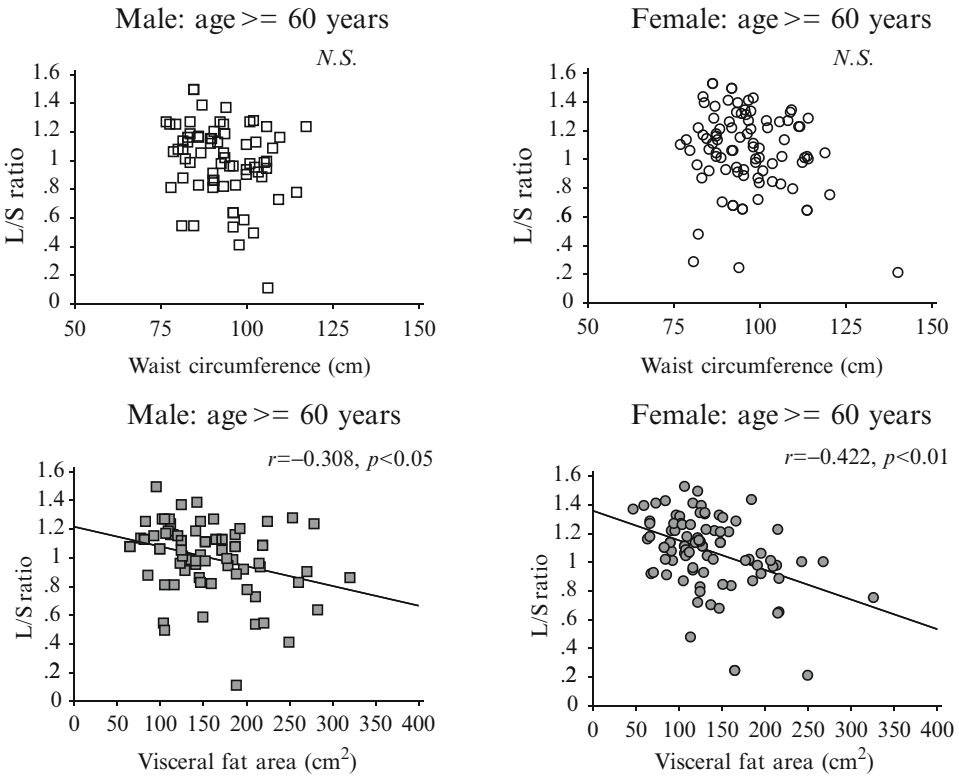

Fig. 136.5 Relationship between liver/spleen ratio (L/S ratio) and waist circumference/visceral fat area in males and females aged ≥60 years. In both groups (males, $n = 78$; females, $n = 93$), there is no correlation between L/S ratio and waist circumference (*upper left and right*, respectively). On the other hand, there is a significant correlation between L/S ratio and visceral fat area determined by abdominal plain CT (*lower left and right*, respectively) (L/S ratio and visceral fat area: males, $r = –0.308$, $p < 0.01$; females, $r = –0.422$, $p < 0.01$)

accumulation in males and females aged <60 years with NAFLD. On the other hand, the relationship between waist circumference and hepatic fat accumulation showed no significant correlation in males or females aged ≥60 years (Fig. 136.5, upper panel), but there was a significant correlation between visceral fat accumulation and hepatic fat accumulation in this age group (Fig. 136.5, lower panel).

Waist circumference is an excellent and easy method to evaluate visceral obesity in NAFLD patients, as for patients with metabolic syndrome. At the same time, it is important to be aware that waist circumference reflects not only visceral fat accumulation but also subcutaneous fat accumulation at the umbilical level. Waist circumference dose not allow us to discriminate between visceral organs (e.g., gastrointestinal tract), subcutaneous abdominal fat, and intra-abdominal fat. In males, the correlation between waist circumference and hepatic fat accumulation indicates that waist circumference reflects visceral fat accumulation, which agrees with the results of previous studies conducted in patients with a variety of metabolic abnormalities, including NAFLD (Targher et al. 2005; Church et al. 2006; Park et al. 2007). A recent study using abdominal ultrasonography showed results similar to those of the present study: waist circumference was correlated with hepatic fat accumulation in males, but not in females (Park et al. 2007). One reason for this may be that, in females, not only visceral adipose accumulation, but also subcutaneous adipose accumulation

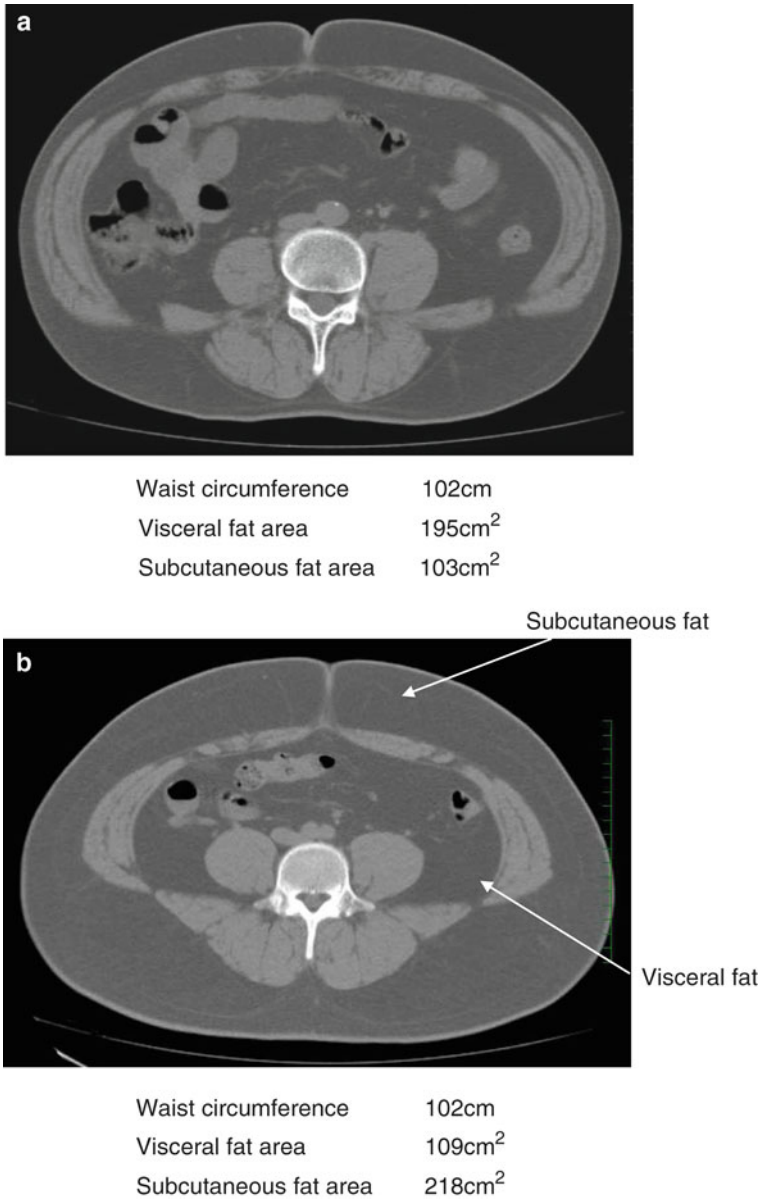

Fig. 136.6 Typical distributions of visceral and subcutaneous fat. Abdominal CT at the level of the umbilicus showing abdominal obesity. Each subject with abdominal obesity shows different distributions of visceral and subcutaneous fat, despite similar waist circumference (**a**), visceral fat-dominant abdominal obesity; (**b**), subcutaneous fat-dominant abdominal obesity)

contributes to waist circumference at the umbilical level. As shown in Fig. 136.6, abdominal CT at the level of the umbilicus shows abdominal obesity. Each subject with abdominal obesity shows different distributions of visceral/subcutaneous fat volume despite similar waist circumference (Fig. 136.6a, visceral fat-dominant abdominal obesity; Fig. 136.6b, subcutaneous fat-dominant abdominal obesity). Ishibashi et al. reported that the ratio between visceral fat area and subcutaneous fat area, and between visceral fat area and total fat area (visceral fat area plus subcutaneous fat area), as measured at the umbilicus, were markedly higher in males than in females ($p < 0.01$) (Ishibashi et al. 2008). Overall, the reasons for the differing results in each sex and age group remain to be elucidated.

136.6 Current Knowledge and Need for Further Studies of Waist Circumference and Hepatic Fat Accumulation

A recent study proposed a novel formula to predict liver fibrosis in patients with non-alcoholic steatohepatitis using the waist/hip ratio (Savvidou et al. 2009). A prospective study reported that 1 year of intense nutritional counseling led to histological improvements in non-alcoholic steatohepatitis in addition to a decrease in waist circumference (Huang et al. 2005). Further studies are needed to clarify the roles of sex, age, and ethnicity on waist circumference as a marker for visceral fat and subcutaneous fat accumulation at an umbilical level. In clinical practice, the investigators should remember that the relationship between waist circumference and hepatic fat accumulation is weaker in females than in males, although recent studies results indicate that waist circumference may be used as a very sensitive marker for hepatic fat accumulation in the general population.

136.7 Conclusions

Waist circumference is a convenient anthropometric measurement for the evaluation for hepatic fat accumulation. This measure might also predict liver enzyme levels, which are affected by the development of fatty liver disease. Investigators should take into account the sex- and age-group differences when evaluating the relationship between waist circumference and hepatic fat accumulation.

136.8 Application to Other Areas of Health and Disease

Since waist circumference is a marker for visceral fat accumulation, many studies suggest that metabolic disorders associated with lifestyle-related diseases and the metabolic syndrome might be evaluated by measuring waist circumference.

Summary Points of Waist Circumference and Hepatic Fat Accumulation

- Waist circumference is a convenient and essential anthropometric measurement that can be used to evaluate fatty liver disease associated with obesity, diabetes mellitus, or the metabolic syndrome.
- A significant association has been found between waist circumference, which is correlated with visceral fat accumulation and hepatic fat accumulation, and liver function.
- The relationship between waist circumference and hepatic fat accumulation is more prominent in males than in females.
- The correlation between waist circumference and hepatic fat accumulation is comparable to that between visceral fat accumulation and hepatic fat accumulation.
- Investigators should be aware of sex- and age-group differences in the relationship between waist circumference and hepatic fat accumulation.

Appendix

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Acknowledgments The authors would like to thank all the medical staff at Eguchi Hospital and Professor Kyuichi Tanikawa (International Institute for Liver Research) for excellent advice.

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Chapter 137
Ultrasonographic Anthropometry: An Application to the Measurement of Liver and Abdominal Fat

Marisa Chiloiro and Giovanni Misciagna

Abstract Non-alcoholic fatty liver disease is a spectrum of disorders characterized by an abnormal accumulation of triglycerides in the liver, and is recognized as the most common hepatic lesion, with an estimated prevalence of 15–39% in more industrialized countries. Many potential risk factors for non-alcoholic fatty liver disease have been identified, such as obesity, insulin resistance, hyperlipidemia and diabetes. Visceral adiposity seems to be the major contributor to a fatty liver in the insulin-resistant state. In fact, epidemiological evidence suggests that visceral adiposity is more associated with a fatty liver than the body mass. Direct assessment of hepatic fat obtained by biopsy is considered the gold standard, but it is a very invasive method. Fatty infiltration of the liver and abdominal fat can also be measured by Computerized Tomography, Magnetic Resonance Imaging, and ^{1}H Magnetic Resonance Spectroscopy. Unfortunately, these accurate methods for measuring fat mass are very sophisticated and expensive and have limited applicability in routine clinical settings. Ultrasound has been proposed as an alternative non-invasive technique for measuring fatty liver and subcutaneous and visceral fat thickness, because it may overcome some limitations of skinfold thickness and more sophisticated anthropometric methods.

Abbreviations

BMI	Body mass index
bc	Biceps skinfold
CRP	C-reactive protein
TC	Computerized Tomography
^{1}H MRS	^{1}H magnetic resonance spectroscopy
FM	Fat mass
FFAs	Free fatty acids
IAF	Intra-abdominal fat
ICC	Intra-class Correlation Coefficient
WC	Waist circumference
WHR	Waist-to-hip circumference ratio
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_137,

NF-kB	Nuclear factor-kB
PCC	Pearson's Correlation Coefficient
si	Suprailiac skinfold
SAT	Subcutaneous Adipose Tissue
tc	Triceps skinfold
ss	Subscapular skinfold
US	Ultrasonography
VAT	Visceral adipose tissue

137.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common hepatic lesion worldwide, with an estimated prevalence of 15–39% in Western countries and 9–13% in the East (Park et al. 2006). It is associated with overweight and obesity, and its distinctive trait is an intrahepatic accumulation of lipids. (Nakao et al. 2002) Many potential risk factors for NAFLD have been identified besides overweight and obesity, with insulin resistance, hyperlipidemia, and diabetes being among the most common. It has been hypothesized that visceral adiposity is a more important predictive factor for a fatty liver than body mass index (BMI) (Fishbein et al. 2006). The diagnosis of NAFLD can be made using different methods: liver biopsy, the gold standard, as well as noninvasive radiological methods, such as computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and ultrasonography (US). Many studies have reported that US, the most simple and cost-effective method among the radiological options, is useful for making a qualitative and quantitative evaluation of fatty liver and visceral and subcutaneous adiposity (Hirooka et al. 2005). The body fat distribution has been assessed using anthropometric measurements, such as skinfolds and waist-to-hip circumference ratios (WHR). Although the WHR is simple to measure and provides a valid estimation of the proportion of abdominal or upper-body fat, it does not distinguish between the deep abdominal (visceral) fat and subcutaneous abdominal fat depots.

The prevalence of obesity and associated metabolic morbidities is dramatically increasing also in childhood (Toriano et al. 1995). The BMI is considered to offer the best combination of weight and height to assess adiposity, and is widely accepted as a measure of overweight and obesity, and of adiposity in adults. However, the BMI has limitations when applied to pediatric populations. The rapid changes in weight and height that occur during growth complicate its interpretation in children. Waist circumference in childhood is a better predictor of the amount of intra-abdominal fat than BMI. The growing incidence of fatty liver in children may be occurring in parallel with visceral obesity. In fact, abdominal obesity contributes to the reduction of hepatic and systemic insulin sensitivity, and likely plays a role also in the pathogenesis of fatty liver disease.

137.2 Non-alcoholic Fatty Liver Disease and Its Measurement By Ultrasound

137.2.1 Definition

The term non-alcoholic fatty liver disease covers a spectrum of liver diseases, ranging from benign, non-progressive, simple hepatic steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH), in which fat in the liver is associated with inflammation and a variable degree of

fibrosis, and that can progress to liver cirrhosis (Angulo 2002). The histological changes in NAFLD are identical to those in alcoholic liver disease, and the former diagnosis can be made in a subject only after excluding the consumption of more than 20 g of alcohol per day. NAFLD includes simple forms of steatosis, either alone (type 1 NAFLD) or with inflammation, but no hepatocyte ballooning or fibrosis (type 2 NAFLD). The term NAFLD is used either when the pathology of the metabolic liver disease is not known or to refer to the full spectrum of fatty liver disease that can also include cases of cryptogenic cirrhosis, where steatohepatitis and steatosis are still present. Furthermore, NAFLD is considered to be one of the phenotypes of the metabolic syndrome, which is characterized by obesity with visceral fat accumulation, diabetes mellitus, hyperlipidemia, and hypertension (Carr et al. 2004).

137.2.2 Prevalence

NAFLD may affect any age and race. The true prevalence of NAFLD is unknown, but it is estimated to affect 15–39% of the general population in different countries. In Italy, the reported prevalence of NAFLD is 20–30% and that of NASH is 2–3% (Clark et al. 2003). The prevalence of NAFLD is higher in patients with obesity, ranging from 57.5% to 74% (Angulo 2002), and with type 2 diabetes mellitus (28–55%) and hyperlipidemia (20–92%). NAFLD affects 2.6% of children, and this figure increases from 22.5% to 52.8% in obese children (Carr et al. 2004). In most case series, the characteristic patient with NAFLD is a middle-aged woman, but in other series there is a higher prevalence of NAFLD in males than in females. Furthermore, many patients with NAFLD are non-obese and non-diabetic, with normal liver tests and lipid profile. Regardless of the body mass index, the presence of type 2 diabetes mellitus significantly increases the risk and severity of non-alcoholic fatty liver disease.

137.2.3 Histological Findings

Liver biopsy features of NAFLD include steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen, hyaline Mallory bodies, and fibrosis. The presence of these features, alone or in combination, accounts for the wide spectrum of non-alcoholic fatty liver diseases. Hyaline Mallory bodies are notably sparse or absent in children with NAFLD. The distribution of lipids may be macrovesicular, with hepatocytes distended by a single vacuole displacing the nucleus, or microvesicular, with numerous droplets surrounding a central nucleus. Widespread microvesicular steatosis is characteristically an acute condition, in which the impairment of fatty acid β-oxidation reflects a more general perturbation of mitochondrial and ribosomal functions, both within and outside the liver. Regardless of the etiology, microvesicular steatosis is widely acknowledged to have a poor prognosis, death being caused by liver failure and extrahepatic causes. Macrovesicular steatosis, by contrast, is typically associated with a longer duration disturbance of the hepatic lipid metabolism, and has up to now been considered a benign condition. Further evidence supporting a role for steatosis in liver progression to cirrhosis comes from the observation that the steatosis of non-alcoholic etiologies is frequently associated with the development of necroinflammation (so-called non-alcoholic steatohepatitis or NASH). The causes of NASH are the same as those of simple steatosis, and include obesity, non-insulin-dependent diabetes mellitus, jejuno-ileal bypass/gastroplasty surgery, parenteral nutrition, bacterial contamination of the small bowel, and drugs. The severity of the steatosis, as in alcoholic steatohepatitis, is one of the main factors associated with steatohepatitis and fibrosis in non-alcoholics.

137.2.4 Pathogenesis

The correlation between the steatosis severity and the necroinflammation/fibrosis in alcoholics and non-alcoholics does not prove that fat is per se causal in the development of more advanced disease. An alternative explanation is that a common mechanism may be responsible for both steatosis and necroinflammation in all forms of fatty liver, with steatosis acting as a surrogate marker of the intensity of the stimulus. A wide variety of mechanisms has been implicated in the necroinflammation that develops after excessive alcohol intake. Recently, evidence has emerged that at least two of these mechanisms play a role in the pathogenesis of NASH: (1) oxidative stress/lipid peroxidation and (2) endotoxin-mediated cytokine release, which explains the striking histological similarity between NASH and alcoholic steatohepatitis, and implicates steatosis as a direct contributor to inflammation and/or fibrosis.

The pathogenesis of NAFLD is still unclear. Hepatic steatosis is due to lipid accumulation, mainly triglycerides, within hepatocytes. The mechanisms leading to lipid accumulation are not completely understood, but they could potentially be either the result of insulin resistance (Bruun et al. 2005) and a decreased disposal of fatty acids due to impaired mitochondrial β-oxidation or a deficient production of very low density lipoproteins. Albeit still inconclusive, some lines of evidence, mainly derived from studies in animal models of fatty liver, suggest that oxidative stress/lipid peroxidation, bacterial toxins, overproduction of tumor necrosis factor-α, alterations of hepatocyte adenosine triphosphate stores and cytochrome P450 Cyp2E1/Cyp4A enzyme activity may play a role in the genesis and progression of NAFLD. Lipid peroxidation seems to increase with the severity of the steatosis. Malondialdehyde, an end product of lipid peroxidation, activates hepatic stellate cells, stimulating collagen production and fibrogenesis. It may also contribute to the inflammation by activating nuclear factor-kB (NF-kB), which regulates the expression of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-8. Another end product of lipid peroxidation, 4-hydroxynonenal, is a strong chemo-attractant for neutrophils.

137.2.5 Ultrasonographic Diagnosis

Fatty infiltration of the liver can be determined by US, CT, MRI, H magnetic resonance spectroscopy (HMRS), and by liver biopsy, the gold standard. However, the sensitivity and specificity of these radiological methods for the detection of fatty infiltration of the liver is generally unsatisfactory.

There are four sonographic signs of diffuse fatty changes in the liver (Gore 1994):

1. A diffuse hyperechoic echotexture (bright liver),
2. An increased liver echotexture as compared with the kidneys,
3. Vascular blurring,
4. Deep attenuation.

In a small retrospective study, a combination of these parameters allowed the diagnosis of fatty liver (defined histologically as fat present in >30% of each lobule) to be made with a sensitivity of 83% and a specificity of 100%. Recently, using both 10- and 3.5-MHz transducers, the frequency-dependent attenuation of an ultrasound beam passing through the liver was well correlated with its fat content (Fusamoto et al. 1991).

To obtain a semiquantitative evaluation of fat in the liver, we adopted a scoring system (Semiz et al. 2007; Toriano et al. 1995). The degree of fatty infiltration of the liver was graded according to the ultrasonographic appearance of the liver echotexture, the hepatic echo penetration, and the clarity

Table 137.1 Cohen's K as a measure of intra- and inter-observer variability of the ultrasonographic partial scores for liver steatosis

Item	Time	Radiologist A	Radiologist B
Contrast between liver and kidney tissue	T_1	0.73	
	T_2	0.43	
		0.43	0.50
Deep penetration of ultrasound	T_1	0.15	
	T_2	0.35	
		0.43	0.47
Clear visibility of blood vessels, specifically veins	T_1	0.07	
	T_2	0.50	
		0.78	0.68

Table 137.2 Pearson's Correlation Coefficient and the intraclass correlation coefficient of the total liver steatosis score between two radiologists

	Pearson *r*		Intraclass *r*	
Time	Radiologist A	Radiologist B	Radiologist A	Radiologist B
T_1	0.87		0.84	
T_2	0.77		0.77	
	0.81	0.77	0.78	0.85

of the hepatic blood vessels, as well as the liver-diaphragm differentiation in echo amplitude. Each criterion was assigned a score indicating the level of fatty liver infiltration. A score of 2 indicated a definite positive (++) fatty liver infiltration for that criterion. A score of 1 was assigned for a probably positive (+) finding based on the criterion. When a negative (-) evaluation for fatty liver was obtained, a score of 0 was assigned to the criterion. The sum of the scores for the three criteria was considered to be an indicator of the severity of fatty infiltration. Thus, the fatty liver score ranged from 0 to 6, whereby a total score of 1–2 indicated mild fat infiltration, a score of 2–4 moderate, and a total score ≥5 severe fat infiltration (absence of steatosis = score 0).

The intra- and inter-observer variations (measured by Cohen's K, Pearson's and the intraclass correlation coefficient) of the partial and total scores that we obtained for the assessment of liver steatosis by ultrasonography are shown in Tables 137.1 and 137.2. The inter-observer variability between two radiologists was evaluated at both times T_1 and T_2, and the intra-observer variability for each radiologist was evaluated between times T_1 and T_2.

137.2.6 Other Imaging Techniques Utilized for the Diagnosis of NAFLD

The most accurate measurement techniques are magnetic resonance imaging and computed tomography, but they are expensive and not available for routine use.

The liver fat content can also be semiquantitatively estimated by MRI as well as CT scans. Normally, the CT attenuation values for the liver range from 50 to 75 Hounsfield units when a non-contrast-enhanced scan is obtained. With increasing hepatic steatosis, liver attenuation values decrease by 1.6 Hounsfield units for every milligram of triglycerides per gram of liver tissue. Thus, in subjects with a fatty liver, the hepatic attenuation is less than that of blood vessels, giving the appearance of a contrast-enhanced scan, when no contrast has been used. When intravenous contrast

is used, both liver and splenic attenuation values increase, but the hepatic values increase to a lesser degree than the splenic values. When a diagnosis of fatty liver is based simply on a qualitative assessment of the differential attenuation during a contrast-enhanced CT scan, the sensitivity and specificity are 54% and 95%, respectively (Jacobs et al. 1998).

Using a cutoff of 20.5 Hounsfield units at 80–100 s after intravenous contrast injection, a fatty liver can be diagnosed with 86% sensitivity and 87% specificity. At 100–120 s, a difference of hepatic and splenic attenuation of 18 Hounsfield units determines a 93% sensitivity and specificity. Thus, the diagnostic accuracy of differential changes in hepatic–splenic attenuation is time dependent and protocol specific. These data were supported by another study in which the sensitivity was even lower (54–71%) (Johnston et al. 1998).

137.3 Abdominal Fat and Its Measurement By Ultrasound

137.3.1 Abdominal Fat

Truncal obesity seems to be a significant risk factor for NAFLD, even in subjects with a normal body mass index (Omagari et al. 2002).

In the last few years, many epidemiological studies have indicated that a regional body fat distribution with abdominal accumulation, regardless of the total body fat as assessed by the BMI, may represent a major independent risk factor for several pathological conditions, specifically, diabetes and cardiovascular disease (Bouchard et al. 1990).

Furthermore, recent findings have shown that central adiposity can be an independent predictor of hepatic steatosis. The body fat distribution was assessed using anthropometric measurements, such as skinfolds and the waist-to-hip circumference ratio. Although the WHR is simple and convenient for epidemiological studies and provides a useful estimation of the proportion of abdominal or upper-body fat, it does not distinguish between the accumulation of deep abdominal (visceral) fat and subcutaneous abdominal fat. Several studies have shown that the detrimental influence of abdominal obesity on metabolic processes is mediated only by the intra-abdominal fat depot (Wajchenberg 2000), in particular, the visceral adipose tissue (VAT).

Abdominal adipose tissue includes distinct anatomical depots: a subcutaneous fat depot and an intra-abdominal fat depot, that can be further subdivided into intraperitoneal and retroperitoneal depots (Wajchenberg 2000). Visceral fat accounts for up to 10–20% of total fat in men and 5–8% in women, and increases with age in both genders.

Fat around abdominal organs in the mesentery and omentum, known as visceral fat, is different from the fat present in subcutaneous areas (subcutaneous fat). The type of fat cells (adipocytes), their endocrine function, lipolytic activity, and response to insulin and other hormones differ between subcutaneous adipose tissue and visceral adipose tissue. Inflammatory cells (macrophages) are more prevalent in visceral than subcutaneous fat (Bruun et al. 2005).

Because of its anatomical position, visceral fat venous blood is drained directly into the liver through the portal vein. This contrasts with subcutaneous fat where venous drainage is through systemic veins. The portal drainage of visceral fat provides direct access of free fatty acids (FFAs) and adipokines secreted by visceral adipocytes to the liver (Fusamoto et al. 1991). Adipokines activate a hepatic immune mechanism with the production of inflammatory mediators, such as C-reactive protein (CRP).

137.3.2 Anthropometric and Ultrasonographic Assessment of Abdominal Fat

The body mass index is a useful indicator of overall adiposity. However, different fat compartments may have a specific metabolic risk Waist circumference (WC) is an easily obtainable but imprecise measure of abdominal adiposity (Poirier and Despres 2003) because it is a function of both the subcutaneous adipose tissue (SAT) and the VAT compartments. Intra-abdominal fat (IAF) can be estimated using anthropometric data. The indices most frequently used are waist circumference, waist-to-hip or waist-to-thigh ratio, truncal skinfold, and predictive equations of IAF derived from anthropometric data. The waist-to-hip ratio is certainly the most popular index in clinical use. For research purposes, however, the accuracy of these indirect methods is inadequate. For example, the waist-to-hip or waist-to-thighs ratios are poor measurements of IAF per se. In addition to IAF, they include subcutaneous fat and gluteal or leg muscle mass, the latter playing a potential role in peripheral insulin sensitivity. Therefore, a precise assessment of VAT requires imaging with radiographic techniques, such as computed tomography or magnetic resonance imaging. Fat accumulated in the lower body (the pear shape) is subcutaneous, whereas fat in the abdominal area (the apple shape) is largely visceral. The localization of fat in women is influenced by several factors, such as heredity and steroid sex hormones. Some researchers suggest that the drop in the estrogen level at menopause is also associated with an increased level of corticoid stress hormones that promotes the accumulation of abdominal fat.

Anthropometry is a dimensional approach that describes the adipose tissue mass. However, adipose tissue mass is not synonymous with fat mass because fat is a chemical not an anatomical entity. It is important to distinguish between *body fat*, an amount of fat, and *body fatness*, a compositional description. The numerical and statistical properties of the amount of fat (kg) differ from those of the composition (proportion or percentage). Although the two are correlated (r = 0.7–0.8), each has a unique specificity. Here, body fat refers to the fat mass (FM) and body fatness to the percentage of fat in the body weight (%Fat).

The anthropometric assessment of body fat and fatness is based on the measurement of skinfold thickness, weight, stature, circumferences, and diameters.

A skinfold is a direct measure of subcutaneous adipose tissue (SCAT) and dermis thickness, and a series of representative skinfold measurements will characterize the average SCAT thickness and provide an estimate of the SCAT mass. Skinfold thicknesses are usually measured as a compressed double fold. Compression varies according to the site, sex, age, nutritional status, and even within groups that are homogeneous for these variables. Ultrasound has been proposed as an alternative to other noninvasive techniques to measure subcutaneous and visceral fat thickness because it may overcome some limitations (see below) of the caliper-based anthropometric measurements (Armellini et al. 1993).

137.3.3 Correlation Between Anthropometric and Ultrasonographic Evaluation of Subcutaneous Fat

Using ultrasound to measure uncompressed SCAT, Kuczmarski did not find this method better than calipers (Fanelli and Koch 1987). To study the correlation between subcutaneous adipose tissue thickness measured by ultrasound, and skinfold thickness measured by calipers, as well as its variation by gender, we studied 260 children between 3 and 6 years of age (Chiloiro et al. 2003). All children were normal weight. Measurements of the triceps (tc), biceps (bc), suprailiac (si), and subscapular (ss) skinfold thicknesses were obtained using Holtain Skinfold Calipers (Holtain Ltd, Crymych, UK). All

Table 137.3 Correlation between calipers and ultrasonographic skinfold thickness measurements

Caliper skinfold	Thickness (cm)	Pearson correlation coefficient
tc	23,313 ± 4,073	$r = 0.33$; $p = 0.003$
bc	14,311 ± 3,216	
ss	20,903 ± 6,420	
si	20,440 ± 5,878	$r = 0.34$; $p = 0.003$
Ultrasonographic skinfold		
tc	16,229 ± 4,782	
bc	13,153 ± 5,083	
ss	16,235 ± 6,408	
si	16,617 ± 4,748	

Table 137.4 Anthropometric data in children (Mean ± SD)

Variables	Values (M ± SD)
Height (m)	1.45 ± 0.12
Weight (kg)	56.04 ± 14.96
BMI (kg/m²)	26.07 ± 3.73
BMI *z*-score	2.01 ± 0.39
Waist circumference (cm)	81.10 ± 10.70
Hip circumference (cm)	93.31 ± 10.65
Waist-to-hip circumference	0.869 ± 0.061

measurements were taken three times at each site, and the mean values were used. Measurements of subcutaneous fat layer were performed using a 7.5-MHz linear-array probe. The skinfold measurements were performed at the same marked sites where the anthropometric measurements were carried out. Our results showed a high correlation between ultrasound and caliper measurements at all sites studied, the highest correlation being found at the triceps site ($R = 0.64$, $p < 0.0001$).

A recent study shows that, in obese children, the correlation between anthropometric and US measurements of skinfold thickness is present for the triceps and suprailiac sites (Semiz et al. 2007). These sites are the ones where adipose tissue accumulates in obese subjects. The lack of correlation in the other sites considered for skinfold thickness evaluations can be explained by the fact that the correlation between caliper and US skinfold thickness is more reliable in non-obese than in obese subjects (Cataldo et al. 1997). In fact, in another work on obese children, we showed a positive correlation between anthropometric and US measurements of skinfold thickness only for triceps and suprailiac skinfolds (Table 137.3). The most relevant anthropometric data on the children we studied are shown in Table 137.4.

137.4 Correlation Between Abdominal Fat and Non-alcoholic Fatty Liver Disease Measured By Ultrasound in Children and Adults

137.4.1 Abdominal Fat and Non-alcoholic Fatty Liver Disease in Children

The prevalence of fatty liver in obese children has been evaluated by ultrasonography. Tominaga et al. (1995) found a 22% overall prevalence of fatty liver in children with a BMI ≥20, and Franzese et al. (1997) also used ultrasound to identify a fatty liver in 38 out of 75 obese children (52.8%).

The high prevalence of a fatty liver in our study (64%) was similar to the figure reported by Sagi et al. (2007) (about 60%) and the prevalence of children with steatosis and altered liver function is similar to that reported by those authors (17% vs. 15.5%). A fatty liver was positively correlated with anthropometric measurements including the BMI, waist and hip circumference, subscapular and suprailiac skinfold thickness, and the duration of obesity, but not with the liver enzymes. It has been shown that the liver enzymes concentration is not able to identify patients with a fatty liver. In fact, altered liver enzymes are present in only 10% of obese children with steatosis (Franzese et al. 1997) and a high percentage of patients with a fatty liver show liver enzymes in the normal range (Fishbein et al. 2003). In another work, (Chiloiro et al. 2008) we examined the relationship between anthropometric and biochemical parameters and a fatty liver at ultrasound in obese children. A total of 94 subjects (59 boys, 35 girls; mean age ± standard deviation = 9.7 ± 2.2 years) were studied. An ultrasonic appearance of hepatic steatosis was diagnosed in 60 out of 94 children (64%); the scoring system assigned 48 out of the 60 children (80%) to the weak steatosis group, nine out of 60 (15%) to the moderate steatosis group, and three out of 60 (5%) to the severe steatosis group.

In the whole sample, a fatty liver (yes/no) was positively associated with anthropometric measurements using logistic regression. These were: duration of obesity (OR = 1.19; CI 95% 1.01–1.42; p = 0.04); z-score BMI (OR = 3.3; CI 95% 1.08–10.2; p = 0.036); subscapular skinfold thickness (OR = 1.11; CI 95% 1.02–1.20; $p = 0.01$); suprailiac skinfold thickness (OR = 1.16; CI 95% 1.05–1.27; $p = 0.002$); waist circumference (OR = 1.11; CI 95% 1.05–1.18; $p < 0.001$); and hip circumference (OR = 1.06; CI 95% 1.01–1.12; $p = 0.012$).

137.4.2 Abdominal Fat and Non-alcoholic Fatty Liver Disease in Adults

In a population survey of subjects 30–89 years of age (Dr Marisa Chiloiro's Thesis for the Board Certification in Radiology, University of Palermo, 2009), the correlation between the fatty liver score and anthropometric parameters (BMI, waist circumference, and visceral and subcutaneous adipose tissue), as well as metabolic alterations that characterize the metabolic syndrome, was evaluated. In addition, the thickness of the subcutaneous and visceral adipose tissue was measured in all the subjects by ultrasound using standard scanning. To measure the subcutaneous fat, epigastric transverse scanning was done down the center of the xypho–umbilical line (Fig. 137.1). The same point was used to measure the visceral fat (Fig. 137.2), between the posterior surface of the abdominal wall and the anterior wall of the abdominal aorta. The thickness was measured in millimeters. In total, 2,966 subjects were examined, to study myocardial infarction and diabetes type 2 and their association with many potential metabolic (arterial pressure, BMI, fasting blood cholesterol, triglycerides, and glucose) and behavioral risk factors (diet, alcohol, and tobacco smoking). All the subjects underwent a standardized ultrasound examination of the liver for hepatic steatosis. The ultrasonographic findings were explored graphically and correlated with the metabolic syndrome variables using Pearson's r and contingency tables (with the aid of STATA 10 statistical software). The thickness of the subcutaneous and visceral adipose tissue, in millimeters, was correlated with the liver steatosis score, as shown in Table 137.5 and in Figs. 137.3 and 137.4. In Table 137.6, it can be seen that the liver steatosis score is directly associated with body weight and BMI, visceral adipose tissue measured by ultrasound, blood triglycerides, glucose, and GPT, and inversely associated with cholesterol HDL. It is not associated with height, total blood cholesterol, alkaline phosphatase, total bilirubin, cholesterol LDL, GOT, and GGT. Finally, the relationship of liver steatosis with systolic and diastolic blood pressure and with subcutaneous adipose tissue is uncertain. The prevalence of fatty

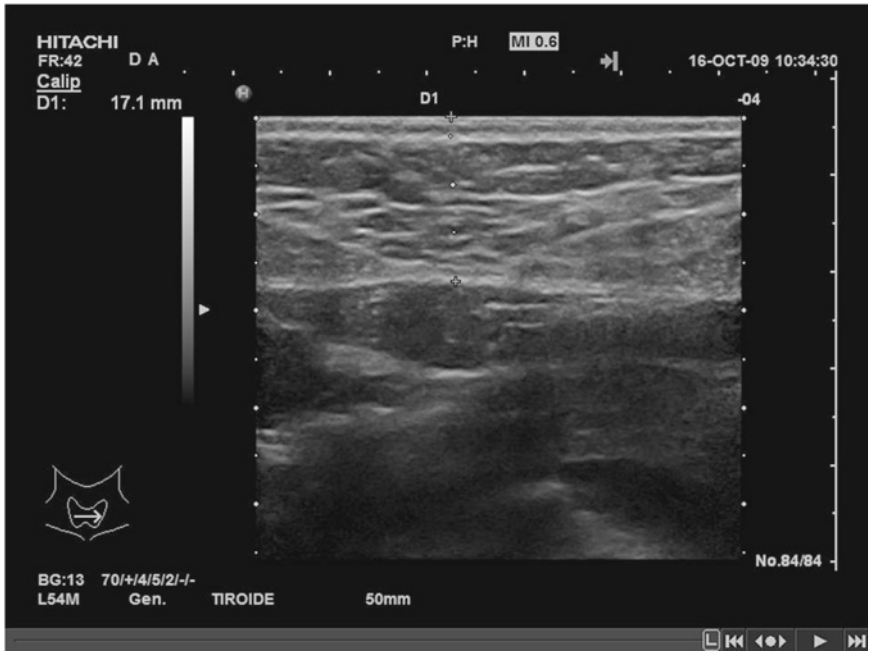

Fig. 137.1 Longitudinal sonogram of the upper abdomen on the xyphoid–umbilical line showing the subcutaneous fat layers. Measurements were taken using electronic calipers placed at the skin–fat and fat–linea alba interfaces

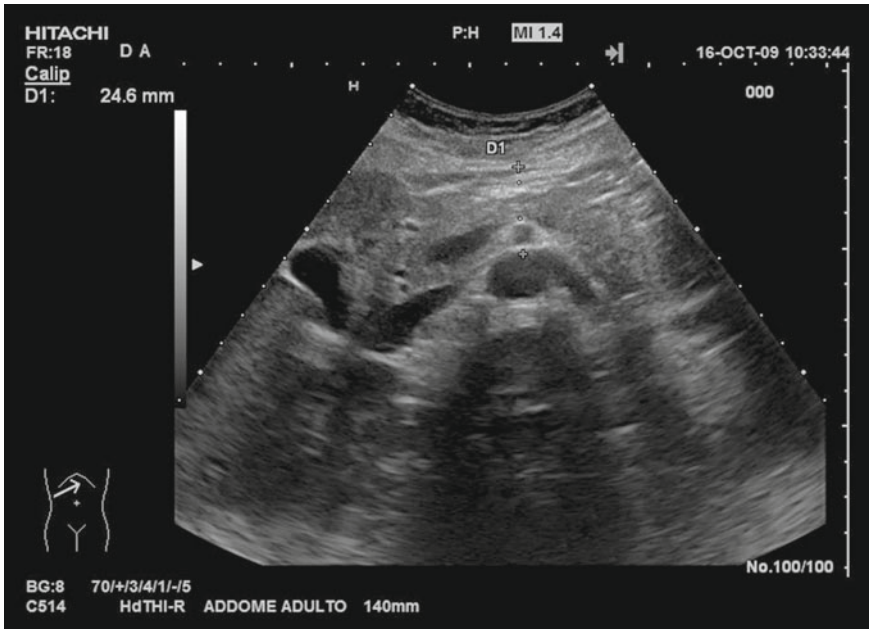

Fig. 137.2 Transverse sonogram just above the center of the xypho–umbilical line displays the visceral fat measured between the posterior aspect of the abdominal wall and the anterior wall of the abdominal aorta

Table 137.5 Correlation of the ultrasonographic total liver steatosis score with anthropometric parameters, and the thickness of abdominal subcutaneous and visceral adipose tissue

		Score of liver steatosis						
	Sex	0	1	2	3	4	5	6
Weight (kg)	M	75.2 ± 12.0	78.8 ± 11.5	82.4 ± 12.6	85.4 ± 13.9	86.0 ± 13.8	89.6 ± 12.7	94.7 ± 16.6
	F	64.4 ± 11.3	70.9 ± 11.3	76.8 ± 15.2	76.3 ± 12.6	77.8 ± 12.2	81.2 ± 14.5	94.4 ± 24.2
Height (cm)	M	167.7 ± 8.5	166.5 ± 8.0	167.4 ± 7.9	167.4 ± 7.4	167.5 ± 7.0	166.2 ± 7.7	167.8 ± 7.6
	F	155.2 ± 7.5	153.0 ± 7.7	153.3 ± 7.8	152.6 ± 7.4	151.7 ± 6.1	152.6 ± 6.5	152.8 ± 7.1
BMI (Kg/m²)	M	26.7 ± 3.6	28.4 ± 3.6	29.4 ± 3.8	30.4 ± 4.2	30.6 ± 4.1	32.4 ± 3.6	33.6 ± 5.1
	F	26.8 ± 4.9	30.4 ± 5.0	32.6 ± 5.6	32.8 ± 5.1	33.8 ± 4.7	34.8 ± 5.4	40.2 ± 8.6
Waist circumference (cm)	M	92.3 ± 9.8	97.7 ± 9.7	99.1 ± 9.8	101.5 ± 10.0	103.0 ± 10.1	106.5 ± 9.2	110.2 ± 11.6
	F	82.6 ± 11.5	90.7 ± 10.7	95.9 ± 12.3	97.8 ± 10.9	98.4 ± 9.1	101.1 ± 10.1	109.2 ± 15.6
Hip circumference (cm)	M	99.8 ± 7.9	102.2 ± 8.0	104.4 ± 8.2	105.2 ± 9.2	106.3 ± 8.6	107.8 ± 8.0	111.7 ± 11.8
	F	100.3 ± 9.8	106.0 ± 10.0	111.3 ± 11.7	111.7 ± 10.8	112.0 ± 10.1	114.5 ± 11.5	123.5 ± 17.1
Systolic blood pressure (mmHg)	M	122.5 ± 18.5	126.0 ± 20.0	123.6 ± 17.0	126.8 ± 17.6	125.5 ± 16.6	127.2 ± 17.2	132.8 ± 18.8
	F	118.6 ± 21.0	122.8 ± 22.0	126.9 ± 14.7	131.9 ± 18.5	130.1 ± 22.6	129.4 ± 21.7	133.6 ± 17.7
Diastolic blood pressure (mmHg)	M	74.1 ± 9.8	75.4 ± 9.7	76.0 ± 8.9	78.1 ± 12.8	77.4 ± 10.2	77.7 ± 8.5	80.9 ± 8.7
	F	72.2 ± 9.8	73.5 ± 10.4	76.5 ± 9.3	74.9 ± 9.2	76.3 ± 9.9	78.2 ± 11.0	80.1 ± 10.2
Cholesterol (mg/dL)	M	194.7 ± 38.6	201.5 ± 42.3	200.9 ± 43.3	202.5 ± 36.9	205.0 ± 39.2	204.5 ± 39.4	203.7 ± 38.7
	F	196.8 ± 35.2	206.5 ± 41.5	209.4 ± 35.6	205.5 ± 39.7	206.4 ± 44.8	210.7 ± 34.2	202.1 ± 46.0
Triglycerides (mg/dL)	M	116.2 ± 76.3	146.9 ± 101.3	155.8 ± 95.7	171.7 ± 129.5	186.7 ± 160.3	180.3 ± 107.6	188.0 ± 133.4
	F	94.8 ± 55.4	131.3 ± 83.4	133.2 ± 62.2	155.7 ± 86.3	158.2 ± 104.3	146.1 ± 43.7	184.1 ± 146.8
Glycemia (mg/dL)	M	108.0 ± 25.9	111.2 ± 22.4	111.2 ± 21.5	113.2 ± 28.2	115.5 ± 27.5	118.9 ± 24.8	127.2 ± 44.2
	F	101.4 ± 20.1	108.1 ± 32.8	114.9 ± 26.5	119.8 ± 41.3	119.9 ± 36.4	127.0 ± 38.6	131.9 ± 46.8
GPT (U/L)	M	17.2 ± 18.3	19.1 ± 12.9	20.8 ± 17.4	21.7 ± 12.6	23.4 ± 12.3	24.8 ± 9.7	25.9 ± 15.4
	F	13.6 ± 11.5	16.6 ± 13.2	17.4 ± 13.6	16.6 ± 12.3	21.0 ± 21.3	20.7 ± 12.1	20.3 ± 9.8
Alkaline phosphatase (U/L)	M	50.9 ± 15.2	50.6 ± 14.0	48.7 ± 16.3	51.1 ± 19.3	49.8 ± 13.2	53.5 ± 19.4	49.4 ± 12.7
	F	49.2 ± 17.9	51.1 ± 16.6	54.7 ± 19.4	59.8 ± 16.8	56.4 ± 14.2	66.5 ± 29.4	55.9 ± 13.9
Total bilirubin (mg/dL)	M	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.5	0.9 ± 0.3	0.9 ± 0.3
	F	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.4

(continued)

Table 137.5 (continued)

		Score of liver steatosis						
	Sex	0	1	2	3	4	5	6
HDL cholesterol (mg/dL)	M	49.1 ± 12.8	47.1 ± 10.6	46.0 ± 10.6	45.5 ± 12.6	45.1 ± 10.9	43.3 ± 7.7	42.7 ± 10.0
	F	58.8 ± 14.8	53.4 ± 12.6	53.2 ± 12.0	48.8 ± 10.0	50.3 ± 14.4	54.1 ± 17.8	47.8 ± 9.3
LDL cholesterol (mg/dL)	M	122.3 ± 32.1	125.0 ± 36.0	123.8 ± 36.7	124.6 ± 33.1	124.4 ± 35.1	125.4 ± 25.3	123.6 ± 34.0
	F	118.9 ± 31.6	126.4 ± 34.7	129.0 ± 29.8	125.6 ± 33.2	123.8 ± 40.1	127.5 ± 31.4	117.4 ± 35.4
GOT (U/L)	M	12.9 ± 11.6	13.7 ± 7.6	14.9 ± 13.1	12.9 ± 4.8	14.1 ± 5.9	14.0 ± 3.8	14.3 ± 5.8
	F	11.5 ± 8.0	13.6 ± 14.7	13.7 ± 11.0	12.5 ± 8.5	14.7 ± 11.7	15.7 ± 13.2	13.3 ± 4.2
GGT (U/L)	M	15.8 ± 13.9	20.2 ± 14.9	23.5 ± 27.4	23.2 ± 24.9	22.7 ± 16.4	19.9 ± 9.2	23.3 ± 17.3
	F	12.1 ± 15.4	15.3 ± 19.0	17.3 ± 30.3	16.7 ± 17.2	14.6 ± 6.3	21.3 ± 17.0	16.4 ± 9.0
Abdominal subcutaneous fat thickness (mm)	M	15.1 ± 5.9	14.5 ± 5.3	17.3 ± 5.5	17.3 ± 5.3	17.7 ± 5.1	17.6 ± 5.0	19.8 ± 6.7
	F	16.6 ± 6.1	19.3 ± 10.0	20.0 ± 5.8	21.9 ± 5.7	21.7 ± 5.3	23.7 ± 6.3	26.9 ± 7.5
Abdominal visceral fat thickness (mm)	M	54.1 ± 15.7	58.6 ± 16.0	63.1 ± 14.2	66.5 ± 16.3	69.9 ± 16.1	76.6 ± 18.2	80.3 ± 21.3
	F	42.3 ± 13.5	48.0 ± 13.1	53.6 ± 13.8	57.5 ± 14.9	59.1 ± 15.7	67.2 ± 17.8	70.8 ± 20.8

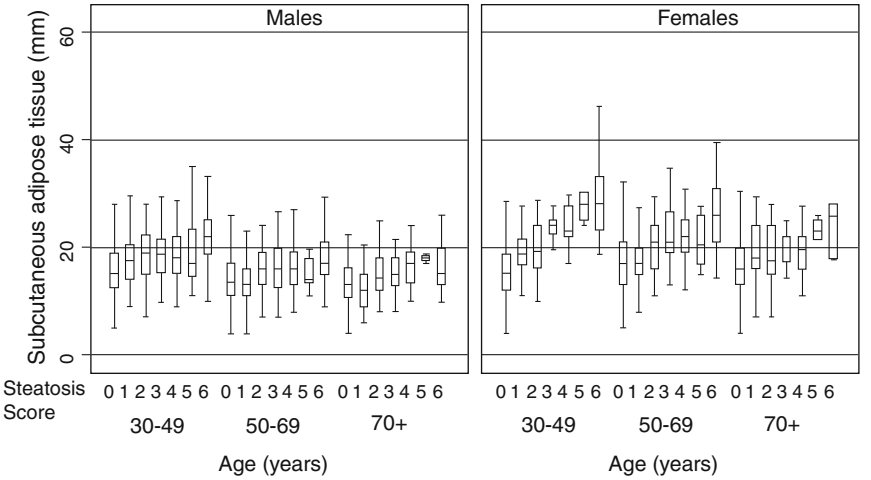

Fig. 137.3 Correlation between the liver steatosis score and subcutaneous adipose tissue, stratified by age and gender

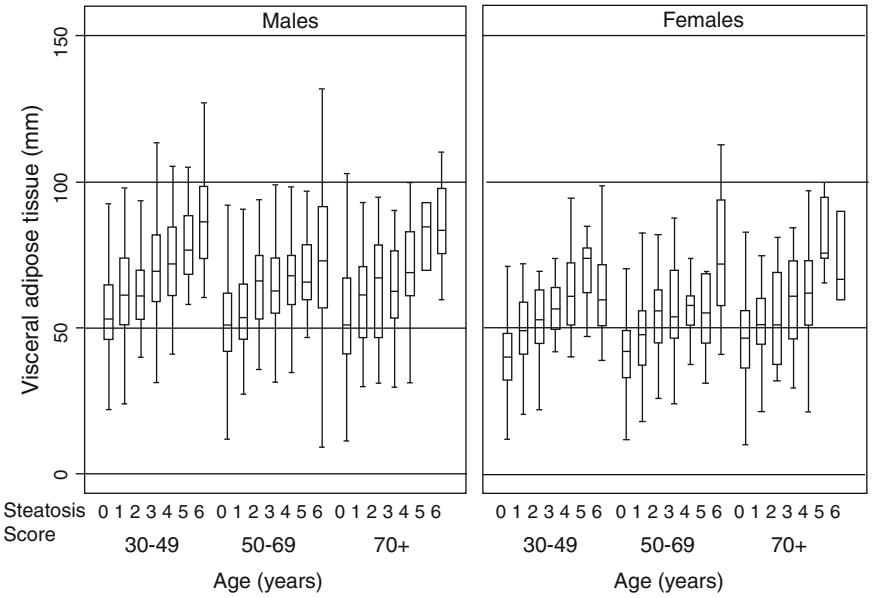

Fig. 137.4 Correlation between the liver steatosis score and visceral adipose tissue, stratified by age and gender

liver in the general population studied is 42.3%, of which 35% is accounted for by non-alcoholic and 7.3% by alcoholic fatty liver disease (anamnestic data). Furthermore, the percentage of subjects with scores ranging from 1 to 6 is similar in non-alcoholic and alcoholic steatosis.

As shown in these tables and in Figs. 137.3–137.5, there is a linear correlation between the fatty liver score, the BMI, and the thickness of the subcutaneous and visceral abdominal fat.

Table 137.6 Correlation (Pearson's r) of the ultrasonographic total liver steatosis score with anthropometric measurements and laboratory variables

	Males		Females	
	r	*p-value*	r	*p-value*
Weight (kg)	0.43	<0.0001	0.49	<0.0001
Height (cm)	−0.004	0.88	−0.14	<0.0001
BMI (kg/m²)	0.49	<0.0001	0.53	<0.0001
Waist circumference (cm)	0.49	<0.0001	0.52	<0.0001
Hip circumference (cm)	0.39	<0.0001	0.47	<0.0001
Systolic blood pressure (mmHg)	0.14	<0.0001	0.22	<0.0001
Diastolic blood pressure (mmHg)	0.20	<0.0001	0.19	<0.0001
Cholesterol (mg/dL)	0.09	0.0001	0.09	0.001
Triglycerides (mg/dL)	0.26	<0.0001	0.34	<0.0001
Glycemia (mg/dL)	0.18	<0.0001	0.30	<0.0001
GPT (U/L)	0.18	<0.0001	0.17	<0.0001
Alkaline phosphatase (U/L)	−0.02	0.37	0.17	<0.0001
Total Bilirubin (mg/dL)	−0.03	0.24	−0.06	0.03
HDL cholesterol (mg/dL)	−0.17	<0.0001	−0.23	<0.0001
LDL cholesterol (mg/dL)	0.02	0.40	0.05	0.07
GOT (U/L)	0.04	0.07	0.09	0.001
GGT (U/L)	0.16	<0.0001	0.10	0.0004
Abdominal subcutaneous fat thickness (mm)	0.025	<0.0001	0.35	<0.0001
Abdominal visceral fat thickness (mm)	0.46	<0.0001	0.47	<0.0001

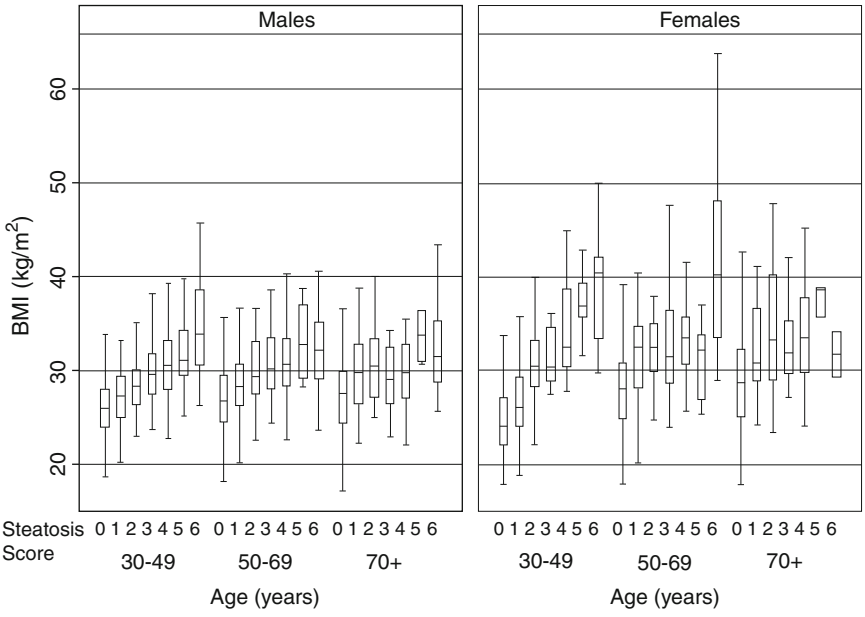

Fig. 137.5 Correlation between the liver steatosis score and the BMI

137.5 Conclusions

The findings presented in this paper show that ultrasonography can be useful to detect fatty liver and abdominal (subcutaneous and visceral) fat accumulation, and that fatty liver and visceral fat, evaluated by ultrasonography, are correlated. Fatty liver and visceral fat accumulation are associated with the metabolic syndrome. Therefore, fatty liver and visceral fat measured by ultrasonography can be useful parameters helping to better characterize the metabolic syndrome, and to evaluate the effects of behavioral and/or clinical interventions. The good agreement between two radiologists in the ultrasound evaluation of fatty liver suggests that sonography can be used for epidemiological studies and clinical research. In the hands of a skilled gastroenterologist or radiologist, ultrasonography could complement the evaluation of liver diseases, including fatty liver. Since ultrasonography cannot distinguish a simple fatty liver from steatohepatitis, that is detected only by liver biopsy, further studies are required to assess the relationship between fatty liver and steatohepatitis graded by histopathology and visceral fat accumulation. Ultrasonographic evaluation of fatty liver and of visceral and subcutaneous abdominal fat can also be used by nutritionists to evaluate body composition, as a noninvasive integration of bioimpedentiometry and DEXA.

Summary Points

- Obesity is highly prevalent in Western industrialized countries and is associated with increased visceral fat and with liver steatosis.
- Standardized measurements of liver steatosis and visceral fat can be made by ultrasonography, and these measurements can be used to monitor the effect of behavioral and drug interventions.
- The relationship between anthropometric parameters and fatty liver measured by ultrasound was evaluated in 94 obese children. A fatty liver was positively associated with the BMI, subscapular and suprailiac skinfold thickness, and waist and hip circumference.
- Liver steatosis and visceral and subcutaneous fat were measured by ultrasonography in a population sample of 2,966 subjects resident in an area of Southern Italy. The grading of liver steatosis is directly associated with the BMI and visceral fat in males and females in all age ranges.

Acknowledgments The authors wish to thank Vito Guerra for the statistical analysis and his assistance in the preparation of the manuscript.

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Chapter 138
Dissecting the Architecture of Bone Strength-Related Phenotypes for Studying Osteoporosis

Xiaojing Wang and Candace M. Kammerer

Abstract This chapter provides a brief overview of methods being used to dissect the underlying architecture of bone strength-related phenotypes, especially with regard to identifying risk factors for osteoporosis, a complex, common disease. The first section comprises a brief background on the known genetic and environmental factors that influence development of osteoporosis. In the next section, we describe the concept of bone strength and how studies of its components may facilitate our understanding of the etiology of osteoporosis. The advantages and disadvantages of several state-of-art two and three dimensional imaging technologies used for assessment of components of bone strength in human populations are described in the third section. These methods include: dual x-ray absorptiometry (DXA), quantitative computed tomography (QCT), quantitative ultrasound (QUS), and magnetic resonance imagining (MRI). In the fourth section, results from the use of different methods of bone assessment on an Afro-Caribbean population are compared. Finally, we describe how these methods could potentially be extended to study other complex diseases.

Abbreviations

aBMD	Areal bone mineral density
BMI	Body mass index
CSA	Cross-sectional area
DXA	Dual x-ray absorptiometry
ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase 1
ESR1	Estrogen receptor-α
LRP5	Low density lipoprotein receptor-related protein 5
MRI	Magnetic resonance imagining
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
SSI	Strength strain index
SXA	Single X-ray absorptiometry

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_138,

TFS	Tobago Family Study
TGFBR3	Transforming growth factor, beta receptor III
vBMD	Volumetric bone mineral density
WNT	Wingless-type

138.1 Introduction

138.1.1 Osteoporosis and Osteoporotic Fracture

Osteoporosis is a systemic skeletal disease characterized by low bone mass and the microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures.

Osteoporosis is prevalent among the elderly, both sexes, and all racial groups. Although most US women under the age of 50 years have normal bone mass (usually measured as bone mineral density, BMD), 27% have low bone density (osteopenia). The most clinically meaningful trait for the consequences of osteoporosis, and the one resulting in serious individual and societal concerns is fracture. In 2000, the estimated worldwide incidence of osteoporotic fractures was nine million, and 56.2 million persons had a fracture-related disability [Fast facts on Osteoporosis, National Osteoporosis Foundation]. Osteoporotic fractures are responsible for considerable pain, decreased quality of life, lost workdays, disability, and even death; greater than 25% of people with hip fractures die within 5 years of fracture. By the age of 80 years, 70% of women are osteoporotic at the hip, lumbar spine, or forearm. Epidemiologic studies from North America have estimated the lifetime risk of common fragility fractures among white women aged 50 years to be 17.5% for hip fracture, 15.6% for clinically diagnosed vertebral fracture, and 16% for distal forearm fracture. The corresponding risks among men are 6%, 5%, and 2.5%, respectively. A British study using the General Practice Research Database estimated the lifetime risk of any fracture to be 53.2% for 50-year-old women and 20.7% for 50-year-old men. Thus, a substantial number of older men and women are at increased risk for fractures.

The prevalence of hip fractures varies widely among and within countries. In general, people who live in latitudes farther from the equator seem to have a higher incidence of fracture. The highest rates of hip fracture are seen among individuals living in northern Europe, especially in Scandinavian countries, where the age-adjusted 1-year cumulative incidence was 903/100,000 for women and 384/100,000 for men in Norway in 1989. Fracture incidence rates are intermediate in the populations of Asia, China, and Kuwait and lowest in populations with African ancestry. Whereas studies in central Norway suggest stabilization in fracture rates in recent years, a study from California reported a doubling of hip-fracture rates among Hispanic patients, whereas no significant change occurred among men or women of African or Asian ancestry. An Australian study concluded that, although the increase in hip-fracture rates during most of the past century may have ended, the number of admissions for hip fracture is still rising because of an aging population. Although fracture incidence in developing countries is lower, this difference is partially explained by demographics; for example, in Latin America, only 5.7% of the population is over 65 years. As the population ages, the incidence of fractures is likely to increase in these countries. Further compounding this expected increase in fracture risk is the poor appreciation of the role of osteoporosis in fragility fracture in some countries. For example, in one Lebanese study, fewer than 10% of hip-fracture patients received any therapy for osteoporosis.

Although fractures are the most clinically meaningful consequence of osteoporosis, they are stochastic events resulting from both bone-related factors (mass, size, architecture, microarchitecture, and intrinsic properties of bone material) and bone-independent factors (falls, protective responses, soft-tissue padding, etc.). Because the pathogenesis of fragility fracture usually involves trauma, it is not necessarily associated with reduced bone strength, and should be used neither synonymously nor interchangeably as a phenotype for osteoporosis. The most commonly used surrogate for bone strength is BMD, especially areal BMD (aBMD) that is measured by dual X-ray absorptiometry (DXA, described in more detail later). In fact, the operational definition of osteoporosis is aBMD of the hip or lumbar spine that is ≤2.5 standard deviations below the mean aBMD of a reference population of adults.

138.1.2 Identifying Genetic and Environmental Factors That Influence Fractures or aBMD

The etiology of osteoporosis involves a complex interplay of environmental and genetic factors. Knowledge of the environmental and genetic risk factors for osteoporosis is important for several reasons: first, it will facilitate our understanding of the pathophysiology of the disorder, as well as identify individuals at increased risk. In addition, such knowledge will contribute to the clinical treatment of individual patients and may even help in the design of individual-specific preventative strategies – one of the goals of personalized medicine. In the short term, identification of specific environmental factors will benefit discovery of additional genes that influence susceptibility for developing osteoporosis; filtering out the effects of environmental 'noise' should increase detection of genetic 'signals'.

138.1.2.1 Environmental Risk Factors

Environmental risk factors of osteoporosis can be grouped into different categories: those that influence the risk of falling and responses to trauma; those that influence the accretion and loss of BMD throughout the life course; and those that influence the skeletal strength independent of BMD. The most important factor influencing BMD is age. Beginning in early adulthood, continuous irreversible bone loss happens throughout the aging process. In fact, bone mass decreases, whereas bone size and area may be enlarged, resulting in weaker bone. Another major risk factor is gender; in general, men have stronger bones than women and, hence, the prevalence of osteoporosis in men is less than in women. However, the relationship between gender and bone is not constant over time, partly due to hormonal changes. For example, in women, BMD decreases sharply after menopause, most likely due to estrogen depletion. By contrast, the strong correlation between higher BMD and elevated prostate cancer rate in older men appears to be related to endogenous levels of hormones, growth factors, and cytokines. Gender differences in bone loss may also be due to other factors, such as calcium scarcity, especially during breast-feeding. The third important risk factor of BMD is body weight (or related factors, such as BMI, body fat mass, and body lean mass). Considerable evidence supports its role as a strong positive determinant of bone strength by exerting continuous stress (loading force) to stimulate bone growth. Geographic ancestry also influences risk; individuals with European or Asian ancestry have lower BMD, whereas individuals of African descent have higher BMD and lower fracture incidences. Other environmental risk factors associated with fracture risk or low BMD include: smoking status, dietary intake, medical history, *etc*.

138.1.2.2 Genetic Risk Factors

Although environmental factors play an important role in osteoporosis, heredity is also important, as indicated in part by the relationship between geographic ancestry and fracture risk or BMD. A trait is heritable if relatives are more similar (e.g., they are more likely to have osteoporosis) than are non-relatives. One method by which to quantify the degree of similarity is to estimate the heritability. This is the proportion of the total phenotypic variation in a trait that is attributable to genes and is usually assessed using data on twins or families. There is substantial evidence that genes influence the risk of osteoporosis and BMD. For example, compared to individuals with no affected relatives, the risk of vertebral fracture among men with one affected first-degree relative is threefold greater (OR: 2.9; 95% CI: 1.4–6.0) and is fourfold greater (OR: 4.4; 95%CI: 1.4–14.4) among those with two or more affected first-degree relatives. Furthermore, as estimated from both twin and family studies, the heritability of bone mineral density (BMD) ranges from 0.5 to 0.8. BMD is heritable in both younger and older individuals (including individuals well into the eighth decade of life), as well as in men and women of different ethnicities.

After determining that fracture risk and BMD are heritable, numerous studies have been performed in attempts to identify specific loci that influence these traits. A variety of study designs and analytical methods have been used, such as linkage analysis of families with a history of osteoporosis, families or sibling pairs drawn from the normal population, and sib pairs who are discordant for BMD values. Linkage analyses methods test for the co-segregation of a specific phenotype with a set of polymorphic genetic markers, and thus enable localization of a putative gene that may influence the specific trait. These linkage studies have revealed numerous loci that may influence BMD, of which the most important to date was the identification of LRP5, a gene that is involved in the Wnt-signaling pathway that plays a central role in controlling embryonic bone development and bone mass. Although numerous loci have been identified, there has been little consistency among these reports.

In addition to linkage studies, many genetic association studies have been performed. These studies test whether alleles or genotype frequencies differ among individuals with or without osteoporosis or whether mean BMD differs among individuals with different genotypes. Association studies can be performed using genotypes on candidate genes, that is, genes in specific biological pathways known to influence BMD, such as those coding for bone matrix proteins, steroid hormones, and regulators of local bone metabolism. Alternatively, association studies can be performed using data on genotypes across the entire genome. Examples of genes that have been robustly associated with BMD across multiple cohorts include: estrogen receptor-α (ESR1), LRP5, vitamin D receptor, and TGFBR3 (transforming growth factor, beta receptor III).

As described above, multiple environmental and genetic factors that influence fracture risk, osteoporosis, and/or BMD have been identified, but not all studies report consistent results for all of the risk factors. In part, these inconsistencies are attributable to the differences in the etiologies of BMD (a measure of bone strength) versus fractures (a measure of bone strength plus from trauma). Furthermore, effects of the known environmental factors and genes do not account for a large proportion of the population variation in risk of osteoporosis. In fact, effects of known genetic variants account for <10% of the estimated heritability of BMD. Because bone is a complex tissue, with multiple components, that changes over time, it is unclear which, if any, bone trait is a good measure (or surrogate) of osteoporosis and fracture risk or whether multiple measures are needed. Thus, other possible reasons for the above inconsistencies include interactions among the environmental (and genetic) risk factors, as well as possible differential effects on different aspects of bone metabolism and/or different bone compartments.

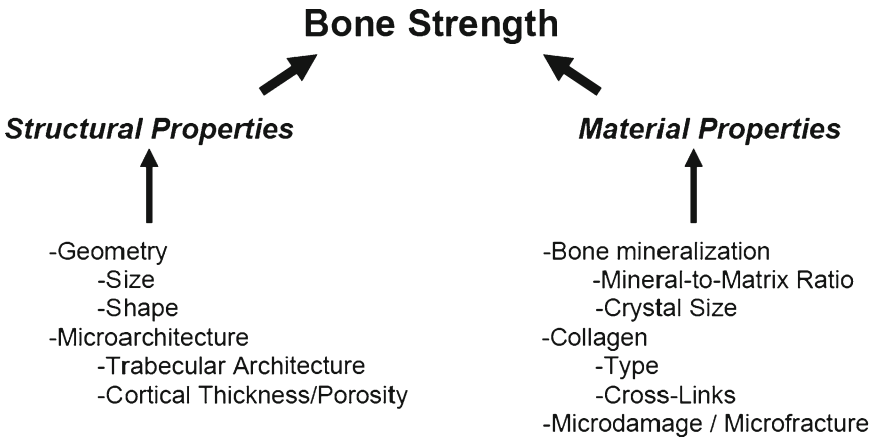

Fig. 138.1 The bone quality framework

138.1.3 Components of Bone Strength

Bone is a geometrically complex and composite material that has an array of mechanical properties; therefore, no simple phenotype is adequate to describe "bone strength." In fact, bone strength is determined by the overall quality of bone, such as bone size, cortical thickness, and trabecular microarchitecture (thickness, number, and connectivity of the trabeculae). Bone strength is usually defined as the "totality of features and characteristics that influence a bone's ability to resist fracture." As depicted in Fig. 138.1, bone strength comprises two components: structural properties and material properties. The structural properties of bone include microarchitecture (trabecular architecture and cortical thickness/porosity) and geometry (size and shape). The microarchitecture of bone is a composite of trabecular architecture (which represents the orientation, thickness, and spacing of the trabeculae, as well as the extent to which the trabeculae are interconnected) and cortical thickness and integrity.

The structural geometric properties of bone, such as the size, thickness, shape, and spatial distribution of bone mass in cross section, also have profound effects on bone strength and fracture propensity independent of BMD. For example, the ability of vertebral bodies to resist compressive forces is directly proportional to their cross-sectional area (CSA), a geometric property. Another important geometric measure is bulking ratio, an indicator of cortical bone instability. It is estimated as the ratio of the femoral neck width to the average cortical thickness. To further assess bone mechanical properties, investigators have also derived composite measures that integrate measures of bone architecture and geometry. One example of such a measure is strength strain index (SSI). It is calculated as the product of section modulus and volumetric cortical BMD normalized to the maximal physiological cortical BMD of human bones. SSI is well acknowledged in the bioengineering field to be a good surrogate measure of bone strength.

Finally, the material properties of bone include its mineral and collagen composition as well as the number, size, and localization of microdamage. Bone turnover (a bone remodeling process accompanied by removal of old bone and its replacement by new bone) rate is a function of the bone renewal process (modeling and remodeling) in which old or damaged bone is reabsorbed and new bone is created to replace it. Bone tissue is composed principally of inorganic bone apatite

crystals that mineralize an organic type I collagen matrix. The degree of mineralization, the material properties of the collagen matrix, crystal size, and the mineral-to-matrix ratio are all important for bone strength.

138.1.4 Assessment of Bone Strength

Considerable progress has been made in the recent years for development of noninvasive assessment of the skeleton, especially for many of the components of bone described above, which has enabled earlier detection of osteoporosis, as well as monitoring its progression and response to therapy. The capability now exists to evaluate the peripheral, central, or entire skeleton as well as the trabecular or cortical bone envelopes accurately and precisely, with the capacity to determine bone strength and predict fracture risk. A variety of methods are currently available to assess geometric and densitometric or even microarchitectural properties of bone: radiographic absorptiometry including both single and dual X-ray absorptiometry; quantitative computed tomography (QCT) including both standard and high-resolution QCT; quantitative ultrasound (QUS); and magnetic resonance imaging (MRI).

138.1.4.1 Key Facts of Radiographic Absorptiometry and DXA

Radiographic absorptiometry was the first quantitative technique to assess integral bone and it is restricted to measurements of appendicular bones, such as metacarpals, phalanges, or calcaneus, which are surrounded by a relatively small amount of soft tissue. Single X-ray absorptiometry (SXA) can be a valuable method in the diagnosis of osteoporosis because the machines used are portable, it is quick, results in low radiation exposure, and provides reasonable assessment of BMD at appendicular sites. It is still used in some studies. However, the precision is low and it is unable to assess bone density at bone sites, such as the hip, that are of major clinical concern.

Dual-energy X-ray absorptiometry (DXA), a two-dimensional measurement, is the most widely used modality for assessment of bone health. This method, which is mostly used for measuring BMD, is sensitive, but not specific, to prediction of fractures in individuals. Studies show that 50–70% of total bone strength can be attributed to aBMD; however, one meta-analysis reported a false positive rate of 15% while using aBMD when predicting hip fracture. The technique is attractive because it is noninvasive, is easily applied for both healthy individuals and patients, and the radiation dose is extremely small. Scanning times, which have been an impediment to its use in pediatric studies, have decreased substantially with newer technology. A further attractive feature is its ability to provide regional body composition analysis, such as body fat, fat-free mass, and bone mineral content for the total body, as well as subcompartments (e.g., legs). However, the DXA measurement device is expensive and not easily transportable. Furthermore, it only provides an overall measure of bone density, and is unable to assess bone health of different bone compartments, such as cortical versus trabecular bone. This latter limitation is especially critical because recent studies indicate that effects of age and other factors differ between cortical and trabecular bone. These differences may be due to the observation that the mineral contents and presumably the metabolism, of these two compartments, differ; for example, mineral tissue makes up 10–35% versus >90% of total tissue volume for trabecular and cortical bone, respectively. This inability to distinguish between bone compartments may explain some of the conflicting results regarding effects of genetic or environmental factors obtained from analyses of BMD in different populations.

138.1.4.2 Key Facts of Quantitative Computed Tomography (QCT)

Quantitative computed tomography (QCT), a three-dimensional imaging technology, can determine the true volumetric density (mg/cm^3) of both trabecular and cortical bone at different skeletal sites simultaneously, as well as measures of skeletal geometry, one of the other major components of bone strength (Fig. 138.1). For assessment of skeletal geometry, QCT imaging permits a direct measurement of vertebral and proximal femoral volumes and cross-sectional areas. The reliability of volume estimates based on projected areas (from radiographs or DXA images) is limited by inaccuracies in the use of simple analytic formulas to describe bone shapes and by errors in the projected areas themselves (caused by patient size or rotation, scoliosis, lordotic curvature, etc.). Thus, a two-dimensional view of a complicated structure does not provide an adequate estimate of its character. Because a volume is imaged, QCT scans may be reformatted along any axis, and geometry can be directly measured in a standardized view. QCT has several essential advantages over DXA; first, QCT measures BMD volumetrically (mg/cm^3) and is independent of bone size. By contrast, DXA provides a measure of areal BMD (g/cm^2) that is confounded by bone size differences. This confounding effect is best illustrated by a comparison with DXA measures of areal BMD in men and women: aBMD is greater in men versus women, but volumetric densities are similar. Thus, gender differences in vertebral bone mass and strength are due to greater bone size in men, not due to differences in volumetric density. A second major advantage of QCT compared with DXA is that it separately measures trabecular and cortical BMD (Fig. 138.2). Both cortical and trabecular BMD influence the mechanical integrity of bone. Measures of trabecular BMD may confer the highest risk for fracture and are more sensitive to changes in bone metabolism. By contrast, DXA yields a measure of integral BMD (i.e., cortical and trabecular) – a "confounded phenotype."

In clinical practice, QCT has been used to assess vertebral fracture risk and follow the progression of osteoporosis and other metabolic bone diseases. Moreover, due to the finer image quality, QCT-based bone measurements have been utilized to evaluate age-related bone loss, sex, and ethnic differences in bone density and geometry at different skeletal sites. However, as with DXA, the equipment to measure QCT is expensive and not easily movable and this limits some of its usefulness for large population-based studies.

138.1.4.3 Key Facts of Quantitative Ultrasound (QUS)

Several attractive features of QUS are low cost, portability, ease of use, and, most important, lower or zero dosage of radiation compared to DXA and QCT. Similar to QCT technology, QUS devices can assess trabecular and cortical bone compartments separately and also measure characteristics of bone strength independent of bone density. QUS measures ultrasound transmission velocity and ultrasound attenuation and both of these parameters are influenced by density and by bone microarchitecture. Because osteoporosis is characterized by decreased bone mass and deteriorated microarchitecture within bone tissue, composite measures of ultrasound transmission velocity as well as ultrasound attenuation may better reflect the bone strength and be closer correlated to clinic disease. However, poor precision and limited assessment of peripheral bone sites have limited the use of this technology as a first-line diagnostic tool in clinical practice.

138.1.4.4 Key Facts of Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is a 3-D imaging method that uses magnetism, rather than ionizing radiation, to produce high-definition images of bone. It has higher resolution than either QCT

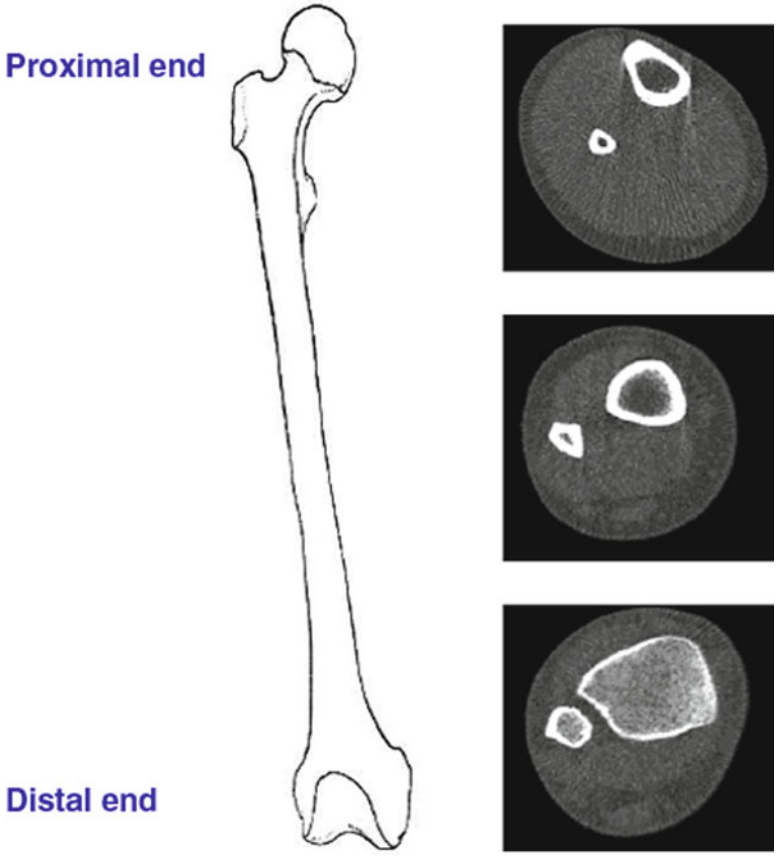

Fig. 138.2 Trabecular and cortical bone compartment measures by QCT. More trabecular bones (*shaded area*) at the distal end compared with more cortical bones (*lighted area*) at the proximal end of long bone

or QUS and produces a positive image of the interstitial space between trabeculae and a negative image of the bone matrix. Evidence from numerous clinical studies has shown that MRI-derived measurements of trabecular microarchitecture reflect the bone morphology changes across age and by disease status (Fig. 138.3). In addition, it successfully discriminates between patients with hip or vertebral fractures and healthy individuals. Despite the merits of MRI, there are two major drawbacks that have hindered the utilization of this technology: high cost and time-consuming procedures.

138.1.5 Dissect the Genetic and Environmental Determinants for Bones: Examples from Tobago Family Study

In this section, we present insights gained from the use of two bone-imaging methods, DXA and QCT. In particular, we present results on the genetic and environmental factors influencing bone architecture from the ongoing Tobago Family Study (TFS). The Tobago Family Study comprises eight multigenerational pedigrees with 471 individuals (283 women and 188 men) ranging in age

Fig. 138.3 Three-D reconstruction of bone microarchitecture by high-definition Micro-CT. *Left*: trabecular bone from healthy individual; *Right*: trabecular bone from osteoporotic individual (Source: http://www.sdu.dk/om_sdu/institutter_centre/klinisk_institut/forskning/forskningsenheder/ortopaedkirurgi/forskningsomraader/eksperimentel%20forskning/microct.aspx?sc_lang=en)

from 18 to 103 years (mean age = 43 years). These families represent a relatively random sample of the Tobago population and were recruited without regard for health outcome; the only criterion was that at least eight living, first-degree relatives were willing to participate in each family. Also, in general, men and women from Tobago have low levels of non-African admixture.

138.1.5.1 Example 1: Mean Bone Change by Age, Sex, Race, and Skeletal Compartments

The incidences of osteoporosis and osteoporotic fracture are known to be lower among individuals of African ancestry than among their Caucasian and Asian counterparts. Mean BMD is typically around 10% higher (about one standard deviation) among individuals of African ancestry versus other ancestral groups, and this difference is not explained by environmental covariates, including body size and physical activity. Furthermore, this difference is present at all ages and in both sexes. For example, Fig. 138.4a, depicts cross-sectional means of total hip aBMD obtained from DXA for men and women at different ages in the TFS, as well as published cross-sectional values for non-Hispanic African Americans and non-Hispanic European Americans in the US NHANES III study. As expected, aBMD decreases across age and men have higher bone density than women for all groups. Furthermore, mean aBMD at the hip was higher among men and women from Tobago versus non-Hispanic European Americans and non-Hispanic African Americans had intermediate values. The higher aBMD among the Tobago population versus African Americans is consistent with their higher average proportion of African ancestry (94% vs. 80%, respectively) based on genetic markers providing information on ancestry. Because 2-D DXA measures are available for many cohorts and some measures have been obtained longitudinally (rather than in cross section, as presented here), these data have been useful to assess age-related changes, as well as differences between genders, ancestral groups, and other environmental and genetic factors.

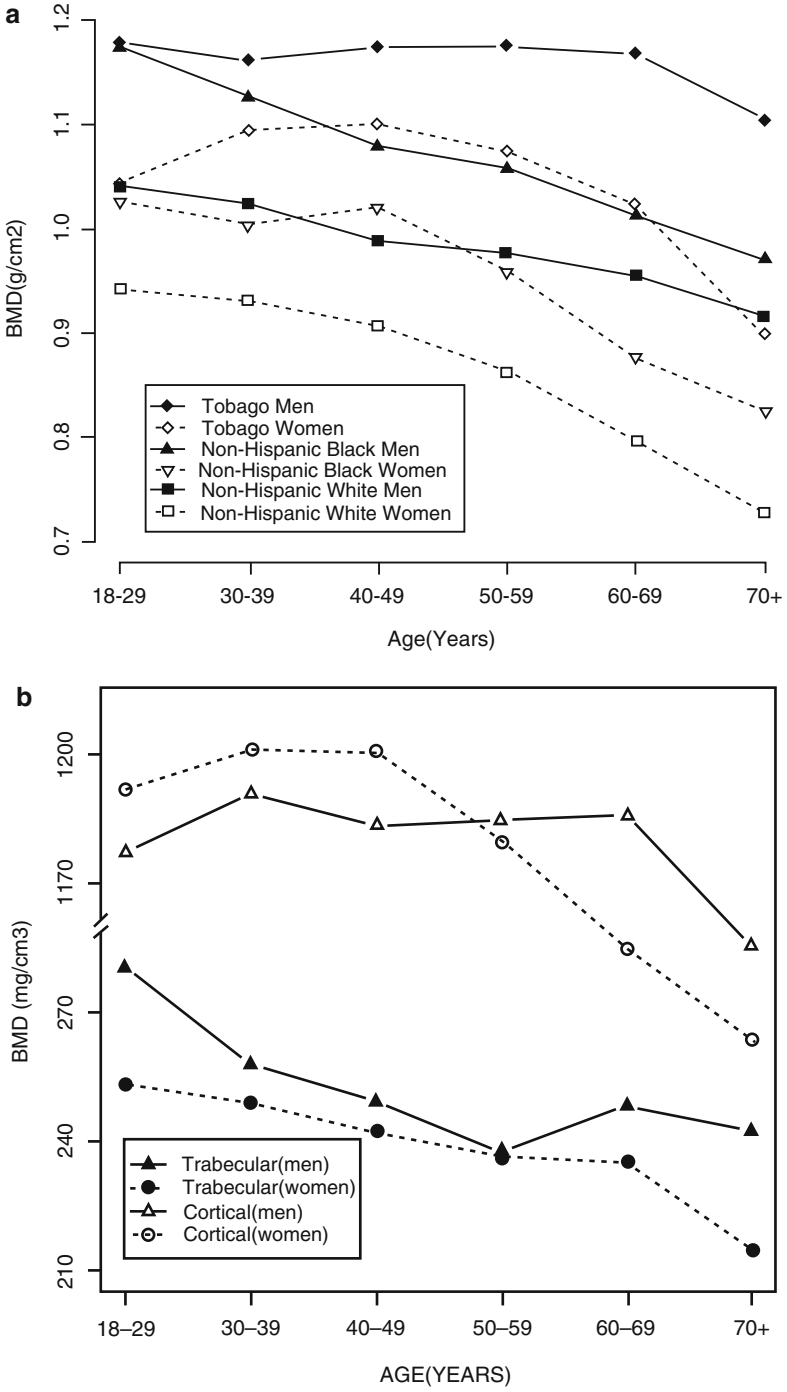

Fig. 138.4 (**a**) Age- and sex-specific means of total hip BMD among Tobagonians and US non-Hispanic whites and non-Hispanic blacks. (**b**) Trabecular and Cortical Mean BMD at Tibia by age and gender among Tobago family members

Table 138.1 Examples of environmental correlates for bone density phenotypes in Tobago family members [a, b, c]

	Age	*Gender*	*Weight*	*Smoking*	*Menopause status*	*Parity*
DXA Areal BMD (g/cm²)						
Lumbar spine	+ **		++ **		—— **	
Femoral neck	— **	+++ *	++ **		—— *	++ ^
Total hip	– *	++++ **	++ **		— *	
pQCT Volumetric BMD (mg/cm³)						
Trabecular, radius	— **	++++ **	++ **	—— ^	—— ^^	
Cortical, radius		– *	– *		— **	+ *
Trabecular, tibia	— **	++++ **	++ **	—— ^^		
Cortical, tibia	– **		– *		— **	++ **

[a] Symbols indicate positive (+) and negative (–) correlation. The strength of the correlation is indicated by the number of symbols: one symbol indicates less than 1% difference; two symbols, a 1–5% difference; three symbols, a 5–10% difference; and four symbols indicate a 10% or greater difference

[b] $^p < 0.10$, $^{^}p < 0.05$, $^*p < 0.01$, $^{**}p < 0.001$

[c] Code female as baseline

As described in the previous section, newer bone-imaging methods allow the assessment of subcompartments of bone, such as using cortical versus trabecular volumetric BMD. Figure 138.4b shows mean volumetric BMD (vBMD) of cortical and trabecular BMD at the tibia. As can be seen, mean trabecular vBMD was again higher in men than women at all ages and generally decreased with increasing age. By contrast, mean cortical vBMD was higher in women than in men until age 50 years, at which point, it decreased markedly in women, but remained fairly constant with advancing age in men, at least until the oldest age group (70+). The patterns observed among the Tobago population are very similar to those reported by Riggs et al. (2004) in US European Americans. These observations illustrate that different bone compartments may have unique features and that phenotypes measured by 3-D image techniques may be more useful for dissecting the underlying genetic and environmental factors.

138.1.5.2 Example 2: Identifying Environmental Factors Influencing BMD Phenotypes

We also mentioned previously that, in addition to age and sex, numerous environmental factors have earlier been reported to influence aBMD, although these results are not always consistent in different populations. In Table 138.1, we present results from an analyses of several environmental factors on measures of aBMD and vBMD obtained in the Tobago Family Study. In general, measures of aBMD and vBMD at different skeletal sites were higher in men than in women, decreased with increasing age, and increased with increasing body weight. Although aBMD and vBMD were measured at different skeletal sites, and, thus, a direct comparison is not possible, there are intriguing differences for other environmental factors. Smoking status was not significant at any aBMD site in the TFS study (although it is significant in some studies), however, it was correlated with cortical, but not trabecular vBMD. Likewise, these results indicate that parity has a strong effect on cortical vBMD, but is only significant for femoral neck aBMD and not total hip or lumbar spine. These results indicate that some environmental factors might only influence one bone compartment (trabecular or cortical) and that the inconsistent results across populations may reflect differences in the relative contribution of trabecular versus cortical vBMD to measures of aBMD (which is a combination of trabecular and cortical BMD).

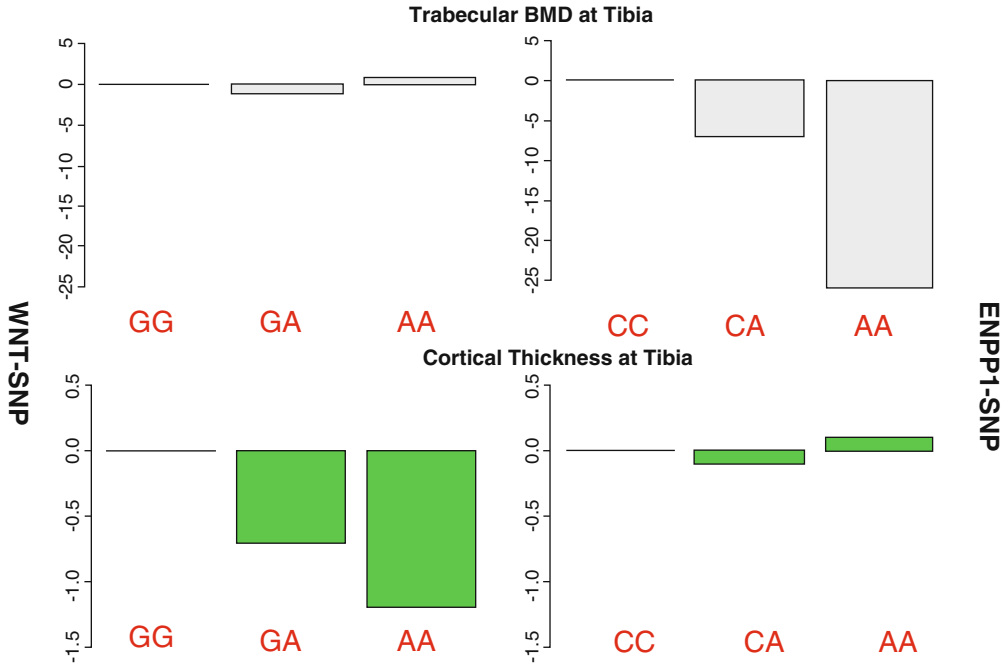

Fig. 138.5 Histogram of adjusted means by genotype for SNPs at WNT and ENPP1 genes. A/C/G/T represents nucleotides of purines (A/G) and Pyrimidines (C/T). *Upper left*: Mean of trabecular BMD by WNT SNP; *Upper right*: Mean of trabecular BMD by ENPP1 SNP. *Lower left*: Mean of cortical thickness by WNT SNP; *Lower right*: Mean of cortical thickness by WNT SNP

138.1.5.3 Example 3: Genetic Effects on Bone Phenotypes

In addition to assessment of environmental factors, analyses of genetic factors influencing different bone compartments (as measured by 3D imaging methods) may reveal insights regarding possible underlying mechanisms. As we described earlier, in general, heritability of aBMD measured by DXA ranges from 40% to 80% of the total population variation, and similar results were obtained for the TFS. However, using data on vBMD measured at the radius and tibia in TFS, heritability of trabecular vBMD was higher ($h^2 \sim 0.5$) than that of cortical vBMD ($h^2 \sim 0.25$). Subsequent analyses indicated that a common set of genes influenced trabecular (or cortical) vBMD measured at both skeletal sites, whereas, at least some of the genes that influenced trabecular vBMD differed from those that influenced cortical vBMD. Figure 138.5 presents specific examples of two genes that have differential effects on different bone compartments. Both genes are members of biological pathways that are involved in bone metabolism. As can be seen, a polymorphism in Wnt10b (one of 19 genes in wingless-type (WNT) family and part of the LRP5 pathway mentioned earlier) is significantly associated with cortical thickness, a measure of bone geometry, but not trabecular vBMD. By contrast, ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1) has significant association with trabecular vBMD, but not with cortical thickness.

In summary, using data from the TFS, we illustrate the use of 2D and 3D imaging methods to assess genetic and environmental factors that influence measures of bone strength. These results indicate that results of 2D imaging methods can be useful because many different populations have been assessed using these methods. However, analyses of data from 3D imaging methods indicate

that metabolism of different bone compartments may intrinsically differ; therefore, imaging technologies which can distinguish these different bone compartments are required for additional insights on the genetic and environmental architecture of bone strength. These results also indicate that single-bone phenotype is not sufficient to assess bone strength. Thus, it is possible these two types of phenotypes represent different characteristics of bone quality.

138.1.6 Application to Other Areas of Health and Disease

The 2-D and 3-D imaging technologies described above can be readily applied to studies of other health-related traits, such as obesity and sarcopenia (loss of muscle mass). Both obesity and sarcopenia are associated with increased risk of other diseases, including cardiovascular disease, diabetes, and osteoporosis, although the fundamental biological pathways by which this occurs are still unclear. Over the past few decades, a variety of genes and environmental factors that influence levels of obesity have been identified, even though much of this research has used body mass index (BMI), a relatively crude measure of obesity. Although BMI, measured as weight in kilogram/(height in meters)^2, takes into account both height and weight, it does not consider the lean-to-fat ratio. For example, two individuals can have the same BMI, but one could have more lean and the other more fat mass. Furthermore, many studies indicate that distribution of fat mass, such as abdominal versus hip fat, is associated with risk of chronic diseases, such as type 2 diabetes. Thus, use of 2D and 3D imaging methods, rather than BMI and waist circumference, should facilitate our understanding of environmental and genetic factors influencing obesity. In fact, more recent studies of visceral fat and intramuscular fat measurements (obtained by 3D methods) indicate that these measures are more highly correlated with risk of diabetes than is assessment of BMI alone. As with measure of BMD, improved definition of obesity again may lead to identification of specific genetic and environmental factors that influence these traits, as well as identification of individuals at risk.

Studies of sarcopenia, a disease associated with degenerative loss of skeletal muscle mass with aging, can be greatly improved by use of 2D and 3D imaging methods as well. Currently, many studies indirectly assess sarcopenia using measures of strength (such as leg strength or grip strength). Although such measures may be clinically important, the use of such a measure is similar to the use of fractures to assess osteoporosis. Studies of lower leg lean muscle mass (measured by DXA), together with measures of muscle attenuation (by CT scan), hold promise as potentially reliable surrogates for muscle quality.

In addition to the use of 2D and 3D imaging methods to assess genetic and environmental risk factors for osteoporosis, obesity, and sarcopenia separately, these methods can be used to assess the intrinsic connections among these body composition measurements. For example, bone strength and muscle mass decrease with increasing age, whereas fat mass increases. Furthermore, at younger ages, lean mass is the main predictor of BMD, presumably in part due to mechanical stresses, whereas, at older ages, fat mass is a better predictor of BMD. In addition to effects of age, Irwin et al. (2009) reported that active exercisers experienced significant decreases in percent body fat, increases in lean mass, and no change in BMD compared to random controls. Finally, evidence is accumulating that these three body compartments may be influenced by a similar set of genes, as well as unique sets of genes. Thus, the use of 2D or 3D imaging methods should greatly facilitate our understanding of the underlying mechanisms and interrelationships among osteoporosis, obesity, and sarcopenia. This knowledge should lead to identification of at-risk individuals and development of preventative strategies and treatment modalities.

Summary Points

- Osteoporosis is a complex disease, which is regulated by multiple risk factors including both environmental and genetic determinants and their interactions;
- Disentangling the effects of genetic and environmental factors on osteoporosis requires expertise in genetic epidemiology and related fields.
- Bone strength is the ability of bone to resist fracture and is composed of both structural and material properties.
- 2-D and 3-D imaging technologies provide different surrogate measures of bone strength, and each imaging method has strengths and weaknesses.
- Analyses of different components of bone strength, such as geometry versus bone architecture, indicate that genes and environmental factors may have differential effects on these components.
- Bone strength cannot be represented by any single measure of bone phenotype so far, but studies of the different components of bone strength may lead to better estimates of individual risk and treatment modalities.

Acknowledgments This work was supported, in part, by grants R03-AR050107 and R01-AR049747 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

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Chapter 139
Body Composition and Lung Function

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and Francesco Fantin

Abstract A growing body of evidence indicates that excess body weight is associated with a wide range of health conditions, including respiratory diseases. Cross-sectional studies have demonstrated an inverse relationship between body mass index and pulmonary function evaluated by spirometry. Longitudinal studies have shown that increases in body weight can lead to a reduction in pulmonary function.

Although the influence of obesity on pulmonary function tests has been examined, there are limited studies that evaluate the influence of body fat distribution on pulmonary function tests in overweight and moderate obesity.

It has been previously shown that body fat distribution has an effect on pulmonary function. In particular, the excess of visceral fat has a negative effect on lung function and is inversely associated with chest wall compliance. A consistent negative association between waist circumference and pulmonary function has been demonstrated in normal weight, overweight and obese subjects, suggesting that the fat mass stored in the abdominal cavity, particularly visceral fat, most likely directly impedes the descent of the diaphragm leading to primarily restrictive respiration impairment.

An increased neck circumference has been suggested as a better sign of obstructive sleep apnoea than waist and BMI.

In the elderly the amount of body fat and a central pattern of fat distribution correlate negatively with lung function, whereas the amount of fat-free mass correlates positively with lung function. The age-related combination of fat free mass loss and fat gain, so called "sarcopenic obesity", may have additive negative effects on pulmonary function.

Abbreviations

FEV1	Forced expiratory volume in 1s
FVC	Forced vital capacity
FM	Fat mass
FFM	Fat-free mass
BMI	Body mass index
WHR	Waist hip ratio

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_139,

COPD	Chronic obstructive pulmonary disease
OSAS	Obstruction Sleep Apnoea Syndrome
MRI	Magnetic resonance imaging
CT	Computer tomography
VAT	Visceral adipose tissue
SCAT	Subcutaneous adipose tissue
SAD	Sagittal abdominal diameter
OR	Odds ratio

139.1 Introduction

Obesity is a chronic disease and is associated with increased mortality.

Multiple health problems are common among the obese and include cardiovascular and metabolic diseases (e.g., non-insulin-dependent diabetes, ischemic heart disease, stroke, and dyslipidemia). Obesity is linked to a wide range of conditions including chronic obstructive pulmonary disease (COPD), asthma, obesity hypoventilation syndrome, pulmonary embolism, aspiration pneumonia, and obstructive sleep apnea (Chen et al. 2002). Fat distribution, more than excess of body fat itself, is linked to reduced lung function (Santana et al. 2001; Nishimura et al. 1995). Fat distribution is usually measured by waist circumference, sagittal abdominal diameter (SAD), and waist-to-hip circumference ratio (WHR). A high WHR is a proxy measurement for an excess of intra-abdominal fat. Body fat percentage, body fat mass, and fat-free mass, evaluated by DXA, and body fat distribution, evaluated by CT and MRI, are more commonly used in studies examining the effects of obesity.

In this chapter, we first describe the relationship between excess body weight and lung function. Second, we discuss the relationship between lung function and body fat distribution evaluated by anthropometry. Finally, we delineate the importance of the effects of age-related body composition changes on worsening of lung function.

139.2 Body Weight and Lung Function

A growing body of evidence indicates that excess body weight is associated with a wide range of health conditions, including respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma (Chen et al. 2002).

Cross-sectional studies have demonstrated an inverse relationship between body mass index (BMI; in kg/m^2) and pulmonary function tests (i.e., FEV1 and FVC) (Wise et al. 1998; Santana et al. 2001; Jones and Nzekwu 2006).

This is of particular importance since FEV1 and FVC are independent predictors of all-cause mortality (Schunemann et al. 2000) and a strong risk factor for cardiovascular disease, stroke, and lung cancer (Cook et al. 1994).

Longitudinal studies have shown that increases in body weight can lead to a reduction in pulmonary function (Nishimura et al. 1995). In an 8-year Italian longitudinal study, Bottai et al. evaluated BMI, spirometry, and carbon monoxide diffusing capacity in over 1,000 subjects from a general population (aged >24 years), observing that most of those who lost weight improved their lung function and those who gained weight reduced their lung function (Bottai et al. 2002) (Table 139.1).

Table 139.1 Key features of the relation between body composition and lung function in older adults

1. Cross-sectional and longitudinal studies have shown that body composition changes with aging, with an increase in fat mass and a decrease in muscle mass.
2. Body fat distribution also changes with age with visceral fat increase and subcutaneous fat decline
3. With aging, there is also loss of muscle mass, a process called sarcopenia, and an increase of the amount of fat inside and around muscles
4. Lung function has been shown to be inversely proportional to fat mass, but positively proportional to fat-free mass in the elderly
5. Sarcopenic obesity may have additive negative effects on pulmonary function

This table lists the key facts regarding relationships between body composition and lung function

A 10-year longitudinal study of middle-aged men in Northern Ireland showed that the decline in lung function was greater in those who had the largest increases in BMI over the study period. The rate of decline in FEV1 increased by 2.9 ml per year per unit increase in BMI over 10 years.

The detrimental effect of weight gain on lung function has been shown to be greater in men than in women, probably due to gender-related differences in fat distribution (Chen et al. 2007).

It must also be considered that a strong relation between underweight and weight loss and pulmonary function worsening has been observed. This is particularly significant in certain clinical conditions, such as COPD (Nishimura et al. 1995), and in the elderly (Tockman 1994). Actually, it should be considered that the relation between body weight and BMI with pulmonary function is not linear and that some important issues should be borne in mind when evaluating the relation between BMI and lung function. First, BMI does not allow distinguishing between fat mass and muscle mass, which have opposite effects on pulmonary function (Wise et al. 1998; Santana et al. 2001). Second, both weight and height are surrogate measures of body size and important predictors for pulmonary function measurements. Third, a unit of body weight or BMI is likely to have less fat mass for underweight persons and for men than for overweight persons and for women (Chen et al. 1993). In addition, body weight and BMI provide no information on the nature of body fat distribution that may play an important role in the association between obesity and pulmonary function (Chen et al. 1993).

139.3 Body Fat Distribution and Lung Function

Several studies have evaluated the relation between indices of body fat distribution and pulmonary function (Santana et al. 2001; Nishimura et al. 1995; Harik-Khan et al. 2001).

It is well known that body fat distribution is an important predictor of adverse health events, such as diabetes, hypertension, hyperlipidemia, and coronary events (Borkan et al. 1986). In central obesity, most of the fat deposits, both subcutaneous (SCAT) and visceral (VAT), are in the abdominal area (Fig. 139.1). It is well known that visceral fat deposits are more strongly correlated with cardiovascular risk than is the degree of adiposity (Després et al. 1990).

Truncal obesity determines a reduction of respiratory muscle strength and function, lung volumes, and peripheral airway size (Sugerman et al. 1997). Abdominal fat may also alter the pressure–volume characteristics of the thorax and restrict the descent of the diaphragm, thereby limiting lung expansion. Reduced ventilation at the lung bases can lead to the closure of peripheral lung units, ventilation-to-perfusion ratio abnormalities, and arterial hypoxemia, especially in the supine position (Caro et al. 1960). The expiratory reserve volume is also reduced and the work of breathing is increased (Caro et al. 1960) (Table 139.2).

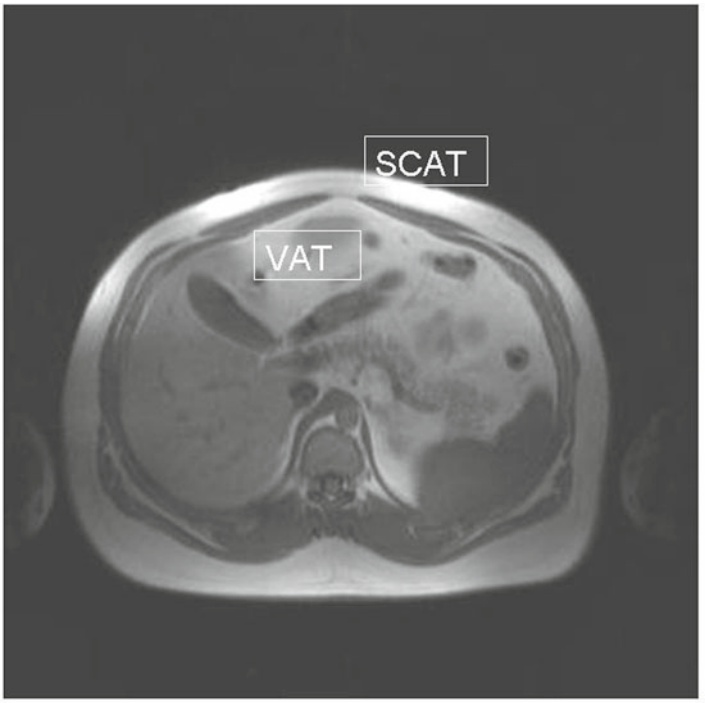

Fig. 139.1 Abdominal fat distribution evaluated by MRI. Transverse T1-weighted MRI image of the abdomen at L3 level, with subdivision of abdominal adipose tissue into subcutaneous adipose tissue (*SCAT*) and visceral adipose tissue (*VAT*)

Table 139.2 Key features of sarcopenic obesity

1. Sarcopenic obesity is a disordered form of body composition characterized by low muscle mass and high level of body fatness
2. Age-related increases in body fatness generally precede the onset of sarcopenia, which appears regardless of level of body fatness
3. The mechanism involved in sarcopenic obesity could be an increased production of TNF-alfa and leptin from adipose tissue, leading to progressive loss of muscle mass and gain in body fat (Roubenoff and Hughes 2000)
4. Prevalence of sarcopenic obesity increases with age, from about 2% to 10% from age 65 to 85 years (Morley et al. 2001)
5. Sarcopenic obesity is more strongly associated with disability and functional limitations than either obesity or sarcopenia (Morley et al. 2001)

This table lists the key facts regarding sarcopenic obesity

It has been shown, at least in obese subjects, that the amount of abdominal fat is inversely associated with chest-wall compliance (Nishimura et al. 1995; Jenkins and Moxham 1991). A consistent negative association between waist circumference and pulmonary function has recently been demonstrated in normal weight, overweight, and obese subjects, suggesting that FM stored in the abdominal cavity, particularly visceral fat, most likely directly impedes the descent of the diaphragm, leading to primarily restrictive respiration impairment (Jenkins and Moxham 1991).

In a cross-sectional study of 1,674 adults, waist circumference was negatively associated with FEV1 and FVC. On average, an increase in waist circumference of 1 cm was associated with a 13-ml reduction in FEV1 and an 11-ml reduction in FVC (Nishimura et al. 1995). Inverse associations

between indices of body fat distribution (i.e., sagittal abdominal diameter and waist circumference) and pulmonary function in men and women with BMI values >25 kg/m^2 were also demonstrated in a random sample of 2,153 healthy individuals with ages ranging from 35 to 79 years (Ochs-Balcom et al. 2006).

In the Baltimore Longitudinal Study of Aging (BLSA), the relation of WHR on FEV1 and FVC was examined in a population of 1,094 men and 540 women (18–102 years) showing that body fat distribution has independent effects on lung function that are more prominent in men than in women (Harik-Khan et al. 2001).

These findings have provided supportive evidence that abdominal adiposity is a better predictor of pulmonary function than weight or BMI.

139.4 Application to Other Areas of Health and Disease

139.4.1 Anthropometry and Obstruction Sleep Apnea Syndrome (OSAS)

It has also been shown that BMI is twice as strong as gender and fourfold stronger than age in predicting OSAS (Fig. 139.2) (Subramanian and Strohl 2004). However, a high amount of fat located in the chest, in the neck, as well as in the abdomen has been clearly shown to be a stronger predictor of OSAS than BMI (Subramanian and Strohl 2004). In a 30-year follow-up study, age, baseline waist circumference, and waist changes were the most powerful predictors of OSAS in old age, in obese as well as in normal-weight men (Carmelli et al. 2000).

An increased neck circumference has been suggested as a better sign of obstructive sleep apnea than other clinical indices and may be up to 77% sensitive and 82% specific for OSAS in patients referred to a sleep clinic (Davies et al. 1992). A prospective study in obese patients with symptoms suggesting sleep apnea showed that neck circumference is more useful as a predictor of obstructive sleep apnea than waist circumference and BMI (Hoffstein and Mateika 1992). Neck circumference (measured in centimeters) is adjusted if the patient has hypertension (4 cm is added), is a habitual

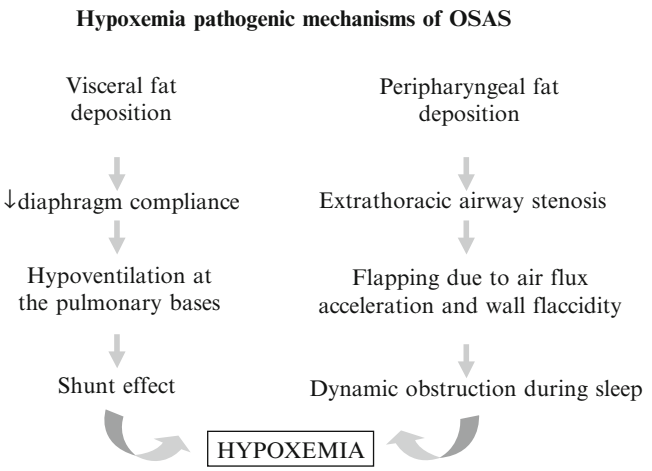

Fig. 139.2 OSAS pathogenic mechanism for Hypoxemia in visceral obesity. Mechanism responsible for respiratory disturbances in visceral obesity

Table 139.3 Key features of OSAS

1. The OSA syndrome is characterized by repeated partial or complete closure of the pharynx, gasping episodes, and sleep fragmentation (Bradley and Floras 2003)
2. Sleep-induced relaxation of the pharyngeal musculature is believed to be the cause of intermittent airway obstruction
3. The physiologic consequences of OSAS are repetitive bursts of sympathetic activity, hypoxia, hypercapnia, increased left-ventricular afterload, and acute hypertension (Bradley and Floras 2003)
4. The daytime hypersomnolence that can occur in obesity is a manifestation of OSAS
5. A person, who has obstructive sleep apnea, often is not aware of the apnea episodes during the night. Frequently, family members witness the periods of apnea

This table lists the key facts regarding Obstruction Sleep Apnea Syndrome

snorer (3 cm is added), or is reported to choke or gasp most nights (3 cm is added). A low clinical probability corresponds to an adjusted neck circumference of less than 43 cm, an intermediate probability (four to eight times as probable as a low probability) to a neck circumference of 43–48 cm, and a high probability (20 times as probable) to a neck circumference of more than 48 cm. Together with the consideration of the severity of symptoms, the clinical-probability estimate helps guide management (Flemmons 2002) (Table 139.3).

139.4.2 Body Composition and Lung Function in the Elderly

With aging, even in the healthy elderly population, a progressive decline in FEV1 and FVC has been observed, independent of smoking or environmental exposure (Enright et al. 1994; Burr et al. 1985). Worsening pulmonary function is clinically relevant because it is associated with increased morbidity and mortality rates (Kannel et al. 1983).

Several factors may contribute to age-dependent decline of lung function.

Cross-sectional and longitudinal studies have shown that body composition changes with aging, with an increase in fat mass and a decrease in muscle mass (Baumgartner et al. 1995).

Even without body weight changes, the amount of fat significantly increases with age (Prentice and Jebb 2001).

In men and women, in both normal weight and obese subjects, body weight tends to increase, peaking at about age 65 years in men and later in women, and then decreasing with further aging (Lissner et al. 1994).

Body fat distribution also changes with age, with visceral fat increase and subcutaneous fat decline.

Aging is also associated with a loss of muscle mass, a process called sarcopenia (Janssen et al. 2002), and an increase of the amount of fat inside and around muscles (Fig. 139.3) (Goodpaster et al. 2001). Both these two changes have been shown to be associated to an increased risk of physical functional decline and disability as well as to an increase in morbidity and mortality (Visser et al. 1998).

Maximal respiratory pressures, an index of the strength of inspiratory and expiratory muscles, decreases with age and is associated with handgrip and FFM (Enright et al. 1994).

Interestingly, in the few reports that investigated the association between the individual components of body composition (i.e., FM and FFM) and lung function, the latter has been shown to be inversely proportional to FM, but positively to FFM (Lazarus et al. 1998).

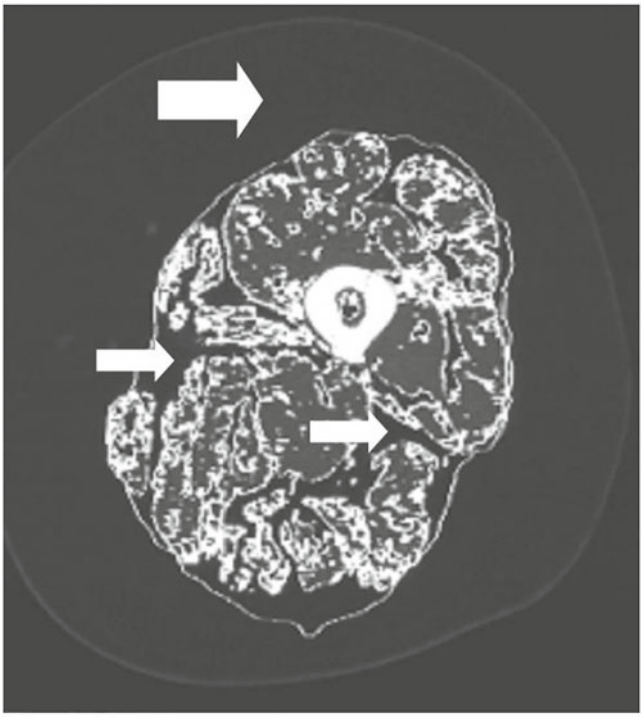

Fig. 139.3 Midthigh CT image of obese subject. Transverse unenhanced CT image obtained at the midthigh in an obese subject depicting subcutaneous (*large arrow*) and intermuscular adipose tissue (*small arrows*). The brighter pixels within the skeletal muscle tissue have attenuation values between 0 and 29 HU and represent low-density (high-fat) muscle. The *darker pixels* have attenuation values between 30 and 100 HU and represent high-density (low-fat) muscle

It may be possible that the loss in muscle and the gain in fat act synergistically to cause disability or metabolic disorders. Recently, the concept of sarcopenic obesity has been proposed (Zamboni et al. 2008) and its relation with physical impairment and disability has been investigated. The concept of sarcopenic obesity should help to understand the complexity of the relation between obesity and mortality and morbidity in the elderly. Sarcopenic obesity may be not recognized with the use of BMI, and, thus, its effect on mortality and morbidity is likely underestimated.

Previous studies have considered the role of body composition changes on lung function decline in the elderly (Santana et al. 2001; Enright et al. 1994; Lazarus et al. 1998; Wannamethee et al. 2005; Tockman 1994). Santana et al. have shown that body composition and fat distribution are associated with lung function in elderly men (Santana et al. 2001). In a population of 97 men aged 67–78 years with BMI ranging from 19.8 to 37.1 kg/m^2, they observed that the amount of body fat and a central pattern of fat distribution correlated negatively with lung function, whereas the amount of fat-free mass correlated positively with lung function (Fig. 139.4) (Santana et al. 2001). This finding has been recently confirmed in a longitudinal study involving 77 elderly men and women evaluated over a 7-year follow-up period, suggesting that the age-related combination of FFM loss and fat gain, so-called "sarcopenic obesity," may have additive negative effects on pulmonary function (Fig. 139.5) (Rossi et al. 2008).

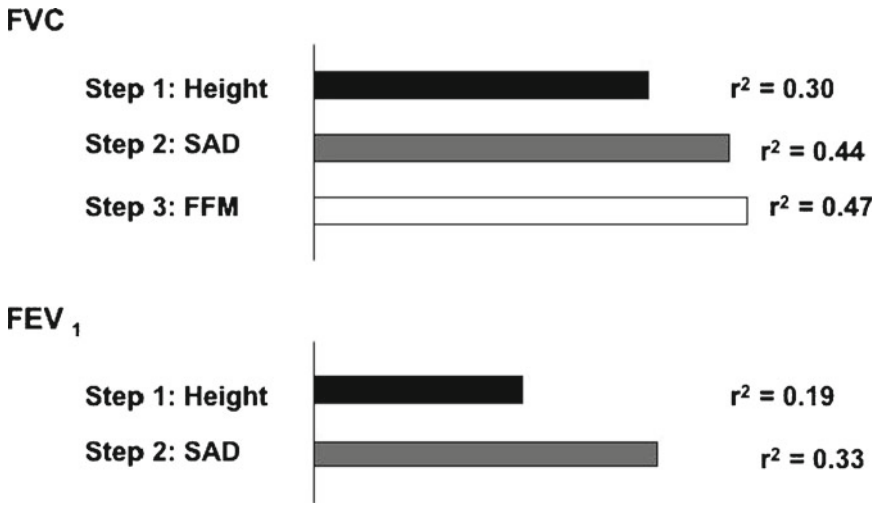

Fig. 139.4 Body composition predictors of lung function in the elderly. Stepwise multiple regression in a population of 97 men, aged 67–78 years with body mass indices (BMIs; in kg/m^2) ranging from 19.8 to 37.1, with use of age, anthropometric measurements, and body-composition variables as independent variables and ventilatory function indices (FEV1 and FVC) as dependent variables (Santana et al. 2001). *FEV1* forced expiratory volume in 1 s, *FFM* fat-free mass, *FVC* forced vital capacity, *SAD* sagittal abdominal diameter

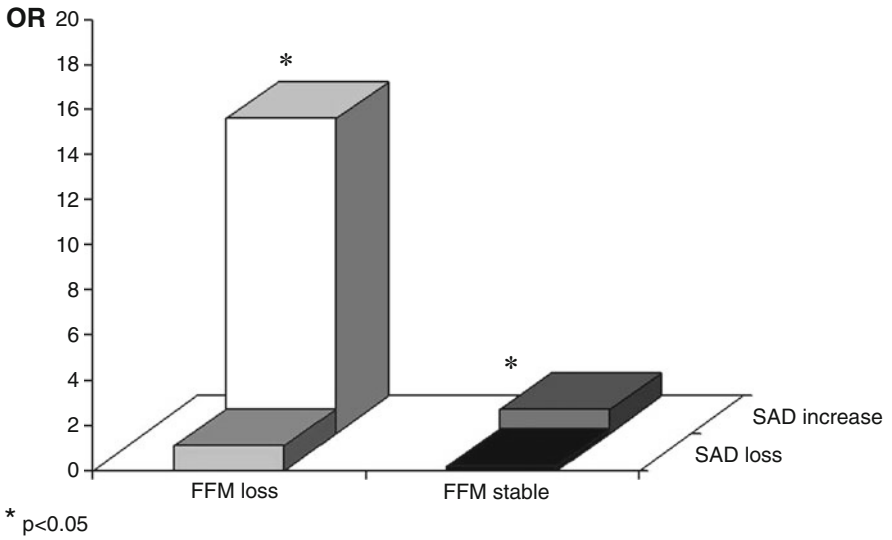

Fig. 139.5 Risk of worsening in FEV1 in the elderly population. Risk of worsening in FEV1 in the elderly population expressed as Odds Ratio (Rossi et al. 2008). *FEV1* forced expiratory volume in 1s, *FFM* fat-free mass, *SAD* sagittal abdominal diameter, *OR* odds ratio

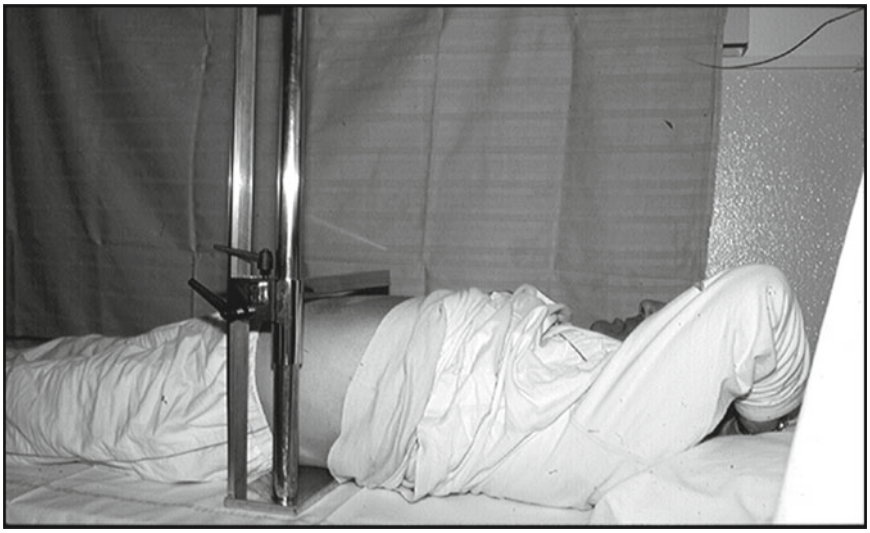

Fig. 139.6 Sagittal abdominal diameter (*SAD*). Sagittal abdominal diameter evaluation with caliper

139.5 Practical Methods and Techniques

139.5.1 Sagittal Abdominal Diameter

Sagittal abdominal diameter (SAD) is defined as the shortest distance between the anterior and posterior trunk at the level of the iliac crest or lowest trunk site. In particular, the measurement is made between the xiphoid process and umbilicus, while the subject breathes softly (Fig. 139.6). The subject should be lying on a rigid surface.

Sagittal diameter can be measured with a Harpender caliper or a CT or MRI scan. Kvist and colleagues showed that sagittal abdominal diameter is highly correlated with visceral fat volume (Kvist et al. 1988) ($r = 0.93$). The caliper must have stability, robustness, and precision.

139.5.2 Neck Circumference

Neck circumference is measured in the midway of the neck, between midcervical spine and midanterior neck, to within 1 mm, with plastic tape. In men with a laryngeal prominence (Adam's apple), it must be measured just below the prominence (Ben-Noun L et al. 2001).

Summary Points

- A growing body of evidence indicates that excess body weight is associated with a wide range of health conditions, including respiratory diseases.
- Both cross-sectional studies and longitudinal studies have demonstrated an inverse relationship between body mass index and pulmonary function evaluated by spirometry.

- The excess of visceral fat has a negative effect on lung function and is inversely associated with the compliance of the chest wall.
- An increased neck circumference has been suggested as a better sign of obstructive sleep apnea than waist and BMI.
- Respiratory function may be affected by body weight, by weight change (both gain and loss), as well as by age-related changes in body composition.
- Age-related combination of fat-free mass loss and fat gain, so-called "sarcopenic obesity," may have additive negative effects on pulmonary function.
- Preventing weight gain, and, in particular, limiting the increase in visceral fat, may be important for reducing the negative effects of aging on lung function.
- In particular, clinicians should be aware that evaluation of body composition should be of clinical relevance even in pulmonary alterations.

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Part XXII
Anthropometry in Special Conditions and Circumstances

Chapter 140
Psychosocial Correlates in the Context of Body Mass Index and Overweight

Helena Fonseca and Margarida Gaspar de Matos

Abstract The potentially serious physical and psychosocial consequences of overweight and obesity have made this condition one of the great contemporary public health issues. However, the earliest and most widespread consequences of adolescent obesity are of psychosocial nature. There is evidence that overweight and obesity in adolescence are associated with significantly lower levels of emotional well-being measures, body image dissatisfaction and social isolation.

Compared with normal weight peers, overweight and obese adolescents express concerns associated with weight more frequently, have a poorer perception of their own health, rate their life satisfaction as lower and are more involved in health compromising behaviours, such as chronic dieting and potentially harmful alcohol consumption. Growing evidence suggests that adolescents with chronic conditions other than obesity, are likely to engage in risky behaviours to at least similar, if not higher rates as their healthy peers, and alcohol has been recognized as the substance most frequently used by young people with a variety of chronic conditions, with little variation by diagnosis. Obesity seems to be similar to other chronic conditions of adolescence, especially in what concerns alcohol use and abuse.

Overweight and obese adolescents should, where possible, be reached with appropriate interventions addressing the broad spectrum of their psychological needs, enhancing their skill development for behavioural change, and providing support for dealing with potentially harmful behaviours.

Abbreviations

BMI	Body Mass Index
EASO	European Association for the Study of Obesity
HBSC	Health Behaviour in School Aged Children
IOTF	International Obesity Task Force
UNWCB	Unhealthy weight control Behaviours
WHO	World Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_140,

140.1 Applications to Other Areas of Health and Disease

There is evidence that a variety of adverse psychosocial factors, including low self-esteem and body dissatisfaction are more common among overweight than among non-overweight teens. A vast number of associations between overweight and psychosocial factors have already been identified, including a poorer self-perceived health status and an increased difficulty in making new friends. Furthermore, when compared with their non-obese peers, overweight adolescents tend to have significantly lower levels of emotional well-being measures. Both potential social isolation and lower levels of emotional well-being may be detrimental to an optimal healthy development of overweight teens.

There is further evidence that overweight youth engage more in weight-control behaviours, both healthy and unhealthy, than their non-overweight peers, with unhealthy weight-control behaviours increasing with perception of body-weight increase. Because most clinicians do not regularly screen for unhealthy weight-control behaviours unless the adolescent is underweight, there is an urgent need to raise their awareness that they need to routinely screen for unhealthy weight-control behaviours when taking care of overweight youth. The design of health-promotion strategies would also benefit from the inclusion of this awareness.

As to date, scarce attention has been paid in surveys to the adolescents who have been excluded from analysis because of missing values for BMI. We know now that these adolescents tend to have poorer body image, poorer health behaviours and poorer social networks. Therefore, a potential bias in the results of studies that do not account for missing BMI may be introduced.

Strategies to prevent adolescent obesity and overweight must take into account a deeper knowledge of psychosocial issues in order to be able to delineate more effective programmes for assessing and treating overweight teens.

140.2 Introduction

In this chapter, the authors focus on behavioural and social correlates of body mass index (BMI) corresponding to overweight and obesity (≥85th and 95th percentiles, respectively) among adolescents.

Obesity results from a chronic energy imbalance such that the rate of energy intake exceeds the rate of energy expenditure. Evidence seems to suggest that in the twentieth century, high-fat food intake has increased and that, at the same time, energy expenditure has declined due to increasingly sedentary lifestyles (Martinez-Gonzales et al. 1999). It is known that obesity is greatly environmentally influenced and that a sedentary lifestyle and sustained physical inactivity may be the main risk factors. Elevated television viewing has already been identified as an important promoting factor for obesity in children. Thus, changes in physical activity and sedentary behaviour seem critical to treating adolescent obesity (Barlow and Dietz 2007).

In 2005, the International Obesity Task force estimated that one out of five European children was overweight (EU Platform 2005). The prevalence of paediatric overweight and obesity increases from north to south with values varying from 10% to 20% in northern Europe to 20–35% in southern European countries.

The potentially serious physical and psychosocial consequences of overweight and obesity have made this condition one of the great contemporary public health issues (Strauss and Pollock 2001; Ebbelling et al. 2002; Lobstein et al. 2004).

The most widespread consequences of adolescent obesity are psychosocial. Adolescence is a very unique and highly individual period in life where important biological and cognitive changes take place. It has been considered a critical developmental period when adolescents are adjusting to

physical changes, establishing their personal identity, seeking greater independence and increasingly relying on peer groups.

Obesity in adolescence carries with it negative connotations leading to important psychosocial problems, in addition to the medical complications (Dietz 1998). Several studies have shown clearly that obese adolescents become targets of early and systematic discrimination and they are ranked lowest as those with whom their peers would like to become friends (Strauss and Pollock 2003, Fonseca and Matos 2005, Fonseca et al. 2009a). Furthermore, they are more prone to develop a negative self-image that appears to persist into adulthood, and low self-esteem (Stunkard 1967). Obese adolescents with decreased levels of self-esteem demonstrated significantly higher rates of sadness, loneliness and nervousness and were more likely to engage in high-risk behaviours such as smoking or alcohol consumption (Strauss 2000). Goodman (Goodman and Whitaker 2002) showed that depressed adolescents are at increased risk for the development and persistence of obesity during adolescence. Other studies also suggested a positive association between depression in adolescence and BMI during adulthood (Pine et al. 2001). However, the nature of the relationship between obesity and mental-health conditions remain unclear.

With the objective of better understanding adolescent obesity, some psychosocial and lifestyle indicators were empirically investigated by the authors using the Portuguese Health Behaviour in School-aged Children (HBSC) data set (Matos et al. 2000, 2003, 2006). The interesting findings may help to better understand overweight adolescents and to what extent they may differ from their peers.

HBSC is a WHO collaborative study started in 1982, now including 41 countries and regions across Europe and in North America (Currie et al. 2008). Data collection occurs every four years. The overall goal of the study is providing evolving information on the health and health-related behaviours of young people as well as their social contexts. In Portugal, data have already been collected three times, in 1998, 2002 and 2006 and included, respectively, 6,903, 6,131 and 4,877 students who were attending the sixth, eighth and tenth grade, corresponding to 11, 13 and 15 years of age, on average. Schools were randomly selected from a national roster of public schools, stratified by region (five Education Regional Divisions). The sampling unit used in this survey was the classroom. In each school, classes were randomly selected in order to meet the required number of students for each grade, which was proportional to the number of same grade mates for each specific region, according to the data provided by the Ministry of Education.

BMI was calculated based on self-reported weight (kg)/height (m^2) using the questions: "How much do you weigh without clothes?" and "How tall are you without shoes?" Adolescents were categorised according to their BMI, based on the standard definition for overweight and obesity and the IOTF-recommended cutoff criteria (Cole et al. 2000).

Measures were defined as has been described in a previous analysis using the HBSC/WHO international survey data. A complete picture of previous uses of the items, their psychometric properties, and measures' validation, can be found in the international study report (Currie et al. 2004).

140.3 Physical Activity and Dieting

According to the research conducted by the authors, obese adolescents were less physically active compared to the non-obese (Fonseca and Matos 2005). Concerning dieting, both females and older teens were revealed to be more likely than males and younger teens to report dieting for weight loss (Fonseca et al. 2009a). Previous studies have already shown dieting to be a more common behaviour among overweight compared with non-overweight adolescents. A large percentage of self-reported overweight (38.0%) and obese (23.1%) adolescents reported not being on a diet because their weight

was fine. Even more striking was the high percentage of non-overweight adolescents (62.5%) reporting being on a diet. There is reason for concern if non-overweight youth are attempting weight loss, as the initiation of frequent dieting is a known risk factor for disordered eating (Patton et al. 1990).

140.4 Body Image

The authors assessed body image using three items: (a) an item measuring *perception of body weight*: "Do you think your body is (1) much too thin, (2) a bit too thin, (3) about the right size, (4) a bit too fat or (5) much too fat?" and (b) a question assessing *other people's perceptions* about one's appearance. Response options included: "they make positive comments," "they make negative comments" and "they do not make comments at all"; and (c) a six-item scale question assessing *body satisfaction/attitude towards appearance*: "Do you think you are (1) very good looking, (2) quite good looking, (3) about average, (4) not very good looking, (5) not at all good looking or (6) don't think about my looks?" Body satisfaction/positive attitude towards appearance was considered when options (1), (2) or (3) were chosen, and body dissatisfaction was considered when options (4) or (5) were chosen.

Identification of perceived body image was used as an interval variable (1–7), with a maximum value meaning a maximum of overweight and a minimum value meaning extreme thinness (Figs. 140.1 and 140.2).

Both obese and overweight adolescents were significantly more likely to report a negative attitude towards appearance and overweight teens were also more likely to report a wish to change something in their bodies (Fonseca et al. 2009a).

BMI, age, involvement in dieting and evaluation of one's physical appearance were found to be key explainers of body image among these adolescents and good predictors of the way these teens view themselves. As we can see in Table 140.1, BMI, involvement in dieting and evaluation of appearance were positively associated, while age was negatively associated (Fonseca and Matos 2005), which alerts us to the need for an early intervention that considers the age differences regarding this topic.

It has already been shown that early onset of obesity has an adverse effect on body image in adult life, and it has been suggested that early onset of obesity increases the risk of body dissatisfaction,

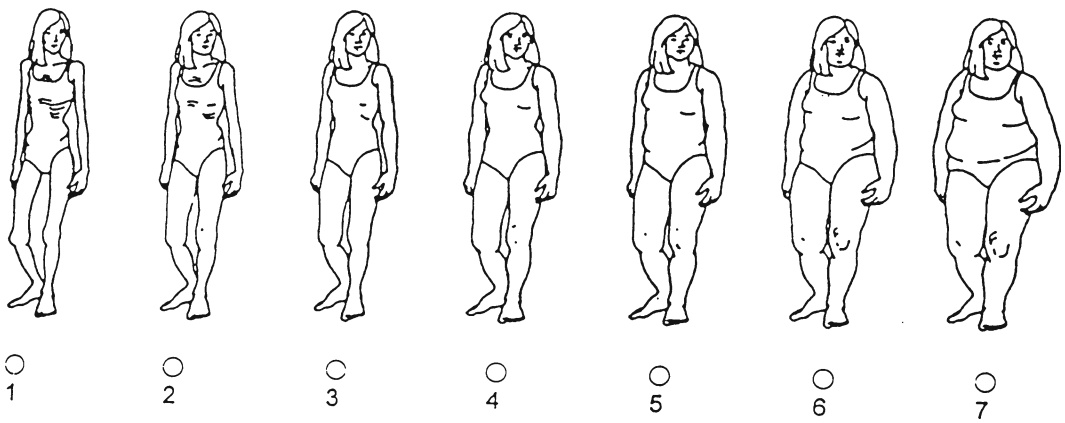

Fig. 140.1 Identification of perceived body image (females). Identification of perceived body image may be used as an interval variable (1–7), with a maximum value meaning a maximum of overweight and a minimum value meaning extreme thinness

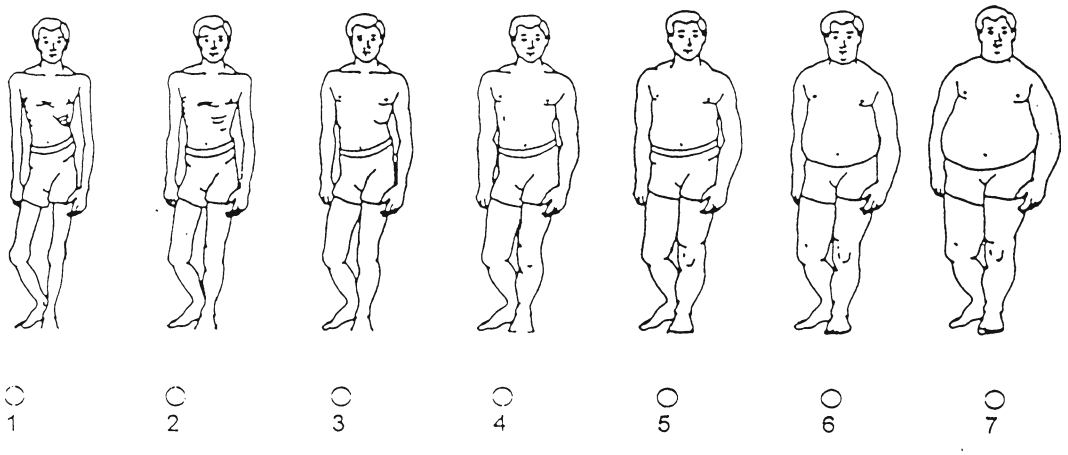

Fig. 140.2 Identification of perceived body image (males). Identification of perceived body image may be used as an interval variable (1–7), with a maximum value meaning a maximum of overweight and a minimum value meaning extreme thinness

Table 140.1 Perception of body image according to body silhouettes (multiple regression) (Reprinted from Fonseca et al. (2005), with permission)

	β	*t*	Significance
BMI	0.491	41.16	0.000
Gender	–0.019	–1.629	0.103 (NS)
Age	–0.413	–34.94	0.000
Physical appearance	0.032	2.718	0.007
Diet behaviour	0.110	9.40	0.000
Constant		32.04	0.000
			$r^2 = 0.349$

BMI, age, involvement in dieting and evaluation of one's physical appearance were found to be key explainers of body image among these adolescents, and good predictors of the way these teens see themselves. BMI, involvement in dieting and evaluation of appearance were positively associated, while age was negatively associated
NS not significant

which in turn impairs self-esteem (Wardle et al. 2002). It has also been shown that a higher BMI is associated with higher body-image dissatisfaction among adolescents, which may impact their psychosocial development in a negative way. The increased risk of body dissatisfaction among obese adolescents suggests another area of investigation into protective factors against overweight and obesity. These results also suggest that strategies to prevent adolescent obesity and overweight must take into account a deeper knowledge of psychosocial issues in order to be able to delineate more effective programmes for assessing and treating overweight teens.

140.5 Association with Psychosocial Factors

A vast number of associations between overweight and psychosocial factors have been identified, including a poorer self-perceived health status (Fonseca and Matos 2005).

Furthermore, when compared with their non-obese peers, overweight adolescents tended to have significantly lower levels of emotional well-being measures, reporting irritability and feeling nervous, more frequently (Fonseca et al. 2009a).

Both potential social isolation and lower levels of emotional well-being may be detrimental to an optimal healthy development of overweight teens.

Overweight adolescents further tended to report more difficulty in making new friends compared to their non-overweight peers (Fonseca et al. 2009a). Being attached to and accepted by the peer group is crucial to young people's development, and those who are not socially integrated are far more likely to exhibit difficulties with their physical and emotional health. Interaction with friends tends to improve social skills and strengthen the ability to cope with stressful events. On the contrary, isolation from peers can lead to feelings of loneliness and poorer emotional health. Interestingly, connection with friends has already been reported as being a protective factor against extreme weight-control behaviours among boys (Fonseca et al. 2002).

In summary, there is evidence that a variety of adverse psychosocial factors, including low self-esteem, body dissatisfaction and depressive symptoms are more common among overweight than among non-overweight teens.

140.6 Quality of Life and Life Satisfaction

To be overweight may represent a major psychosocial burden for an adolescent. Social stigma and marginalisation may, in fact, be a substantial challenge to their social and emotional well-being. A study of obese children and adolescents showed lower health-related quality of life compared with young people of a similar age who had cancer (Schwimmer et al. 2003) and was able to determine the large negative impact this chronic health condition may have on the adolescent.

One possible way of assessing life satisfaction is through the measurement technique known as the *Cantril ladder* with ten steps: the top of the ladder indicates the best possible life and the bottom the worst possible life (Cantril 1965). Adolescents who entered in the HBSC study were asked to indicate the step of the ladder at which they would place their lives at the moment (Fig. 140.3), by answering the question: "Here is the picture of a ladder: The top of the ladder '10' is the best possible life for you, and the bottom '0' is the worst possible life for you. In general, where on the ladder do you feel you stand at the moment?" Life satisfaction revealed to be higher among boys, decreased with progression in age and is lower among adolescents with a higher BMI.

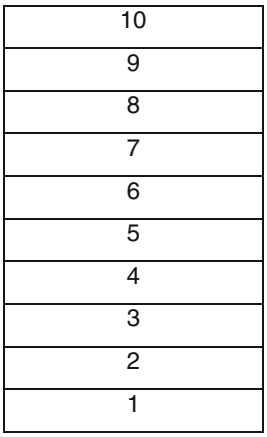

Fig. 140.3 Life satisfaction. Adolescents can be asked to indicate the step of a ladder at which they would place their lives at the moment (the *top* of the ladder indicates the best possible life and the *bottom*, the worst possible life). Overweight and obese adolescents tend to place themselves on a lower step compared with their non-overweight peers

140.7 The Concept of Obesity as a Chronic Condition

Growing evidence suggests that adolescents with chronic conditions other than obesity are likely to engage in risky behaviours to at least similar, if not higher rates, as their healthy peers (Sawyer et al. 2007), and alcohol has been recognised as the substance most frequently used by young people with a variety of chronic conditions, with little variation by diagnosis.

Many papers have been published about specific psychosocial factors associated with obesity in young people. Higher rates of health-risk behaviours, including smoking, among adolescents who diet (whether obese or not) have been reported by some authors. It has also been shown that overweight adolescents are more likely to engage in unhealthy behaviours, such as chronic dieting and binge eating.

Weekly drinking increases substantially in the general population between ages 13 and 15, and alcohol has already been recognised as the substance most frequently used by young people with a variety of chronic conditions. The exposure of obese adolescents to alcohol-consumption patterns associated with heightened risk of injury was studied by the authors who, based on the results of their research, have developed the concepts of the existing literature and propose that obesity is similar to other chronic conditions of adolescence, especially related to alcohol use and abuse (Fonseca et al. 2009a).

In the HBSC survey, alcohol use was assessed by the question: "How many times a week do you usually drink any alcoholic drink?" Response options included: "never," "less than once a week," "once a week," "2–4 days a week," "5–6 days a week," "once a day," "everyday" or "everyday, more than once," while alcohol abuse was assessed with the question: "Have you ever had so much alcohol that you were really drunk?" Response options included: "no, never," "yes, once," "yes, 2–3 times," "yes, 4–10 times" or "yes, more than 10 times."

Obese adolescents reported more regular drinking (drinking alcohol every day more than once) than their non-overweight peers (3.6% vs. 1.2%). They also reported having got drunk more than 10 times, significantly more often than non-obese teens (5.3% vs 2.4%) (Fonseca et al. 2009a).

140.8 Association with Unhealthy Weight-Control Behaviours

Recently, there has been growing attention in the literature to the tendency of different weight-related behaviours and disorders to simultaneously co-occur in the same individuals. Significantly higher percentages of overweight youth have been described to engage in binge eating and unhealthy weight-control behaviours than non-overweight youth (Neumark-Sztainer et al. 2002). Excessive weight-related concerns and behaviours have potentially serious consequences for adolescents in their impact on dietary intake, physical growth and psychosocial development and the development of disordered eating. Strong correlates of disordered eating have been found, including overweight status, low self-esteem, depression, suicidal ideation and substance use.

Concerns with weight, body shape and dieting with the purpose of losing weight are common among adolescents and have been suggested as risk factors for eating disorders. Although weight concerns are less common among males, these concerns are becoming more prevalent. Internalisation of the thin-ideal body image for girls in Western culture results in dissatisfaction with weight and shape, because the ideal body shape and weight are unattainable for most women. According to Stice's theory (Stice et al. 1996), one should expect overweight females to be more dissatisfied with their weight because they are far away from the ideal weight and shape. Thus, it is not surprising that several cross-sectional studies have reported a positive association between weight and engagement in bulimic behaviours. Moreover, family, peer and media pressures to be thin also increase or sustain

Table 140.2 Examples of healthy and unhealthy weight-control behaviours

Healthy weight-control behaviours	Unhealthy weight-control behaviours
Drink more water	Vomiting
Eat less sweets	Laxative use
Eat more fruits/vegetables	Diet pills/teas use
Drink less soft drinks	Smoking more cigarettes
Exercise more	Fasting/skipping meals

The different types of weight-control behaviours tend to present at different degrees, and some of them may be/become extreme

body dissatisfaction by repeatedly reminding women how far away they are from the ideal shape and weight. However, the development of eating disorders is even more complex and is believed to be related to personal factors, family and peer influences and sociocultural pressures.

Weight-control strategies may range from healthy behaviours, such as moderate dieting and exercise, to potentially harmful behaviours, such as vomiting, laxative or diet-pill use and skipping meals (Table 140.2). Correlates of unhealthy weight-control behaviours have been assessed using the Portuguese HBSC Portuguese data set (Fonseca et al. 2009b). The authors found that overweight youth and females engaged more in weight-control behaviours, both healthy and unhealthy than respectively their non-overweight peers and males. Moreover, UNWCB seemed to increase with perception of body-weight increase (Fonseca et al. 2009b).

The gender difference that was found may be understood because of the earlier growth spurt in females and the subsequent increase in percentage of body fat. Another possible explanation is the increased burden put on a girl's body image by society, which may lead to an increased concern about this topic. UNWCBs were also more prevalent among younger youth (13-year olds). Because the question regarding weight-control behaviour was not asked to the sixth graders (11-year-olds), the authors wonder whether they might start even earlier. It would be of interest to further investigate at what age UNWCBs tend to start.

Concrete thinking is still the dominant way of thinking during the first years of adolescence with important implications in behavioural competences. This may explain a higher involvement of younger youth in UNWCB, in an attempt to achieve a faster and more effective control of their weight.

It is well acknowledged that unhealthy weight-control behaviours are unlikely to be effective in weight control and may even inadvertently place youth at risk for further weight gain. Should overweight younger girls be targeted as a specific high-risk group for unhealthy weight-control behaviours? We envisage early adolescence as a window of opportunity for prevention in this regard.

In addition, UNWCBs were significantly higher among those who were dieting and among those who, although not being on a diet, considered they should be. It has already been shown from longitudinal research that the relative risk for dieters to develop an eating disorder is significantly higher than that for non-dieters after a 1-year period (Patton et al. 1990). The association found by the authors between dieting and UNWCB points in the same direction and may have important implications in clinical practice.

Alcohol and drug use have already been described as directly and significantly associated with disordered eating. The authors have further found in their research that UNWCBs were more prevalent among those reporting drinking everyday (Fonseca et al. 2009b). This correlation is understandable as risk factors tend to cluster. As far as we are aware of, a possible interaction between alcohol abuse and UNWCB had not been described in the literature so far. The implications of this potential interaction are huge for clinical practice: adolescents who are referred for alcohol abuse should start being screened for UNWCB and vice versa. The significant positive correlation found between healthy and unhealthy weight-control behaviours suggests that, when young people engage in weight-control behaviours, they try by all their means every kind of strategy, either healthy or

unhealthy. This knowledge may contribute to increase parents' and teachers' awareness for prompt identification of this kind of practices and adequate referral.

Obesity is a large public-health problem in adolescence; thus, a relatively large proportion of youth may be at risk for developing weight concerns and unhealthy weight-control behaviours. Unfortunately, most paediatricians do not regularly screen for unhealthy weight-control behaviours unless the adolescent is underweight. These findings support the need to raise awareness among clinicians that unhealthy weight-control behaviours are a quite common weight-control strategy. Because they are associated with both medical and psychological health risks, routine screening is warranted. Special attention needs to be directed towards youth at greatest risk for disordered eating, including overweight youth.

140.9 Gender Differences

Usually, females are more likely than males to report dieting for weight loss. Females also seem at increased risk regarding higher body dissatisfaction and lower satisfaction with life. Moreover, more weight-control behaviours, both healthy and unhealthy, have been described among females than among males. A better understanding of gender determinants of obesity may inform its prevention and treatment.

140.10 Methodological Considerations

Measuring health through self-reporting on a questionnaire such as HBSC has both strengths and limitations. Among the strengths, one should mention the fact of being standard, enabling comparisons between individuals and countries, noninvasive and ensuring anonymity. However, it limits the depth and coverage of measurements, as compared with qualitative methods. The cross-sectional nature of the study design does not enable us to draw conclusions about the direction of causality between overweight and obesity and the identified associated adverse psychosocial factors. Whether factors such as low self-esteem, poor body image, or even depression lead to obesity or whether obesity causes them, remains unclear. A third limitation is the high percentage (10.8%) of missing BMI values, which may introduce a potential bias. Associations between missing BMI values and a range of demographic, body image and emotional well-being variables have been studied that suggest that those subjects with missing values for BMI tend to have a poorer body image, poorer health behaviours and poorer social networks (Fonseca et al. 2009c). Missing values for BMI were significantly predicted by a younger age, sedentary lifestyle, having a poor body-satisfaction assessment, paternal absence, lack of friends of the opposite sex and poor perception of academic achievement. Implications for potential bias in the results of studies that do not account for missing BMI should be taken into account.

In most studies, pubertal indicators also lack not allowing to adjust for the timing of maturation. Adjustment for the timing of maturation is important, because overweight status in girls is strongly associated with earlier maturation while, for boys, early maturation is associated with a low BMI. Finally, the findings are based entirely on adolescents' self-reports and self-perceptions and biases. Although BMI is considered a reasonable measure with which to assess fatness in children and adolescents, once, subjective indicators of weight and height are used to obtain a BMI score biases in perception and reporting cannot be ruled out. Some authors have suggested that self-report could lead to a fairly good BMI rating, slightly underestimating the proportion of overweight adolescents, while others have questioned the reliability of this procedure.

140.11 Implications and Future Directions

Some of the adverse psychosocial factors that have been discussed throughout this chapter may help us to be more aware of the specific well-being concerns and behaviours among overweight youth. More consistent and comprehensive monitoring of health status, including life satisfaction, mental health and risk-taking behaviours would provide stronger evidence for clinical and preventive efforts that aim to mediate the effect of obesity on the lives of adolescents. The fact that overweight and obesity in adolescence appears to be associated with decreased life satisfaction should inform paediatricians and healthcare planners about intervention strategies and priorities.

A deeper understanding of the social aspects of growing up and becoming an adult being overweight is needed. How does the experience of being overweight as a teen impact one's capacity of engaging in age-appropriate social networks? Are efforts to develop a robust personal identity affected by the fact of being obese? Qualitative studies may help providing some insight into these important questions.

Since most obese adolescents remain obese as adults, this age group is a very important group to reach through preventive programmes addressing issues of health promotion, including body satisfaction, sociability, diet and sedentary lifestyles. One of the implications of this knowledge is the need for early identification, assessment and management of adolescents who exceed a healthy weight for height, gender and age, which would enable healthcare practitioners to start prevention and management of adolescent overweight and obesity earlier, thus decreasing the potential for associated medical and psychosocial problems.

Obesity prevention and treatment efforts might benefit from addressing the broad spectrum of the psychosocial implications of being overweight as a teen, enhancing skill development for behavioural change and providing support for dealing with potentially harmful behaviours, including exposure to alcohol consumption. A better understanding of determinants of obesity may further inform its prevention and treatment.

Health-promotion strategies should be able to enhance the capacity of overweight youth to negotiate the social demands of adolescence.

Summary Points

- Obesity in adolescence carries with it negative connotations leading to important psychosocial problems, in addition to the medical complications.
- A higher BMI is associated with higher body-image dissatisfaction among adolescents, which may impact their psychosocial development in a negative way.
- Overweight adolescents become targets of early and systematic discrimination, being more prone to develop a negative self-image and a low self-esteem.
- A vast number of associations between overweight and psychosocial factors have been identified, including an increased difficulty in making new friends and a poorer self-perceived health status.
- Furthermore, obese adolescents are at greatest risk for disordered eating. Because unhealthy weight-control behaviours are associated with important medical and psychological health risks, the clinician who cares for obese adolescents should routinely screen for unhealthy weight-control behaviours.
- As to date, scarce attention has been paid in surveys to those who are excluded from analysis because of missing values for BMI. Those who do not report their weight and/or height tend to have a poorer body image, poorer health behaviours and poorer social networks.

- Prevention and management of adolescent overweight and obesity should start earlier, thus decreasing the potential for associated medical and psychosocial problems.
- It is necessary to develop health-promotion strategies that enhance the capacity of overweight youth to negotiate the social demands of adolescence.

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Chapter 141
Body Composition Studies in Critical Illness

Lindsay D. Plank

Abstract The systemic inflammatory response which is common to critically ill patients with major traumatic injury or severe sepsis precipitates a metabolic response which leads to rapid and marked derangements in body composition. Our laboratory, designed to measure total body protein (TBP), total body fat (TBF), total body and extracellular water (TBW and ECW), and total body potassium (TBK) in these patients while under the care of the intensive care unit (ICU), has characterized these derangements over a 3-week period from soon after admission to the ICU. Of the 33 patients studied, 21 were admitted to the ICU with blunt injury and 12 with peritonitis secondary to perforation of an abdominal viscus. Body composition assessments were carried out using in vivo neutron activation analysis, dual-energy X-ray absorptiometry, tritium and bromide dilution, and whole-body counting as soon as patients were haemodynamically stable. These measurements were repeated at regular intervals for 21 days. Massive TBP loss occurred which was derived principally from proteolysis of skeletal muscle in the early catabolic phase with later contribution from visceral organs. An aggressive approach to nutritional support of these patients ensured that TBF was unchanged over the course of the study. Trauma patients had retained >6 L and sepsis patients >12 L of resuscitative fluids, mainly in the extracellular compartment, by the time they were haemodynamically stable. After this time diuresis occurred, but in elderly patients (>60 years) the period of ECW expansion was markedly prolonged compared to younger patients (<40 years). The time course of changes in TBK, a measure of the cellular mass of the body, followed a very similar profile to that of TBP. The catabolic features of trauma and sepsis were very similar reflecting the impact of a systemic inflammatory response which is initiated by quite different insults.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
BCM	Body cell mass
DXA	Dual-energy X-ray Absorptiometry
ECW	Extracellular water

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_141,

FFM	Fat free mass
FFMn	Normally hydrated FFM
ICU	Intensive care unit
ISS	Injury severity score
IVNAA	In Vivo Neutron Activation Analysis
SIRS	Systemic Inflammatory Response Syndrome
TBF	Total body fat
TBK	Total body potassium
TBP	Total body protein
TBW	Total body water
TBWn	TBW content of FFMn

141.1 Introduction

Critically ill patients in intensive care present formidable problems for the investigator interested in quantifying the body compositional changes associated with severe illness. All the standard methods for body composition measurement must be re-evaluated in view of the extreme compositional abnormalities seen in these patients. Since the early work of Cuthbertson (1945) it has been recognized that the metabolic sequelae of critical illness include massive erosion of body protein stores, expansion of the body water space, and consumption of body fat stores. Cuthbertson's work more than 60 years ago focused on injured patients and he showed that in the early phase after their injury these patients were in a hyperdynamic state, consuming protein and fat stores at a high rate, and conserving water and salt. This response is characteristic also of the patient admitted to the intensive care unit (ICU) with a severe infection. Indeed, patients surviving resuscitation after major trauma remain at risk of progressive organ failure and death from what appears to be an uncontrolled inflammatory process. This systemic inflammatory response is as if the patient is infected yet a septic cause is usually not identifiable. The term *systemic inflammatory response syndrome* (SIRS) was proposed by the expert consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine (Bone et al. 1992) to describe this generalized inflammatory process. This consensus meeting provided definitions of *SIRS*, *sepsis*, *severe sepsis*, and *septic shock* which have been widely accepted as they standardized terminology which previously lacked precise definition (Table 141.1). These conditions can be considered to form a continuum associated with increasing mortality, typically of the order of 50% for septic shock (Rangel-Frausto et al. 1995).

A number of scoring systems have been developed which grade the severity of critical illness and provide prognostic information. The *Acute Physiology and Chronic Health Evaluation* (APACHE) II score (Knaus et al. 1985) and its sequel APACHE III (Knaus et al. 1991) are most commonly utilized and take into account current biochemical and physiologic indices as well as age and co-morbidity. APACHE II scores, which are calculated within the first 24 h of admission, may range from 0 to 71 with higher scores indicating more severe disease and higher risk of death. For patients with traumatic injury the *Injury Severity Score* (ISS) (Baker et al. 1974) grades each injury, allocated to one of six body regions, on a scale of 1–5 (5 being life-threatening) and sums the highest scores (squared) for the three most severely injured body regions. Hence, ISS may range from 0 to 75.

Our studies of critically ill patients admitted to intensive care have enrolled patients with major trauma or severe sepsis.

Table 141.1 Key features of critical illness: trauma and sepsis

1. Characterized by a systemic inflammatory response or presence of systemic inflammatory response syndrome (SIRS)
2. SIRS describes an abnormal host response characterized by a generalized activation of the inflammatory reaction in organs remote from the initial insult
3. *SIRS* is manifested by two or more of the following:
   Temperature > 38°C or <36°C
   Heart rate > 90 beats/min
   Respiratory rate > 20 breaths/min
   White blood cell count > 12.0×10^9/L, <4.0×10^9/L, or > 10% immature forms (bands)
4. *Sepsis* denotes SIRS plus a documented infection (positive culture for organism)
5. *Severe sepsis* denotes sepsis associated with organ dysfunction, hypoperfusion abnormalities (e.g., lactic acidosis, oliguria, or an acute alteration in mental status), or hypotension
6. *Septic shock* denotes sepsis with hypotension, despite adequate fluid resuscitation, plus hypoperfusion abnormalities
7. *Multiple organ dysfunction syndrome* develops as the extreme manifestation of SIRS and is a consequence of the host response
8. These conditions form a hierarchical continuum associated with progressively higher mortality

This table lists key facts relating to critically ill patients with trauma or sepsis including useful definitions

141.2 A Body Composition Laboratory for Studies in Critical Illness

Since the early 1980s we have maintained a body composition facility designed for critically ill patients which is located within a short distance of the ICU. In this laboratory a compartmental analysis of the body is undertaken in which total body protein (TBP), total body fat (TBF), and total body water (TBW) are measured. TBP is further subdivided into skeletal muscle protein and visceral protein. TBW is also subdivided into extracellular water (ECW) and intracellular water. An estimate of cellular mass of the body is obtained by measurement of total body potassium (TBK). A hoist weighing system consisting of an electrically operated block and tackle attached to a load cell and to a frame that supports a canvas sheet on which the patient lies is used to transfer the patient from the bed to the scanning machines and the body weight is measured during the transfer. These measurements can be performed on patients soon after their admission to the ICU, once they reach haemodynamic stability at which time requirements for inotropic support have stabilized.

141.2.1 Total Body Protein

TBP is measured using prompt-gamma in vivo neutron activation analysis (IVNAA). A whole-body scanning technique is used where the patient is passed through two opposed neutron fields generated by ^{238}Pu/Be sources placed above and below the patient (Mitra et al. 1993). Gamma rays produced from the interaction of neutrons with nitrogen nuclei in the patient are detected using bilaterally placed sodium iodide crystals and suitable calibration allows estimation of total body nitrogen. TBP is calculated from total body nitrogen, by multiplying by 6.25 using the fact that nitrogen in the body is almost exclusively confined to protein at a mean level of 16%. Precision of 2.5% for TBP is achievable with this approach when dual scans of approximately 30 min each (depending on patient height) are used. We have assessed accuracy by scanning anthropomorphic phantoms composed of mincemeat and lard

Table 141.2 Accuracy and precision of the measurement of TBP in association with massive fluid overload

		Mass of protein by IVNAA (g)			
Mass of mincemeat phantom (kg)	Mass of protein by chemical analysis (g)	Normal hydration	Moderate fluid overload	Severe fluid overload	ANOVA[b]
43[b]	5,918 ± 126[c]	6,036 ± 54	6,017 ± 65	6,163±51	ns
		3.4% (2.1–4.8)[d]	4.2% (2.5–5.8)	3.4% (2.1–4.8)	
62[e]	8,624 ± 177	8,552 ± 65	8,640 ± 66	8,597±87	ns
		3.4% (2.3–4.6)	3.4% (2.3–4.5)	4.5% (3.0–6.1)	
75	10,348 ± 211	9,977 ± 80	10,176 ± 87	10,217±73	ns
		3.1% (1.9–4.4)	3.3% (2.0–4.6)	2.7% (1.6–3.8)	
87	11,744 ± 253	11,530 ± 106	11,382 ± 79	11,521±116	ns
		3.6% (2.1–5.0)	2.7% (1.6–3.8)	3.9% (2.3–5.5)	

Results are shown for mass of TBP measured by in vivo neutron activation analysis (IVNAA) and compared with chemical analysis in anthropomorphic phantoms prepared from mincemeat with and without additional fluid (Hill et al. 1993, Table 2, p. 8, Copyright © (1993) Springer, Heidelberg. With permission)

[a]F test for IVNAA protein measurements

[b]This phantom received 3,200 s scans

[c]Mean ± SEM

[d]CV with 95% confidence interval

[e]This phantom received 20 IVNAA scans at each degree of hydration

with and without additional fluid to simulate the conditions that pertain in the patient situation. These phantoms contained a skeleton prepared from calcium phosphate. Each phantom was scanned 15 times in its entirety over approximately 2,000 s to give total counts of nitrogen. Administration of 3–6 L of physiological saline (depending on phantom size) provided moderate overhydration and 6–12 L, severe fluid overload. The results of this simulation (Table 141.2) indicate that accuracy of within 4%, compared to chemical analysis, was obtained and this was not compromised by high levels of fluid overload. Precision of between 2.7% and 4.5% was obtained, depending on phantom size.

141.2.2 Total Body Fat

A whole-body dual-energy X-ray absorptiometer (GE-Lunar model DPX+, Lunar Radiation Corporation, Madison, WI) is used to measure TBF. This technology partitions the body into TBF, fat-free soft tissue, and bone mineral. A fundamental assumption is that the soft tissue is normally hydrated (Pietrobelli et al. 1998) and the massive fluid changes experienced by the typical ICU patient may compromise the validity of the TBF measurements. We have assessed accuracy using the mincemeat and lard anthropomorphic phantoms of known fat content (measured by chemical analysis) and with different levels of over hydration (Table 141.3). It can be seen from the Table that precision for TBF was excellent (around 1.3%) while increasing degrees of fluid overload resulted in increased measured TBF. These increases do not exceed 2.5%. Increasing fluid overload is associated with reduction in the fat fraction to the extent predicted for normal saline by Pietrobelli et al. (1998).

141.2.3 Total Body Water

TBW is obtained by dilution of tritium-labeled water. However, it should be recognized that TBW measurements in critically ill patients are more difficult to obtain than in normal subjects or even the vast majority of sick patients. The fluid accumulation characteristic of ICU patients often includes

Table 141.3 Accuracy and precision of the measurement of TBF in association with massive fluid overload

		Mass of fat by DXA[a] (g)			
Mass of mincemeat phantom (kg)	Mass of fat by chemical analysis (g)	Normal hydration	Moderate fluid overload	Severe fluid overload	ANOVA[b]
43	11262 ± 97[c]	9805 ± 32	10184 ± 49	10125 ± 34	p<0.0001
		1.3% (0.8–1.8)[d]	1.9% (1.2–2.6)	1.3% (0.8–1.8)	
62[e]	16411 ± 140	14641 ± 36	14798 ± 37	15005 ± 36	p<0.0001
		1.1% (0.7–1.5)	1.1% (0.7–1.5)	1.1% (0.7–1.5)	
75	19691 ± 168	19518 ± 67	19777 ± 75	19926 ± 84	p<0.002
		1.3% (0.8–1.8)	1.2% (0.6–1.8)	1.6% (1.0–2.2)	

Results are shown for mass of TBF measured by dual-energy X-ray absorptiometry (DXA) and compared with chemical analysis in anthropomorphic phantoms prepared from mincemeat with and without additional fluid (Hill et al. 1993, Table 3, p. 9, Copyright © (1993) Springer, Heidelberg, with permission)

[a]Fat result dependent on composition of material used as bone equivalent so comparison with chemical analysis in this study does not reflect the in vivo situation

[b]F test for DXA fat measurements

[c]Mean ± SEM

[d]CV with 95% confidence interval

[e]This phantom received 20 DXA scans at each degree of hydration

collections of free fluid within body cavities (ascites, pleural effusions, intraluminal gut fluid, etc.) where mixing of isotope via the circulation is slow. Under these circumstances the period of isotope equilibration can be expected to be variably prolonged from the 2 to 3 h period sufficient in normally hydrated individuals. There may be loss of isotope in urine, nasogastric aspirates, and from fluid via surgical drains during this period of equilibration. In addition, the patients are all receiving IV fluids at moderate infusion rates. These fluids cannot be withheld over the period of isotope equilibration and by virtue of their non-instantaneous mixing with body water lead to a dilution effect in plasma water. Finally, the TBW itself may be changing during the period of isotope equilibration due to imbalance between gains and losses. Streat et al. (1985) addressed these issues and showed that after a 4-h equilibration time the volume of distribution was essentially constant after due consideration was taken of all losses and gains. By sampling of blood at 4, 5, and 6 h after injection of 3.7 MBq of tritiated water a measurement precision of 0.9% was achievable. A correction of 4% for non-aqueous hydrogen exchange is generally applied to the tritium dilution space in order to derive TBW. In the ICU situation, given the often quite massive fluid overload, it is likely that this correction is less than 4% and no correction was applied by Streat et al. (1985).

141.2.4 Extracellular and Intracellular Water

ECW is estimated by the dilution of sodium bromide provided as an intravenous injection of 50 mL of 5% solution. Bromide is distributed very similarly to chloride in the body (Wallace and Brodie 1939) and the "bromide space" is widely used as a measure of ECW volume. The advent of high-performance liquid chromatography as a very sensitive technique for assaying stable bromide (Miller et al. 1989) has effectively eliminated the need to use the radionuclide ^{82}Br which has an inconveniently short half-life (36 h). Bromide is known to penetrate some tissue cells, especially erythrocytes (Edelman and Leibman 1959; Pierson et al. 1978) and a correction needs to be applied for this. ECW can be determined using the formula (Bell et al. 1984):

$$\mathrm{ECW} = 0.90 \cdot 0.95 \cdot \mathrm{Br\ dose} / [\mathrm{Br}]_s$$

where 0.90 is the correction factor for intracellular penetration, 0.95 is the Donnan equilibrium factor for univalent anions, and $[Br]_s$ is the bromide concentration in protein-free serum ultrafiltrate after correction for the basal concentration. As for TBW estimation, equilibration appears to be complete after 4 h. However, it should be noted that a measurable increase in the bromide space beyond a rapid equilibration phase lasting a few hours may occur because of slow permeation of bromide into the CSF particularly (Moore et al. 1968; Pierson et al. 1978). ECW at the time of injection is calculated from the mean of three values derived from 4, 5, and 6 h serum samples by a manner exactly analogous to the method used for TBW. In trauma patients studied by Monk et al. (1996), the overall mean precision for the measurement of ECW varied from 6.9% when a single sample was taken to 4.0% when three samples were taken.

141.2.5 Skeletal Muscle Mass

Regional analysis of the whole-body DXA scanning images is used to estimate appendicular skeletal muscle mass using the method of Heymsfield et al. (1990). In this approach, the fat-free mass (FFM) of the limbs less the mass of wet bone of the limbs (1.82 × appendicular bone mineral content) is assumed to approximate limb skeletal muscle mass. Application of the method to critically ill patients requires a correction to the measured FFM (see below) to account for the deviation from normal hydration of lean tissue commonly seen in these patients. Total skeletal muscle mass is calculated from appendicular muscle mass by multiplying by 1.26, a factor established from the CT scanning of normal subjects (Wang et al. 1996). Protein content of total skeletal muscle is assumed to be 17% (Snyder et al. 1975).

141.2.6 Visceral Mass

Visceral tissue mass is derived from hydration-corrected whole-body FFM (see below) by subtracting the masses of wet bone and total skeletal muscle. The protein content of the visceral compartment is derived from TBP by subtracting the protein in skeletal muscle and the protein content of wet bone. The latter is assumed to be 26% of wet bone mass (Snyder et al. 1975).

141.2.7 Derivation of Hydration-Corrected Fat-Free Mass

Measured FFM (i.e., body weight – TBF) is composed of normally hydrated FFM (FFMn) plus additional fluid such that:

$$\mathrm{FFM} = \mathrm{FFMn} + \mathrm{TBW} - \mathrm{TBWn}$$

where TBW - TBWn represents the deviation of measured TBW from the water that accompanies FFMn. Rearranging this equation:

$$\mathrm{FFMn} = \mathrm{FFM}(1 - \mathrm{TBW}/\mathrm{FFM}) / (1 - \mathrm{TBWn}/\mathrm{FFMn})$$

where TBWn/FFMn is the ratio of TBW to FFM in healthy subjects, found to equal 0.73 in 176 healthy volunteers measured in our laboratory using the techniques described above. An analogous equation applies for hydration adjustment of the FFM of the limbs provided the measured whole-body hydration (TBW/FFM) applies also to the appendicular FFM.

141.2.8 Total Body Potassium

TBK is measured by analysis of the gamma spectrum emitted from naturally occurring K^{40} using a shadow shield counter (Beddoe and Zuidmeer 1986). This radioisotope, which is present in constant proportion (0.012%) in all natural potassium, emits penetrating gamma rays (1.46 MeV) which can be measured by radiation detectors placed around the body. With suitable calibration, the total mass of potassium can be estimated from the measured intensity of the emitted gamma radiation. Precision of better than 3% for this measurement in adults is possible with counting times of 15–30 min providing adequate shielding is provided to reduce natural background radiation levels (cosmic rays and radioactive contaminants in construction materials). Given that TBK is almost wholly (>97%) intracellular, changes in this quantity will tend to reflect changes in cellular mass. The relationship between TBK and body cell mass (BCM) can be determined based on the original assumptions of Moore et al. (1963). By assuming an average ratio for the intracellular K to intracellular N of 3 mmol K/g N and that one quarter of wet cell weight is protein, the BCM can be derived from TBK as follows:

$$\begin{aligned} \text{BCM} &= 6.25 \cdot 4 \cdot \text{TBK} / 3 \\ &= \text{TBK} \cdot 8.33 \end{aligned}$$

where no correction is made for extracellular potassium. However, the quantification of the BCM is dependent on the assumptions that it has an average K:N ratio of 3 in all states of sickness and health and that protein comprises 25% of cell mass even in intensive care patients. In the latter situation the model assumed above is unlikely to hold and it is preferable to assess changes in BCM by monitoring TBK directly.

141.3 Sequential Changes in Body Composition in Critically Ill Patients

We have conducted longitudinal studies of the changes in body composition that occur in critically ill patients with major trauma or severe sepsis. Patients were recruited for these studies soon after admission to the ICU and informed consent was obtained from the patient or, more usually, from their next of kin. As soon as they were haemodynamically stable (day 0), patients were transported to the laboratory for body composition measurements which were repeated 5, 10 and 21 days later. Major trauma patients were also measured on day 15. The criteria for the diagnosis of severe sepsis were those of the American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) consensus statement (Bone et al. 1992). Patients admitted to the ICU with major blunt trauma and an ISS ≥16 were eligible for the study. Twelve patients with generalized peritonitis secondary to perforation of an abdominal viscus completed the protocol. All underwent urgent surgery and were then treated in the ICU. Clinical details are given in Table 141.4. Complete clinical data and results of this study have been published elsewhere (Plank et al. 1998, 2000). Two of the 12 patients died (on postoperative days 24 and 28) but the other 10 survived and left hospital in a median time of 29.5 days. The median time from enrolment to the first body composition scan was 2 days (range 1-4 days). Twenty-one patients admitted to our ICU with major trauma completed the protocol. Eighteen sustained a major blunt head injury and three suffered blunt abdominal trauma. Clinical details are given in Table 141.4. The median time from enrolment to the first body composition scan was 3 days (range 0-5 days). Seven of the 21 patients developed septic complications while in the ICU.

Table 141.4 Characteristics of trauma and sepsis patients

	Trauma	Sepsis
Male/female	18/3	6/6
Age (year)	21 (16–70)	67 (25–76)
ISS	34 (16–59)	
APACHE II		21.5 (12–34)
Days on ventilator	6 (0–24)	9 (2–24)
Intensive care stay (days)	9 (2–26)	13 (3–29)
Hospital stay (days)	35 (12–78)	29.5 (12–120)

Results are medians (range). ISS: injury severity score, APACHE: acute physiology and chronic health evaluation

Demographic and clinical data of 21 patients with major blunt trauma and 12 patients with severe sepsis (With kind permission from Springer Science+Business Media: Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma, p. 631, Plank and Hill (2000), Table 1, © 2000 by the Société Internationale de Chirurgie)

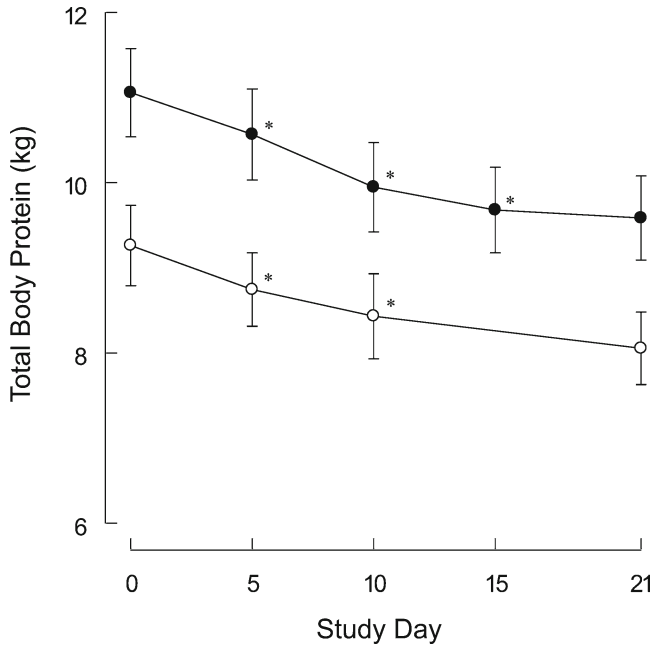

Fig. 141.1 Sequential measurements of total body protein (TBP) in trauma and sepsis. Total body protein in 21 patients with major trauma (*closed circles*) and 12 patients with severe sepsis (*open circles*) measured over a 21-day period after onset of illness (mean ± SEM). In both groups, 13% of the initial body protein was lost over the study period. * = a significant ($p < 0.05$) change from preceding measurement (With kind permission from Springer Science+Business Media: Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma, p. 631, Plank and Hill (2000), Fig. 1, ©2000 by the Société Internationale de Chirurgie)

141.3.1 Total Body Protein Changes

The trauma patients were younger and heavier than the sepsis patients and their absolute body protein stores higher**.** Total protein lost over the 21-day study period averaged 1.47 ± 0.20 (SEM) kg in the trauma patients ($p < 0.0001$) and 1.21 ± 0.13 kg in the sepsis patients ($p < 0.0001$) which for both groups amounted to 13% of day 0 TBP (Fig. 141.1). In both groups losses were greatest during the first 10 days, amounting to approximately 1.0% and 0.9% of TBP/day in trauma and sepsis, respectively.

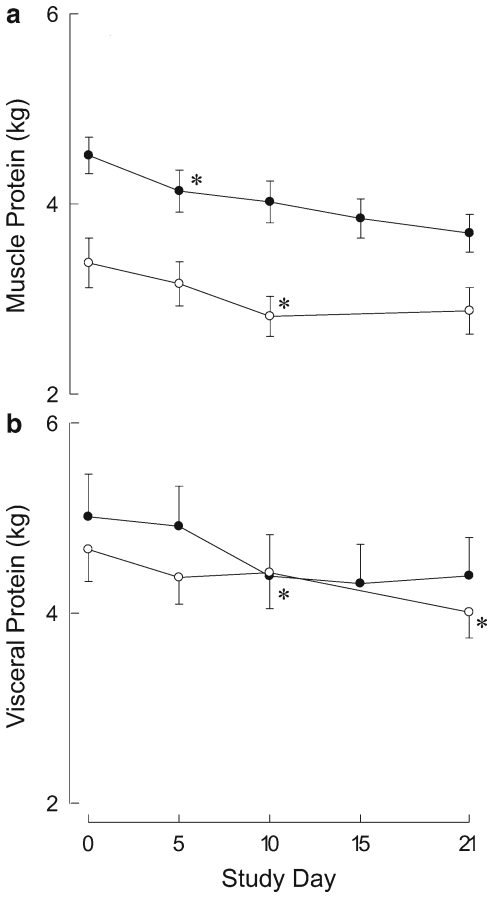

Fig. 141.2 Sequential measurements of skeletal muscle and visceral protein in trauma and sepsis. Skeletal muscle protein (**a**) and visceral protein (**b**) in 21 patients with major trauma (*closed circles*) and 12 patients with severe sepsis (*open circles*) measured over a 21-day period after onset of illness (mean ± SEM). Approximately 70% of the total protein lost over the first 5–10 days was derived form skeletal muscle. * = a significant ($p < 0.05$) change from preceding measurement

141.3.2 Changes in Skeletal Muscle and Visceral Protein

During the first 5 days of the study in the trauma patients and during the first 10 days in the sepsis patients, approximately 70% of the total protein lost came from skeletal muscle (Fig. 141.2). After these times a greater contribution to the protein lost was derived from visceral tissues.

141.3.3 Total Body Fat Changes

In both the trauma and sepsis patients TBF remained essentially unchanged throughout the 21-day study period (Fig. 141.3). The preservation of TBF stores reflects the results of aggressive enteral and/or intravenous feeding adopted with these patients as soon as clinically acceptable.

141.3.4 Total Body Water Changes

The changes in TBW that occurred over the 21-day study period are shown in Fig. 141.4 with estimated pre-illness values. Once haemodynamic stability had been reached (day 0), TBW began to return toward normal. In the trauma group, despite the mean value of TBW returning to the pre-trauma

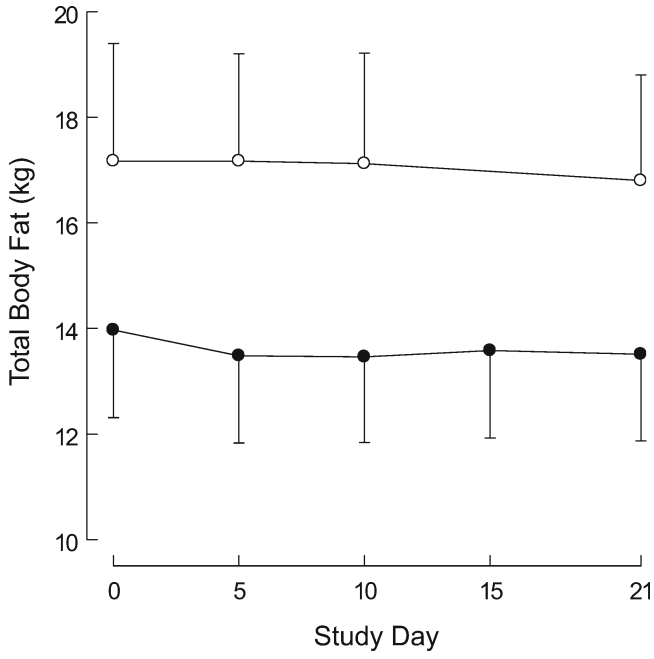

Fig. 141.3 Sequential measurements of TBF in trauma and sepsis. Total body fat in 21 patients with major trauma (*closed circles*) and 12 patients with severe sepsis (*open circles*), measured over a 21-day period after onset of illness (mean ± SEM). In both groups, TBF was preserved over the course of the study

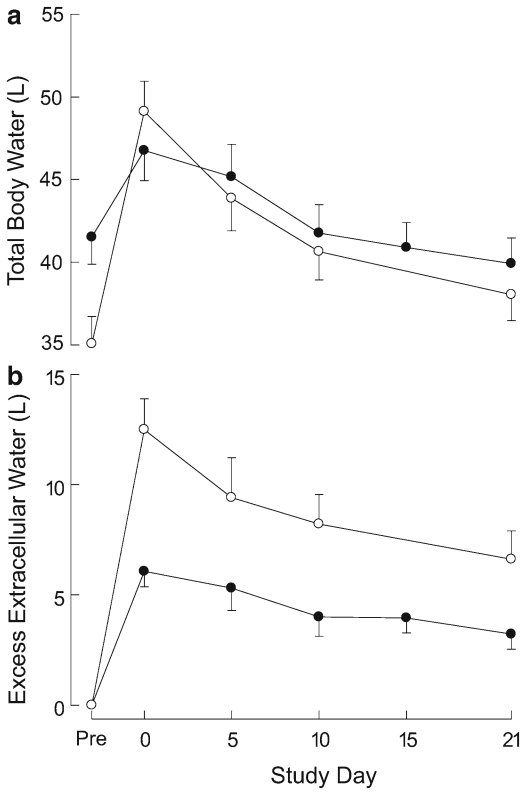

Fig. 141.4 Sequential measurements of TBW and excess extracellular water (ECW) in trauma and sepsis. Total body water (**a**) and excess ECW (**b**) in 21 patients with major trauma (*closed circles*) and 12 patients with severe sepsis (*open circles*), measured over a 21-day period after onset of illness with estimated pre-illness values (mean ± SEM). Total body water accretion is largely extracellular and amounts to >6 L in trauma and >12 L in sepsis at the end of the early resuscitation phase (With kind permission from Springer Science+Business Media: Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma, p. 632, Plank and Hill (2000), Fig. 2, © 2000 by the Société Internationale de Chirurgie)

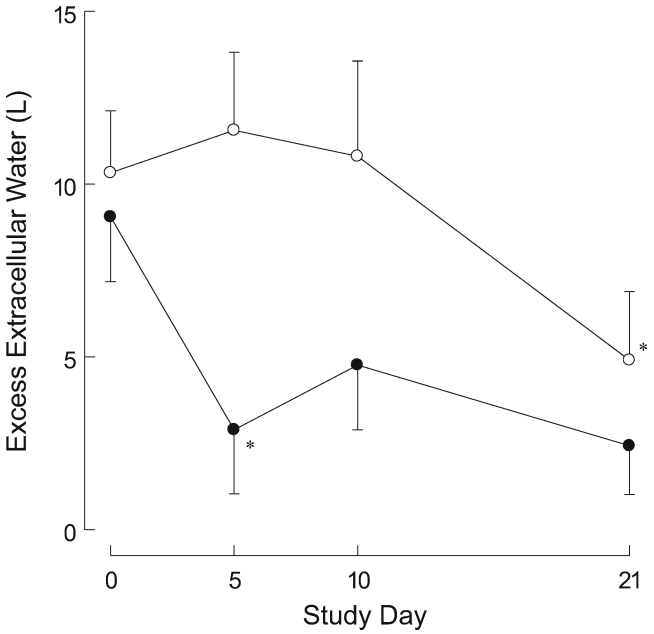

Fig. 141.5 Sequential measurements of excess ECW in young and elderly patients with sepsis. Excess ECW in 6 young (<40 years, *closed circles*) and eight elderly patients (>60 years, *open circles*) with severe sepsis, measured over a 21-day period after onset of sepsis (mean ± SEM) showing the prolonged period of fluid sequestration in the elderly patients. * = a significant ($p < 0.05$) change from preceding measurement (From Cheng et al. (1998). Copyright © (1998) American Medical Association. All rights reserved)

level by day 21, relative overhydration of the FFM was still present, indicated by the slightly elevated TBW:FFM ratio (0.74 ± 0.01). At day 21 in the sepsis group, this overhydration was more marked (0.77 ± 0.01) despite these patients having lost an average of 10.8 ± 1.4 L of water. These changes during and post-resuscitation can be largely accounted for by changes in ECW as shown in Fig. 141.4 where the excess over normal levels of ECW is shown. The volume of excess ECW accumulated was calculated from the difference between the measured ECW and the ECW predicted from the FFM of the patient corrected for abnormal hydration, using the ratio of ECW to TBW found in health, as described in detail elsewhere (Cheng et al. 1998). Over the first 2–3 days of resuscitation the trauma patients gained 6 L of fluid and the sepsis patients 12.5 L.

In elderly patients with sepsis (age > 60 years) the period of ECW expansion is more prolonged than in their younger counterparts (age < 40 years) and appreciable mobilization of the excess ECW does not occur for at least 10 days (Fig. 141.5). This highlights the need for close vigilance of elderly patients recovering from sepsis in terms of fluid balance and sodium restriction.

141.3.5 Changes in Total Body Potassium

Measurements of TBK over the 21-day study period in a subgroup of the trauma and sepsis patients decreased essentially in parallel with those of TBP (Fig. 141.6). The higher absolute TBK seen in the trauma group reflects the greater skeletal muscle mass in this group.

141.4 Applications to Other Areas of Health and Disease

In disease states where large fluid shifts occur, the simple 2-compartment model of body composition (TBF and FFM) is of limited value. In these conditions, which may include patients with end-stage renal or liver disease, heart failure patients, and those in the early postoperative phase after a

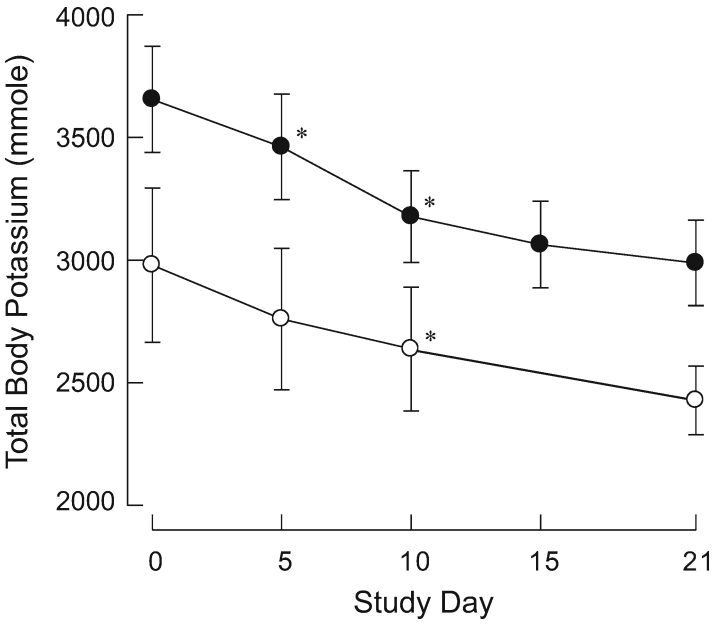

Fig. 141.6 Sequential measurements of total body potassium (TBK) in trauma and sepsis. Total body potassium in 18 patients with major trauma (*closed circles*) and 5 patients with severe sepsis (*open circles*), measured over a 21-day period after onset of illness (mean ± SEM). The changes in TBK track closely the changes in total body protein (TBP). * = a significant ($p < 0.05$) change from preceding measurement

major surgical operation, detailed compartmental analysis is invaluable for understanding the type and magnitude of the compositional derangements that occur. We have utilized such measurements to construct an energy balance where the changes in TBF, TBP, and total body glycogen (estimated from the other measured compartments), expressed as energy equivalents, over a defined time period for which accurate energy intake data was available, allows total energy expenditure to be calculated (Franch-Arcas et al. 1994). For predicting resting energy expenditure, equations which rely on body weight or FFM are unreliable in situations where fluid overload is present. In such cases, the measurement of body water spaces may allow correction of these compartments to "dry" or normally hydrated values. The availability of TBK as a measure most closely related to the energy-metabolizing "core" of the body provides an even more valuable approach to evaluating resting metabolic expenditure (Monk et al. 1996). Direct measurement of TBP has application for assessing response to therapies designed to promote anabolism in both critical illness and other catabolic conditions such as weight-losing cancer and liver disease.

Summary Points

- Body composition of critically ill patients with trauma or sepsis in the ICU is highly deranged.
- Massive proteolysis occurs, initially largely of skeletal muscle with contribution of visceral tissue as the clinical course progresses.
- The catabolic features of trauma and sepsis are very similar reflecting the impact of a systemic inflammatory response which is common to both groups of patients.
- The loss of body protein continues in the face of adequate nutrition support.
- Lipolysis is not evident when energy requirements are met by appropriate nutritional intake.

- Massive fluid overload is characteristic of these patients with 10 L of additional fluid not uncommon in the early resuscitation period.
- Diuresis of this fluid excess is more difficult in older than younger patients with a prolonged period of fluid sequestration evident in the former group.
- The time course of changes in TBK, a measure of the cellular tissue compartment of the body, follows a very similar profile to that of TBP.

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Chapter 142
Anthropometry and Infectious and Parasitic Diseases

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Abstract Anthropometric data are used to assess and predict performance, general health and survival of individuals and also can reflect the economic and social well being of populations. They are associated with the prognostic of several chronic pathologies such as risk of hypertension, diabetes mellitus, cardiovascular disease, arthritis and other diseases. Nutritional anthropometry is widely recognized as the measurements used to assess either physical growth or body composition. Some infections diseases suffer direct influence of anthropometric parameters and nutritional status, and also they may cause loss of appetite, malabsorption, increased catabolism that could exacerbate the malnutrition and further impaired immunity development. Several evidences indicate that chronic heavy infections represent a hidden risk factor for anemia in infants, growth retardation, delayed motor development, poor cognitive abilities and reduced school performance. Moreover, several studies suggest that the association between polyparasitism and malnutrition could be due either to direct effect of intestinal parasites on growth or to the effect of undernourishment on the immune response leading to an increased susceptibility to infection. Although the malnutrition has been classically associated with failure of immune response to eliminate the infectious agents due to increased frequency or sometimes severity of infections, children suffering several infections can die even with a very good nutritional appearance. In this chapter the authors have made some considerations about the association between parasitic and infectious diseases and alterations on anthropometric parameters.

Abbreviations

BCG	Bacillus Calmette-Guerin
BMI	Body mass index
CD4 T cells	Helper T cell MHC II restricted
CL	Cutaneous leishmaniasis
CRP	C-reactive protein
HA	Height-for-age

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_142,

HAZ	Height-for-age Z score
HIV	Human Immunodeficiency Virus
IFN-γ	Interferon-gamma
IGFBP3	IGF binding-protein 3
IGF-I	Insulin-like growth factor
IL-1	Interleukin-1
IL-6	Interleukin-6
ML	Mucosal leishmaniasis
MUAC	Mid-upper arm circumference
MUACZ	Mid-upper arm circumference for age
PBMC	Peripheral blood mononuclear cells
SD	Standard-deviation
Th1	Helper T lymphocyte type 1
TNF-α	Tumor necrosis factor-alpha
VL	Visceral leishmaniasis
WA	Weight-for-age
WAZ	Weight-for-age Z score
WH	Weight-for-height
WHZ	Weight-for-height Z score

142.1 Introduction

Anthropometry is a widely used, inexpensive, and noninvasive measure of the general nutritional status of an individual or a population group. It is used to assess and predict performance, general health, and survival of individuals and also can reflect the economic and social well-being of populations. Anthropometric data have been utilized and associated with the prognostic of several chronic pathologies. For example, individuals with large measures of subcutaneous adipose tissue are reported to be at increased risk for hypertension, diabetes mellitus, cardiovascular disease, arthritis, and other diseases. Moreover, anthropometry is widely used to measure general health in children. Although initially genetically programmed, both height and weight are strongly affected by social and environmental conditions, making growth a useful marker of health and living conditions.

Some infectious diseases directly influence anthropometric parameters, especially in developing countries, where parasitic infections are common and influence decisively the growth of children (Fig. 142.1). Nutritional anthropometry is recognized widely as an effective means of assessing nutritional status, especially at the level of the population, and the measurements taken are used to assess either physical growth or body composition. The former is a reflection of nutrient adequacy during development, the latter an indicator of the excess or deficit of energy and protein (Stenphenson et al. 2000a; Bethony et al. 2006). Protein-energy malnutrition is usually defined by low anthropometry, and the three indices commonly accepted based on height and weight measurements are height-for-age (HA), weight-for-age (WA), and weight-for-height (WH) and a value below the -2 standard deviation (SD) value (*Z*-score) or a fixed percent of median of the growth reference distribution as low or 'malnourished'. The main critic about nutritional anthropometry is the observation that a lower height and weight of children found in the studies in less-developed countries could be left to consider the children who show these characteristics due to its genetic profile (Stenphenson et al. 2000a; Bethony et al. 2006).

Malnutrition is estimated to cause about 12 million deaths of children less than 5 years annually. In association with infectious and parasitic diseases, it is the major obstacle to health in developing

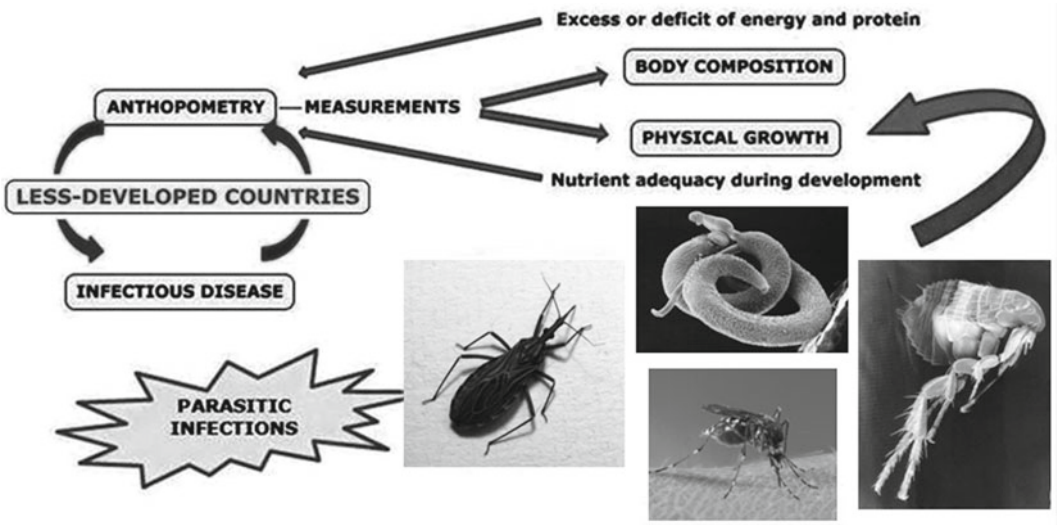


Fig. 142.1 Vicious circle of anthropometric measurement and infectious and parasitic diseases. The *circle* represents the relationship between anthropometric measures and diseases, especially parasitic infections common in children living in less developed countries, where malnutrition associated with poverty increases the chances of the individual to become sick because of the inability to fight against the infectious pathogens. There is a close relationship between the incidence of parasitic/infectious diseases and the level of intake of necessary nutrients for adequate development

countries, where the prevalence of parasitic infections is maximum before 5 years, reaching a relatively stable asymptote in adulthood. Protozoan and helminthic infections are widespread and antagonistic to certain aspects of intestinal physiology and thus of importance with respect to nutritional status in humans. In children of those countries, polyparasitism is very common, and frequently they are more heavily infected than the adults, being consequently more susceptible to suffer severe morbidity (Bethony et al. 2006) (Box 142.1).

It is important to point out that the host defense against the parasites depends on nutritional conditions and also that some infections may cause loss of appetite, malabsorption, and increased catabolism that could exacerbate the malnutrition and further impaired immunity development. Although the malnutrition has been classically associated with failure of immune response to eliminate the infectious agents, due to increased frequency or sometimes severity of infections, children suffering several infections can die even with a very good nutritional appearance. The explication to this remains speculative. Anthropometrical parameters truly represent nutritional status, and a worse nutritional status always increases severity of infections. In this chapter, the authors have discussed some parasites and infectious diseases that influence or can be influenced by the nutritional status and the importance of anthropometric analysis in this area of knowledge.

142.1.1 Amebiasis

Entamoeba histolytica infection remains an important cause of morbidity and mortality mainly in countries where malnutrition has high prevalence and the sanitation infrastructure and health educations are not adequate. Recently, it was demonstrated that IFN-α production, a Th1 cytokine involved in the protection against several infections, is linked to nutritional status and predicts susceptibility of children to *E. histolytica* (Table 142.1). The authors showed that peripheral blood mononuclear

Box 142.1 Highlights of the interplay among anthropometry and immunity to infectious and parasitic diseases

Thymus Size and Health

- The thymus is responsible for T-cell differentiation.
- In infancy, its size has been considered a strong and independent risk factor for mortality.

Immunological findings in small-for-gestational age and low-birth-weight infants and in elderly of the developing world

- Increased risk of death in the immediate postpartum period, thymic atrophy, prolonged impairment of cell-mediated immunity, reduced number and proliferative response of T-lymphocytes to mitogens, and deficient phagocyte functions are common in small-for-gestational age and low-birth-weight infants.
- In developing countries, the elderly present a higher risk of acquiring infectious diseases due to the cumulative effects of immunosenescence and malnutrition.

Immunological findings during nutrient depletion

- Nutritional deficiency is commonly associated with parasitic infections and a significantly impaired development, differentiation, and activation of the immune system. It can affect immune-cell trafficking, phagocytosis, cytokine production, and immune effector function, favoring infections and body energy consumption.

This box lists the immunological findings in special conditions related to anthropometry

cells of children with both weight-for-age *Z*-score (WAZ) and height-for- age *Z*-score (HAZ) <–2 produce less IFN-γ when stimulated *in vitro* with antigen-soluble amebic extract, indicating the importance of nutritional status for parasite control (Haque et al. 2007).

142.1.2 Giardiasis

In relation to giardiasis, data showed that children infected with different species of *Giardia* (*G. lamblia, G. intestinalis*, or *G. duodenalis*) present more significant deficit in height-for-age (HAZ), weight-for-height (WHZ), weight-for-age (WAZ), and mid-upper-arm circumference for age (MUACZ) than uninfected children (Table 142.1). Furthermore, giardiasis causes iron-deficiency anemia, micronutrient deficiencies, malnutrition, and growth retardation in children (Silva et al. 2009). It is recognized that *G. lamblia* infection may destroy the brush borders of enterocytes and impair the activity of mucosal enzymes, causing carbohydrate and lipid malabsorption. The pharmacological treatment of giardiasis is able to improve significantly the body-weight gain and fat-free mass of children.

142.1.3 Leishmaniasis

Leishmaniasis is ranked as one of the most neglected parasitic diseases and has strong links with poverty. It remains a major public health problem despite the vast amount of research on *Leishmania* pathogens, which cause a spectrum of diseases ranging from self-healing cutaneous lesions to

Table 142.1 Association between anthropometry and different parasitic diseases

Disease	Anthropometric variables[a]	Reference
E. histolytica[b] (diarrhea/ dysentery)	There is positive correlation among IFN-α production by PBMC, HAZ, and WAZ has been described. Low levels of IFN-α was associated with risk of *E. histolytica* diarrhea/dysentery in children from Dhaka, Bangladesh	Haque et al. (2007)
Giardiasis	Children infected with *Giardia lamblia* have lower means of HAZ, WHZ, WAZ, and MUACZ than uninfected children. Giardiasis causes iron-deficiency anemia, micronutrient deficiencies, malnutrition, and growth retardation in children, which can be ameliorated by the treatment	Carvalho-Costa et al. (2007) Silva et al. (2009)
Cutaneous and Mucosal Leishmaniasis	Plasmatic levels of selenium, zinc, and iron were decreased in patients with cutaneous leishmaniasis, probably in response to immunoregulatory cytokines; ML and CL are more frequent in patients with malnutrition	Machado-Coelho et al. (2005) Kocyigit et al. (2002)
Visceral Leishmaniasis	Deficit in WAZ and HAZ scores; hypoalbuminemia; inversion of the albumin/globulin ratio; decreased body mass index and mid-upper-arm circumference-for-height; low weight at birth; lower value of *Z*-scores for total and free insulin-like growth factor (IGF-I) and for IGF-binding-protein 3 were associated with a higher chance of developing active visceral leishmaniasis	Gomes et al. (2007) Maciel et al. (2008)
Malaria	Stunted and underweight and wasted African children had a more than twofold higher risk of dying by malaria	Müller et al. (2003)
Malaria in Pregnant Women	Fetal growth retardation in weight and length present from 30 weeks' gestation; placental or peripheral parasitemia at delivery were associated with reduced newborn weight, length and head circumference, wasting and stunting	Kalanda et al. (2005)

[a] Available parameters linked to higher risk of described disease

[b] Etiologic agent more frequently associated with diarrhea and dysentery

Abbreviations: *HAZ* Height-for-age *Z*-score, *IFN-γ* Interferon-gamma, *IGF-I* Insulin-like growth factor, *MUACZ* Mid-upper-arm circumference for age, *PBMC* Peripheral blood mononuclear cells, *WAZ* Weight-for-age *Z*-score, *WHZ* Weight-for-height *Z*-score

progressive and often fatal disease. It is known that the nutritional status might influence the outcome of *Leishmania* spp. infection, especially in children aged less than 5 years. In this context, the prejudicial interaction between malnutrition and the development of cutaneous, mucocutaneous, and visceral diseases has been described, but it is more evident in patients with the classical form of visceral disease, which is characterized by fever, hepatosplenomegaly, pancytopenia, hypoalbuminemia, and hypergammaglobulinemia (Machado-Coelho et al. 2005; Gomes et al. 2007).

An important reduction in plasma levels of selenium, zinc, and iron was observed in patients with cutaneous leishmaniasis, probably in response to immunoregulatory cytokines (Table 142.1). Furthermore, in a study carried out in southeast Brazil using a total of 2,820 patients diagnosed with American cutaneous leishmaniasis, data found that individuals with mucosal leishmaniasis (ML) presented 3.4 times more chances of being malnourished than patients with cutaneous lesions (CL). ML occurred 4 times more frequently in patients with malnutrition than in well-nourished individuals (Machado-Coelho et al. 2005).

In relation to visceral leishmaniasis (VL), in a *Leishmania chagasi* endemic area of Brazil, a decrease in body mass index (BMI) and mid-upper-arm circumference for height was observed in children with VL, and a decreased birth weight was associated with a higher chance of developing severe disease (Table 142.1). In addition, higher albumin concentrations and birth weight protected

against disease. In another study, also conducted in endemic area for VL in Brazil, it was found that children with active form of disease presented more pronounced weight loss and a deficit in WAZ and HAZ compared with oligosymptomatic, asymptomatic patients and non-infected children. Serum albumin levels also were significantly reduced in children with active (2.7 ± 0.22 g/dl) or oligosymptomatic (2.97 ± 0.34 g/dl) VL compared with asymptomatic (4.22 ± 0.07 g/dl) and control (4.36 ± 0.03 g/dl) children, indicating that VL can affect the nutritional condition of patients. It is important to comment that the deficit in height and weight was not a risk factor to infection by *Leishmania* in that geographic area. Moreover, the serum ferritin concentration in the active VL group was 11, 18.6, and 22.7 orders of magnitude higher compared with oligosymptomatic, asymptomatic and control individuals, respectively (Gomes et al. 2007). Insulin-like growth factor (IGF-I) production is regulated by nutritional status. It was demonstrated that, in patients with active form of VL or oligosymptomatic patients, the levels of IGF-I and also its ligand IGF binding-protein 3 (IGFBP3) were significantly reduced in relation to controls or asymptomatic patients (Table 142.1). IGF-I is mainly produced in the liver (Gomes et al. 2007). Thus, it is possible that the cytokine-induced inflammation can decrease IGF-I production by liver cells, since its biosynthesis is inhibited by mediators, such as TNF-α, IL-1, and IL-6, which are produced in the course of VL. On the other hand, the alterations in liver induced by those inflammatory cells may impair the production of IGF-I and IGFBP3. Overall, these results suggest that, in leishmaniasis, malnutrition is likely to occur previous to infection (cutaneous and visceral leishmaniasis) impacting on the outcome of disease, and also to be reinforced at least during visceral form of disease, since a marked reduction in fat reserves and muscle mass related by TNF-α production occurs.

142.1.4 Malaria

The relationship between malnutrition and malaria is an unsolved and complex issue. *Plasmodium falciparum* infection may cause malnutrition, whereas malnutrition itself may modulate susceptibility to malaria. There is no direct association between malnutrition and malaria mortality, but stunted, underweight, and wasted African children had a more than twofold higher risk of dying than non-malnourished infected children (Table 142.1). Although children living in an endemic area of malaria showed clinical symptoms of disease during the first 10 years, the effect of malaria on nutritional status appears to be greatest only in the first 24 months, suggesting that, subsequent to infection, children aged under 2 years became underweight or stunted (Nyakeriga et al. 2004). Moreover, in a study carried out with pregnant women in Chikwawa District, Southern Malawi, a rural area endemic to malaria, the mean birth weight, length, and head circumference were significantly lower in babies of mothers with placental or peripheral *P. falciparum* parasitemia at delivery. Furthermore, univariate analysis showed that placental and/or peripheral presence of parasite was associated with wasting and stunting (Kalanda et al. 2005). These alterations could be due to placental insufficiency, leading to intrauterine growth restriction.

142.1.5 Tuberculosis

About one-third of the world's population carries the bacterium that causes tuberculosis, *Mycobacterium tuberculosis*, and roughly 10% of these people will go on to develop the disease. Because drug courses can last for a year or more, most people do not complete their treatment, and the growth of resistance is therefore inevitable.

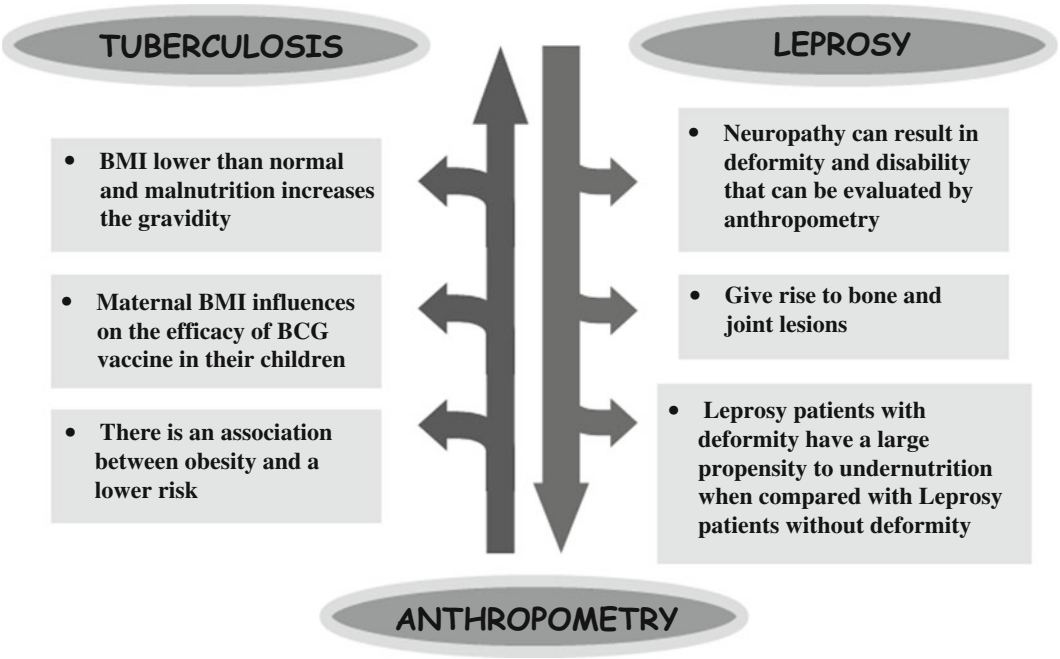


Fig. 142.2 Relationships among anthropometry, tuberculosis, and leprosy. Anthropometric measurements influence the prognosis of infection caused by *Mycobacterium tuberculosis*. However, in relation to leprosy, an opposite effect has been observed, and the disease and the degree of deformity have a decisive influence on the anthropometric parameters

A better understanding of the relationship between the tubercle bacilli and our body is probably an important issue for the discovery of new interventions seeking for solutions to problems that arise when we interact with this pathogen. Although there are many studies about the morbidity and mortality of tuberculosis at a worldwide level, many researchers continue to look for answers about the metabolic, physiological, and immunological processes involved in the control of the infection and in a positive prognostic for the host or in the spread of the pathogen in the body and dissemination of disease, occasioning many times the death of the patient.

In terms of anthropometric characteristics, the BMI invariably has been associated to mortality. One value of BMI lower than normal represents an increase in the risk when it refers to tuberculosis. Moreover, malnutrition is associated with higher incidence and increase in the gravidity of the clinical status of tuberculosis, according to radiographic visualization of lungs of infected individuals (van Lettow et al. 2004).

Important items that have been monitored and are the focus of recent research on the effectiveness of current vaccine used against tuberculosis and the search for new strategies for vaccination. The *Mycobacterium bovis* BCG vaccine presents efficacy that can range from 0% to 80%, depending on the geographic region evaluated. One of the possible explanations for this variation could be the maternal anthropometric characteristics (Moore et al. 2004). This speculation comes from studies that showed a negative correlation between the immune response of children and adolescents against mycobacterial antigens and the BMI of their mothers (Fig. 142.2). Furthermore, the antenatal and postnatal environments show a decisive influence in the capacity to mount a protective immune response against tuberculosis (Table 142.2). The season of birth can be important to a subsequent effective response against *Mycobacterium tuberculosis*. In countries where there are well-defined seasons with periods of wet and dry weather, there is a decrease in energy intake and available food

Table 142.2 Different aspects of anthropometric measures in relation to tuberculosis and leprosy

Tuberculosis		Leprosy	
Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death	Bernabé-Ortiz (2008) Van Lettow et al. (2004)	Given that individuals may be cured and yet suffer lifelong deformities and disability, the number of individuals with nerve damage would be a better indicator for elimination of leprosy	Greve et al. (1994)
Birth weight, prenatal undernutrition, and postnatal environment have influence on vaccination against tuberculosis	Moore et al. (2004)	Computerized podometric evaluation of the insensible feet of leprosy patients showed a close relation between points of increased pressure and areas with deficient sensation	Greve et al. (1994)
Micronutrient supplementation to patients with active tuberculosis and HIV improves their health by increasing $CD4^+$ count, increasing their weight, and improving the efficacy of their drug treatment	Swaminathan et al. (2008)	BMI and mid-upper circumference have been demonstrating that cured leprosy patients with residual deformity have a larger propensity to undernutrition than cured leprosy patients without deformity	Diffey et al. (2000)
There is an association between obesity and a lower risk to become infected by tubercle bacilli. A cholesterol-rich diet accelerates bacteriologic sterilization in pulmonary tuberculosis.	Pérez-Guzmán et al. (2005)	The inclusion of nutritional-status evaluation by anthropometry as part of the initial screening of leprosy patients prior to instituting socioeconomic rehabilitation has been proposed as a strategy that can help in the prioritization of these patients	Vaz et al. (2001)

This table summarizes important published data concerning anthropometric measurements and their influence on the risk of infected people to be sick, on immune response, and point out that, in untreated *Mycobacterium leprae*-infected patients, the disease impacts on the nutritional status and also on quality of life, promoting deformities and disability

from the previous harvest in the wet seasons. In the same way, the wet season represents the time in which there is a higher demand for female exhaustive labor in agriculture. Consequently, the variations of available food and increased daily efforts in the life of mothers influence the birth weight of their children and the response of these children to the prophylactic action of BCG vaccine against tuberculosis.

Weight loss is one of the fundamental signs both in HIV-positive and HIV-negative tuberculosis patients. Malnutrition and wasting are associated with tuberculosis and HIV infection. Coinfection with one pathogen may potentially exacerbate the wasting that occurs in the other (van Lettow et al. 2004). Since HIV-infected adults with pulmonary tuberculosis had significantly low micronutrients and BMI, this subgroup may potentially benefit from nutritional interventions. Several studies have revealed that micronutrient supplementation to patients with active tuberculosis and HIV improves their health by increasing CD4 T-cells' count, increasing their weight, and improving the efficacy of their drug treatment, in addition to decreasing opportunistic infections (Table 142.2).

Tuberculosis and leprosy show different aspects about association with anthropometry. For tuberculosis, the great majority of research works has established a relationship of the effects of anthropometry, especially weight and height represented by BMI, with the gravity of disease. The risk of mortality has a negative correlation with anthropometric indicators of nutritional status. For leprosy, it is the inverse, as many studies have observed an influence of the disease on anthropometric measurements (Fig. 142.2). It is important to note that tuberculosis, as much as leprosy, remains a serious threat to public health in less developed countries (Diffey et al. 2000; Walker and Lockwood 2007).

Although obesity has association with diabetes and cardiovascular-associated diseases, which represent predisposing factors to the increase of incidence of tuberculosis, it is important to note that there is an association between obesity and a lower risk to become infected by tubercle bacilli (Pérez-Guzmán et al. 2005). Both clinical and experimental studies have shown that a cholesterol-rich diet helps the host against infection by tuberculosis (Table 142.2).

Endogenous reactivation is becoming a major source of tuberculosis disease among the older generations. Although treatment of latent infection is a possible strategy against this endogenous reactivation, the decision to is not always easy to make in a high-prevalence setting, especially in view of the limitations in the currently available diagnostic and treatment tools. The cost-effectiveness of such screening is likely to be improved if BMI can be taken into consideration. Aggressive measures may also be indicated against elderly malnutrition to reduce the risk of reactivation of tuberculosis, and nutritional supplementation in this regard. It may therefore be worthwhile to explore the potential impact of ongoing changes in our body build on the future tuberculosis trend.

142.1.6 Leprosy

Leprosy has plagued human populations for thousands of years and puzzled scientists since the identification of its etiological agent, *Mycobacterium leprae*, by Hansen in 1873. Ancient texts describe the existence of leprosy in China, India, and Egypt in around 600 BC, and skeletal remains bearing hallmarks of the disease have been found in Egypt (Monot et al. 2005). The disease causes skin lesions and neuropathy. Secondary complications of the neuropathy can result in deformity and disability, with skin, mucosal, eye, and nerve involvements (Diffey et al. 2000). Computerized podometric evaluation of the insensible feet of leprosy patients showed a close relation between points of increased pressure and areas with deficient sensation. The use of this anthropometric type of evaluation may be an important instrument in preventing plantar ulcers, because we can see the exact point of increased pressure. This fact is confirmed by qualitative analysis that demonstrated the coincidence between plantar ulcers and points of increased pressure (Greve et al. 1994).

The maintenance of the treatment with the multidrug therapy is a fundamental strategy to reduce the current socioeconomic problems of the leprosy. After introduction of multidrug treatment, there was an expressive decrease in leprosy incidence that was also more restricted to very young and very old patients. Leprosy remains a stigmatizing disease. However, multidrug therapy has led to the understanding that leprosy can be effectively treated before disability. Since 1985, 14 million individuals have received multidrug therapy (Walker and Lockwood 2007).

Some of the most important problems associated with leprosy are the disability and the difficulties in the socioeconomic rehabilitation of patients. Leprosy continues to give rise to bone and joint lesions, which may ultimately become crippling (Fig. 142.2). This has, in fact, been listed as a priority area for leprosy program planners. Moreover, when some authors compare leprosy patients, with or without deformity, these problems become still more expressive (Monot et al. 2005; Walker and Lockwood 2007). Anthropometric parameters, such as BMI and mid-upper arm circumference, have

demonstrated that cured leprosy patients with residual deformity and their household members have a greater propensity to undernutrition than cured leprosy patients without deformity (Table 142.2). Surprisingly, many of the household members of cured leprosy patients with deformity who presented this greater propensity were not sick but only infected by *Mycobacterium leprae*, since, despite 90% of the people who maintain contact with these patients become infected, only 8% will be sick.

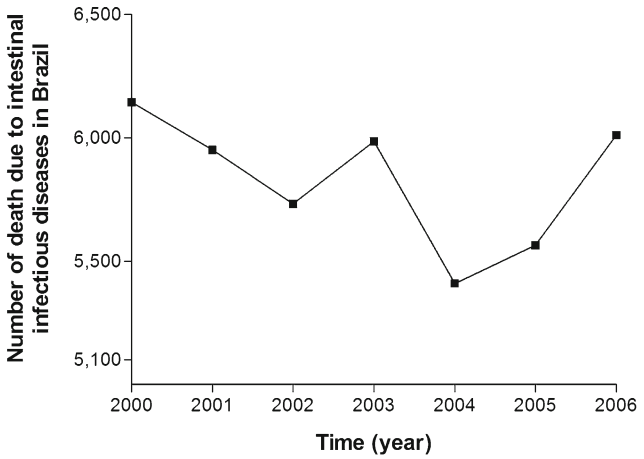
The inclusion of nutritional-status evaluation by anthropometry as part of the initial screening of leprosy patients prior to instituting socioeconomic rehabilitation has been proposed as a strategy that can help in the prioritization of these patients. This is important because, when economic resources are limited the processes of rehabilitation need to be addressed in those most in need (Table 142.2). In much of Asia and Africa, the focus on elimination as a target has resulted in inappropriate programs with the sole purpose of reducing the number of cases on the treatment register, instead of improving the quality and effectiveness of leprosy services. In spite of the effectiveness of the available treatment, many patients develop deformity, especially those related to the impairment of the peripheral nervous system. Once those individuals are cured and yet suffer lifelong deformities and disability, the number of individuals with nerve damage would be a better indicator for control of leprosy (Greve et al. 1994).

142.2 Geohelminths and Anthropometry

The geohelminths are among the most common etiologic agents of human infections and often occur together within the same host. Geohelminth infections occur predominantly in the developing countries of the tropics and subtropics areas, where it is estimated that there are currently one billion people infected. The geohelminths include the common whipworm, *Trichuris trichiura*; the large intestinal roundworm, *Ascaris lumbricoides*; and two species of hookworms, *Ancylostoma duodenale* and *Necator americanus*. Hookworms and *Ascaris* inhabit the small intestine, whereas *Trichuris* is a parasite of the colon. They can live in the gastrointestinal tract for up to several years (Stephenson et al. 2000a).

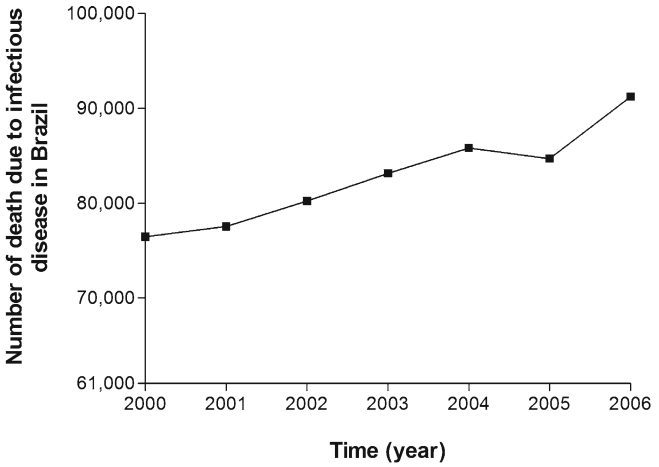
Intestinal parasitic infections remain a serious public global health problem. Although the predictors of stunting are multifactorial, intestinal parasitic infections, notably helminthic infections, are acting as factors associated to low nutritional status, along with sanitary and socioeconomic conditions to increase morbidity and mortality in children and various other functional consequences, including impaired cognitive development and impaired growth (Stenphenson et al. 2000a). In Brazil, intestinal diseases caused by protozoan and helminthic parasitism (Fig. 142.3) and infectious diseases (Fig. 142.4) still lead to great number of death annually (Ferreira et al. 2006; Buschini et al. 2007).

The World Health Organization now recommends that, in areas where infections are endemic (prevalence of 20–30%) and anemia is prevalent, hookworm control (using chemotherapy) needs to be included in strategies designed to improve the health, development, and nutritional status of girls and women. Intestinal parasite infections can be controlled with anthelmintic drugs in conjunction with education and improvement of sanitary conditions. Intervention studies have shown that infection with as few as ten roundworms is associated with deficits in growth and physical fitness in school-aged children and those moderate whipworm infections can cause growth retardation and anemia. Fortunately, many of the growth and nutritional deficits caused by these infections are reversible with the use of anthelmintics. For example, the treatment of intense infections with whipworm has shown a positive impact on anthropometric parameters and iron status of schoolchildren



Source: Ministry of Health/MH - Information System for Notifiable Diseases – ISND/Brazil

Fig. 142.3 Deaths due to intestinal infectious diseases in Brazil. In Brazil, the mortality rates due to intestinal infectious diseases including amebiasis and giardiasis still remain an important cause of death. Source: Ministry of Health, Division of Health Surveillance: Mortality Information System and demographic base of the Brazilian Institute of Geography and Statistics (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2008/c17.def)



Source: Ministry of Health/MH - Information System for Notifiable Diseases – ISND/Brazil

Fig. 142.4 Deaths in consequence of infectious diseases in Brazil. Annual mortality rates due to infectious diseases by year, Brazil, 2000–2006. Source: Ministry of Health, Division of Health Surveillance, Mortality Information System (MIS) and demographic base of the Brazilian Institute of Geography and Statistics (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2008/c17.def)

and preschool children. However, although control strategies relying on targeted delivery of benzimidazole anthelmintic are generally effective at eliminating adult worms, reinfection occurs quickly, and frequent treatments may be necessary for sustained improvement in the health of at-risk populations.

Epidemiologic evidence in many different countries has shown that for *Ascaris* and *Trichuris*, heavy infections will occur predominantly among school-aged children and, hence, a window period of susceptibility to morbidity from these parasites during childhood. For hookworm, heavy infections

also can occur during childhood but, probably, increasing intensity occurs more commonly with age. Evidence indicates that chronic heavy infections with geohelminths represent a hidden risk factor for maternal iron-deficiency anemia and fetal growth retardation, anemia in infants, growth retardation, delayed motor development, poor cognitive abilities, reduced school performance, and an impaired immune response (Stephenson et al. 2000b; Bethony et al. 2006). In several studies, the association between polyparasitism and malnutrition can be due either to the direct effect of intestinal parasites on growth or to the effect of undernourishment on the immune response, leading to an increased susceptibility to infection.

142.2.1 Trichuriasis

The common whipworm *Trichuris trichiura* occurs where fecal contamination occurs on warm and damp soil; it affects an estimated 800–1,000 million individuals worldwide. Children with *Trichuris* colitis have numerous systemic sequelae that are similar to those caused by other kinds of inflammatory bowel disease. Growth retardation is a prominent feature, and it is proportional to the intensity of chronic infection. The basis by which whipworms impair physical growth during childhood is unknown. Among the mechanisms proposed are direct intestinal protein losses, anorexia and increased catabolism resulting from TNF-α production, and reduced host circulating levels of IGF-I (Cooper et al. 1997; Duff et al. 1999; Drake and Bundy 2001) (Table 142.3). Even less well known are the mechanisms by which *Trichuris* impairs cognition and school performance (Drake and Bundy 2001).

Several studies showed that *T. trichiura* infection may contribute to vitamin A and zinc deficiencies caused by reduced retinol and zinc intake, respectively, due to anorexia and/or vomiting, malabsorption, and increased requirement and loss due to diarrhea. On the other hand, the zinc deficiency is associated with increased susceptibility toward gastrointestinal nematodes, likely through a weakening of the gut epithelial barrier, allowing greater penetration and establishment of the larval stages as well as a profound impairment of the gut immune response. Heavy *Trichuris* infections cause iron-deficiency anemia and growth retardation, both of which are associated with poor cognition and low school performance (Stephenson et al. 2000a, b; Drake and Bundy 2001; Bethony et al. 2006) (Table 142.3).

142.2.2 Ancylostomiasis

The two major species of hookworms are *Ancylostoma duodenale* and *Necator americanus*, and more than 700 million people worldwide are infected with hookworms. The adult hookworms attach via their buccal capsule to the intestinal mucosa, rupture capillaries, and feed on blood. The pathogenesis of hookworm infection is mainly a consequence of the blood loss, which occurs during attachment and feeding. In a large number of developing countries, hookworms are the leading cause of iron-deficiency anemia, hypoproteinemia, and growth delay, which is proportional to worm burden (Table 142.3). During heavy infections, sufficient blood (and plasma protein) loss can result in depletion of host iron and protein reserves, leading to physical and mental retardation and sometimes deaths in children, as well as adverse maternal–fetal outcomes. The processes of growth retardation and deficits in attention and intellectual development that occur during chronic, heavy hookworm infections in childhood are possibly due to the development of clinical iron deficiency (Hotez et al. 2004, 2005; Bethony et al. 2006) (Table 142.3).

Table 142.3 Harmful effects of the association between helmintic infections and malnutrition. Association between malnutrition and different helmintic infections

Pathogen/disease	Nutritional variables[a]	References[b]
Trichuris trichiura Trichuriasis	Can lead to intestinal protein losses, anorexia and increased catabolism resulting from host tumor-necrosis-factor production, and reduced host circulating levels of insulin-like growth factor I Contribute to vitamin A and zinc deficiencies caused by reduced retinol and zinc intake, respectively Heavy infections cause iron-deficiency anemia and growth retardation, both of which are associated with poor cognition and impair school performance	Bethony et al. (2006) Drake and Bundy (2001) Stephenson et al. (2000a) Stephenson et al. (2000b) Cooper et al. (1997)
Ancylostoma duodenale *Necator americanus*	Hookworms can lead to iron-deficiency anemia, hypoproteinemia, and growth delay, which is proportional to worm burden	Bethony et al. (2006) Hotez et al. (2005) Hotez et al. (2004) Stephenson et al. (2000a)
Ancylostomiasis	Chronic heavy hookworm infections in childhood with clinical iron deficiency can lead to processes of growth retardation and deficits in attention and intellectual development Hookworm infection can cause levels of undernutrition that are greatest among younger children and decrease with the age	
Ascaris lumbricoides Ascariasis	The Ascariasis contributes to impairment of growth and cognitive development in children by; different ways: 1. I impairing host nutrition by causing malabsorption of protein, lactose, fat, and some fat-soluble vitamins, including vitamin A, through a process of villous atrophy; 2. Producing a battery of peptide serine protease inhibitors that *in vitro* can block the action of pancreatic trypsin, chymotrypsin, and elastase; and 3. Causing different degrees of intestinal mucosal epithelial cell damage, because they can elicit mechanical damage and lumen obstruction if they reach the biliary tree or become entangled and matted into a bolus of worms.	Payne et al. (2007) Bethony et al. (2006) Stephenson et al. (2000a) Ferreira et al. (2006) Buschini et al. (2007)

This table summarizes the effects of parasite infections on nutritional status and anthropometric parameters, such as deficient growth and deficits related to biochemistry functions and cognitive development

[a] Possible consequences in nutritional status with the presence of described disease

[b] Recent works which discuss the issues

142.2.3 Ascariasis

Ascaris lumbricoides (roundworm) infects 0.8–1.2 billion people worldwide, and it is the major cause of disease burden, especially in developing countries, with an estimated loss of from 1.2 to 10.5 disability-adjusted life years per infected person. The role of *A. lumbricoides* in determining malnutrition has been extensively studied. *A. lumbricoides* infection, even in the absence of obvious symptoms of disease, can impair linear growth. Data showed higher prevalence of stunting and underweight among high-school children infested by *A. lumbricoides*. This persistent intestinal parasitic infestation seemed to be associated with physical growth retardation and low nutritional indices, such as height-for-age Z score (HAZ) and weight-for-age Z score (WAZ).

Ascariasis may affect growth in different ways, depending on its long-term effects (Table 142.3). Several studies showed that large parasite burdens in ascariasis can lead to intestinal obstruction and

also to decreased appetite and food intake. It was demonstrated that adult *Ascaris* worms impair the absorption of vitamin A and fat, leading to nutritional deficiencies, whereas vitamin A deficiency may reduce the immune response to intestinal parasites, leading to higher worm burdens. Furthermore, there is substantial evidence that ascariasis contributes to impairment of growth and cognitive development in children and thus has important long-term consequences if not prevented or treated (Stephenson et al. 2000a; Payne et al. 2007).

In summary, the *A. lumbricoides* infection may lead to the following disease classification: (1) reversible growth faltering in children and/or reduced physical fitness in children and adults, which lasts for the duration of the infection; this deficit in health is recovered completely once the individual loses the infection; (2) permanent growth retardation, which is a lifelong consequence of infection, occurring only in children; this deficit might be recovered, but only partially, even if the individual loses the infection completely; (3) clinically overt, acute illness (such as intermittent abdominal pain or discomfort, nausea, anorexia, or diarrhea) of short duration and mild-moderate severity, sufficient for the infected individual to seek medical attention; (4) acute complications (including intestinal obstruction and its complications, biliary or pancreatic disease, appendicitis, and peritonitis) of sufficient severity for the affected individual to be hospitalized; and (5) mortality caused by acute complications (5% case fatality rate) (Stenpheson et al. 2000a; Bethony et al. 2006; Payne et al. 2007).

142.3 Applications to Other Areas of Health and Disease

Anthropology is one of the interdisciplinary scientific fields that is gaining much attention since it can have applications in many different areas of knowledge. Its use is not restricted directly to the assessment of nutritional status or indirectly to indicate either a state of immune incompetence or susceptibility to disease. In many chapters of this hand book, the reader can come across many different applications including the study of human development, fetal growing, and diagnostic comprehension of genetic, cardiovascular, hematological diseases, and others.

Infectious and parasitic diseases are mostly endemic in underdeveloped and developing countries, including Brazil, a tropical developing country, where many infectious diseases including tuberculosis, leprosy and leishmaniasis present high incidence (Table 142.4). Hence, we need to consider that some infectious agents including parasites can persist chronically in the human body without provoking a strong host response. In fact, many patients remain well in spite of the infection. Conversely, patients with heavy infection or those in the initial infective stage may have symptoms. Frequently, parasites degenerate and die in human tissues. By contrast, some parasites live for a long time in the human body, from several years to decades and produce chronic inflammation. Furthermore, many patients have repeated and cumulative infections. Because of persistent or lifelong exposure to para-

Table 142.4 New cases of infectious diseases in Brazil by year, 2000–2007

Disease	2000	2001	2002	2003	2004	2005	2006	2007	Total
Tuberculosis	81,182	73,771	77,493	78,596	77,678	76,741	71,870	72,179	609,510
Leprosy	43,196	45,646	49,149	51,680	50,271	49,145	44,764	41,367	375,218
Visceral Leishmaniasis	4,858	2,544	2,448	2,971	3,573	3,591	3,650	3,201	26,836

Source: Ministry of Health/MH – Information System for Notifiable Diseases – ISND/Brazil
Source: Ministry of Health, Division of Health Surveillance, Information System for Notifiable Diseases (http://tabnet.datasus.gov.br/cgi/tabcgi.exe?idb2008/d0202.def)

sites and their excreta, cancer may develop. For example, hepatocellular carcinoma or bladder cancer develops in patient with schistosomiasis. Some parasitic diseases that affect the lungs and urinary bladder will be discussed in the appropriate sections of individual parasitosis. Some parasites reach the peritoneal space during their migratory life cycle and they inadvertently reside there and produce inflammatory reaction.

Infection intensity is a key factor to understand the morbidity of the patients; although light infections are often asymptomatic, heavy infections cause an array of morbidities, including dietary deficiencies and delayed physical and cognitive development. In this way, chronic heavy infections represent a hidden risk factor for anemia in infants, growth retardation, delayed motor development, poor cognitive abilities, reduced school performance, and an impaired immune response.

Infection, inflammation, or increased oxidative stress may also increase catabolic loss of certain nutrients. For example, infection with most microorganisms leads to activation of macrophages and neutrophils by microbial products or by pro-inflammatory mediators produced by damaged cells. The release of the pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-1beta and IL-6, result in induction of the systemic acute-phase response. This response will lead directly to responses by the central nervous system (e.g., induction of fever and production of cortisol to down-regulate inflammation) and the liver, which includes the increased production of positively regulated acute-phase proteins (e.g., C-reactive protein or CRP) and the decreased synthesis of other proteins, which results in decreased serum retinol concentration and serum iron and zinc concentrations. The decreased serum retinol concentrations during infection could lead to decreased tissue concentrations of vitamin A. It is unclear whether these reductions in the serum micronutrient concentrations lead to decreased transport to target tissues.

Additionally, parasitic infections contribute to iron-deficiency anemia and nutritional deficiencies. Micronutrient deficiencies may be produced by infectious diseases in one of the following five ways: (1) decreasing food intake (anorexia); (2) impairing nutrient absorption; (3) causing direct micronutrient losses; (4) increasing metabolic requirements or catabolic losses; and (5) impairing transport to target tissues.

Thus, serious acute infections, particularly those that involve the gastrointestinal tract, impair linear growth. Chronic infections can also impair linear growth. Opportunistic infections may have accounted for diminished growth in some, but not all, children. For example, *Helicobacter pylori* can cause a chronic bacterial infection of the stomach and duodenum and, in some cases, can cause gastric or duodenal ulcer disease. Acute and chronic infections may impair linear growth due to micronutrient deficiency. For example, diarrhea and acute respiratory infections have been associated with the development of vitamin-A deficiency.

Summary Points

- There is a strong relationship between malnutrition, severity of infections, and infant mortality, especially in developing countries where parasitic infections are common.
- Undernutrition is not necessarily caused by inadequate food intake. There are malnourished people in rich countries, for example, patients receiving long-term care and those hospitalized.
- There is a negative correlation among anthropometric parameters, immune-response development, and health. Poor nutrition can lead to reduced immunity, increased susceptibility to disease, and impaired physical and mental development.
- Nutritional status of the host can be modified by increased demands of the parasites or by specific effects, for example, mucosal mechanical obstruction, blood loss, and others. Hence, chronic and uncontrolled infections can increase malnutrition status creating a continuous cycle of malnutrition and infection.

- Geohelminths may alter food intake, digestion and absorption of nutrients, and increased catabolism due to production of cytokines, such TNF-α, IL-1, and IL-6. These parasites can also lead to intestinal protein losses, deficiencies of vitamin A, zinc, and iron, anemia, hypoproteinemia, and growth retardation.
- Some parasites, such *Ascaris lumbricoides*, may affect growth in different ways, and may impair host nutrition by causing malabsorption of protein, lactose, fat and some fat-soluble vitamins, including vitamin A and also by direct mechanical damage and lumen obstruction.
- There is a prejudicial association between malnutrition, low values of anthropometric measures, and the outcome of cutaneous, mucocutaneous, and visceral diseases, but this is more evident in patients with the classical form of visceral disease.
- Lower BMI value represents an increased risk to tuberculosis. A negative correlation among anthropometric indicators of nutritional status and mortality by tuberculosis has been found.
- Leprosy continues to give rise to bone and joint lesions which may ultimately become crippling. Computerized podometric evaluation of the insensible feet of leprosy patients showed a close relation between points of increased pressure and areas with deficient sensation.
- Anthropometric parameters, such as BMI and mid-upper-arm circumference, have indicated that cured leprosy patients with residual deformity have a greater propensity to undernutrition when compared to cured leprosy patients without deformity.

Key Features

Table 142.5 Key features of parasitic and infectious diseases

1. Parasitology is the study of parasites and their relationships with their hosts.
2. Parasitism is a relationship in which the parasites physiologically depend on the host.
3. Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites, or fungi; the diseases can be spread, directly or indirectly, from one person to another.
4. Unsanitary living conditions, poor nutrition, low education and economic levels, inadequate public health politics, and compromised immune response of people contribute to the high prevalence of parasitic and infectious diseases in tropical and subtropical countries.
5. Nutritional status influences the immunological defense against infectious and parasitic diseases.
6. Malnutrition plays an important role in susceptibility to infections.
7. The World Health Organization has considered malaria, leishmaniasis and leprosy as major human tropical diseases.

This table lists the key features of parasitic and infectious diseases including the concepts of parasitism, infectivity and their relationship to other areas of knowledge, and the importance of nutritional status and anthropometric parameters to efficient defense by the host

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Chapter 143
Body Composition in Spinal Cord Injured–Paraplegic Men

Yannis Dionyssiotis

Abstract Spinal cord injury-induced paraplegia causes an extreme and sudden immobilization of the lower limbs. The effects of spinal cord injury in paralyzed areas are well documented. Immobility leads to a changing pattern of loading in the paralyzed areas, which respond by alteration in structure. Subjects lose muscle mass and bone and gain fat mass, especially in the lower limbs. In addition, studies have shown that the demineralization and the deterioration of body composition are more severe in the sublesional regions of the subjects and in tetraplegics compared with paraplegics. Clinical studies also indicated that neurological injuries are associated with the development of a rapid and severe osteoporosis that is not only due to a compromised biomechanical function but also could have a central nervous system origin. In this chapter, factors influencing body composition in paraplegia and rehabilitation intervention are also discussed.

Abbreviations

BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
DEXA	Dual energy X-ray absorptiometry
FM	Fat mass
FFM	Fat free mass
LM	Lean mass
NLoI	Neurological level of injury
SCI	Spinal cord injury
pQCT	Peripheral quantitative computed tomography

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_143,

143.1 Introduction

Human body composition measurement to quantify nutritional and health status has become important as evidence accumulates identifying relative body fat as a significant predictor of mortality (Seidel et al. 1996; Bender et al. 1998; Van Der Ploeg et al. 2003).

Spinal cord injury (SCI) causes immobilization associated with profound changes in the body composition in spinal cord injured (SCI) patients. There is loss of lean tissue mass (LM) and bone, but gain in fat mass (FM), and regional changes. The potential risks involved with these changes in body composition have implications for the health of the SCI individual (Jones et al. 1998). Disorders such as carbohydrate intolerance, insulin resistance, lipid abnormalities, and heart disease occur prematurely and at a higher prevalence in the SCI population and may be related to adverse changes in body composition that result from immobilization and skeletal muscle denervation from SCI (Spungen et al. 2003).

Body mass index (BMI, kg/m2) was used in many studies as a surrogate measurement of obesity. It is a very simple measurement of fat requiring only the measurement of height and weight; however it does not distinguish the individual components of weight. The applicability of conventional BMI cut-off values is questioned (Buchholz 2005; McDonald et al. 2007). According to the literature, several studies have shown that anthropometric measures tend to underestimate fat percentage when compared with able bodied individuals. BMI is an insensitive marker of obesity in subjects with SCI and measuring fat with BMI in chronic paraplegic patients is not enough to determine a subject's body fat percentage (Olle et al. 1993).

Fat free mass (FFM) is often used to standardize or index physiological variables, such as resting metabolic rate and strength (Van Der Ploeg et al. 2003). Skeletal muscle is the main component of FFM, representing 50% of the non-fat component in the total body (Clarys et al. 1984; Modlesky et al. 2004). In the assessment of nutritional status, disease risk, danger of illnesses, physical function, atrophic effects of aging and muscle-wasting diseases, the exact quantification of the amount of skeletal muscle is important (Forbes 1987; Mojtahedi et al. 2008).

A decline in bone mineral density (BMD) and bone mineral content (BMC) has been detected radiologically in the paralyzed limbs of patients as early as 6 weeks after SCI. The dramatic reduction in BMD or BMC has been well documented in chronic SCI patients. Bone loss generally involves the pelvis and lower extremities in paraplegic patients, while in tetraplegic patients the upper extremities are also involved. SCI patients display a specific form of demineralization characterized by an exclusively sublesional topography in which the head of tetraplegics (upper and lower body paralysis) and the upper limbs of paraplegics (lower body segment paralysis) are preserved (Jiang et al. 2006).

143.2 Imaging Techniques

Changes in body composition in SCI patients can be assessed with various techniques including isotope-labelled water (Jones et al. 1998), total body potassium counting (Lussier et al. 1983; Spungen et al. 1992), anthropometric measures (Bulbulian et al. 1987), hydrodensitometry (Lussier et al. 1983; Sedlock 1990), dual photon absorptiometry (DPA) (Spungen et al. 1992; Changlai 1996) and dual energy X-ray absorptiometry (DEXA) (Jones et al. 1998). However, some of these methods are not particularly suitable for use in the SCI population.

The hydrodensitometric model was regarded as the "gold standard" for body composition assessment. This model partitions the body into two compartments of constant densities (FM: 0.9007 g/cm3 and FFM: 1.100 g/cm3) and assumes that the relative amounts of the FFM components [water, protein, protein, bone mineral (BM), and non-BM] are fixed (Brozek et al. 1963; Van Der Ploeg et al. 2003).

Hydrodensitometry is clearly inappropriate for individuals who deviate from these fixed and/or assumed values (e.g., children, elderly, and obese), and its application is therefore somewhat limited (Womersley et al. 1976; Schutte 1984; Lohman 1986; Fuller et al. 1996).

Recently, DEXA has gained acceptance as a reference method for body composition analysis (Mahon et al. 2007; LaForgia et al. 2009). Originally designed to determine bone density, DEXA technology has subsequently been adopted for the assessment of whole body composition and offers estimation rapidly, non-invasively and with minimal radiation exposure (Van Der Ploeg et al. 2003; Dionyssiotis et al. 2008). DEXA also has the advantage of being a three-compartment model that quantifies: (1) bone mineral density and content (BMD, BMC), (2) FM and (3) lean mass (LM), half of which is closely correlated with muscle mass and also yields regional as well as total body values (Rittweger et al. 2000).

143.3 Pathophysiological Context

Complete SCI causes inactivation and consequently unloading of affected skeletal muscle (Van Der Ploeg et al. 2003). Studies performed on the skeletal muscle in paraplegics following SCI indicate marked changes in muscle morphology and in metabolic and contractile properties, and on the plasticity of the muscle in the present condition. Disuse was thought to be the mechanism responsible for the skeletal muscle atrophy in paraplegics, but muscle fibres following SCI begin to change their functional properties early post injury. It is evident that other co-factors such as spasticity and microvascular damage, contribute to the induction of the marked morphological and enzyme histochemical changes seen in the paralyzed skeletal muscle (Scelsi 2001). Small fibers, predominantly fast-twitch muscle, and low mitochondrial content have been reported years after injury in cross-sectional studies. These data have been interpreted to suggest that human skeletal muscle shows plasticity (Castro et al. 1999).

Actually, little is known regarding the nature and time frame of the influence of complete SCI on human skeletal muscle, because in cross-sectional studies, different groups of few subjects have been examined and the data was analyzed on different time periods in the chronic phase of paralysis. Muscle fibre cross-sectional area (CSA) has been suggested to decline from 1 to 17 months after injury and thereafter to reach its lowest point. Conversion to type II fibres has been suggested to occur between 4 months and 2 years after injury, resulting in even slow-twitch muscle becoming predominantly fast twitch thereafter (Castro et al. 1999). Metabolic enzyme levels in skeletal muscle might be expected to be reduced after SCI because of inactivation. In support of this contention, succinic dehydrogenase (SDH) activity, a marker of aerobic-oxidative capacity, has been reported to be 47–68% below control values in fibres of tibialis anterior muscle years after injury (Scelsi 2001). Conversely, force loss during repetitive contractions evoked by surface electrical stimulation (ES) of skeletal muscle in humans does not appear to be altered within a few months of injury (Shields 1995), but it is greater a year or more after SCI (Hillegass and Dudley, unpublished observations). The greater fatigue, when evident, has been partially attributed to lower metabolic enzyme levels (Scelsi 2001).

Muscle atrophy in paraplegics is of the central type and depends on the disuse and loss of upper connections of the lower motor neuron, sometimes associated with the loss of anterior horn cells

and trans-synaptic degeneration. The last alteration may be responsible for the denervation changes seen in early stages post SCI. In the later stages of paraplegia (10–17 months post SCI), diffuse muscle atrophy with reduction of the muscle fascicle dimension is associated with fat infiltration and endomysial fibrosis. In all stages post SCI, almost all patients showed myopathic changes, such as internal nuclei, fibre degeneration and cytoplasmic vacuolation due to lipid accumulation (Scelsi 2001).

The mechanisms that underlie bone loss after SCI remain poorly elucidated and controversial. Disuse may play an important role, but factors that are independent of mechanical loading of the skeleton also appear to be important. Possible influential non-mechanical factors may include poor nutritional status, disordered vasoregulation, hypercortisolism (either therapeutic or stress-related), alterations in gonadal function, endocrine disorders, and neural factors (Jiang et al. 2006).

Mechanical stress is one of the determinants of BMD, bone morphology and bone strength. Osteocytes embedded in the bone matrix respond to the mechanical load and to changes in bone metabolism (Doty 1981; Cowin et al. 1991; Lanyon 1993).

The gap junction of the long processes of osteocytes plays an important role in transmitting the mechanical load through intracellular signal transmitters (cAMP and cGMP) and extracellular signal transmitters (PGE2, IGF-I, IGF-II, and TGF-b) to induce bone formation by osteoblasts and inhibition of bone resorption by osteoclasts, or a combination of the two (Rodan et al. 1975; Palumbo et al. 1990; Duncan 1995; Jiang et al. 2006). Therefore, disuse accelerates bone resorption, leading to fragile bones. Sympathetic nervous system (SNS) dysfunction after SCI is attributable to loss of supraspinal control that occurs with disruption of spinal cord pathways (Teasell et al. 2000).

Maintenance of homeostasis within the body is a function of the autonomic nervous system and is interrupted when central nervous system (CNS) communications are interrupted. With high-level spinal cord injuries the SNS is disproportionately involved when compared with the parasympathetic nervous system. In a complete high-level SCI, functioning in the isolated spinal cord below the lesion becomes independent of supraspinal control and has been termed “decentralization” of the SNS (Claus-Walker and Halstead 1982; Karlsson et al. 1998).

Today there is clinical evidence that the sympathetic regulation of bone does exist in humans and plays a clinically important role in diseases characterized by excessive sympathetic activity (Schwarzman 2000). SCI is a dynamic process that is related to alterations in both the central and peripheral SNS. Also, changes in the autonomic nervous system are proposed to cause attrition of SCI bone, via changes in vascular tone and flow (Levasseur et al. 2003).

Sympathetic denervation in SCI may cause arteriovenous shunts and a slowdown of intraosseous blood flow, thus increasing bone resorption. Anatomically, in SCI above the mid-thoracic SNS outflow is crucial to the development of clinical features of SNS dysfunction. It has been observed that the higher the level of the SCI, the greater the degree of clinical manifestations of SNS dysfunction (Teasell et al. 2000).

Vascular modifications below the neurological lesion play a role in the bone resorption after SCI by inducing a local modification of the endosteal surface. The decrease of gas exchanges and blood could promote osteoclast formation because of local hyper pressure, thus accelerating bone resorption (Chantraine et al. 1979).

This clear predominance of bone demineralization in the highly vascularized metaphyseal–epiphyseal areas of the long bones constitutes an additional argument. However, there is indeed a significant local vascularization at the level of these areas, which would be particularly affected by a secondary intramedullary blood stasis due to the sublesional vasomotor disorder (Teasell et al. 2000).

143.4 Methodological Considerations

143.4.1 Paraplegia Related Alterations in Lean Mass, Fat Mass, and Body Mass Index

143.4.1.1 Body Mass Index (BMI) in Spinal Cord Injury – Paraplegia

Similar body mass indices were found between paraplegics and controls, although there were significant decreases in the lean muscle mass of the paraplegics (<16%). The analysis of body composition with DEXA has also revealed large increases in fat in people who do not appear obese, yet they carry large amounts of fat tissue and in the group of paraplegic subjects FM was 47% higher (Jones et al. 2003). Furthermore, where authors performed research on the usage of the BMI in anthropometric measurements, the conclusion was that BMI, widely used as an obesity measurement tool, is not capable of distinguishing the weight components among people, so that the fat percentage is degraded in the paraplegic population in comparison to the control group (Bulbulian et al. 1987) (Fig. 143.1).

In a study which investigated a chronic paraplegic population, BMI values were statistically decreased compared to controls (Dionyssiotis et al. 2008), while others found no significant difference in relation to controls (Maggioni et al. 2003; Mamoun et al. 2004). Moreover, BMI values in both paraplegics and controls were below values considered to indicate obesity (BMI > 27.8) (Statement NIOSH/CDC, 1987; Schulte et al. 2007; Dionyssiotis et al. 2008). This finding may be acceptable for the control group examined, but raises questions regarding the paraplegics. Literature has shown that paraplegics are obese (Kocina 1997). Nevertheless, there are studies which demonstrate the usefulness of BMI as an indicator of obesity in body composition in people with SCI (Gupta et al. 2006). However, these studies included both tetraplegics and middle-aged people, unlike the Greek study which included relatively young individuals (Dionyssiotis et al. 2008). The latest studies show that the criteria of BMI are not effective in assessing obesity in people with SCI (McDonald et al. 2007) (Figs. 143.2 and 143.3).

As with the healthy population, BMI values are positively correlated with obesity in the SCI population. This emerged from a study, conducted by whole body DEXA Norland X-36, only when the

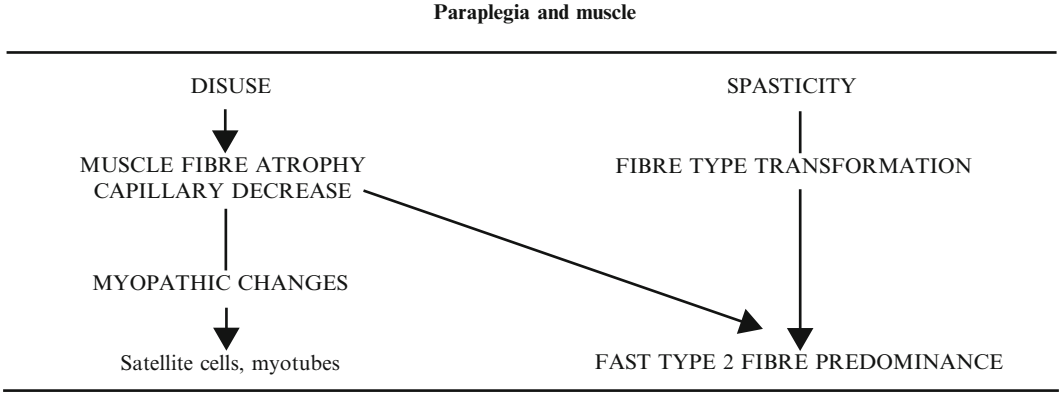

Fig. 143.1 Paraplegia alterations in muscles. Spinal cord injury-induced paraplegia affects muscles in both ways: through disuse and spasticity (Reprinted from Scelsi 2001. With permission)

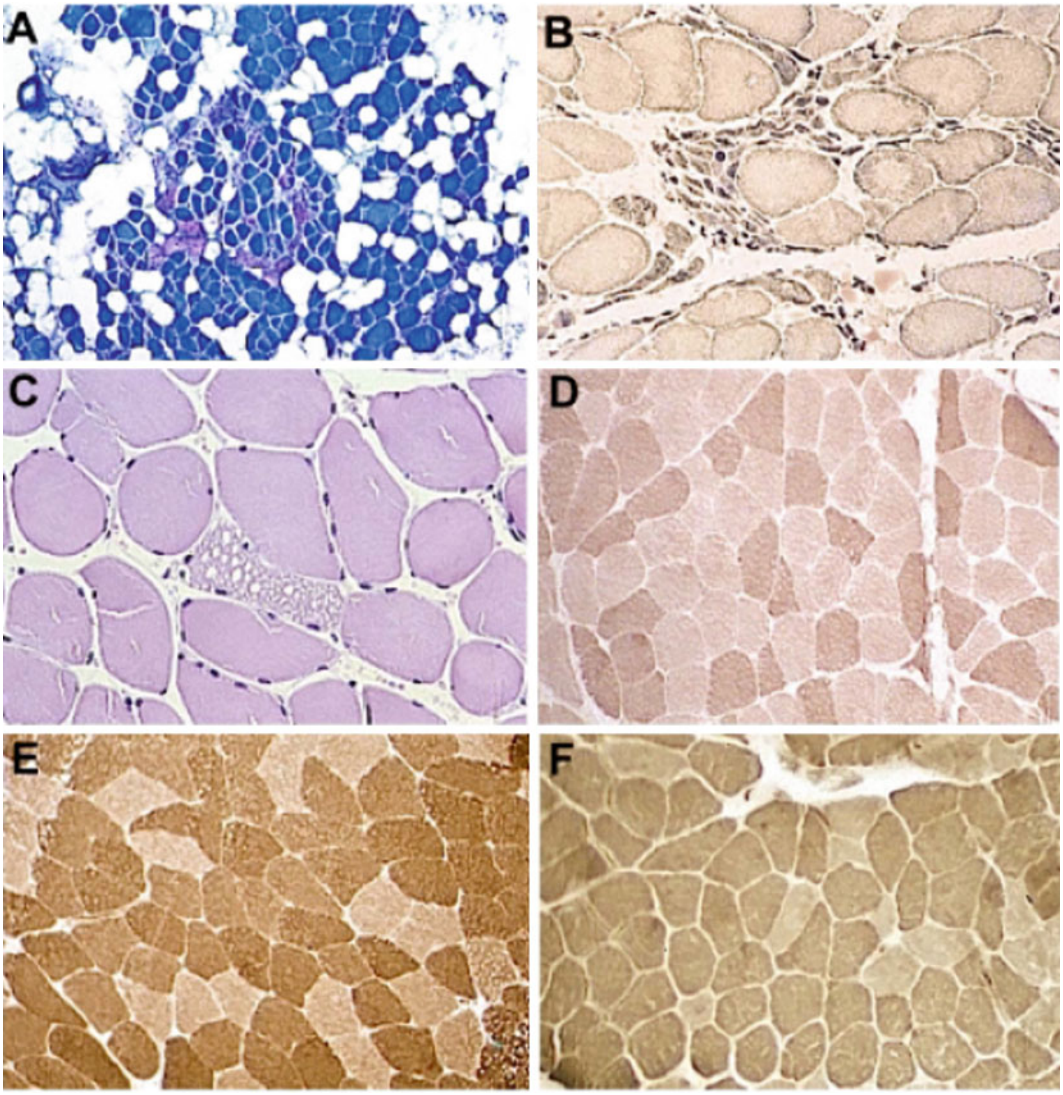

Fig. 143.2 Paraplegia and muscle (1). (**a**) Fascicular atrophy with increase of perimysial fatty tissue in the rectus femoris muscle. Fifteen months post SCI. Giemsa. X 60. (**b**) Pattern of denervation in groups of angulated atrophic fibers in the rectus femoris muscle. One month post SCI. DPNH diaphorase. X 250. (**c**) Numerous lipid vacuoles in the muscle fiber cytoplasm. Six months post SCI. H&E. X 250 D. Normal type I and type II (*dark*) fiber distribution in the quadriceps femoris muscle. Eighteen days post SCI. Myosin ATPase pH 9.4. X 150. (**e**) Some areas of type 2 fiber predominance in the rectus femoris muscle. Nine months post SCI. Myosin ATPase pH 9.4. X 150. (**f**) Diffuse type II fiber predominance in the soleus muscle. Seventeen months after SCI. Myosin ATPase pH 9.4. X 150 (Reprinted from Scelsi 2001. With permission)

findings of total fat in paraplegics were correlated with BMI. Employing whole body DEXA Norland XR-36, it was found that the total FM was statistically, significantly higher for any given BMI value in paraplegics compared with controls (Dionyssiotis et al. 2008), a finding that strongly supports the studies held by the whole body DEXA Hologic QDR-2000 method (Spungen et al. 2000, 2003).

The studies illustrated statistically, significantly higher total FM and fat percentages for any given unit of BMI in paraplegics in comparison to controls. Increased fat per BMI unit was found in a

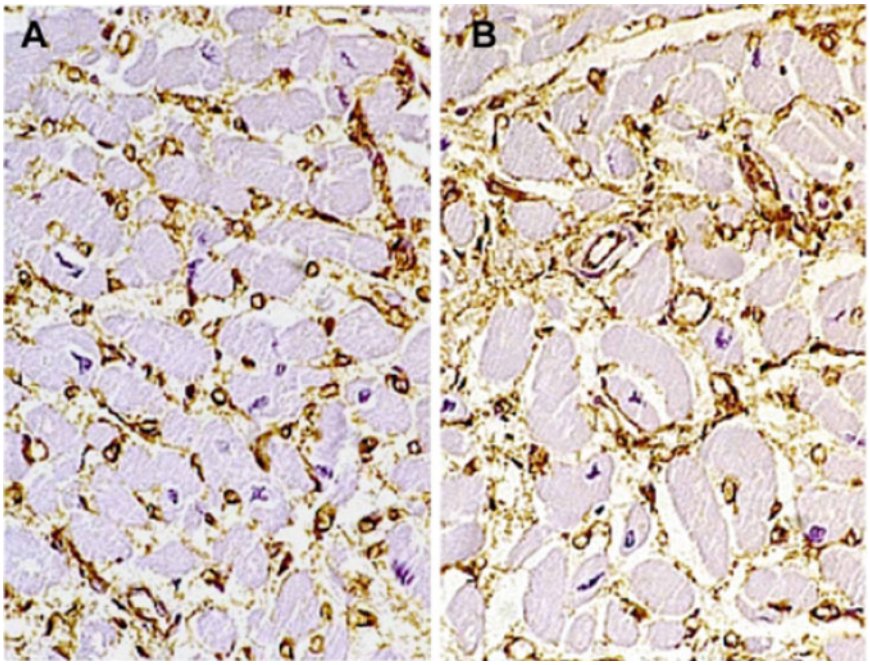

Fig. 143.3 Paraplegia and muscle (2). (**a**) Normal capillary distribution in a paraffin embedded transverse section of muscle fibers from an healthy subject. Rectus femoris muscle. Immunohistochemical reaction for CD 36. X 60. (**b**) Reduction in the number of capillaries and marked dilatation of the lumen of small blood vessels in gastrocnemius muscle. Twelve months after SCI. Immunohistochemical reaction for CD36. X 60 (Reprinted from Scelsi 2001. With permission)

study, also by the above authors, of monozygotic twins, one with SCI compared with the non-SCI co-twin (Spungen et al. 2000). Adjustments in classifications of normal, overweight, obese, and morbid obesity by BMI are needed for persons with SCI (Groah et al. 2009).

In addition, in an analysis between paraplegics with high and low neurological level injuries (NLoIs), a lack of statistically significant differences in BMI was highlighted. However, when data from the analysis undertaken in areas measured by whole body DEXA were compared in the same patients, there were differences between paraplegics with high and low NLoI. This finding is new and reinforces those views on the inaccuracy of BMI usage in the analysis of body composition of paraplegics (Dionyssiotis 2008; Dionyssiotis et al. 2008).

BMI of the male paraplegic group was slightly greater than that of the male tetraplegic group (25.2 vs. 24.7 kg/ m2; $p < 0.01$). The proportion of overweight or obese was comparable between men with SCI and that observed in men in the US general population. Distribution of BMI by level of injury was similar, with 37.5% and 40.5% of the male tetraplegic and male paraplegic groups, respectively, falling into the recommended BMI range. Approximately 50% in each male group were overweight by BMI, and 12.5% and 10.8%, respectively, were classified as obese. Overall, when compared with the general population-observed distribution by BMI, a greater proportion of men with SCI fell into the desirable BMI range and fewer fell into the obese category (Groah et al. 2009).

No differences were found in BMI between paraplegics in the acute phase of injury and control. This finding is in accordance with other studies reported in chronic paraplegic patients and controls, in which despite the same BMI, the body composition and the distribution of fat and FFM were altered in patients with SCI, with the FFM being statistically, significantly lower in paraplegic

Table 143.1 Regional (*upper and lower limbs*) and total body composition results in controls vs. total paraplegic group

		Control group $n = 33$	Paraplegics $n = 31$	
Whole body DEXA	Parameters	Mean value ± SD	Mean value ± SD	*p*-Value
Upper limbs	BMC, g	449.88 ± 57.3	465.15 ± 65.71	N.S
	Lean, g	6,570.21 ± 1,498.81	6,082.03 ± 1,615.13	N.S
	Fat, g	2,025.32 ± 874.04	2,316.87 ± 1,500.12	N.S
Lower limbs	BMC, g	1,213.84 ± 149.37	886.26 ± 178.81	< 0.0005
	Lean, g	19,692.73 ± 3,242	11,094.3 ± 2,174.64	< 0.0005
	Fat, g	6,909.91 ± 2,497	8,203.3 ± 3,433.02	N.S.
Total body	BMC, g	3,322.7 ± 302.84	3,016.74 ± 368.38	0.001
	Lean, g	56,655 ± 8,781.05	42,211.2 ± 6,509.2	< 0.0005
	Fat, g	19,015.8 ± 6,553.84	23,071.8 ± 9,485	0.001

Values of measured parameters (bone mineral content (BMC), lean and FM) in paraplegics and controls using whole body DEXA in upper and lower limbs and total body composition (Reprinted (modified and translated) from Dionyssiotis 2008)

patients in total body composition and in the lower, but not the upper limbs. As far as the FM is concerned, it was statistically, significantly higher (kilograms and %) in the total body composition in the upper and lower limbs (Maimoun et al. 2006) (Table 143.1).

These findings show that using the BMI does not contribute substantially in determining the body composition of paraplegics, but that it shows a lower percentage of fat in this population – a finding that agrees with other studies and shows that the anthropometric measurement with BMI in paraplegics underestimates fat in body composition when measurements are compared with healthy subjects (Jones et al. 1998).

143.4.1.2 Total Body Composition Alterations

The body composition is significantly altered during the first 6 months after the injury according to studies conducted in paraplegics who noticed remarkable muscle atrophy between the first and the third month after injury, without further loss until the following 6 months (Rossier et al. 1991; Uebelhart et al. 1995; Baldi et al. 1998; Castro et al. 1999). The corresponding percentages were 10.7% in the lower limbs and 5% in the total body composition in six young paraplegic men, while the LM increased by 19.6% in the upper limbs. In a perspective study of 1 year, muscle mass is dramatically diminished during the first months after the injury in the lower limbs (in 15 weeks), while in the same time period the fat content tended to increase. The total lean muscle mass is reduced by approximately 9.5% within 6 months, while the lean muscle mass of the lower limbs is reduced by 15.1% within a year after the injury. Nevertheless, authors phrased that LM is better preserved in patients who develop spasticity (Wilmet et al. 1995) (Fig. 143.4).

In another study the population of paraplegics was estimated with DEXA and furthermore anthropometric skinfold measurement was performed. The anthropometric measurement underestimated significantly the FM in the paraplegics' population. The total and regional body composition (FM; fat-free mass, FFM) was estimated in 13 SCI patients and total FM was found to be significantly higher and LM lower in comparison to the controls. In the group of paraplegics the regional FM was higher in the lower limbs and the trunk (Maggioni et al. 2003).

In active paraplegic men FM was found to be 16–24% compared to 15% for normal men (Kocina 1997). In chronic paraplegics who had suffered injury 2 years earlier, the amount of skeletal muscle in the FFM of the soft tissue was studied at the mid-shaft of the femoral bone using a magnetic resonance

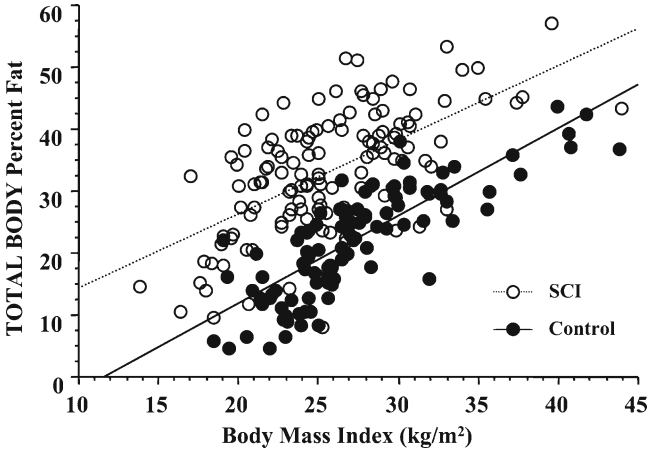

Fig. 143.4 The relation of total body percent fat with body mass index (BMI) for spinal cord injured and controls. Relationship of total body percent fat with BMI for the spinal cord injury (SCI) and control groups (SCI: $r = 0.60$, $p < 0.0001$, control: $r = 0.81$, $p < 0.0001$). The subjects with SCI had, on average, a 13 ± 1% increase in percent fat for any given BMI compared with the control subjects (Reprinted from Spungen 2003. With permission)

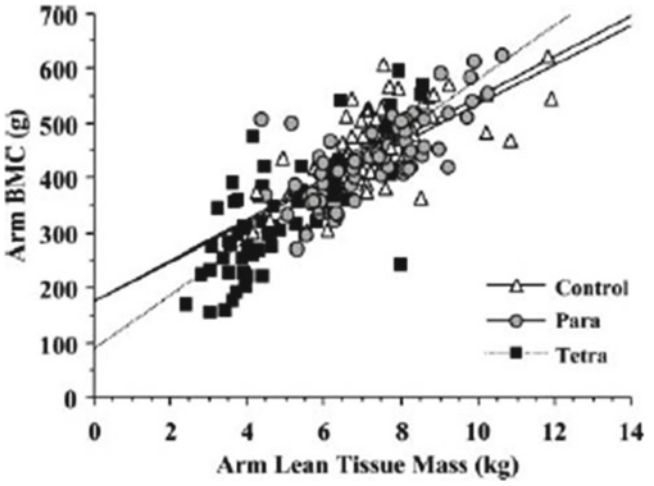

Fig. 143.5 The relation of arm bone mineral content (BMC) with arm lean tissue mass for tetraplegics (tetra), paraplegics (para) and controls. Relationship of arm BMC with arm lean tissue mass for Tetra, Para, and control (Tetra: $r = 0.76$, $p < 0.0001$; Para: $r = 0.73$, $p < 0.0001$; control: $r = 0.73$, $p < 0.0001$). There were no significant interaction effects or slope differences among Tetra, Para, and control groups (Reprinted from Spungen 2003. With permission)

imaging (MRI) technique and with DEXA and compared with similar normal population. Muscle mass and fat-free soft tissue mass were statistically, significantly lower in paraplegics, but the paraplegic group showed a lower ratio of muscle to fat-free soft tissue mass tissue in relation to controls (Modlesky et al. 2004). Using the MRI technique, an 18–46% loss was observed in the thigh surface in complete paraplegics in the acute phase of 6 weeks, with an additional loss of about 8–15% during the next 18 weeks (Castro et al. 1999). The percentage of FM in subjects with low paraplegia was comparable to controls at 20%, although in higher NLoI, the rate of fat ranged from 30% to 36% in 37 SCI patients studied using radioisotope methodology (Nuhlicek et al. 1988). In 133 men with chronic SCI, 13 ± 1% more fat per unit of BMI and higher values of FM in paraplegics' upper limbs and lower rates of LM were found compared with controls (Spungen et al. 2003) (Fig. 143.5).

Table 143.2 Arms' measured parameters in controls and paraplegic groups

Whole body DEXA parameters		Control group $n = 33$ Mean value ± SD	High Paraplegics $n = 16$ Mean value ± SD	Low Paraplegics $n = 15$ Mean value ± SD	*p*-Value
ARMS	BMD, g/cm^2	0.76 ± 0.11	0.66 ± 0.10	0.76 ± 0.12	0.008
	BMC, g	449.88 ± 57.3	454.86 ± 68.10	476.13 ± 63.53	0.391
	Lean, g	6.570 ± 1.499	6.150 ± 1676	6.007 ± 1.602	0.451
	Fat, g	2.025 ± 874	1.951 ± 962	2.658 ± 1839	0.186

Values of measured parameters BMC, BMD, lean and FM) in both paraplegic groups and controls using whole body DEXA in the upper limbs (Reprinted (modified and translated) from Dionyssiotis 2008)

The strong influence of the duration of injury to both the lower limbs and body composition study has been reported in a study of monozygotic twins where one brother had complete paraplegia and his twin brother was normal. The reduction in LM was as greater as longer the duration of the paralysis (Spungen et al. 2000, 2003).

A statistically significant decrease of 26% in total muscle mass in paraplegics compared with controls was found within 5 years of injury. Moreover during the same period in paraplegics the total amount of fat was statistically, significantly increased by 21% (Dionyssiotis 2008). Similarly, others found that the total muscle mass decreases by about 9.5% within 6 months, while the muscle mass of the lower limbs is reduced by 15.1% 1 year after the injury (Wilmet et al. 1995). The increased rate of fat by 29% which was found in the Greek study of paraplegics with a low NLoI (Dionyssiotis 2008) is substantially similar to a former study (increased rate of fat in paraplegics 20%) of a group of paraplegics that also included high paraplegics (Nuhlicek et al. 1988). The difference is due to the participation of high paraplegics in their study which reduced the percentage. In a mixed paraplegic population (complete and incomplete paraplegics) the percentage of LM, but not absolute LM, in the upper limbs of paraplegics was significantly lower than controls, suggesting that the higher amount of absolute FM in paraplegics was responsible for this result (Spungen et al. 2003). In contrast, the Greek study of the analysis of LM and FM in paraplegics' upper limbs and controls did not show any significant differences (Dionyssiotis et al. 2008). However, when paraplegics were analyzed according to the NLoI, values of fat in high paraplegics' upper limbs were similar to controls and lower in comparison with values of fat in the low paraplegics group. However these results were not statistically significant. In the same study further investigation of the relationship of muscle mass in both upper limbs of paraplegic groups revealed that the high paraplegics have 2% more muscle mass than the low paraplegics. Also, the corresponding relationship concerning the fat revealed a decrease in fat by 26.6% in the upper limbs of the high paraplegics compared with the low paraplegics. Taking into consideration that the upper limb is only theoretically a non-weight bearing bone in paraplegics, an explanation of this finding could be that high paraplegics are trying to overcome their handicap through an arm overuse (high mechanical forces) reducing regionally adiposity and inducing LM. So the question is if the higher FM values in low paraplegics' arms are responsible for the higher values in BMD (Dionyssiotis 2008; Dionyssiotis et al. 2008) (Table 143.2).

In a prospective 1-year study it was seen that LM is better preserved in patients who develop spasticity (Wilmet et al. 1995). Other authors also reached the same conclusion as Gorgey and Dudley 2003. The latter study included patients with incomplete SCI. This conclusion, however, has been questioned by other researchers and has not been verified by studies involving patients with complete paraplegia (Eser et al. 2005). Spasticity does not constitute a maintaining factor of the

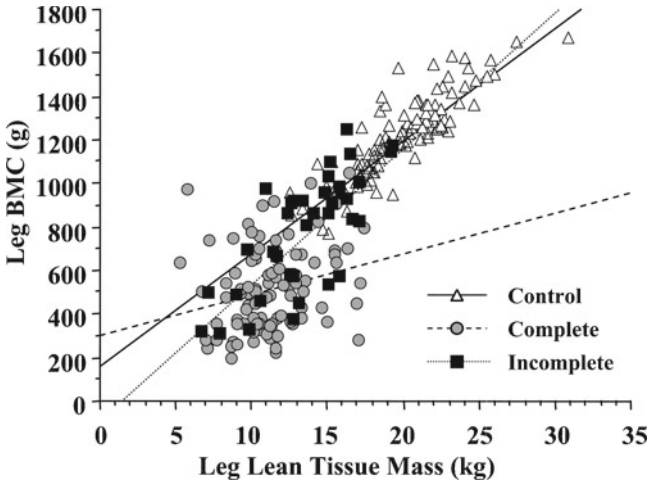

Fig. 143.6 Relationship of leg BMC with leg lean tissue mass for those with complete or incomplete SCI and controls. Relationship of leg BMC with leg lean tissue mass for those with complete (an absence of sensory or motor function below the neurological level, including the lowest sacral segment) or incomplete (sensory or motor function below the neurological level, including the lowest sacral segment) spinal cord injury (SCI) and controls (complete: $r = 0.25$, $p < 0.01$; incomplete: $r = 0.74$, $r < 0.0001$; control: $r = 0.86$, $p < 0.0001$). Those in the complete group had significantly less BMC per unit of lean tissue mass than the other two groups (slopes: complete = 0.061 vs. incomplete = 0.553 and control = 0.747; $p < 0.01$) (Reprinted from Spungen 2003. With permission)

muscle system and we believe that the importance of neurogenic damage is highlighted, so that either the myopathic muscle does not recognize stimuli due to its degeneration or it recognizes them incorrectly (Dionyssiotis 2008) (Fig. 143.6).

In addition, the strong influence of the duration of injury to the lower limbs and body composition has been reported in monozygotic twins, where one brother had complete paraplegia and his twin brother was normal (Spungen et al. 2000). The authors concluded that the longer the duration of paralysis, the greater the decrease in muscle mass. In the group of high paraplegics a strong relationship between duration of paralysis and both total body and upper limbs fat was found (Spungen et al. 2003). Despite the similar paralytic effect on body composition and the similar duration of paralysis in both paraplegic groups of this study, the explanation of that strong correlation may be due to the outcome of higher frequency of standing and increased mobilizing in the group of low paraplegia and the possible use of gait orthoses and standing frames that results in increased energy consumption and obesity reduction. Nevertheless, this explanation is simplistic considering the complex pathophysiology with regard to hormonal influences, the injury and the neurogenic factor in body composition of paraplegics (Dionyssiotis 2008).

143.4.2 Spinal Cord Injury Induced Paraplegia and Bone

SCI always results in substantial and rapid bone loss. In SCI patients, the demineralization predominates on the long bones of the lower limbs. The most affected sites are the trabecular metaphyseal–epiphyseal areas of the distal femur and the proximal tibia (Jiang et al. 2006). The predominant finding of SCI on bone is a large loss of bone during the first year of injury due to disuse osteoporosis, predisposing to an increased prevalence of fractures (Spungen et al. 2003). An ongoing demineralization

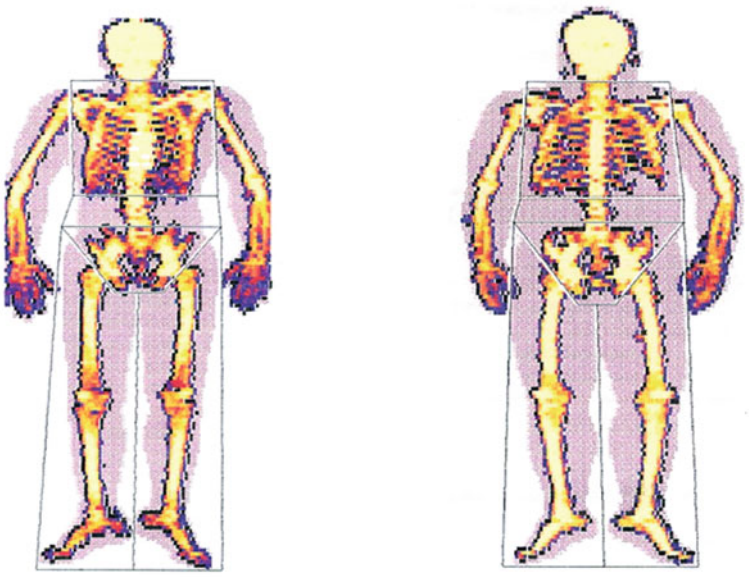

Fig. 143.7 Whole body Norland XR-36 in paraplegic (*left*) vs. control subject and values of the measured parameters. Whole body and regional distribution of fat mass (FM), lean mass (LM), BMC and BMD from paraplegic subject Thoracic 12 (*left picture*) and healthy man using whole body DEXA Norland X-36 and values of measured parameters (Reprinted from Dionyssiotis 2008)

in the tibia was demonstrated 3 years after trauma (Biering-Sörensen et al. 1988) and a progressive bone loss in SCI over 12–16 months prior to stabilizing (Lazo et al. 2001) (Fig. 143.7).

Duration of paralysis, related loss of bone in the lower limbs of monozygotic twins with chronic paraplegia in comparison with their able-bodied co-twins is also reported (Bauman et al. 1999). A longitudinal study of 15 acute SCI patients revealed that BMD in the calcaneus and proximal tibia was decreased by 7.5% and 5.3% in 6 weeks after injury, respectively (Warden et al. 2002). Cancellous bone is more affected than cortical bone after SCI. In a prospective study, six acute tetraplegics were followed up for 12 months, and the trabecular and cortical BMDs of the tibia were found to be decreased by 15% and 7%, respectively (Frey-Rindova et al. 2000). In a cross-sectional study (Dauty et al. 2000) of 31 SCI patients more than 1 year after injury, a significant demineralization at the distal femur (-52%) and the proximal tibia (-70%) was demonstrated and this is in accordance with the findings of other authors (Biering-Sorensen et al. 1990; Finsen et al. 1992). Similarly, in another cross-sectional study of eight SCI patients, a reduction of 35.3% in BMD of the tibial trabecular bone occurred within the first 2 years after SCI, whereas there was only a 12.9% reduction in tibial cortical bone (de Bruin et al. 2000). Bone loss in the proximal tibia of acute SCI patients is about 5.3–15%, whereas in chronic SCI patients a range of 15–52% was reported (Biering-Sorensen et al. 1990; Demirel et al. 1998; Dauty et al. 2000; Warden et al. 2002).

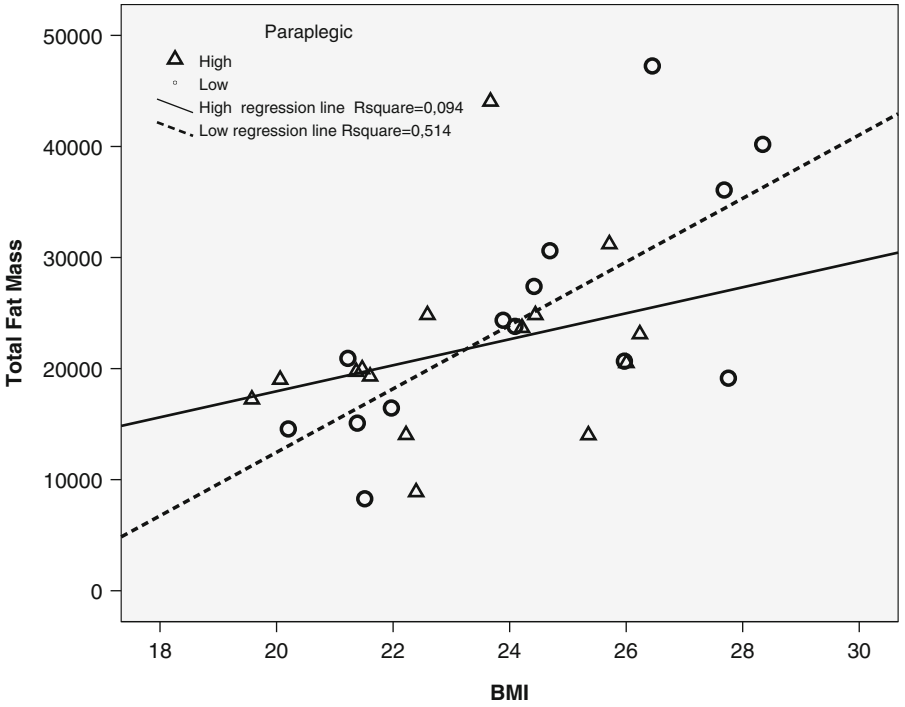

Fig. 143.8 The relation of total FM with BMI for paraplegics with high and low levels of injury. Relationship of total FM with BMI for paraplegic subjects (high paraplegics above thoracic (T) seven neurological level of injury (NLoI) vs. low paraplegics T8-T12 NLoI. According to the level of neurological injury during analysis between paraplegic subjects no statistically significant differences in BMI were found. When we correlated data from the analysis undertaken in body composition measured by the method of whole body DEXA we found strong correlation of total FM with BMI only in low paraplegic group. This finding is new and reinforces those views on the impossibility of use of BMI in the analysis of body composition of paraplegic subjects (Reprinted (modified and translated) from Dionyssiotis 2008)

143.4.3 Factors that Appear to Influence Bone in SCI Individuals

1. The level of the lesion and thus the extent of impairment of motor and sensory functions may be taken into account first, because tetraplegics are more likely to lose more bone mass throughout the skeleton than paraplegics (Tsuzuku et al. 1999). A reduction of lower limb BMC in chronic paraplegics vs. controls was found independently of the NLoI. Lower limb BMC was negatively correlated with the duration of paralysis in the total paraplegic group, but after investigation according to the NLoI this relationship was due to the strong correlation of high paraplegics leg BMC with the duration of paralysis, meaning that the NLoI determines the extent of bone loss (Dionyssiotis et al. 2009). However, similar severity of demineralization in the sublesional area was shown between paraplegics and tetraplegics, and the extent of the bone loss may be variable (Demirel et al. 1998; Tsuzuku et al. 1999; Dauty et al. 2000) (Fig. 143.8).
2. In addition, in those SCI individuals with complete lesions (an absence of sensory or motor function below the neurological level, including the lowest sacral segment) bone loss is more severe than subjects with incomplete lesions (partial preservation of motor and/or sensory function(s) below the neurological level, including the lowest sacral segment) (Garland et al. 1992; Demirel et al. 1998; Sabo et al. 2001). In a cross-sectional study of 11 patients with complete SCI and 30

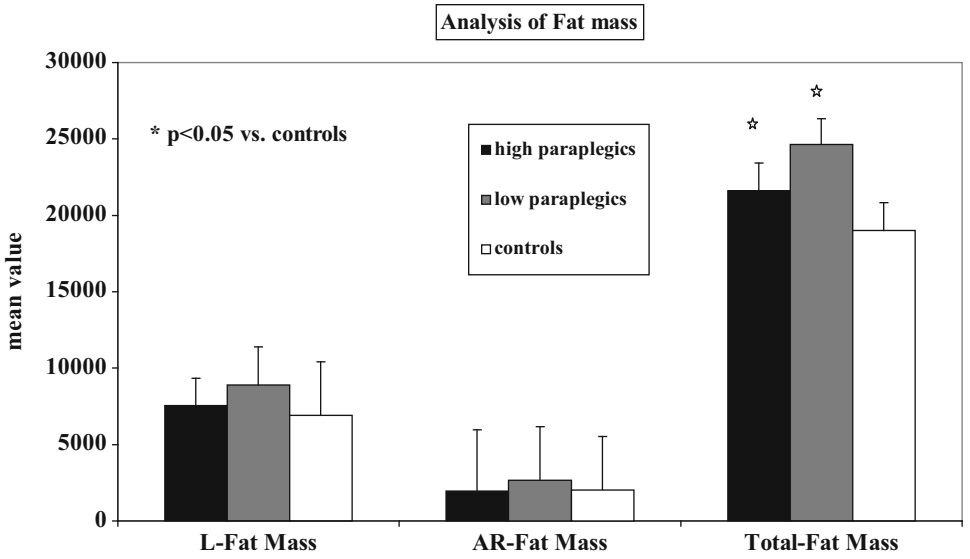

Fig. 143.9 Fat mass analysis in the two paraplegic groups and controls in upper limbs region (AR-FM), lower limbs region (L-FM) and total body composition (Total – FM). Fat mass analysis in the two paraplegic groups and controls in legs, arms and total body. Analysis of FM in paraplegics' arms and legs vs. controls did not show any significant differences. Total body fat value was statistically significant increased in paraplegic subjects 23,071 ± 9,485 vs. 19,015.± 6,553 in controls ($p = 0.05$) (Reprinted (modified and translated) from Dionyssiotis 2008)

patients with incomplete SCI, more significant osteopenia was observed in patients with complete SCI than in patients with incomplete SCI (Demirel et al. 1998).

3. Inconsistent results have been reported regarding the effect of muscle spasms on BMD in SCI patients. Those with spasticity were found to have higher BMD when compared with flaccid individuals (Demirel et al. 1998), and a significant correlation between the degree of spasticity measured with modified Ashworth scale and BMD was reported. Thus, it was concluded that spasticity may be protective against bone loss in SCI patients (Eser et al. 2005). Conversely, other investigators have not established a correlation between BMD and muscle spasticity (Panin et al. 1971; Gross et al. 1987; Biering-Sorensen et al. 1990; Wilmet et al. 1995; de Bruin et al. 2000) (Figs. 143.9 and 143.10).
4. Studies also emphasize the contribution of aging to bone loss in complete SCI patients. Moderate correlation between age and femoral BMD was observed in a cross-sectional study of 30 patients with SCI of 1-year duration or less (Kiratli et al. 2000). On the other hand, bone loss in eight pairs of identical male twins with SCI of duration ranging from 3 to 26 years appeared to be independent of age (Bauman et al. 1999; Wood et al. 2001)
5. Muscular loading of the bones has been thought to play a role in the maintenance of bone density. The ability to stand or ambulate itself does not improve BMD and does not prevent osteoporosis after SCI, although exercise increases site-specific osteogenesis in able-bodied individuals (Kunkel et al. 1993). There was only one study demonstrating that standing might reduce the loss of trabecular bone after SCI. In this prospective study of 19 acute SCI patients, the patients involved in early loading intervention exercise lost almost no bone mineral, whereas the immobilized patients lost 6.9–9.4% of trabecular bone (de Bruin et al. 1999) (Fig. 143.11).

Muscles rather than body weight achieve the greatest loads on bone (Frost 1987). It is difficult to translate in vivo bone strains from animal work to a gross loading environment for humans.

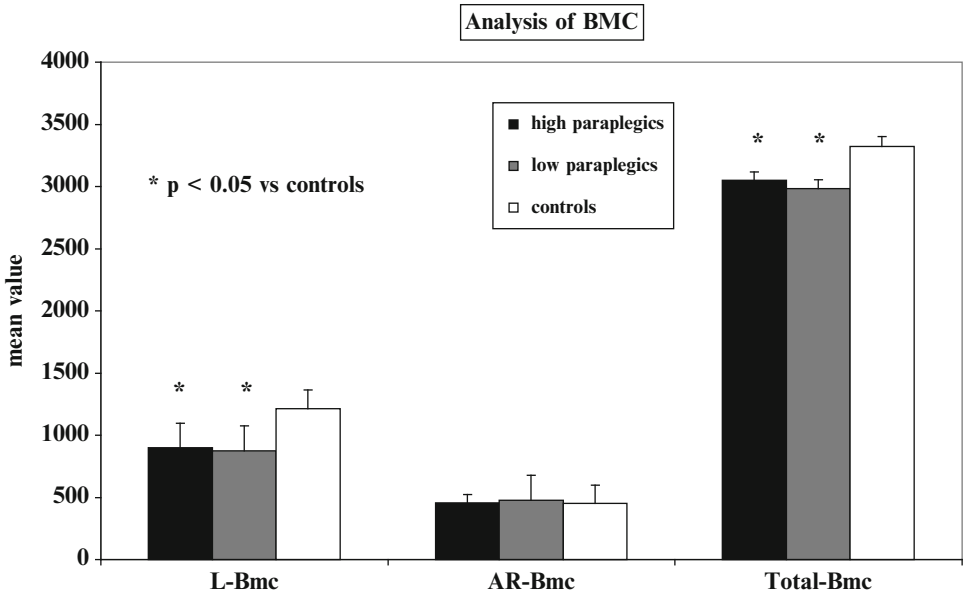

Fig. 143.10 Analysis of bone mineral content (BMC) in the two paraplegic groups and controls. Analysis of BMC in high and low level paraplegics and controls. A statistically significant reduction was observed in BMC in total body composition (3,016 ± 368 vs. 3,322 ± 302, $p = 0.001$) and paraplegics' lower limbs (886 ± 178 vs. 1,213 ± 149, $p < 0.001$) in comparison with able-bodied males (Reprinted (modified and translated) from Dionyssiotis 2008)

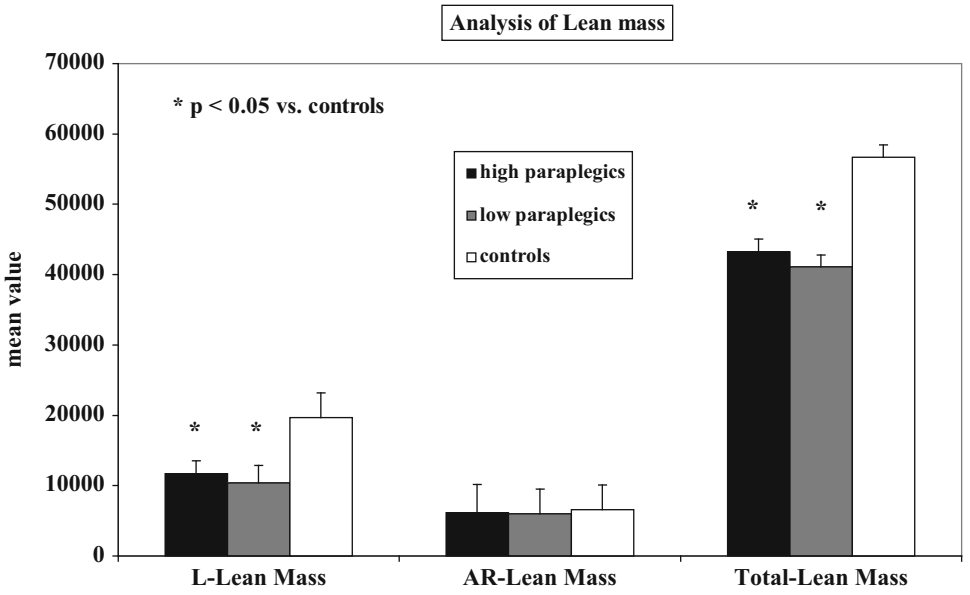

Fig. 143.11 Analysis of lean mass (LM) in the two paraplegic groups and controls. Analysis of LM in high and low level paraplegics and controls. A statistically significant reduction in total LM ($p < 0.001$) in paraplegics' total body and lower limbs composition in comparison with able-bodied males (42,211 ± 6,509 vs. 56,655 ± 8,781 and 11,094 ± 2,174 vs. 19,692 ± 3,242, respectively) was observed (Reprinted (modified and translated) from Dionyssiotis 2008)

However, the pioneering work in animal models (Frost 1988) suggests that if the active–resistive standing exercise can indeed transmit loads at an appropriate frequency and strain-rate, compressive loads approaching 240% body weight may have the potential to be osteogenic (Frost 1990, 1995).

Functional electrical stimulation (FES) cycling (Ragnarsson et al. 1988) and quadriceps muscle training (Belanger et al. 2000) have been able to increase force-generating capability and to improve muscular endurance with training after SCI (Ragnarsson et al. 1988). Conversely, cycling with FES has been reported to induce only small improvements in BMD (Bloomfield et al. 1996; Mohr et al. 1997) as well as having no effect (Leeds et al. 1990; BeDell et al. 1996) on lower extremity BMD measurements in individuals with SCI. Additionally, neither passive standing, ambulation with long-leg braces, nor ambulation with FES have yet to exhibit any improvement in lower extremity BMD in chronically injured subjects (Sloan et al. 1994; Needham-Shropshire et al. 1997). The subject population of previous BMD studies were comprised almost exclusively of individuals with chronic rather than acute SCI. These interventional BMD studies may have utilized sub-threshold mechanical stimuli. The use of relatively low bone loading regimens is not unexpected due to the extensive atrophy of chronically paralyzed muscle (Shields 2002, 2007) and concerns of fracture which have been reported to occur with physical interventions (Valayer-Chaleat et al. 1998; Frey-Law and Shields 2004).

6. The duration of paralysis has also been shown to affect the degree of bone loss in the sublesional areas (Lohman 1986; Modlesky et al. 2004). Studies report inverse relationships between the duration after injury with lower limb percentage-matched BMD and trunk percentage-matched BMD (Clasey et al. 2004). In addition upper limb FM and lower limb BMD were correlated with the duration of paralysis in total paraplegic group, but after investigation according to the NLoI (NLoI). This association was due to the strong correlation of high paraplegics' lower limbs BMD with the duration of paralysis. The explanation of this strong correlation could possibly be that despite the similar paralytic effect on bones in all paraplegic patients and the similar duration of paralysis in the two paraplegic groups, this difference is possibly a result of higher incidence of standing in the group of low paraplegics and direct effect of loading lower limbs and walking with orthoses. The association of the duration of paralysis with parameters below and above the NLoI raises the question of the existence of a hormonal mechanism as an influential regulator in paraplegics' body composition (Dionyssiotis et al. 2008).
7. The role of leptin: the hormone leptin is secreted by fat cells and helps regulate body weight and energy consumption (Fruhbeck et al. 1998). The amount of leptin in the circulation is positively correlated with the percentage of fat in people (Maffei et al. 1995). In paraplegics, when compared with healthy subjects, higher levels of leptin have been found, possibly due to greater fat tissue storage (Bauman et al. 1996). Leptin activates the sympathetic nervous system (SNS) through a central administration. The disruption of the sympathetic nervous system may modify the secretion and activity of the leptin, because the sympathetic preganglionic neurons become atrophic in high paraplegics (Elias et al. 1998; Correia et al. 2001). The irritation thus, below the NLoI, from the leptin is disturbed. In addition, extensive obesity is known to reduce lipolytic sensitivity (Haque et al. 1999; Horowitz et al. 1999; Horowitz and Klein 2000). Given that in a high level of neurological paraplegia there is a problem of disorder of the autonomic nervous system, and in combination with the existence of scientific evidence, that the hormone leptin activates the sympathetic nervous system through central control, it was formulated that the closure <of paths> of the central nervous system disrupts the effect of leptin and possibly increases the risk of obesity in paraplegic patients with high-level injury (Krassioukov et al. 1999; Jeon et al. 2003).

However, after separation of SCI subjects into those with an injury above or below Thoracic (T) 6, leptin levels were significantly higher in the former group. T6 appears to be the lowest level of injury in most patients with SCI to develop autonomic dysreflexia. With SCI above the level of T6, there is reduced SNS outflow and supraspinal control to the splanchnic outflow and the lower-extremity blood vessels. Multiple regression analysis showed that serum leptin levels in men with SCI correlated not only with BMI but also with the neurologic deficit. This finding supports the notion that decentralization of sympathetic nervous activity relieves its inhibitory tone on leptin secretion, because subjects with tetraplegia have a more severe deficit of sympathetic nervous activity (Wang et al. 2005).

143.4.4 Steady State After Injury

Is there a time after injury where bone loss ceases? Some authors reported that approximately 2 years after SCI, a new steady state level between bone resorption and formation would be re-established (Chantraine et al. 1986; Biering-Sorensen et al. 1990), whereas others (de Bruin et al. 2005) found that there was no sign of a new steady state in bone formation in the lower extremities 2 years after the SCI. Using peripheral quantitative computed tomography (p QCT) has been shown that different parameters reach the steady state at different time and levels in the same bone (Dionyssiotis et al. 2009). It still remains controversial whether or not a new steady state of bone remodelling is re-established after SCI.

143.4.5 Effect of Paralysis in Bones Above and at the Neurological Level of Lesion

There is no demineralization of the upper limbs in paraplegics. On the contrary, a minor increase of BMD (6%) in the humerus was reported in a cross-sectional study of 31 male chronic paraplegics 1 year post injury. With reliance on the upper limbs to provide movement for activities of daily living in the SCI population, this area could be subjected to greater site-specific loading, and thus increasing osteogenesis, than in the corresponding able-bodied population. At the lumbar spine, the trabecular bone demineralization remains relatively low compared to the cortical bone demineralization of long bones (Dauty et al. 2000). Normal (Chantraine et al. 1986; Biering-Sorensen et al. 1988; Kunkel et al. 1993) or even higher than normal (Ogilvie et al. 1993) values of BMD in the lumbar spine have been reported, a phenomenon which is named dissociated hip and spine demineralization (Leslie and Nance 1993). One reason for preservation of bone mass in the vertebral column is because of its continued weight-bearing function in paraplegics. In a cross-sectional study of 135 SCI men, BMD in the lumbar spine was found to be stable with an insignificant decline in the tetraplegic population at 1 ± 5 years post injury in the 20–39-year age group, whereas in the 40–59-year age group and the 60+-year age group, bone mass in the lumbar spine remained unchanged or even increased with age (Szollar et al. 1997). However, several factors may affect the results of BMD measurement: lumbar spine arthrosis, bone callus, vertebral fracture, aortic calcification, osteosynthesis material, etc. Degenerative changes in the spine may be the most possible reason to give falsely higher values of BMD (Dauty et al. 2000). An interesting question is why we do not see osteoporotic vertebral fractures in SCI patients to the extent it occurs in post-menopausal osteoporotic women or senile osteoporotic men?

143.5 Conclusion

Another critical question that arises is how best to proceed programmatically to promote optimal body weight and composition to reduce disease risk. Typical management options include dietary change, physical activity, and pharmacologic options. First-line self-management is often dietary changes for improved weight control and disease prevention. To achieve benefits, many individuals with SCI would have to follow stringent diets with lower total energy intake and an emphasis on nutrient-rich foods (Groah et al. 2009).

143.6 Applications to Other Areas of Health and Disease

Paraplegia related alterations of body composition are very important. Not only fractures because of bone loss but other diseases such as coronary heart disease, non-insulin-dependent diabetes mellitus and lipid abnormalities exist in paraplegics with higher prevalence. The increased fat percent in the body and the immobilization play a significant role in these diseases. Research about body composition in paraplegia is very important to quantitate and monitor body composition changes and to modify our therapeutic interventions in this specific population.

Summary Points

- Healthy BMI values often underestimate body fat in men with spinal cord injury and may mask the adiposity.
- BMI and total body fat were interrelated in SCI, as in the control population, but the line was shifted to the left, indicating that total body fat mass and percent were significantly greater at any given unit of BMI in persons with SCI than in controls.
- Upper limbs' analysis according to the neurological level of injury unmasked similar fat values in high paraplegics and controls vs. higher values in low paraplegics.
- Spasticity did not defend skeletal muscle mass and bone. This result supports the concept that after spinal cord injury the myopathic muscle could not recognize correctly the stimulation because of the neurogenic injury.
- Studies indicated marked atrophy of paralyzed muscles after spinal cord injury suggesting a preferential atrophic response in the antigravity muscles. One explanation is that paraplegics mostly transfer much of the weight-bearing demands of daily activities to their upper extremities. This reduced the weight-bearing of the affected paralyzed muscles triggering a cycle of added muscle atrophy and acts synergistically with the continuous catabolic action caused by the neurogenic factor.
- Spinal cord injury induces bone loss in paraplegics. A decline in bone mineral density as well as bone mineral content is expected in paralyzed segments.
- The duration of paralysis is positively correlated with the degree of bone loss. Duration of paralysis is positively correlated with total fat mass in total paraplegic group. This correlation was found to be stronger for high paraplegics in specific regions (upper limbs) and in total body composition.
- While it is possible that different stimuli are necessary to cause adaptations in muscle and bone after SCI, it is also possible that osteoporosis, unlike muscle atrophy, is essentially irreversible

once established. Prevention rather than treatment may have the greatest potential to alleviate this significant SCI complication.

- Muscles and bones are related tissues. Strategies that help paraplegics to bear weight, to stand or walk therapeutically should be added early in the rehabilitation program to gain benefits according to muscles and bones.

Key Points

Table 143.3 Key points of Spinal Cord Injury (SCI) induced paraplegia

Key points in body composition in SCI – paraplegia
Body mass index values often underestimate body fat in men with spinal cord injury
Subjects lose muscle mass and bone and gain FM especially in lower limbs
Osteoporosis is essentially irreversible once established
Paraplegia related alterations are associated with unloading but also could have a central nervous system origin
Spasticity did not defend skeletal muscle mass and bone
Important issues in paraplegia related changes in body composition

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Chapter 144
Anthropometry of Head Circumference, Limb Length and Dementia

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Abstract Recent research findings suggest that dementia in late life may have its origin in early life. Head circumference (HC) and limb length are recognized to be determined at least in part by factors operating in childhood and remain stable into late life; these measurements may, therefore, be valuable proxy markers for early life environment particularly, it appears, early life nutrition. In this chapter, we review the research evidence for relationships between specific attained anthropometric measures – HC, leg length (LL), arm span and height – and other markers of early life environment, followed by associations between these measures and cognitive outcomes in later life (cognitive impairment and dementia). Smaller HC has been found to be associated with adverse cognitive outcomes including dementia and has been assumed, in this respect, to be a marker of brain "reserve." However, shorter LL and arm span have also been found to be associated with dementia and cognitive impairment. Shorter standing height measured both in early/mid and late life has found to be associated with adverse cognitive outcomes including dementia; however, due to the impact of spinal curvature and kyphosis on trunk length that occur with advancing age, limb length is a more reliable indicator of earlier stature. Several studies have suggested that associations between anthropometric measures and cognitive outcomes are modified by gender or apolipoprotein E genotype. Overall, for the prediction of disorders such as dementia, HC and limb length provide potentially important proxy information on childhood environment and are very cheap, easy, and quick to measure in epidemiological research.

Abbreviations

AD	Alzheimer disease
Apo E4	Apolipoprotein E e4 allele
CASI	Cognitive Abilities Screening Instrument
CERAD	Consortium to establish a registry for Alzheimer's disease
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder 4th edition
GH	Growth hormone
GIT	Groningen Intelligence Test

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_144,

HC	Head circumference
LL	Leg length
MMSE	Mini-Mental State Examination
NINCDS-ADRDA	National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for the diagnosis of AD
WHO	World Health Organization
WLT	Word Learning Task

144.1 Introduction

There has been a growing research interest in associations between the early life environment and late life cognitive impairment. Educational level (Stern et al. 1994; Evans et al. 1997), area of residence (Hall et al. 2000; Yano et al. 2000), parental occupation (Kaplan et al. 2001; Wilson et al. 2005) and household size in childhood (Moceri et al. 2001; Borenstein et al. 2005) have been found to be potentially important in the etiology of dementia. One possible explanation is that an adverse early life environment might affect maturation of the brain (Dekaban 1978), and increase vulnerability to later neurodegeneration. However, one of the weaknesses of research in this area is that information on the quality of the early life environment can only be evaluated by individuals' reports, which are clearly subject to recall bias in the context of a disorder, which impairs memory. Furthermore, it is very difficult in late life interviews to ascertain childhood nutritional status, a risk factor for dementia of particular potential interest.

Anthropometric measures such as HC and limb length have received recent research attention as proxy markers for early life environment, which may be particularly useful for dementia research because: (1) these involve direct measurement and are, therefore, not affected by recall bias; (2) they can be applied very easily, cheaply and quickly and (3) measurement error can be potentially minimized. The review of the literature carried out for this chapter aimed to clarify the evidence for associations with early life environment and cognitive outcomes in late life. For these purposes, we focused on HC, LL, arm span and height as the anthropometric measures most frequently investigated. After outlining the significance of early life environments as etiological factors for late life cognitive impairment and dementia, HC and limb length in adulthood are briefly discussed as proxy markers for early life environment. This is followed by reviews on the four most used anthropometric measures at late life with respect to dementia: HC, LL, arm span and height. Finally information is presented on modification effects of gender and apolipoprotein E e4 allele (apo E4) on these measures.

144.2 Early Life Environment and Late Life Cognition or Dementia

There has been growing interest on the early life environments as etiological factors for late life cognitive impairment and dementia. This hypothesis was based on the assumption that structural and functional brain capacity is developed mainly in childhood and adolescence (Schmand et al. 1997) and may have an influence on later cognitive outcomes. The mechanism underlying the protective effect of increased brain capacity has been hypothesized in terms of "cognitive reserve": that is, the ability of individuals with increased reserve to cope with more advanced brain pathology, so that

they remain free of dementia symptoms for longer than those with less reserve (Stern et al. 1992). Level of education has been considered as one of the major determinants or markers of cognitive reserve at early life and "cognitive reserve" theory arose from the well replicated observation that higher education is associated with lower risk of dementia (Stern et al. 1994; Evans et al. 1997). The neuronal activation associated with educational exposure has been suggested as enhancing synaptic complexity, neuronal reserve and resistance to harmful insults on cognition (Garibotto et al. 2008). Cognitive reserve theory is supported by observations that higher education in people who develop dementia is associated with evidence of more advanced underlying disease: namely, more severe brain changes (Stern et al. 1992) and worse prognosis (Wilson et al. 2000).

Other early life factors found to be associated with dementia also relate to adverse home situations. Parental manual occupation and lower education, representing lower familial social class, were associated with an increased risk of dementia (Kaplan et al. 2001; Wilson et al. 2005). Higher number of sibling size, which has been found to predict final educational attainment (Downey 2001), has also been found to be associated with dementia (Moceri et al. 2001; Borenstein et al. 2005). Rural childhood residence, where less educational opportunities can be expected, was associated with later development of dementia (Hall et al. 2000; Yano et al. 2000). Childhood undernutrition, known to be correlated with lower household socio-economic level, has been suggested to be associated with reduced brain synaptogenesis and complexity of dendritic branching (Dobbing 1984), which might account for later associations with risk of dementia: that is, that the early life environment may not only modulate later ability to compensate for slowly progressing neurodegenerative disorders (i.e. affecting age of onset of the clinical dementia syndrome), but also may affect the brain's underlying vulnerability to pathology (i.e. affecting the absolute risk of dementia). This is supported by a finding from a cohort of elderly Nuns that linguistic ability (derived from pieces of writing submitted on entering the order in early adult life) was negatively associated with Alzheimer pathology at postmortem, regardless of intervening dementia diagnosis (Snowdon et al. 1996).

However, an important weakness of studies which seek to characterize the childhood environment much later in life is the necessary reliance on individual's self-reported information, and the problem of recall bias when cognition disorders (generally affecting memory even in mild "preclinical" cases) are the focus of the research. This is particularly the case for more complex aspects of early life environment such as nutritional status.

144.3 Head Circumference and Limb Length as Proxy Markers for the Early Life Environment

Recently some anthropometric measures have been received research attention as proxy markers for early life environment. Head circumference has attracted particular interest, for obvious reasons, in dementia research. The cranial vault approaches maximum proportions by age 7 and, therefore, HC measurements in adulthood largely reflect brain growth in the early years of life (Gale et al. 2003). Active and substantial neuronal growth also occurs in that period. However, it can also be importantly reduced by undernutrition, and effects of nutritional restriction at key stages in development may be less amenable to later catch-up, thereby giving rise to effectively permanent deficits to brain structure and/or function (Dobbing 1984). Smaller HC measured in late life has been found to be associated with lower educational level and childhood rural residence (Kim et al. 2008a, b), and is also known to be highly correlated with intracranial volume (Jorgenson et al. 1961).

Within general epidemiology, the use of limb length measurements in adulthood as proxy markers for childhood exposures has been present for some time, particularly LL (Gunnell 2002).

Like skull circumference, skeletal growth progresses in parallel with maturation of the brain (Ho et al. 1980), and LL has been found to be highly correlated with HC in elders (Kim et al. 2008a). Longitudinal studies have found that LL measured in childhood is strongly associated with socioeconomic status (Gunnell et al. 1998). A British birth cohort study suggested that attained adult LL was particularly associated with diet in infancy, especially breast feeding and energy intake at age 4, whereas trunk growth was more strongly associated with later childhood stressors such as parental separation (Wadsworth et al. 2002). Adverse childhood socioeconomic circumstances have been found to be associated with shorter LL in both younger and older adults (Kim et al. 2003; Webb et al. 2008). Studies of arm span or demispan have shown similar results to those with LL (Kim et al. 2003; Jeong et al. 2005), although the number of reports are less. Total height, on the other hand, appears less valuable than limb length as proxy marker for early life environments. Adult height has been found to be associated with adverse childhood socioeconomic status (Webb et al. 2008), while height in late life failed to reflect this (Schooling et al. 2008). This is likely to be due to intervening risk of spinal curvature and kyphosis with advancing age which mean that total height becomes less strong a marker of earlier stature (Bannerman 1997). Limb length, on the other hand, is much less affected by these processes and remains a better marker even into advanced old age.

Overall, HC and limb length have been found to be determined in childhood and remain stable into late life and, therefore, are potentially valuable proxy markers for early life environments, particularly early life nutrition, with the following advantages in late life epidemiological research: (1) they remove the risk of recall bias, (2) they can be applied very easily, cheaply and quickly, and (3) measurement errors can be minimized, particularly for LL.

144.4 Head Circumference and Late Life Cognition

Studies on the associations between HC and cognitive outcomes including dementia and Alzheimer disease (AD) are listed and their characteristics are summarized in Table 144.1. Eight of 14 studies listed were carried out in the USA, although the ethnicity of the participants was diverse including those with Caucasian, Hispanic, African and Asian backgrounds. Most used data from community-based surveys apart from one case control study. The method for measuring HC was almost identical across the studies that it was measured by placing a plastic tape over the eyebrows and passing it around the head above the eyebrows and over the most posterior protuberance of the occiput. The mean HC ranged 55.9–58.5 cm in men and 54.2–55.7 cm in women. Outcomes included cognitive function (measured by various tests), dementia and AD. Three studies were prospectively designed and, therefore, cognitive decline and incident AD were considered as outcomes.

The first study found no association between HC and AD. However, it was reported that smaller HC was associated with poorer cognitive function in AD cases, but not in non-cases (Graves et al. 1996). However, the remainder found significant associations between smaller HC and worse cognitive function (Reynolds et al. 1999; Gale et al. 2003; Kim et al. 2008b), increased risk of cognitive decline (Gale et al. 2003), increased prevalence of dementia or AD (Schofield et al. 1997; Mortimer et al. 2003; Kim et al. 2008a; Llibre Rodriguez et al. 2008; Mortimer et al. 2008; Scazufca et al. 2008) and increased incidence of AD (Borenstein Graves et al. 2001; Borenstein et al. 2005). Some effect modification has been reported with two studies finding that the associations were stronger, and/or only significant, in women (Schofield et al. 1997; Kim et al. 2008a) or in the presence of the apo E4 (Borenstein Graves et al. 2001; Borenstein et al. 2005; Kim et al. 2008b). One case-control study reported negative results, in that the association between smaller HC and AD was no longer significant after adjustment for age and education (Espinosa et al. 2006).

Table 144.1 Studies on the associations between head circumference (HC) and cognitive outcomes

Source	Country/ethnicity	Study type	Sample number	Mean HC	Cognitive outcomes	Evaluation methods	Comments
Graves et al. (1996)	USA/Japanese American	Community based cross-sectional	1985	Median 55.7 cm	Cognitive function, AD	CASI, NINCDS-ADRDA	Smaller HC was associated with poorer cognitive function in AD cases, but not in non-cases nor with probable AD
Schofield et al. (1997)	USA/White, African American, Hispanic	Community based cross-sectional	649	Men 56.9 cm, Women 54.7 cm	AD	NINCDS-ADRDA	Smaller HC was associated with AD, statistically significant in women but not in men
Reynolds et al. (1999)	USA	Community based cross-sectional	825	Men 58.5 cm, Women 55.7 cm	Cognitive function	MMSE	Every 1 cm increment in HC was associated with a reduction of 20% in the risk of low MMSE score in non-demented elderly
Borenstein Graves et al. (2001)	USA/Japanese American	Prospective cohort	1869	55.9 cm	Incident AD	NINCDS-ADRDA	Small HC predicted earlier onset of AD in the presence of apo E4
Tisserand et al. (2001)	Netherlands/ unknown	Community based cross-sectional	818	Men 58.0 cm, women 55.5 cm	Cognitive function	GIT, Stroop tests, WLT, MMSE	HC was related to tests on intelligence, global cognitive function, and information processing speed, but not memory in non-demented elderly
Gale et al. (2003)	UK/unknown	Retrospective cohort	215	At birth 34.7 cm, adult 57.3 cm	Cognitive function and decline	AH4 test, Wechsler Memory Scale	Adult but not at birth HC was associated with higher cognitive performance and less cognitive decline
Mortimer et al. (2003)	USA/Caucasian female	Prospective cohort	294	Mode 54–55 cm	Dementia	Nonstandard criteria	Combination of small HC and low education increase the risk of dementia
Borenstein et al. (2005)	USA/Japanese American	Prospective cohort	1859	55.8 cm	Incident AD	NINCDS-ADRDA	Small HC was associated with incident AD in the presence of apo E4
Espinosa et al. (2006)	USA/unknown	Case control	1051	Men 57.8 cm, Women 55.3 cm	AD	NINCDS-ADRDA	AD patients had significantly smaller HC compared to controls, but it was no longer significant after adjustment
Kim et al. (2008a)	Korea/Korean	Community based cross-sectional	916	Men 55.9 cm, Women 54.2 cm	Dementia, AD	DSM-IV	Smaller HC was independently associated with dementia and AD, but only in women

(continued)

Table 144.1 (continued)

Source	Country/ethnicity	Study type	Sample number	Mean HC	Cognitive outcomes	Evaluation methods	Comments
Kim et al. (2008b)	Korea/Korean	Community based cross-sectional	1902	55.3 cm	Cognitive function	MMSE	Smaller HC was associated with lower scores on MMSE, but only in the presence of apo E4
Llibre Rodriguez et al. (2008)	Cuba/unknown	Community based cross-sectional	2944	55.6 cm	Dementia	DSM-IV, 10/66 dementia diagnosis algorithm	Smaller HC was associated with both dementia diagnoses
Mortimer et al. (2008)	USA/Caucasian female	Prospective cohort	294	54.7 cm	Dementia, AD	Nonstandard criteria	Smaller HC was associated with less education in persons at risk for dementia or AD
Scazufca et al. (2008)	Brazil/unknown	Community based cross-sectional	2005	54.4 cm	Dementia	DSM-IV	Smaller HC was associated with dementia

AD Alzheimer disease; *CASI* Cognitive Abilities Screening Instrument; *NINCDS-ADRDA* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for the diagnosis of AD; *MMSE* Mini-Mental State Examination; *GIT* Groningen Intelligence Test; *WLT* Word Learning Task; *apo E4* apolipoprotein E e4 allele; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorder 4th edition

The associations between smaller HC and adverse cognitive outcomes have been supported by neuroimaging findings. Smaller intracranial brain volumes measured directly by magnetic resonance imaging have been found to be associated with worse cognitive function in healthy elderly (MacLullich et al. 2002), with AD (Wolf et al. 2004), and with and increased risk of cognitive decline in people with AD (Mori et al. 1997).

In summary, smaller HC has been found to be associated with a range of adverse cognitive outcomes including dementia in late life. This may reflect its role as a component of brain reserve, possibly even through spatial restrictions imposed by smaller intracranial volume on brain size and function. However, final brain size and HC are at least in part determined by genetic makeup and may be associated with other aspects of brain development besides simple size limitations. Measurement and consideration of parental HC might be useful to control for genetic determinants in the future although this presents substantial logistic challenges. It is also important to recognize that the associations between HC and cognitive outcomes could be modified by demographic or genetic factors.

144.5 Leg Length and Late Life Cognition

Studies on the associations between LL and cognitive outcomes including dementia and AD are listed and their characteristics summarized in Table 144.2. The six studies identified were from various countries with diverse ethnicities. All studies involved analysis of community-based survey data. For measuring LL, five studies applied iliac crest height (from the uppermost part of the iliac crest to the ipsilateral lateral malleolus in standing position) and one study used knee height (from sole of the foot to the anterior surface of the thigh, with the ankle and knee each flexed to a 90° angle). Two studies were prospectively designed. Cognitive outcomes included cognitive function and decline, prevalent/incident dementia and/or AD.

The first study of LL and dementia was from South Korea. It was reported that shorter LL was associated with dementia and AD, but the association was only significant in women after adjustment for age and education (Kim et al. 2003). The same study group recently reported similar results, and also found the associations were independent of HC despite a significant correlation between LL and HC (Kim et al. 2008a). A larger prospective study from the USA subsequently found similar results in that the associations between shorter LL and incident dementia and AD were also only significant in women, although a formal test for statistical interaction did not reach statistical significance (Huang et al. 2008). A prospective study from the UK with African-Caribbean population reported that shorter LL was significantly associated with cognitive impairment, but not with cognitive decline (Mak et al. 2006) and found no gender modification. A recent study from Brazil also found an association (Scazufca et al. 2008), while another from Cuba found no significant association after adjustment for age, education and family history of dementia (Llibre Rodriguez et al. 2008).

In summary, shorter LL has found to be associated with dementia and cognitive impairment mirroring the findings for HC. It is possible that both HC and LL are proxy measures for the same underlying risk factors. However, the association between LL and dementia was not accounted for by HC in one analysis (Kim et al. 2008a), so it is also possible that LL is associated with specific early-life stressors and has an independent causal pathway. Similar to the results of HC studies, gender modification of the associations between LL and dementia have been reported in a few studies. As with HC studies, genetic or familial confounding, although unlikely, has not been ruled out.

Table 144.2 Studies on the associations between leg length (LL) and cognitive outcomes

Source	Country/ethnicity	Study type	Sample number	Mean LL	Cognitive outcomes	Evaluation methods	Comments
Kim et al. (2003)	Korea/Korean	Community based cross-sectional	746	Men 89.9 cm, women 84.0 cm	Dementia, AD	DSM-IV, NINCDS-ADRDA	Shorter LL was associated with dementia and AD, only significant in women
Mak et al. (2006)	UK/African Caribbean	Community based cross-sectional	290	Men 96.9 cm, women 91.1 cm	Cognitive function and decline	Items from CERAD and WHO batteries	Shorter LL was associated with cognitive impairment, but not with cognitive decline
Huang et al. (2008)	USA/unknown	Prospective cohort	2798	52.9 cm for knee height	Incident dementia and AD	DSM-IV, NINCDS-ADRDA	Shorter LL was associated with higher risks of dementia and AD, only significant in women
Kim et al. (2008a)	Korea/Korean	Community based cross-sectional	916	Men 86.5 cm, women 79.8cm	Dementia, AD	DSM-IV	Shorter LL was associated with dementia but only in women independent of HC
Llibre Rodriguez et al. (2008)	Cuba/unknown	Community based cross-sectional	2944	85.2 cm	Dementia	DSM-IV, 10/66 dementia diagnosis algorithm	Shorter LL was associated with both dementia diagnoses, but lost significance after adjustment
Scazufca et al. (2008)	Brazil/unknown	Community based cross-sectional	2005	88.5 cm	Dementia	DSM-IV	Shorter LL was associated with dementia

AD Alzheimer disease; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorder 4th edition; *HC* head circumference; *NINCDS-ADRDA* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for the diagnosis of AD; *CERAD* Consortium to establish a registry for Alzheimer's disease; *WHO* World Health Organization

144.6 Arm Span and Late Life Cognition

Analyses of associations between arm span and cognitive outcomes including dementia and AD are listed and their characteristics are summarized in Table 144.3. These studies have been less frequent than those of HC or LL with only three detected to date: two from South Korea and one from the USA. All studies analyzed community-based survey data: two cross-sectional and one prospective. For measuring arm span, demispan (the distance from the sternal notch to the middle finger tip along the outstretched arm) was usually used. Cognitive outcomes included cognitive function, and prevalent/incident dementia and AD.

The first study of arm span and dementia was from Kwangju, South Korea, and found that shorter arm span was associated with dementia and AD. The association, in common with that for LL, was only significant in women after adjustment for age and education, although a test for gender interaction did not reach statistical significance (Kim et al. 2003). The second study was from Jeonbuk province in South Korea and a different sample. This also found that shorter arm span was associated with cognitive impairment and dementia, although with no gender interaction (Jeong et al. 2005). A recent prospective study from the USA found significant associations between shorter arm span and both dementia and AD in both men and women (Huang et al. 2008).

In summary, shorter arm span has found to be associated with adverse cognitive outcomes including dementia. These results were consistent with those of HC and LL, although with less obvious gender interactions. In the Kwangju sample, arm span was very highly correlated with LL (Pearson's correlation coefficient = 0.73) (Kim et al. 2003). Arm span may, therefore, also be a proxy measure for early life environment, although this has not been formally investigated.

144.7 Height and Late Life Cognition

Studies of associations between height and cognitive outcomes are listed and their characteristics summarized in Table 144.4. Of the five studies identified to date, two used historical cohort study designs with adult height as an exposure, two were community-based cross-sectional studies and one was a case control study. Cognitive outcomes included cognitive function, and prevalent dementia and AD.

The first analysis of adult height and late life cognitive function was carried out on data from a Japanese American population and found a "dose dependent" association between shorter height measured in 1965–1968 and cognitive impairment 3 decades later (Abbott et al. 1998). In a recent larger study from Israel, height measured in midlife was associated with prevalent dementia and AD, again in a dose dependent pattern (Beeri et al. 2005). A cross-sectional survey from Kwangju, South Korea using sitting height as an exposure reported different findings, in that shorter sitting height was associated with prevalent dementia, but lost significance after adjustment for age and education (Kim et al. 2003). However, another South Korean study in a different sample reported significant associations between shorter height and both cognitive impairment and dementia (Jeong et al. 2005). A recent case-control study from the USA found that shorter height was associated with AD in men, while it was only significantly associated with AD in the absence of apo E4 in women (Petot et al. 2007).

In summary, shorter standing height measured both in mid- and late-life has been found to be associated with adverse cognitive outcomes including dementia. However, sitting height in late life was not independently associated with dementia (Kim et al. 2003), which suggests that limb length may explain most of the standing height associations with trunk length compromised as a measure in late life because of spinal curvature and kyphosis, as mentioned earlier (Bannerman 1997).

Table 144.3 Studies on the associations between arm span and cognitive outcomes

Source	Country/ethnicity	Study type	Sample number	Mean arm span	Cognitive outcomes	Evaluation methods	Comments
Kim et al. (2003)	Korea/Korean	Community based cross-sectional	746	Men 83.4 cm, women 76.4 cm	Dementia, AD	DSM-IV, NINCDS-ADRDA	Shorter arm span was associated with dementia and AD, only significant in women
Jeong et. al. (2005)	Korea/Korean	Community based cross-sectional	235	Men 83.1 cm, women 76.2 cm	Cognitive function, dementia	MMSE, DSM-IV	Shorter arm span was associated with cognitive impairment and dementia
Huang et al. (2008)	USA/unknown	Prospective cohort	2798	86.6 cm	Incident dementia and AD	DSM-IV, NINCDS-ADRDA	Shorter arm span was associated with higher risks of dementia and AD

AD Alzheimer disease; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorder 4th edition; *NINCDS-ADRDA* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for the diagnosis of AD; *MMSE* Mini-Mental State Examination

Table 144.4 Studies on the associations between height and cognitive outcomes

Source	Country/ethnicity	Study type	Sample number	Mean height	Cognitive outcomes	Evaluation methods	Comments
Abbott et al. (1998)	USA/Japanese American men	Retrospective cohort	3733	163.5 cm	Cognitive function	CASI	Adult short height was associated with late-life cognitive impairment
Kim et al. (2003)	Korea/Korean	Community based cross-sectional	746	Sitting height, men 74.0 cm, women 66.1 cm	Dementia, AD	DSM-IV, NINCDS-ADRDA	Shorter sitting height was associated with both dementia diagnoses, but lost significance after adjustment
Beeri et al. (2005)	Israel/unknown	Retrospective cohort	1881	168.1 cm	Dementia, AD	DSM-IV, NINCDS-ADRDA	Adult short height was associated with late life dementia and AD
Jeong et al. (2005)	Korea/Korean	Community based cross-sectional	235	Men 163.2 cm, women 148.2 cm	Cognitive function, dementia	MMSE, DSM-IV	Shorter height was associated with cognitive impairment and dementia
Petot et al. (2007)	USA/unknown	Case-control	580	Men 174.4 cm, women 161.4 cm	AD	NINCDS-ADRDA	Shorter height was associated with AD in men. In women, it was associated with AD only in the absence of apo E4

CASI Cognitive Abilities Screening Instrument; *AD* Alzheimer disease; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorder 4th edition; *NINCDS-ADRDA* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for the diagnosis of AD; *MMSE* Mini-Mental State Examination; *apo E4* apolipoprotein E e4 allele

For this reason, associations between skeletal dimensions and cognitive outcomes may be obscured in older people if the former are limited to standing height, and limb lengths are more suitable in these age groups as markers of dementia risk.

144.8 Gender Modification

Several studies have reported modification by gender of associations between anthropometric measures and cognitive outcomes. With respect to HC, the associations between smaller HC and dementia and/or AD were significant only in women in two studies. One study was from the USA with diverse ethnicities, such as white, African-American and Hispanic (Schofield et al. 1997), and the other study was from South Korea (Kim et al. 2008a). Therefore, this phenomenon was found in various ethnicities. Possible explanations include the following: (i) The correlation between HC and intracranial volume has been found to be less strong in men (Willerman et al. 1991), so that differential misclassification might have occurred. (ii) There may be gender differences in vulnerability to stressors occurring during the period of brain maturation that sex hormones may have a role in brain development and early vulnerability (MacLusky and Frederick 1981). iii) Additionally there were particular characteristics in the South Korean study. That is, different early life social conditions for male and female children of the older generation in that country (possibly in common with other East Asian countries) should be considered. Male gender preference was highly prevalent at the time when the participants were growing up, due to strongly held Confucian patriarchal traditions in Korea. It was, therefore, common practice for parents to provide education and/or nutrition preferentially to male children, particularly in families with lower socio-economic status (Kim et al. 2008a). However, this does not explain similar findings emerging from US cohorts (Schofield et al. 1997) where gender preference is unlikely to have been so pronounced.

In terms of limb length, shorter LL and arm span were significantly associated with dementia and AD only in women in a Korean sample (Kim et al. 2003). Shorter LL was significantly associated with incident dementia and AD only in women, while shorter arm span was significantly associated with them in both genders in a US sample. Possible explanations include the following: (1) Health states in adult or late life could mediate the associations. Shorter limb length has been found to be associated with cardiovascular disease in adulthood (Han et al. 1997; Davey Smith et al. 2001). Higher overall cardiovascular mortality in men might possibly account for a later gender difference through differential survival. (2) Skeletal growth terminates approximately 2 years earlier in women compare to men, and may. Therefore, be more closely related to brain maturation and the early life environment. (3) The male gender preference hypothesis raised above for associations with HC could also applied to those with limb length.

In summary, there is some evidence to suggest that there might be gender differences in the relationships between these markers of early life status and risk of dementia. As well as methodological issues, this may reflect different causal pathways or different strengths of association between anthropometric measures and underlying brain vulnerability. However, replication has frequently been incomplete and further research is required.

144.9 Modification by Apolipoprotein E Genotype

Three studies of HC have reported modification by the presence/absence of the apo E4. A US cohort study of Japanese Americans found that small HC predicted earlier onset of AD more strongly in the presence of apo E4 (Borenstein Graves et al. 2001). A follow-up study of the same cohort also found

that small HC was associated with incident AD more strongly in the presence of this allele (Borenstein et al. 2005). Recently a South Korean study also found that smaller HC was associated with poorer cognitive function only in the presence of apo E4 (Kim et al. 2008b). Interestingly, the participants of all three studies were of East Asian ancestry, while studies of HC and dementia in other populations have not mentioned apo E interaction.

These data suggest that effects of adverse early life environments on the development of poorer cognitive outcomes may be strengthened in the presence of this genetic vulnerability marker. Gene–environment interactions may be an important consideration, but require further replication.

144.10 Applications to Other Areas of Health and Disease

The associations between these anthropometric measures and cognitive impairment may have a neuroendocrinological basis, which might link the findings to those from other disorders. Particularly, growth hormone (GH) levels are associated with both anthropometry and cognitive function: (1) cognitive impairments have been found in GH deficient men (Deijen et al. 1996); (2) GH replacement therapy has been found to improve cognitive function in adults with childhood-onset GH deficiency (Deijen et al. 1998) and (3) binding sites for GH are found in various brain areas, particularly in hippocampus, a brain structure affected at an early stage in AD (Van Dam et al. 2000). Sex hormones are also potentially linked with both anthropometry and cognition: Specifically, decreased LL has been found to be associated with later menarche (dos Santos Silva et al. 2002), and lower early life cognitive function has been found to be associated with earlier menopause (Richards et al. 1999).

Summary Points

- Recent research findings suggest that risk of dementia in late life may be substantially influenced by early life factors.
- Early life environmental factors relevant to this issue include education, parental occupation, sibling size and rural/urban living area. However, this information acquired in late life may not be accurate because of recall bias.
- Childhood nutrition, one of the variables on early life environments, is an important factor for the risk of dementia. However, it is very difficult to estimate previous childhood nutritional status directly in later life.
- There have been accumulating evidence that HC and limb length are determined substantially in childhood and remain stable into late life and, therefore, they could be reliable proxy markers for early life environment particularly in terms of early life nutrition.
- Smaller HC has been found to be associated with adverse cognitive outcomes including dementia in late life, hypothesized as a component of brain reserve.
- Shorter LL has also been found to be associated with dementia and cognitive impairment.
- Shorter arm span has found to be associated with adverse cognitive outcomes including dementia.
- Shorter standing heights measured both in adult and elderly has found to be associated with adverse cognitive outcomes including dementia.
- Several studies have reported that associations between anthropometric measures and cognitive outcomes are more prominent in women. If genuine, these might reflect differences in the risks for or causal pathways to dementia particularly in the aspects of early life environment and nutritional status.
- Some studies of HC and dementia have reported that the associations were stronger in the presence of the Apo e4 allele, but more replication is needed.

Key Features

Table 144.5 Key facts on early life environments and dementia

1. Adverse environments in early life are associated with increased risk of dementia and cognitive impairment in late life
2. These factors include education, parental occupation, household size, living area
3. There are indirect evidences suggesting associations between early life nutrition and cognitive development which may influence risk of dementia much later in life.

Table 144.6 Key facts on anthropometry of HC, limb length and dementia

1. As well as genetic influences, HC and limb length have important environmental determinants in childhood and remain stable from adolescence/early adulthood into late life
2. Smaller head size and shorter limb length are proxy markers for lower early life socio-economic status: for LL particularly reflecting nutrition in infancy
3. Both factors have been associated with adverse cognitive outcomes including dementia
4. There have been several reports that these associations are modified by gender or apolipoprotein E4 genotype

Acknowledgements This research was supported by a grant of the Korea Health 21 R&D, Ministry of Health and Welfare, Republic of Korea (A050174).

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Chapter 145
Anthropometry in Special and Selective Conditions and Circumstances: Anthropometry as Measure of Risk in COPD Patients

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Abstract In the last decade, Chronic Obstructive Pulmonary Disease (COPD) has been redefined and newly approached not only as an airway-disease condition, but as a multi-component disease including extra-pulmonary manifestations, such as peripheral muscle weakness and malnutrition.

The evaluation of body composition (as a part of nutritional assessment) fairly integrates the simple body mass index (BMI) measure by measuring the individual's active metabolism (fat free mass, FFM). Indeed, BMI and FFM are both parameters correlated with many COPD-strong outcomes. In several epidemiological studies of COPD population admitted to both in- or outpatient rehabilitation programmes, the estimated prevalence of weight loss ranges from 17% to 53%. Nonetheless, weight reduction, together with FFM depletion, is a common feature in emphysema as well as in chronic bronchitis.

A nutritionally depleted patient is usually defined by a BMI of ≤ 20 kg/m^2. Several studies aimed at evaluating the prognostic value of BMI in COPD patients have documented that BMI ≤ 25 kg/m^2 and weight reduction of >3 kg/m^2 are strong predictors of mortality. Moreover, other studies confirmed that FFM and measurement of the cross-sectional area of muscle mass (mid-thigh and mid-arm) also correlate to survival rates.

In future research, studies looking at other anthropometric, metabolic and functional factors able to predict the long-term survival should be welcomed in patients with other diseases, such as pulmonary fibrosis, similarly leading to chronic respiratory failure.

Abbreviations

AMA	Arm muscle area
BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BODE INDEX	Body mass index (B), obstruction (O), dyspnea (D) and exercise endurance (E)
CCHS	Copenhagen City Heart Study

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_145,

CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
ECW	Extracellular water
FEV_1	Forced Expiratory Volume in the first second
FFM	Fat free mass
FFMi	FFM index
FM	Fat mass
HR	Hazard ratio
HRQL	Health related quality of life
IBW	Ideal body weight
ICW	Intracellular water
LTOT	Long term oxygen therapy
LVRS	Lung volume reduction surgery
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
NETT	National Emphysema Therapy Trial
$PaCO_2$	Arterial Carboxide Pressure
PaO_2	Oxygen Arterial Pressure
PEmax	Maximal Expiratory Mouth Pressure
RR	Relative risk
TBW	Total Body water
TSF	Triceps skinfold thickness
VO_2 %/Kg	Percentage of oxygen consumption for kilogram

145.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is no longer considered a disease affecting the airways, but a multi-component disease with several systemic consequences.

Even if the dysfunctional characteristics of COPD, such as flow obstruction and expiratory limitation, are still considered as the cardinal features for intervention strategies, recent evidence suggested that COPD be considered a complex disease including extra-pulmonary manifestations, such as peripheral muscle weakness and malnutrition.

Abnormalities in body composition and alteration in body weight (i.e. loss in body mass and/or muscle wasting) are highly prevalent in the advanced stages of this illness. The extra-pulmonary manifestations of COPD are probably linked to several chemical mediators of inflammation which in turn have direct effects on muscle performance and composition. This characteristic may strongly complicate the whole clinical management of the disease.

In this chapter we will review the main aspects dealing with measures of body composition and nutritional status in COPD and their likely significance in clinical practice (Table 145.1).

Table 145.1 Key points of nutritional measure in COPD

- Nutritional status should be always integrated as a measures of health in patients with COPD
- Both BMI and FFM provide useful and integrated information to the individual's nutritional status
- Change in body mass is fairly related with change in prognosis in COPD individuals

This table lists the main features and evidence related to the likely significance of assessing body measure in patients suffering from COPD

145.2 Assessment of Body Composition and Nutritional Status in COPD: Methods and Techniques

The complexity of COPD as a disease, including extra-pulmonary manifestations, has frequently recalled the clinical features of peripheral muscle weakness and malnutrition (Table 145.2).

The terms "malnutrition" and "cachexia", meaning nutritional depletion and wasting of body mass, have frequently been reported in the clinical history of COPD. Weight loss may have multiple causes, including a reduction in dietary intake, the effect of the increased energy cost of breathing due to the abnormal respiratory mechanics and the effects of chronic systemic inflammation. Muscle wasting is an important systemic manifestation, since the loss of more than 40% of metabolically active tissue causes death. The imbalance between protein synthesis (anabolism) and protein breakdown (catabolism), leads to hyper-metabolism and may be the consequence of mild systemic inflammation in COPD.

Systematic nutritional assessment is nowadays considered as an essential component of any integrated management of COPD patient. The measurement of the body weight only is certainly useful as a screening tool in the first step of nutritional evaluation, but this measurement does not provide qualitative data regarding body composition; thus, it cannot be sufficient to describe the patients' nutritional status.

In order to study this topic in depth, body composition should be analysed to detect malnutrition by focusing the assessment on the body cell mass (BCM), which represents the active metabolic contractile tissue. The imbalance between the fat mass (FM) and the fat free mass (FFM) is a marker of body composition alteration which, in patients with low FFM, represents malnutrition. Nonetheless, body composition alterations are not necessarily associated with change in body weight.

Several studies stated that measuring FFM allows muscle wasting to be detected, whilst the FFM index (FFMi), calculated as FFM/height^2, further characterizes nutritional depletion. FFM has a strong relationship with pulmonary diffusing capacity in these patients. To date, there is no guideline that dictates criteria to categorize FFM or FFMi; consequently, clinicians usually dichotomize these parameters by using the cut-off value suggested by Schols and colleagues, which is equal to 15 kg/m^2 for women and 16 kg/m^2 for men (Schols et al. 1993).

Muscular tissue depletion, as demonstrated by a reduction in FFM, is significantly associated with selective atrophy of type II muscle fibres (see Fig. 145.1) (Gosker et al. 2002). The atrophy of these fibres – which are efficient for short bursts of speed and power and use both oxidative and anaerobic metabolism – drives the impairment of the skeletal muscles of patients with COPD. It has been clearly demonstrated that it occurs very frequently in severe hospitalized patients, as well as in outpatients with moderate to severe airflow obstruction. From a clinical point of view, loss of FFM in COPD is associated with impairment in respiratory muscle strength, although a partial contributor

Table 145.2 Extra-pulmonary manifestations of COPD

Cardiac manifestations (ischaemic heart disease and congestive cardiac failure)
Metabolic syndrome
Normocytic anaemia
Reduced bone mineral density (osteoporosis)
Progressive muscle weakness
Cachexia: loss of fat-free mass
Pulmonary hypertension
Mood disturbance (depression)

This table lists the most prevalent co-morbidities and extra-pulmonary diseases which affect the advanced COPD patient

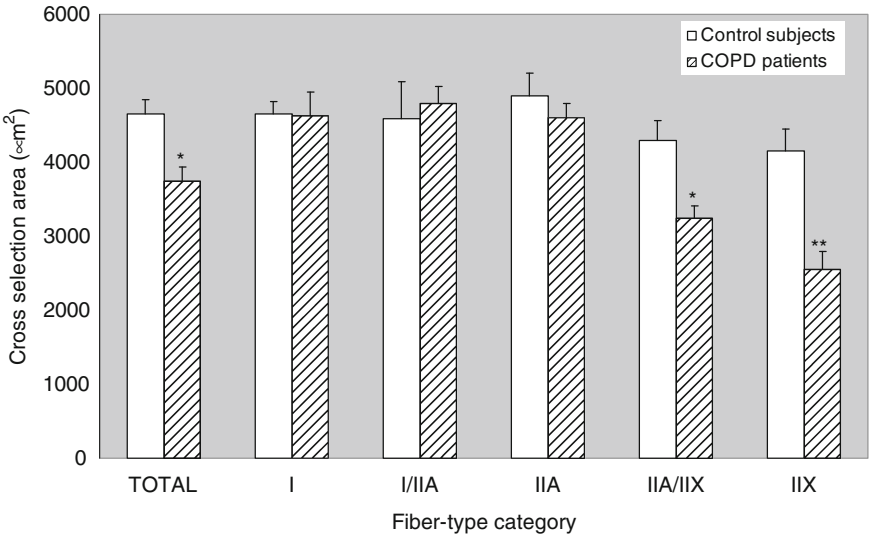

Fig. 145.1 Type-specific muscle fibre in specimens from COPD patients and controls. In malnourished COPD patients there is a significant reduction in total muscle fibre section area (as assessed from a quadriceps specimen) with a relative reduction of type-II fibre. Results are expressed as mean ± SE. $^{*}p < 0.05$ and $^{**}p < 0.01$ (vs. control) (Modified and adapted from Gosker et al. 2002)

Table 145.3 Body and nutritional abnormalities in COPD

Reduction in FFM
Reduction in FM
Atrophy of type II muscle fibres
Reduction of TSF
Reduction of mid-thigh and mid-AMA

This table summarizes the most typical changes of body and muscle characteristics in the malnourished COPD patient
FFM fat free mass; FM fat mass; TSF triceps skin fold thickness; AMA arm muscle area.

to the weakness of these muscles is undoubtedly the mechanical disadvantage owing to hyperinflation and the changes in chest wall shape. FFM depletion is also responsible for other important clinical manifestations of COPD such as peripheral muscle weakness (Engelen et al. 2000), impairment in exercise capacity and general worsening of health status. Indeed, alteration in body composition, independent of weight loss, seems to be an important predictor of worsening the perceived Health Related Quality of Life (HRQoL) (Mostert et al. 2000). Interestingly enough, normal-weight COPD patients with low FFM always report lower level of HRQoL as compared with underweight patients with normal FFM. Table 145.3 summarizes body and nutritional abnormalities, which can affect COPD patients with muscle depletion.

From a practical point of view, assessment of FFM can be obtained using different techniques, including hydro-densitometry and isotopic dilution with the deuterium and sodium bromide method. These techniques provide the values of intracellular (energy-exchanging part) and extracellular (role of support and transport) water compartments by measuring the total (TBW) and the extracellular (ECW) body water. The intracellular water (ICW) is detected as the difference between TBW and ECW. This method is complex and cannot be used on a wide scale. So far, this method has been used in a group of clinically stable COPD patients (Baarends et al. 1997) to show that the ECW/ICW ratio

was similar in normal weight and underweight individuals. However, this ratio increased in patients with low FFM, thus showing that the intracellular compartment, which relates to muscles and other tissues, was even more depleted than expected.

An easier method to assess FFM is bioelectrical impedance analysis (BIA). A low intensity alternate electric current is applied through electrodes to the ankle and the wrist, and the resistance opposed by the body tissues to its flow is then measured. FFM is then indirectly calculated from this measurement, since the resistance opposed by the FM to the electric current flow is higher than the impedance of the FFM. BIA is highly reproducible in patients with COPD. The only fluctuation detected is a slightly higher resistance and a consequently lower estimated FFM in the fasting state. Several algorithmic rules have come from different patient populations to calculate FFM by way of BIA, but attention has to be paid to choose an algorithm that is appropriate for the population studied.

Schols and colleagues specifically applied both the above-mentioned techniques in patients with COPD (Schols et al. 1991), demonstrating an excellent association between the impedance and the deuterium dilution results in estimating FFM.

Finally, the real nutritional status can also be estimated by skinfold anthropometry. The measurement of skinfold thickness can be taken at four body sites, specifically on the triceps brachii, on the biceps brachii, over the subscapular area, or on the suprailiac area. This measurement is a simple and widely used method to assess FM. Total FM is estimated using equations or tables, and FFM is obtained by subtracting FM from body weight. Triceps skinfold thickness (TSF) and mid-arm circumference (MAC) can be used to calculate mid-arm muscle circumference (MAMC), which estimates muscle mass as:

$$\mathrm{MAMC} = \mathrm{MAC} - (\pi \mathrm{TSF}) .$$

Alternatively, arm muscle area (AMA) can be calculated as:

$$\mathrm{AMA} = \mathrm{MAMC}^2 / 4\pi .$$

It should be recognized that this method is based on the assumption that the measured fat layer represents a constant fraction of total body fat. However, this is no longer true in elderly subjects where FM is predominantly located in the central and internal parts of the body. Thus, in patients with COPD the measurement of skinfold thickness tends to underestimate FM while overestimating FFM, when compared with the deuterium dilution method (Schols et al. 1991).

In two studies (Hunter et al. 1981; Schols et al. 1991), TSF was <90% of the standard in 62% and 76% of COPD patients and MAMC was <90% of the standard in 50% and 53%, respectively. The AMA was 79% of the standard in outpatients and 62% of standard in patients with acute respiratory failure. Despite its well-known limitations, this method may suggest depletion of both FM and FFM in COPD population.

For a long time, study results have reported differences in anthropometry and nutritional status that are significantly linked to two specific patterns of body composition, which correspond to the clinical subtypes of COPD. These phenotypes are the emphysematous type (*pink puffer)* and the chronic bronchitic type (*blue bloater*). It is well recognized that the emphysematous patient is more breathless, has marked hyperinflation and frequently manifests a major degree of weight loss. In contrast, the bronchitic patient has more severe central cyanosis with no marked weight loss; in fact this type is often overweight and occasionally manifests weight loss in the terminal phase of the disease. Recent data indicate that these two clinical subtypes of COPD are associated with different levels of impairment of skeletal and respiratory muscles, as a consequence of different manifestations of metabolic alterations.

A previous paper (Openbrier et al. 1983) clarified the differences in the anthropometric characteristics between the two clinical subtypes of COPD, highlighting that somatic depletion is particularly

evident in pink puffer compared to blue bloater patients. Moreover, in the emphysematous patient group, the authors found a strong correlation between the degree of airflow obstruction (FEV_1, forced expiratory volume in the first second) and the somatic depletion ($r = 0.699$, $p < 0.001$) as well as the single-breath lung diffusing capacity ($r = 0.605$ $p < 0.019$). Unfortunately, this study included only 18 patients, 14 with emphysema and 4 with chronic bronchitis and, consequently, was not powered to detect a clinically significant difference, if any, in the outcome analysed.

In a more recent paper, Engelen and colleagues (2000) have shown that whole body and extremity FFM were lower in both the emphysematous and chronic bronchitis patients compared to controls, but the trunk FFM was lower than in controls only in emphysematous patients. Therefore, FFM as calculated at the extremities seems to be similar in the two COPD phenotypes, whereas trunk FFM is not. In both groups, however, absolute skeletal muscle function and muscle function per kilogram of whole body FFM were lower than in healthy people, with no difference in the two clinical subtypes. The authors have concluded that wasting of extremity FFM is associated with skeletal muscle weakness and is unrelated to the COPD subtype, although marked differences in whole body composition can be demonstrated between the emphysematous patients and the patients suffering from chronic bronchitis.

145.3 Body Mass as Outcome Measure and Prevalence of Weight Loss in COPD Patients

During the last decade, the influence of the BMI on different epidemiological and functional aspects of COPD has become an area of increasing interest in research. In order to consider body weight as a valuable outcome in COPD, the relationship between body weight and other common COPD-related parameters has been studied. The measurement of height, weight and weight changes provides an initial assessment of the nutritional condition of the patient. However, clinicians should remember that some degree of weight change frequently occurs in patients with severe respiratory failure, due to fluid retention.

Physicians usually make use of two simple and well-known methods to compare the weight of the patient with the physiological values. The first approach compares actual body weight, calculated by the Metropolitan Insurance Company tables, to the Ideal Body Weight (IBW) as derived from height, size and sex. Nutritional depletion occurs when body weight is less than 90% of the IBW (Metropolitan Life Insurance Company 1983).

The second approach uses the Body Mass Index (BMI) or *Quetelet Index*, which is easily calculated by dividing the patient's weight in kilograms by the patient's height in squared meters (kg/m^2). In vivo measurements have demonstrated that the BMI formula is a valid gauge of change in body mass.

On the basis of BMI, patients can be categorized as underweight, normal weight, overweight and obese. The US Department of Agriculture and the Department of Health and Human Services, in a report called *Nutrition and Your Health*, proposed a BMI between 18.5 and 24.9 kg/m^2 as a healthy weight target, while underweight people are characterized by a BMI lower than 18.5 kg/m^2 and overweight and obese people have a BMI greater than 25 and 30 kg/m^2 respectively (US Department of Agriculture and US Department of Health and Human Services 2000). However, the same report states that a BMI above or below the healthy range may actually correspond to a healthy status and, conversely, having a BMI which falls inside the healthy range may not necessarily mean being healthy, because the body composition may be abnormal even in the presence of a physiological BMI. Therefore, the assessment of body composition should always integrate the calculation of BMI.

This assessment is particularly relevant in specific clinical conditions, such as cachexia or muscle wasting, where the weight loss is distributed dissimilarly between FFM e FM. In fact, in cachexia most of the weight loss behave to FFM, the active metabolic contractile tissue, whereas in muscle wasting the loss of BCM and FM are balanced. Thus, cachexia is always accompanied by muscle wasting, but muscle wasting does not always lead to cachexia (Vandenbergh et al. 1967; Wilson et al. 1989; Schols et al. 2005).

Moreover, measurement of body weight, BMI and nutritional status can be defined by involuntary weight loss, when a loss of 10% during the previous 6 months is categorized as severe malnutrition.

A close relationship between poor muscle condition, reflected by a reduction in the actual body weight or a low BMI, and a reduction in the maximal aerobic capacity has been observed in several studies. Furthermore, reduced body mass has an independent negative effect on muscle aerobic capacity in COPD patients, as manifested by a decrease in maximal oxygen consumption, a reduction in the lactate threshold and a slowing down of the oxygen consumption kinetics.

Many studies concerning the prevalence of low body weight in COPD individuals with different disease severities have been performed by using diverse methods to detect the underweight condition.

Schols and colleagues (1993) reported data on the prevalence of the underweight condition and body composition in a group of 255 patients, consecutively admitted to a pulmonary rehabilitation programme. Their results indicate that the depletion of body weight, associated with a reduction in FFM detected by the MAMC measurement, was most pronounced in moderate to severe stable COPD. In particular, a reduction in the actual body weight (<90% of IBW) was present in 46% of patients suffering from chronic hypoxemia, while a prevalence of nutritional alteration was found in 27% of normoxyemic patients with severe COPD (FEV_1 between 35 and 50% of predicted) and in 41% of patients with very severe airflow obstruction ($FEV_1 < 35\%$).

Another study (Braun et al. 1984) showed that the prevalence of nutritional depletion affected 27% out of the 60 outpatients with COPD referred to rehabilitation. Moreover, the measurement of the triceps skinfold was below 60% of standard in one-third of patients. In this study, the body weight is related to the FEV_1, the lung diffusing capacity and the percentage of oxygen consumption per kilogram, at rest (VO_2%/kg).

Furthermore, three very substantial recent epidemiological studies which involved a large number of people with COPD in China (Zhong et al. 2007), the Netherlands (Vermeeren et al. 2006), and Latin America (Montes de Oca et al. 2008) provided data on the prevalence of weight loss.

The Chinese study collected data from 25,627 subjects of whom 8% were COPD and found that the percentages of patients with a BMI < 18.5 kg/m^2, between 18.5 and 23.9 kg/m^2, between 24 e 27.9 kg/m^2 and >28 kg/m^2 were 21%, 9.5%, 6% and 5.4% respectively (significant trend, $p < 0.001$).

The COSMIC study in the Netherlands, which involved 39 outpatient centres and 389 moderate to severe stable COPD patients, resulted in 27% prevalence of nutritional depletion (pre-defined by a BMI ≤ 21 kg/m^2 and/or FFMi ≤ 15 and ≤ 16 kg/m^2 for females and males respectively). Moreover, weight depletion as assessed by the BMI (18% vs. 10%, respectively, $p < 0.01$) and the FFMi (40% vs. 20% $p < 0.001$) was significantly prevalent in females rather than in males (see also Fig. 145.2). No difference between depleted and non-depleted COPD patients has been recorded in FEV_1% of predicted value, in perceived dyspnoea, and in disease-specific health status measured by the St. George's Respiratory Questionnaire.

The Latin America data from the PLATINO study (Proyecto Latino-americano de Investigacion en Obstrucción Pulmonar), which involved 759 COPD patients and 4,555 subjects without, showed that, a higher proportion of underweight (6% vs. 2.9%) and normal weight (31% vs. 24.5%) categories were present among COPD. The proportion of overweight was similar in the two groups

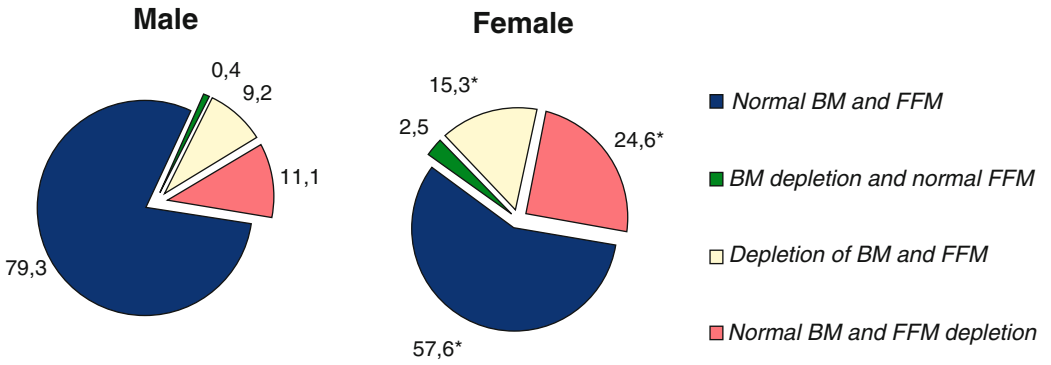

Fig. 145.2 Prevalence of different depletion categories stratified by gender. Gender may partially influence the distribution of different categories of depletion in COPD patients. Results are expressed as percentage. *$p < 0.05$ (between males and females) (Modified and adapted from Vermeeren et al. 2006)

(39.9% vs. 41%), whereas obese individuals were lower among COPD (23% vs. 31.4%). Factors associated with lower BMI in men with COPD were older age, current smoking and a severe or very-severe degree of the disease. In women with COPD, current smoking and a lower level of education were associated with lower BMI, whereas dyspnoea and wheezing were associated with higher BMI.

In a prospective observational study Mazolewski and co-workers (1999) aimed at defining the incidence and the clinical meaning of nutritional deficiencies in patients with COPD. They studied 51 end-stage emphysematous patients who had undergone video-assisted thoracoscopic surgery for lung volume reduction and found that the BMI was below the normal range in 53% of the population. The important clinical consequence of their analysis is that 26% of the patients with low BMI required prolonged ventilatory support for more than 24 h, compared to the 4% of the patients with a normal BMI. This data was also associated with a different length of stay in hospital (15.9 vs. 11.8 days) in the two groups.

On the other hand, data from one of the most famous epidemiological studies (the so called Copenhagen City Heart Study – CCHS) (Vestbo et al. 2006) did not show a higher prevalence of underweight patients among 1,898 COPD patients studied, when compared to healthy people. This result was confirmed even when considering the sub-groups of severe patients or women. In addition, the pattern of distribution of FFM was different as compared to BMI. In the whole cohort of patients, 83.8% had normal or high BMI and a FFMi above the 10th percentile, as referred to the cut-off values (14.62 and 17.05 kg/m^2 in women and men, respectively). In addition, 13.1% of the cohort showed normal or high BMI and a FFMi below the 10th percentile, 0.7% had a low BMI and a FFMi above the 10th percentile, and 2.4% had a low BMI and a FFMi below the 10th percentile. Thus, a higher proportion of subjects with low FFMi had a normal BMI compared to subjects that matched low FFMi with low BMI.

The results from CCHS controvert findings by Schols and colleagues (1993) but discrepancies between populations can be explained by some differences in the sources of patients examined. In particular, Vestbo and colleagues identified COPD people by way of a population survey, whereas Schols and co-workers included COPD patients in their study after a complete assessment performed before their referral for inpatient rehabilitation programme. Importantly, the Dutch study demonstrated differences in body composition even in the early stages of COPD, when patients are not generally considered to have associated muscle wasting.

145.4 BMI, Weigth Change and Nutritional Status as Predictors of Survival in COPD

In patients with end-stage COPD, the underweight condition has been investigated so far as a negative predictive factor of survival. A study of Vandenbergh and co-workers (1967) observed that 5-year mortality was higher in COPD patients who lost weight (80%) in contrast to those whose weight was stable (50%).

Other studies, using both prospective and retrospective design, then examined and confirmed the relationship between the nutritional status, as assessed by weight, height and BMI, and the increased risk of mortality in COPD (see also Fig. 145.3).

Wilson and co-workers (1989) retrospectively analysed a cohort of 779 male patients with moderate to severe COPD and normal values of oxygen arterial pressure (PaO_2), by using the data available from the National Institutes of Health Intermittent Positive Pressure Breathing Trial. By way of a Cox proportional hazards model they found that a significant borderline association ($p = 0.055$) exists between the body weight, expressed as a percentage of the IBW, and survival with the strongest correlation in men with moderate airflow obstruction. In fact, from their analysis, 25% of the patients examined turned out to be underweight (weight < 90% IBW) and, in the sub-group of patients with a FEV_1 of less than 35% of predicted, 51% were undernourished as compared with 20% in the less severely obstructed patients ($FEV_1 > 47\%$ of predicted). Thus, it seems that the severity of airway obstruction is associated with an increased risk of under-nutrition. However, since different studies provide different conclusions about the relationship existing between nutritional status, mortality and severity of airflow obstruction, more research is still needed for an agreed-upon definition and accurate assessment of the nutritional status.

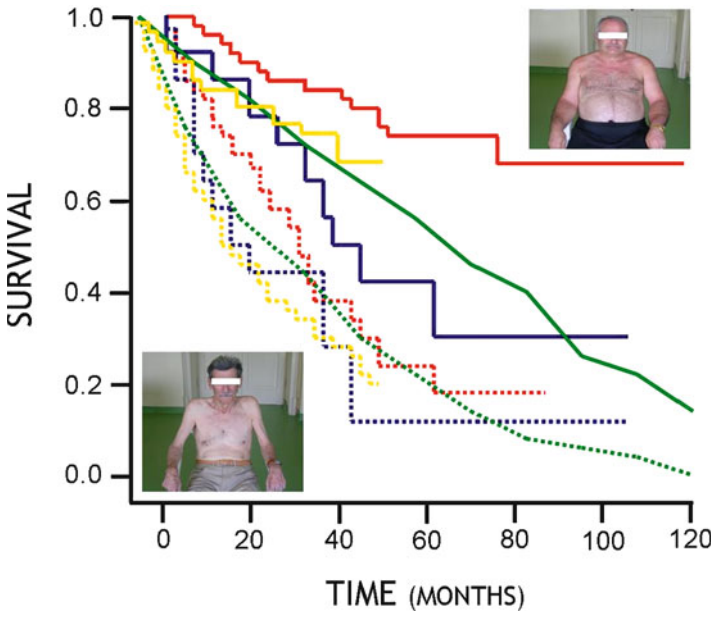

Fig. 145.3 Survival in COPD of different body mass. Graph displays the Kaplan-Meyer survival curves from underweight (BMI ≤ 20 kg/m², *Modify as lines, and photo bottom left*) and normal/ overweight (BMI ≥ 25 kg/m² *Modify as lines, and photo top right*) COPD phenotypes (Modified and adapted from Budweiser et al. 2007, Schols et al. 1998, Chailleux et al. 2003 and Marti et al. 2006).

Two subsequent retrospective studies, investigating different COPD populations, provided evidence of a relationship between low BMI and mortality, independent of the FEV_1. In a cohort of 348 severe Canadian COPD subjects including patients with hypoxemia and recruited for a study regarding the effectiveness of the negative pressure ventilation, Gray-Donald and colleagues (1996) found that 18% of patients were underweight and that the poor nutritional status, detected as a low BMI, and the use of home supplementation of oxygen were strong predictors of death, independently associated with reduced survival in a follow-up that lasted 3–5 years. Degree of airway obstruction (FEV_1), maximal expiratory mouth pressure (PEmax), age, smoking status and gender were factors not associated with survival.

A relevant retrospective study of Schols and co-workers (1998) in 400 COPD stable patients under rehabilitation, and without any nutritional support therapy, demonstrated that body weight is a significant prognostic factor in COPD. The authors found that survival decreased significantly in both underweight and normal weight patients when compared with those who were overweight and obese ($p < 0.0001$). Furthermore, a multivariate analysis which investigated the risk of death, showed that the BMI (Relative Risk (RR) 0.928 with 95% Confidence Interval, CI 0.894 to 0.963, $p < 0.0001$) together with age ($p < 0.0001$) and low PaO_2 ($p < 0.05$) were significant independent predictors of increased mortality. After stratification of the COPD population by BMI quintiles, a threshold equal to 25 kg/m^2 was identified as the cut-off value below which the mortality risk increased significantly.

A subsequent study by Landbo and co-workers (1999) prospectively investigated a cohort of 2,132 Danish patients with COPD (1,218 men and 914 women). The prevalence of nutritional depletion, defined as patients with BMI < 20 kg/m^2, was higher in females (15.5% vs. 5.1% in males) and the RR of death, adjusted for smoking, chronic mucus hyper-secretion, FEV_1 and gender, was significantly increased in underweight subjects, in contrast to overweight and obese patients. This result was particularly evident in the sub-groups of patients with moderate and severe airway obstruction (see Fig. 145.4).

However, when analysing the COPD-related cause of mortality, patients with BMI < 20 kg/m^2 showed a RR equal to 3.34 (95% CI 1.94–5.83) in men and 2.45 (95% CI 1.42–4.22) in women, compared to patients with BMI ≥ 30 kg/m^2 (RR 0.60 with 95% CI 0.29–1.25 in men, and 0.34 with 95% CI 0.12–0.97in women). These findings suggest that abnormal eating habits, either manifested as obesity or cachexia, increases all-cause mortality in mild to moderate COPD patients. Similar results were found for COPD-related causes of death, with the strongest association in the sub-group of patients with severe COPD (RR of 7.11 with 95% CI 2.97–17.05 in patients with low BMI as compared with those with high BMI). The authors then concluded that low BMI is an independent risk factor for mortality in subjects with COPD and that the association is strongest in subjects with severe COPD.

More recently, the study of Budweiser and co-workers (2007) which involved 188 COPD patients with chronic hypercapnic respiratory failure (FEV_1 31.0% of predicted, arterial carboxide pressure ($PaCO_2$) equal to 56.3 mmHg) and under home mechanical ventilation, did confirm the negative role of baseline BMI (Hazard Ratio – HR 5.07 with 95%CI 2.92–8.20, $p < 0.0001$), together with lung residual volume, and blood gases to predict mortality. Similar to the study by Schols (Schols et al. 1998), authors found that a weight gain and a consequent increase in the BMI to the level of 25 kg/m^2 is associated to improved survival at the 5-year follow-up.

Two other recent studies were conducted (Chailleux et al. 2003; Marti et al. 2006) to detect factors that predict survival in patients with COPD with chronic hypoxiemic respiratory failure and the need for Long Term Oxygen Therapy (LTOT) for a minimum of 18 h/day. The first study in temporal order investigated a cohort of 4,088 severe COPD patients, with both chronic bronchitis and/or emphysema, requiring domiciliary LTOT. This study analysed data collected from the *Observatoir*

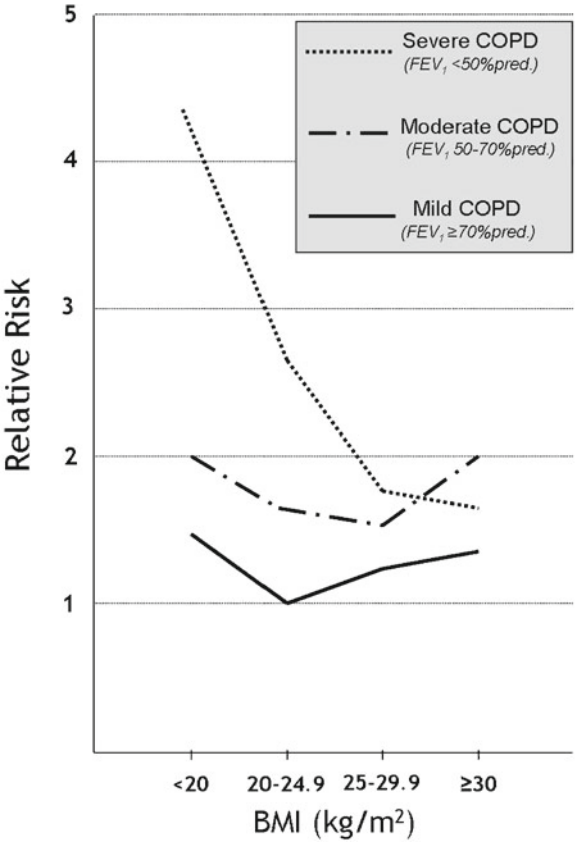

Fig. 145.4 Relative risk (RR) for all-cause mortality in COPD patients. Graph displays the risk of all-cause mortality in COPD patients with different degree of airway obstruction. Taken the reference risk at 1 in the phenotype with BMI 20–24.9 and Mild obstruction, the risk increases according to the decrease in BMI, especially in the most severe individuals (Modified and adapted from Landbo et al. 1999)

de la Association Nationale pour le Traitement a Domicile de l'Insuffisance Respiratoire Chronique, a national French database. Authors assessed the prognostic value of nutritional depletion on the rates of survival and hospitalization and found that the prevalence of malnutrition, defined as a BMI < 20 kg/m^2, was around 23% in men and 30% in women and that BMI is a risk factor for mortality independent of age, FEV_1, PaO_2 and gender. The 5-year survival rates were 24%, 34%, 44% and 59% for patients with BMI values < 20 kg/m^2 (95% CI 21–27), 20 ≥ 24 kg/m^2 (95% CI 32–36), 25 ≥ 29 kg/m^2 (95% CI 41–48) and ≥ 30 kg/m^2 (95% CI 53–64), respectively. The RR of death, using a BMI ≥ 30 kg/m^2 as the reference value, was 40% greater in the sub-group of patients with BMI 25 ≥ 29 kg/m^2, 80% in those with BMI 20 ≥ 24 kg/m^2, and 140% in those with a BMI < 20 kg/m^2. Again, the best prognosis among COPD under domiciliary LTOT was observed in overweight and obese individuals. Moreover, this study demonstrates that low BMI is the most powerful predictor of duration and rate of hospitalisation, independent of baseline blood gas levels and respiratory function. Indeed, the mean time spent in hospital was 29,6 ± 40,4 days/year in patients with BMI < 20 kg/m^2 versus 17,5 ± 30.1 days/year in those with BMI ≥ 30 kg/m^2. This result further corroborates the clinical significance of BMI as an outcome measure in COPD.

The other study by Marti and colleagues reported data from a retrospective Spanish study in 128 severe COPD (126 males), treated with LTOT and admitted in a tertiary teaching hospital, aimed at evaluating outcomes which can predict reduction in survival. This retrospective design reported data in the cohort in a time frame of 10 years. Based on the correlation analysis, BMI <25 kg/m^2, the number of co-morbid conditions, as assessed by the Charlson index, age ≥ 70 years and presence of cor pulmonale were positively associated with all-cause mortality. Low BMI and presence of

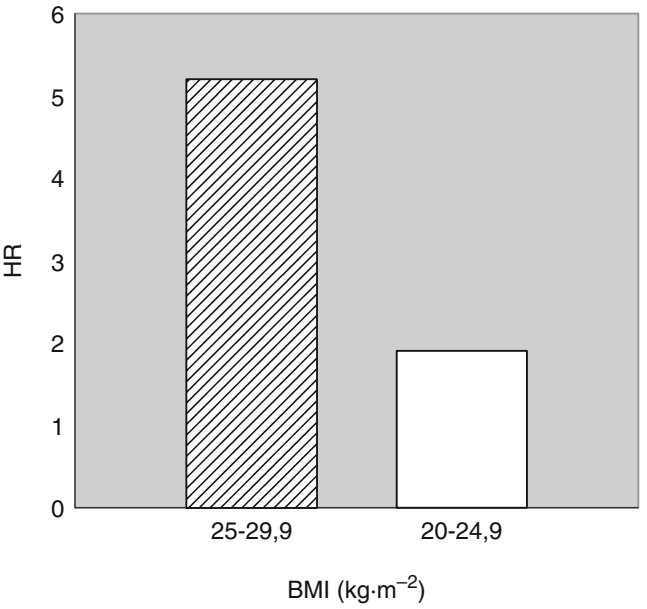

Fig. 145.5 Relative risk for all-cause mortality in the most severe COPD patients. Bars display the risk of all-cause mortality (as assessed by hazard ratio – HR) in the categories of both BMI 25–29.9 and BMI 20–24.9 among very severe COPD patients undergoing domiciliary long-term oxygen therapy (LTOT) (Modified and adapted from Marti et al. 2006)

co-morbidities still remained the only significant predictive factors associated with death when the analysis was restricted to respiratory mortality. In particular, BMI 20 ≥ 24.9 kg/m^2 or <20 kg/m^2 had a increased risk for all-cause mortality (see Fig. 145.5) and for respiratory cause of death (HR 2.07 with 95%CI 1.42–5.07, and 4.95 with 95%CI 2.04–12.01, $p < 0.01$).

In order to evaluate the additional prognostic importance of weight change, Prescott and colleagues (2002) reported data on unselected population of COPD (n = 1,612) participating in the CCHS over 15 years. They confirmed the role of baseline BMI to predict survival. In particular, they studied the mortality rate due to COPD taking the sub-group of patients with a BMI 20 ≥ 24.9 kg/m^2 as the reference value, and found that the RR of death was reduced by 34% and 28% in the sub-groups of patients with BMI between 25 ≥ 29 kg/m^2 and ≥30 kg/m^2 respectively. Not surprisingly, the risk increased by 68% in those COPD with BMI < 20 kg/m^2. They also performed an analysis that investigated the relationship between weight change in BMI units (e.g. for a subject 170 cm tall, 1 unit change in the BMI is equal to 3.89 kg.) and mortality, taking 1 kg/m^2 as the reference value of change in the BMI; a gain between 1 to 3 kg/m^2 or >3 kg/m^2 was associated with a mortality risk reduction by 17% and 5% respectively, whereas a reduction in BMI units between 1 to 3 kg/m^2 or >3 kg/m^2 increased this risk by 31% and 114% ($p < 0.001$) respectively. These findings suggest, after adjusting for age, smoking habits, baseline BMI, and lung function, that weight loss > 3 BMI units would be associated with a significantly higher mortality risk in COPD patients.

Martinez and coworkers (2006) explored the factors predicting mortality in patients with a narrow specific emphysema phenotype and candidate to LVRS inside the National Emphysema Therapy Trial (NETT). A total of 609 patients with severe airflow obstruction and hyperinflation were evaluated for risk factors such as markers of emphysema detected by CT scan, demographic, clinical and physiological data, BMI and changes of the modified BODE index (Celli et al. 2004), which is considered one of the most sensitive outcome predicting risk of death in COPD populations, where the higher the score, the higher the risk. Interestingly enough, in this study, as shown in the above-mentioned study on BODE index by Celli, the BMI, when taken as a single outcome measurement, did not show any significance to predict death. Indeed, taking the 60% of BMI distribution as a reference value, the upper quintile distribution of values (= mean BMI > 28 kg/m^2) showed a HR of 0.86

(95%CI 0.62–1.21, $p = 0.40$) whereas the lower quintile distribution of values (= mean BMI <21.4 kg/m^2) showed a HR of 1.32 (95%CI 0.98–1.78, $p = 0.06$). However, it is worth noting that the modified BODE index score has been shown to be a valid independent predictor of survival in these patients with severe emphysema. Taking the values of BODE between 1 and 6 as a reference category, BODE score 7 ≥ 10 showed a HR of 1.48 (95%CI 1.07–2.05, $p = 0.02$), meaning a significant increase in the risk of mortality in COPD patients with BODE index score above 6. It is difficult to draw a definitive interpretation from this apparent discrepancy of results; the lack of significance of BMI alone in predicting survival might depend on the particular population of severe COPD here included. On the other hand, it is likely that a multi-component index such as the BODE (which also includes BMI) might better reflect the power of prediction in the same population. For sure, further research will clarify this aspect.

Finally, even if BMI alone has been demonstrated to be a valid factor correlated to mortality risk in COPD, three other studies underlined the additional predictive role of body composition and muscle mass area.

To assess the association between FFM and mortality, Schols and coworkers (2005) studied 412 patients with moderate to severe COPD over 5 years. They stratified their cohort into three different pre-defined categories according to different patterns of tissue-depletion: low BMI with normal or above-normal FFMi (semi-starved), low FFMi with normal or above-normal BMI (muscle atrophy) and low BMI with low FFMi (cachectic). While the first two categories were equally distributed among stages of the disease, a higher prevalence of cachexia (29% in men and 27% in women) was seen in the sub-group of patients more severe COPD. Furthermore, while patients with muscle atrophy and cachexia reported similar and worst survival rate, the group of semi-starved (or no impairment) had significantly higher rate of survival. Thus, patients with low FFM had greater mortality risk than all the others, and FFM appears to be a better independent predictor of survival with respect to the BMI and the FM (RR 0.90, 95% CI: 0.84–0.96, $p = 0.003$). Therefore, this study supports the need to include assessment of body composition, as an important marker of disease severity, in COPD staging and phenotyping.

Two recent prospective studies (Marquis et al. 2002; Soler-Cataluña et al. 2005) aimed to assess the prognostic value of muscle mass depletion in severe COPD concluded that, in addition to the prognostic role of BMI level, measurement of the muscular cross-sectional area and the circumference of the mid-thigh as measured by means of the usual CT scan method, may also have a significant role in predicting the patient's survival.

145.5 Applications to Other Areas of Health and Disease

Weight loss and muscle wasting are recognized as critical features that may have an adverse impact on the natural history of COPD patients, influencing both morbidity and mortality. Several studies have documented that BMI ≤ 25 kg/m^2 is a strong predictor of mortality in these patients. The role of low body weight as a determinant of poor survival in COPD patients could be linked to several factors, such as respiratory and peripheral muscle weakness. However, it is still possible that the progressive decline in BMI as shown in patients with COPD, is a marker of advanced disease corresponding to a currently unknown factor also responsible for the decline in pulmonary function.

Recent findings indicate that the assessment of body composition and nutritional status provide additional information compared to BMI alone and help in categorizing COPD patients.

Future research will need to systematically integrate the body composition measure in the whole assessment of COPD patients. Furthermore, a similar approach and assessment should be investigated

even in patients other than COPD, such as idiopathic pulmonary fibrosis. Indeed, in respiratory diseases characterized by lung fibrosis, we still do not know which anthropometric, metabolic or functional factors can predict the long-term outcomes. In addition, all those respiratory conditions leading to chronic respiratory insufficiency might include in their assessment and phenotyping description, some of the body composition parameters which could also be used to identify who are most likely at risk of death.

Therefore, a more extensive knowledge on this topic could then help clinicians to identify patients at risk who may benefit more from life-sustaining interventions, such as domiciliary oxygen.

Summary Points

- Chronic respiratory diseases, COPD in particular, often present with extra-pulmonary manifestations, of which malnutrition and concomitant muscle wasting are most important
- The evaluation of body mass (BMI) and composition (FM and FFM) is an essential part of COPD patient's assessment, and these measures fairly correlate with strong outcomes such as long-term survival
- Several methods of increasing complexity may indirectly (skinfold thickness, MAC or muscle-circumference) or directly (hydro-densitometry, isotopic dilution, BIA) provide information on the FFM status in COPD
- BMI reduction already reflects poor muscle condition and correlates with individual's reduction in maximal aerobic capacity. A cut-off of ≤ 21 kg/m^2 is nowadays considered a threshold limit of nutritional depletion in COPD patients. FFM evaluation, however, may further inform about this status, being the cut-off of ≤ 14.62 kg/m^2 in men and of ≤ 17.05 kg/m^2 in women the threshold of normality
- Longitudinal change of an individual's BMI may variably predict the risk of subsequent survival in the COPD population. Anthropometry can therefore help to detect clinical aspects of COPD patients which are essential in defining specific phenotype and in addressing further interventions

Conflict of Interest Declaration All the authors declare to have no actual and potential conflicts of interest.

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Chapter 146
Anthropometry in Congenital Adrenal Hyperplasia

Henrik Falhammar, Anna Nordenström, and Marja Thorén

Abstract Congenital adrenal hyperplasia (CAH) is a monogenic disorder of the adrenal cortex with cortisol deficiency and androgen excess affecting anthropometric parameters throughout the entire life. Glucocorticoids are the mainstay of therapy and anthropometry is vital in judgment and adjustment of the treatment. Treatment involves a difficult balance, in which both over- and under-substitution will result in an increased risk of short final height. Hence, the majority of patients with CAH have attained a final height below their potential. However, improvements in management have resulted in more patients reaching their target height. Earlier, obesity was common in CAH. Nowadays the situation may have improved, weight in these patients does not differ from that in the general population. However, the shorter stature of CAH patients results in an elevated body mass index (BMI) in most reports on both children and adults, and patients aged >30 years may have a higher waist to hip ratio. BMI may give an unreliable estimate of body fat in CAH since, females in particular may experience high androgen levels leading to increased muscle mass. Moreover, owing to the exposure to raised androgens during fetal life, many girls and women with CAH show more gender-atypical behavior regarding choice of profession and leisure time interests with increased physical activity as a consequence. These individuals may then show an elevated BMI as a result of increased muscle (lean) mass, but without increased fat mass. On the other hand, in overtreatment with glucocorticoids, lean mass may be low and BMI may underestimate fat mass. Dual energy X-ray absorptiometry (DXA) provides a more accurate and reliable way of measuring fat and lean mass in males and females affected by CAH. DXA has demonstrated increased fat mass in CAH, but sometimes also, especially in women, increased lean mass.

Other anthropometric characteristics of females with CAH are a lower ratio of the length of the index finger to the ring finger compared to female controls of the same ethnicity, indicating a more masculine-typical ratio. The virilization of external genitals seen predominantly in classic CAH includes a longer clitoris than normal unless operated upon. Benign testicular adrenal rest tumors are common and in about one third of patients may reach a size large enough to become palpable.

In conclusion, anthropometry is a central part of the management of CAH; however, due to the special features of CAH, the interpretations of anthropometry may differ.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_146,

Abbreviations

ACTH	Corticotropin
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CRH	Corticotropin-releasing hormone
FH	Final height
NC	Non-classic
PCOS	Polycystic ovary syndrome
SV	Simple virilizing
SW	Salt-wasting
TH	Target height

146.1 Introduction

Congenital adrenal hyperplasia (CAH) is a monogenic disorder of the adrenal cortex with cortisol deficiency and androgen excess affecting anthropometric parameters throughout life (Table 146.1). Glucocorticoids are the mainstay of therapy and anthropometry is vital in the judgment and adjustment of the treatment (Table 146.2). Height, weight, and different measurements of fat and lean mass

Table 146.1 Key features of monogenic disorders

1. A disease controlled by a single defective gene
2. Considered to be relatively rare, however, the global prevalence at birth is about 1/100
3. Over 10,000 human diseases are considered to be monogenic
4. Inherited (passed on from one generation to another) in a simple pattern
5. Inheritance patterns for monogenic disorders are usually autosomal dominant, autosomal recessive, or X-linked
6. CAH is considered to be one of the most common monogenic disorders inherited in an autosomal recessive pattern

This table lists the key facts of monogenic disorders including its frequency and inheritance
CAH congenital adrenal hyperplasia

Table 146.2 Key features of congenital adrenal hyperplasia

1. CAH is potentially fatal because of cortisol deficiency if not correctly diagnosed and treated promptly with glucocorticoids
2. Girls with CAH are born with different degrees of virilization of external genitalia (ambiguous genitalia) due to elevated prenatal androgens, except in the mild non-classical variant
3. Females exhibit clitoral hyperplasia if not previously subjected to surgery
4. A high risk of not obtaining target height, that is, most individuals will not reach their target height as it is very difficult to obtain the optimal glucocorticoid dose
5. Increased central obesity
6. Increased fat mass, but also sometimes, especially in older women, increased lean mass
7. Decreased index-to-ring finger ratio

This table lists the key facts of congenital adrenal hyperplasia (CAH) focusing on anthropometric features of CAH

are measured regularly in individuals with CAH. A large number of studies have been published on children and young adults with CAH; however, the majority is quite small. By contrast, studies including older adults with CAH are rare. This chapter will commence with an overview of the pathophysiology and clinical presentation of CAH, followed by a more detailed description of the different results found in anthropometric measurements in children and adults affected by CAH. Moreover, suggestions on how, which and when anthropometric measurements should be performed will be given.

146.2 Overview of Congenital Adrenal Hyperplasia

CAH occurs due to total loss or impairment of one of the five steroidogenic enzymes in the adrenal cortex responsible for cortisol production. The most common impairment, 21-hydroxylase deficiency, accounts for approximately 95% of all cases. The enzyme 21-hydroxylase controls the synthesis of cortisol and aldosterone (Fig. 146.1), and mutations in the cytochrome P450 (*CYP21A2*) gene will determine the degree of deficiency, with a generally good correlation with the phenotype. For a more extensive review, see White and Speiser (2000) and Merke and Bornstein (2005). Classical CAH due to a 21-hydroxylase deficiency is divided into salt-wasting (SW) and simple virilizing (SV) types. In SW CAH, both cortisol and aldosterone production are severely impaired, while in SV CAH mainly cortisol is affected. Via lack of negative feedback to the pituitary gland and the hypothalamus, low serum cortisol levels will stimulate corticotropin (ACTH) and corticotropin-releasing hormone (CRH) production. ACTH stimulates both adrenal growth and adrenal androgen production, the latter being the reason why females with classic CAH are born with virilized external genitalia (Table 146.3). Non-classic (NC) CAH exhibits milder symptoms of androgen excess, and females do not have virilized external genitalia at birth. Patients with NC CAH show no obvious cortisol and aldosterone deficiency. The symptoms and signs in female NC CAH may be indistinguishable from those found in polycystic ovary syndrome (PCOS) with oligomenorrhea, hirsutism,

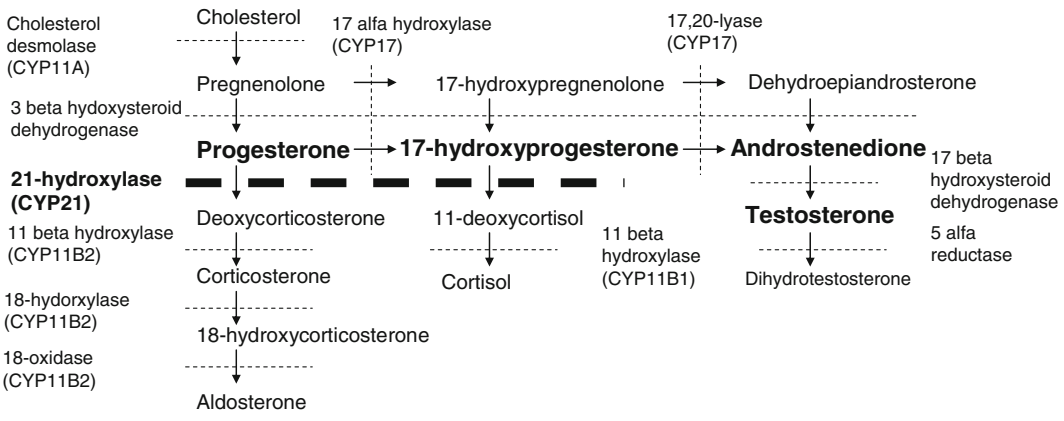

Fig. 146.1 Steroid biosynthetic scheme in the adrenal cortex. The pathways of cortisol, aldosterone, and androgens with their steroid precursors are shown. The different enzymes involved in steroid synthesis are included. The enzyme 21-hydroxylase is most frequently affected in congenital adrenal hyperplasia and is highlighted together with precursors and androgens usually being elevated in this condition

Table 146.3 Key facts of virilization

1. Development of male sex characteristics in females or increased male characteristics in boys before pubertal time
2. In females, the signs are:
   (a) facial hair and increased body hair (hirsutism);
   (b) accelerated growth and bone maturation;
   (c) acne;
   (d) deepening of the voice;
   (e) male-pattern baldness; and
   (f) increased size of clitoris (hypertrophy): in newborn girls, 'scrotalization' of the labial skin, and different degrees of fusion of the labiae, forming a common urogenital sinus, can be found
3. Caused by excess androgen production, that is, testosterone and similar hormones or intake of androgens, namely, use of anabolic steroids
4. CAH is one of the most common causes of virilization

This table lists the key facts of virilization including signs and causes

infertility, and ovaries with increased stroma and multiple follicles (Falhammar et al. 2008). Males with NC CAH are usually found through family studies or because of symptoms of premature pubarche and acne (Merke and Bornstein 2005; Falhammar et al. 2008).

Patients with the salt-losing form of CAH are typically diagnosed during the first weeks of life, while SV CAH has been diagnosed as late as 15 years of age and NC CAH at 6–32 years of age, but occasionally at a very late age (Falhammar et al. 2007a; Falhammar and Thorén 2005). Males with SV or NC CAH are sometimes diagnosed later than females with SV or NC CAH. During the last decades, a number of countries have initiated neonatal screening programs with 17-hydroxyprogesterone, detecting predominately classic CAH due to 21-hydroxylase deficiency. In the Swedish program, one out of 10,500 children is affected (Thilén et al. 1998). Similar frequencies have been found in other populations with an overall incidence of one in 15,000 newborns for classic CAH (White and Speiser 2000; Merke and Bornstein 2005). However, a few geographically isolated populations have a higher incidence of classic CAH, the highest being the Yupik Eskimos in Alaska with an incidence of one in 280 (Merke and Bornstein 2005). In contrast to classic CAH, NC CAH due to 21-hydroxylase deficiency is considered to be the most frequent autosomal recessive genetic disorder in man, with 0.1% of the general Caucasian population affected and higher frequencies in Hispanics and Yugoslavs (1–2%) and in Ashkenazi (Eastern European) Jews (3–4%) (White and Speiser 2000).

Compared to 21-hydroxylase deficiency, the other forms of CAH are rare. The incidence of 11-beta hydroxylase deficiency is about one out of 100,000 in the general population (White and Speiser 2000). This variant of CAH exhibits elevated levels of the steroid precursors deoxycorticosterone (DOC) and 11-deoxycortisol (Fig. 146.1). DOC is a strong mineralocorticoid, and the affected patients show not only virilization but also decreased serum potassium and a raised blood pressure. CAH due to 3-beta-hydroxysteroid dehydrogenase deficiency is even rarer, and females may have only mild virilization of the external genitalia while males exhibit ambiguous genitalia (undermasculinization). Levels of dehydroepiandrosterone and 17-hydroxypregnenolone are elevated (Fig. 146.1).There are more rare variants of CAH, but, in this chapter, we will primarily refer to 21-hydroxylase deficiency when discussing CAH.

Since the introduction of glucocorticoid treatment in the 1950s, these medications have remained the mainstay of treatment in CAH, supplementing the cortisol deficiency and suppressing the ACTH production and leading to restrained androgen production. All patients with CAH due to a 21-hydroxylase deficiency display some degree of aldosterone deficiency, which is, however, clinically apparent only in the SW and SV forms. Fludrocortisone, a mineralocorticoid, is usually added as well, since it may reduce the glucocorticoid dose needed. Unfortunately, supraphysiological doses of

glucocorticoids are often required to suppress the adrenal androgens, and the hypercortisolemia carries the risk of such adverse effects as short stature in adulthood, obesity, insulin resistance, elevated liver function tests, osteoporosis, and fractures (Falhammar et al. 2007a,b, 2009).

146.3 Anthropometry at Birth

In healthy infants, boys are larger at birth than girls in terms of birth weight, length, and head circumference. Infants with CAH have been studied in order to determine whether or not this difference is caused by prenatal exposure to androgens.

Data on birth weight are not entirely consistent. Two studies including 92 and 101 subjects, respectively, demonstrated significantly higher weights compared to reference populations (Jääskelainen et al. 1997; Balsamo et al. 2006), whereas, in one study of 89 children, a modest decrease was found (Völkl et al. 2006). Furthermore, differences in birth weight between classic and non-classic (NC) CAH cases have been found. In an Italian study of infants at 38–41 weeks of gestation ($n = 101$), patients with the classical forms were significantly heavier than the NC patients, the mean weight in females being 3.4 ± 0.4 versus 3.2 ± 0.7 kg and in males 3.5 ± 0.4 versus 3.2 ± 0.7 kg. NC patients were in turn not different from controls (Balsamo et al. 2006). An increased birth weight (+ 0.8 SDS) was also displayed in Finnish infants with early diagnosed, that is, severe forms of CAH, compared to infants with less severe forms (+ 0.2 SDS) diagnosed later during childhood (Jääskeläinen and Voutilainen 1997). Moreover, differences between the two classical forms have also been demonstrated in that patients with the more severe SW form weighed less than those with the milder SV form (Balsamo et al. 2006).

Birth length is increased in infants with CAH and has been reported to be + 0.38 and + 0.39 SDS in females and males, respectively (Völkl et al. 2006). In the latter study, the severity of the disease was not indicated. Balsamo et al. reported that birth length was significantly higher in classic CAH than in NC CAH. In females, the mean birth length was 50.3 ± 1.5 cm in classic CAH and 49.8 ± 2.1 cm in NC CAH. The corresponding means in males were 51.2 ± 1.7 and 49.7 ± 2.1 cm. It has been reported that the *CYP21A2* genotype was positively correlated with gestational length in girls but not in boys (Gidlöf et al. 2007). Gestational age may therefore contribute to the differences seen in birth weight and length.

It is a well-known fact that androgens stimulate skeletal maturation and growth of muscle mass and reduce fat mass. It is likely that the differences in birth length and birth weight, although modest between healthy and CAH infants as well as between classic and NC CAH ones, are attributable to dissimilarities in prenatal adrenal androgen exposure. Possible impacts of other hormonal differences, such as in hydrocortisone concentrations, remain to be explored.

146.4 Postnatal Growth and Final Height

The majority of patients with CAH attain a final height (FH) below their height potential. Treatment in CAH is a difficult balance, where both over- and undersubstitution will result in an increased risk of short FH. Overtreatment with glucocorticoids will result in a decreased growth rate and short stature. On the other hand, undertreatment will result in an androgen excess and growth acceleration and also advanced bone maturation and early epiphysis closure and therefore a short FH. The trend over time has been to use lower doses of hydrocortisone (the preferred glucocorticoid until FH has been achieved), which has resulted in a better FH for individuals with CAH (Hoepffner et al. 2008).

146.4.1 Growth

Growth is a sensitive tool for assessing hormonal control in CAH.

Undiagnosed and untreated patients with milder forms of CAH, that is, SV, who are able to survive past the neonatal period, or NC show an increased growth velocity. Typically, the growth acceleration is obvious from age 3–6 and is accompanied by other symptoms of androgen excess, such as adult/apocine sweating, acne, and pubic hair. It is more common that boys are not diagnosed, as they generally do not demonstrate ambiguous genitalia, and they are often described as big and strong with good muscles. The accelerated bone age results in premature closure of the epiphysis and therefore short stature. The early closure of the growth plate may compromise limb growth even more, resulting in a relatively long trunk (high sitting height) (Young et al. 1989).

Interestingly, several reports indicate that growth velocity and possibly bone maturation either do not seem to be affected or are only moderately affected by excess androgens during the first 12–18 months of life (Claahsen-van de Grinten et al. 2006; Thilén et al. 1995).

146.4.2 Final Height

A meta-analysis of height outcome in 561 CAH patients from 18 centers showed an overall mean weighted FH of -1.37 SDS (no trend for when the articles were published was found). Patients with an early diagnosis had a better outcome (–1.11 SDS) than those with a late diagnosis (–1.61 SDS), and females had a better outcome than males (–1.24 vs. –1.57 SDS). Final height SDS minus target height SDS calculated for all the 204 patients for whom target height (TH) was available gave –1.21 SDS. There was a good correlation between early diagnosis and compliance and FH (Eugster et al. 2001). However, there are contradictory reports concerning the positive effect of early diagnosis on FH, which may reflect different treatment policies. Longer lasting synthetic glucocorticoids as well as high doses of hydrocortisone result in a risk of overtreatment and a shorter FH (Bonfig et al. 2007; Balsamo et al. 2003). This may be the explanation for the conflicting reports as to which form of CAH has the most compromised FH: SW (Trinh et al. 2007) or SV (Balsamo et al. 2003; Manoli et al. 2002). Hence, patients with good hormonal control have been reported to be taller (Trinh et al. 2007; Eugster et al. 2001). In a Swedish survey of 61 women with CAH, the majority of whom had received slightly supraphysiological glucocorticoid doses, the mean FH was 160 cm as compared with 167 cm in controls, and there was no difference in height between older and younger patients (Falhammar et al. 2007a).

It appears that patients with CAH predominantly lose height potential during the first year of life and during puberty. Therefore, it is important to keep the glucocorticoid doses as low as possible throughout childhood and especially during these vulnerable periods (Van der Kamp et al. 2002; Bonfig et al. 2007; Manoli et al. 2002; Girgis and Winter 1997). The addition of mineralocorticoid substitution in patients with SW CAH is also beneficial for reaching TH by reducing the demand for glucocorticoids (Balsamo et al. 2003). Moreover, FH is also dependent on the timing of puberty and hormonal control. Pubertal growth has been reported to be early by, on the average, 2 years (Hargitai et al. 2001) and possibly early in boys (especially with SW) and timely in girls (Trinh et al. 2007; Bonfig et al. 2007). The pubertal growth spurt is reported to be diminished to different extents in both (Hargitai et al. 2001; Stikkelbroeck et al. 2003a; van der Kamp et al. 2002; Manoli et al. 2002).

Body proportions have been reported to be within the normal range in CAH, with the exception of one patient (out of three studied) with the NC form and late diagnosis (Young et al. 1989).

146.5 Weight

Obesity was previously considered to be a common side effect of glucocorticoid treatment in patients with CAH. With time, the management of this therapy has improved. In more recent reports, no difference in weight was found in either adult males or females compared to controls (Stikkelbroeck et al. 2003b; Falhammar et al. 2007a). Similar results have been reported in children (Isguven et al. 2008). In a Swedish study, females with CAH aged 30 years or more were, however, 8 kg heavier than females with CAH aged 18–29 years, while there was no significant difference between younger and older age-matched female controls (Table 146.1) (Falhammar et al. 2007a). This could possibly indicate that patients with CAH (at least female ones) increase their weight more during aging, compared with the general population.

146.6 Body Mass Index

Although weight does not differ between patients with CAH and controls, the shorter stature in patients results in an elevated body mass index (BMI) according to the majority of reports (Stikkelbroeck et al. 2003b; Jääskeläinen and Voutilainen 1996; Isguven et al. 2008), but not all (Cameron et al. 1995), in both children and adults with CAH. However, in the recent Swedish study mentioned above where adult females with CAH were compared with age- and sex-matched controls, only the patients with CAH ≥30 years of age exhibited an elevated BMI, whereas younger adult patients with CAH had BMIs similar to those of controls (Falhammar et al. 2007a) (Table 146.1). The BMI range was, however, wide in both patients and controls (18–48 kg/m^2 and 18–40 kg/m^2). In patients, 11% were even underweight (BMI <19.9 kg/m^2), 56% were normal (BMI 20–24.9 kg/m^2), 18% were overweight (BMI 25–29.9 kg/m^2), 8% were obese (BMI 30–39.9 kg/m^2), and 5% were extremely obese (BMI ≥ 40 kg/m^2). Thus, patients with obesity (BMI ≥30) were a minority (18%).

To avoid adult obesity, the management from infancy and onward is extremely important. Overtreatment during infancy, with high doses of glucocorticoids, was reported to increase the risk of obesity in childhood despite adequate treatment for several years thereafter (Knorr et al. 1988). Prepubertal children had increased BMIs also when growth was not negatively affected. In normal children, BMI increases rapidly to a peak in infancy, and then reverses before increasing again later in childhood. An early age for this rebound is considered a reliable indicator of future adult obesity. Children with CAH were reported to have an earlier adiposity rebound by, on the average, 3 years compared with the normal population, and BMI SDS was greater than 1 in all but one patient in spite of no change in height SDS (Cornean et al. 1998).

Contributing factors predisposing to obesity in childhood are glucocorticoid dosing, bone age delay, and parental obesity. The relative risk of obesity, defined as BMI >2 SDS, was reported to be 4.86 in children and adolescents with obese parents (Völkl et al. 2006).

146.7 Anthropometric Estimations of Body Fat

146.7.1 Body Circumferences

Measurements of body circumferences have not been reported widely in CAH. Visceral obesity is an established risk factor for cardiovascular disease and type 2 diabetes, and waist circumference and the waist-to-hip ratio are established anthropometric measurements used for estimating truncal fat.

We reported similar waist circumferences in both younger (18–29 years) and older (30–63 years) female patients with CAH and age- and sex-matched controls (Falhammar et al. 2007a). The waist-to-hip ratio was, however, elevated in the older women with CAH compared to controls. Both in adult females with CAH and in controls, the waist-to-hip ratio was increased in the older compared with the younger group (Table 146.4). We have found similar results in adult males with CAH.

In a study of eight boys and nine girls affected with CAH aged 1.6–10.5 years, waist, hip, upper arm, and femur circumferences were increased compared to controls (Isguven et al. 2008). The waist-to-hip ratio was, however, increased in girls, while it was decreased in boys.

146.7.2 Skinfold Thickness

Another simple measure that correlates with body fat, skinfold thickness has occasionally been used in studies of individuals with CAH. At least in children, skinfold thicknesses have been demonstrated to be increased at all locations measured (biceps, triceps, subscapula, suprailiac, and femur, and the sum of all) compared to controls (Isguven et al. 2008). Prepubertal children had increased skinfold thickness also when growth was not negatively affected (Cornean et al. 1998).

146.8 Limitations of Anthropometric Measurements for Assessment of Body Fat in Adults with CAH

BMI can be unreliable as an estimate of body fat, especially in people with CAH. If undiagnosed or poorly controlled, especially females with CAH will experience high androgen levels, leading to muscular hypertrophy (Fig. 146.2). Moreover, probably due to the exposure to raised androgens during fetal life, girls and women with CAH show more gender-atypical behavior regarding choice of profession and leisure time interests than controls (Frisén et al. 2009). In fact, 74% were interested in rough sports (100% in the most severe genotypes), such as ice hockey and soccer. These individuals may display an elevated BMI due to increased muscle (lean) mass but no increased fat mass. Conversely, in physically very inactive patients or in those on severe overtreatment with glucocorticoids (exogenous Cushing's syndrome), lean mass may be low and BMI may underestimate fat mass. Hence, a more reliable method of estimating body fat, but also lean mass, is needed in combination with anthropometric measurements in individuals with CAH.

146.8.1 Dual-Energy X-Ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA), which has been used in some studies on CAH patients (Cameron et al. 1995; Stikkelbroeck et al. 2003b; Falhammar et al. 2007a), provides a fairly accurate, reliable, and simple way of measuring fat and lean mass in males and females affected by CAH. Unfortunately, not all DXA machines can measure body composition because DXA equipment is used primarily for bone measurements and to enable measurements of fat and lean body mass additional software is necessary. In addition, the whole body must be measured and not just the central parts, which is the case with some DXA machines used solely for bone measurements.

Table 146.4 Anthropometry and blood pressure in adult females with congenital adrenal hyperplasia

	Patients <30 year (n = 27)	Controls <30 year (n = 27)	P value[a]	Patients ≥ 30 year (n = 34)	Controls ≥ 30 year (n = 34)	P value[b]	P value, patients[c]	P value, controls[c]
Height (cm)	161.4 ± 1.3	168.0 ± 1.2	<0.001	158.6 ± 1.2	165.7 ± 0.98	<0.001	NS	NS
Weight (kg)	60.7 ± 2.5	64.4 ± 1.9	NS	68.7 ± 2.8	67.0 ± 2.3	NS	0.021	NS
BMI (kg/m^2)	22.4 (17.7–41.8)	21.9.(17.5–33.8)	NS[d]	24.4 (20.7–48.3)	23.7 (19.4–39.9)	0.019[d]	0.003[d]	NS[d]
Waist (cm)	76.0 (65.0–97.0)	77.0 (65.0–102.0)	NS[d]	82.0 (70.0–130.0)	82.0 (65.0–125.0)	NS[d]	<0.001[d]	NS[d]
Waist to hip ratio	0.77 ± 0.009	0.78 ± 0.012	NS	0.84 ± 0.012	0.81 ± 0.011	0.037	<0.001	0.049
Total fat (kg/m^2)	6.3 (2.5–14.9)	7.1 (3.3–22.4)	NS[d]	8.5 (4.5–25.7)	8.3 (4.2–18.6)	NS[d]	0.002[d]	NS[d]
Total fat (%)[e]	31.0 ± 1.8	34.1 ± 1.4	NS	38.5 ± 1.8	36.1 ± 1.5	NS	0.003	NS
Truncal fat (kg/m^2)	3.0 ± 0.35	3.3 ± 0.28	NS	4.9 ± 0.44	4.0 ± 0.35	NS	0.002	NS
Truncal fat (%)[f]	28.1 ± 2.1	32.5 ± 1.6	NS	36.6 ± 1.7	34.4 ± 1.8	NS	0.002	NS
Total lean (kg/m^2)	14.7 ± 0.28	14.1 ± 0.22	NS	15.7 ± 0.31	14.6 ± 0.22	0.006	0.031	NS
Lean arms (kg/m^2)	1.5 (1.1–2.1)	1.5 (1.2–2.7)	NS[d]	1.7 (1.3–3.1)	1.5 (1.3–2.5)	0.008[d]	0.013[d]	NS[d]
Lean legs (kg/m^2)	2.0 ± 0.11	5.0 ± 0.17	NS	5.2 ± 0.11	4.9 ± 0.098	NS (0.054)	NS	NS
Total fat to lean ratio	0.47 ± 0.041	0.57 ± 0.052	NS	0.66 ± 0.045	0.58 ± 0.039	NS	0.005	NS
BP supine (mm Hg)[g]	110/71	115/69	NS/NS[d]	110/75	115/75	NS/NS	NS/NS[d]	NS/NS (0.075)[d]
BP standing (mm Hg)[g]	120/75	115/70	NS/NS[d]	115/79	113/73	NS/NS	NS/0.047[d]	NS/NS[d]

Table illustrating anthropometry, body composition (by DXA), and blood pressure measured in female patients with congenital adrenal hyperplasia and age-matched controls <30 and ≥30 years of age (mean ± SEM or median and range). Body-composition data were calculated in 24 patients and 26 controls <30 years and in 32 patients and 34 controls ≥30 years. Fat mass and lean body mass data are adjusted for body height (kg/m^2) (From Falhammar et al. (2007a), Copyright 2007, The Endocrine Society)

Body composition data were calculated in 24 patients and 26 controls younger than 30 year and in 32 patients and 34 controls 30 or older. Fat mass and lean body mass data are adjusted for body height (kg/m^2)

NS not statistically significant ($P \geq 0.05$); BP blood pressure

[a] Comparison between patients and controls younger than 30 year

[b] Comparison between patients and controls at least 30 year old

[c] Comparison between patients younger than 30 and 30 year old or older

[d] Mann-Whitney U test; χ^2, with Yates correction

[e] Percentage of total body mass

[f] Percentage of total truncal mass

[g] The three patients on antihypertensive medication were excluded

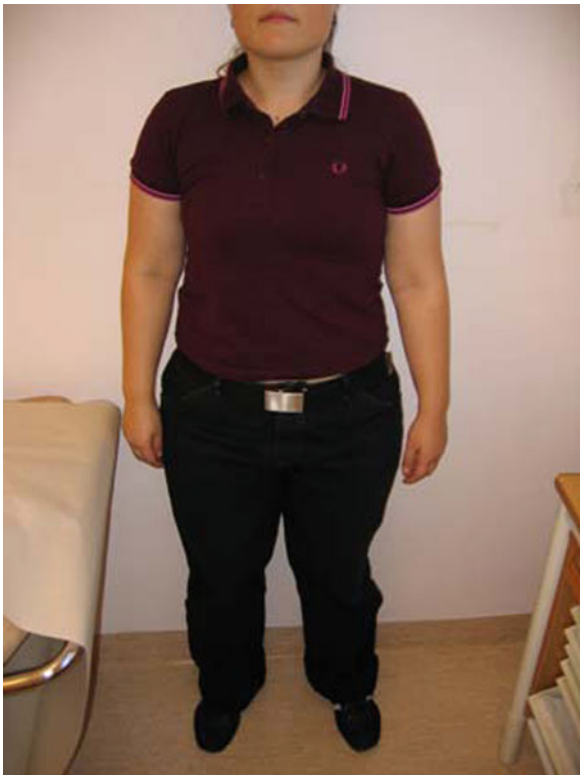

Fig.146.2 An adult woman with CAH. This figure illustrates a short woman with classic CAH, poor compliance to glucocorticoid medication, and signs of muscular hypertrophy. Her serum testosterone was markedly elevated (16 nmol/L; reference interval in adult females 0.3–3.0 nmol/L, in adult males 10–30 nmol/L)

Cameron et al. investigated the total fat-to-lean ratio in male and female children, adolescents, and young adults with CAH, aged 8–32 and found a higher ratio in patients with CAH than in their controls (Cameron et al. 1995). Stikkelbroeck et al. assessed male and female patients 17–25 years of age and found an increased total fat mass, but not lean mass, in patients with CAH compared to age- and sex-matched controls, especially when adjusted for the shorter height in CAH patients (Stikkelbroeck et al. 2003b). By contrast, we found no difference with respect to controls in adult females with CAH under 30 years of age in either total or regional fat or lean mass (Table 146.4). Surprisingly, in the older patients with CAH (≥30 years of age), total and arm lean mass adjusted for height were found to be elevated, whereas different measurements of fat mass did not differ from age-matched controls. Moreover, older women with CAH demonstrated more fat and lean mass than younger women (Table 146.4). Both the younger and older cohorts were modestly overtreated with glucocorticoids as evidenced by suppression of adrenal androgens (Fig. 146.3). It cannot be ruled out, though, that some of the older patients may have been undertreated in the past with ensuing stimulation of muscle mass by elevated adrenal androgens. However, in both women with CAH and their controls, the strongest correlation between total lean mass adjusted for height turned out to be fat mass adjusted for height (Fig. 146.4). This correlation was even stronger if only older women with CAH were studied.

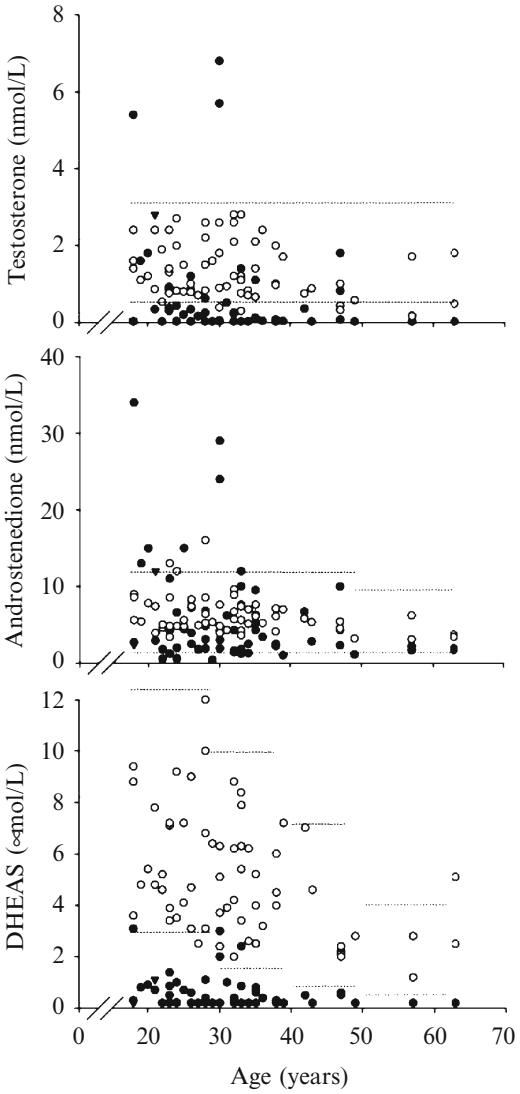

Fig.146.3 Serum androgens in adult women with congenital adrenal hyperplasia and controls. Figure illustrating different androgen levels in women affected by CAH (congenital adrenal hyperplasia) and age- and sex-matched controls. (●) CAH women, those on antiandrogen excluded. (▼) CAH women on antiandrogen. (○) Controls. $P < 0.001$ between CAH women and controls in all comparisons. Reference limits for the different androgens and different age intervals are indicated by *dotted lines* (From Falhammar H et al. (2007a). Copyright 2007, The Endocrine Society)

146.8.2 Bioelectrical Impedance Analysis

Bioelectrical impedance analysis is a noninvasive, inexpensive method of measuring total body fat. Body-fat percentage using bioelectrical impedance analysis was significantly elevated in children with CAH compared to controls (27.3% vs. 11.5%) (Isguven et al. 2008). However, when available, DXA measurements are preferred due to the possibility of measuring regional fat and lean mass distribution.

146.9 Shoe Size

Shoe sizes, as a measurements of foot length, have been demonstrated to be smaller in young adult males with classic CAH than in healthy controls (40.6 ± 1.5 vs. 43.9 ± 1.0; $P < 0.001$), probably reflecting their shorter stature by 12.1 cm compared to controls (Stikkelbroeck et al. 2003b).

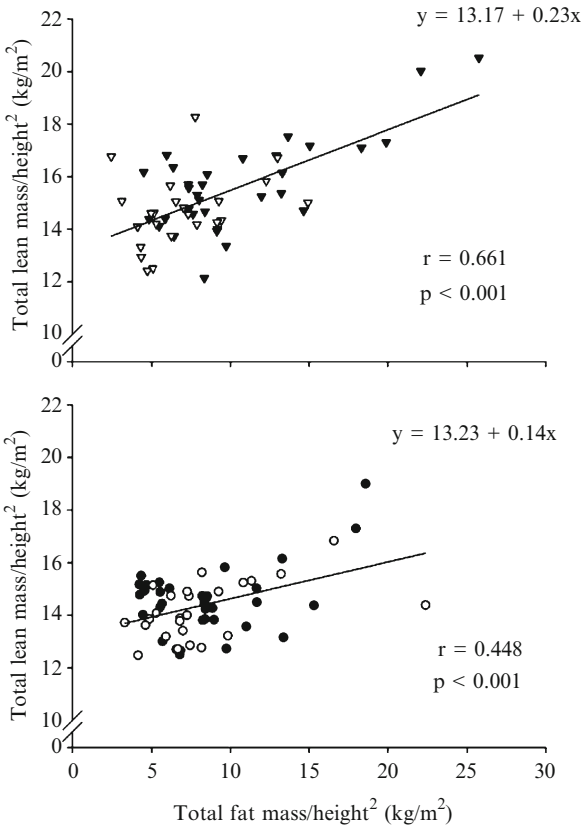

Fig.146.4 Correlation between total lean mass/height^2 and total fat mass/height^2 in adult women with congenital adrenal hyperplasia. Figure illustrating correlation between muscle (lean) mass and fat mass, both adjusted for the shorter height in individuals with CAH (congenital adrenal hyperplasia). (▼) CAH women ≥30 years old. (▽) CAH women <30 years old. (●) Controls ≥30 years old. (○) Controls <30 years old (From Falhammar H et al. (2007a). Copyright 2007, The Endocrine Society)

146.10 Ratio of the Second and Fourth Finger Length

Since first published in 1875, males have consistently been demonstrated to have, on average, a lower ratio of the length of the index finger to the ring finger (2D- to-4D ratio) than females (McIntyre 2006). As early as the end of the first trimester of gestation, this sex difference can be found. Constant means of the 2D-to-4D ratio for males and females have been reported from at least 2 years of age through adulthood. It can be assumed that the sex difference in the 2D-to-4D ratios is a result of androgen status. Hence, the 2D-to-4D ratio has been suggested as a marker of intrauterine androgen exposure.

Since females with CAH are exposed to high intrauterine levels of androgens, they have been considered to be a model for testing the hypothesis that prenatal androgens can affect the 2D-to-4D ratio. If the hypothesis is correct, these females should display a smaller 2D-to-4D ratio than healthy women.

In one study, the 2D-to-4D ratio was measured on both hands in females with CAH (aged 7–44 years) and control females (aged 12–44). Females with CAH exhibited lower 2D-to-4D ratios, indicating more masculine-typical ratios compared to female controls, although the difference did not reach statistical significance on the left hand (Fig. 146.5). No differences between females with CAH and female controls were found in the absolute length of any of the four fingers measured (Brown et al. 2002).

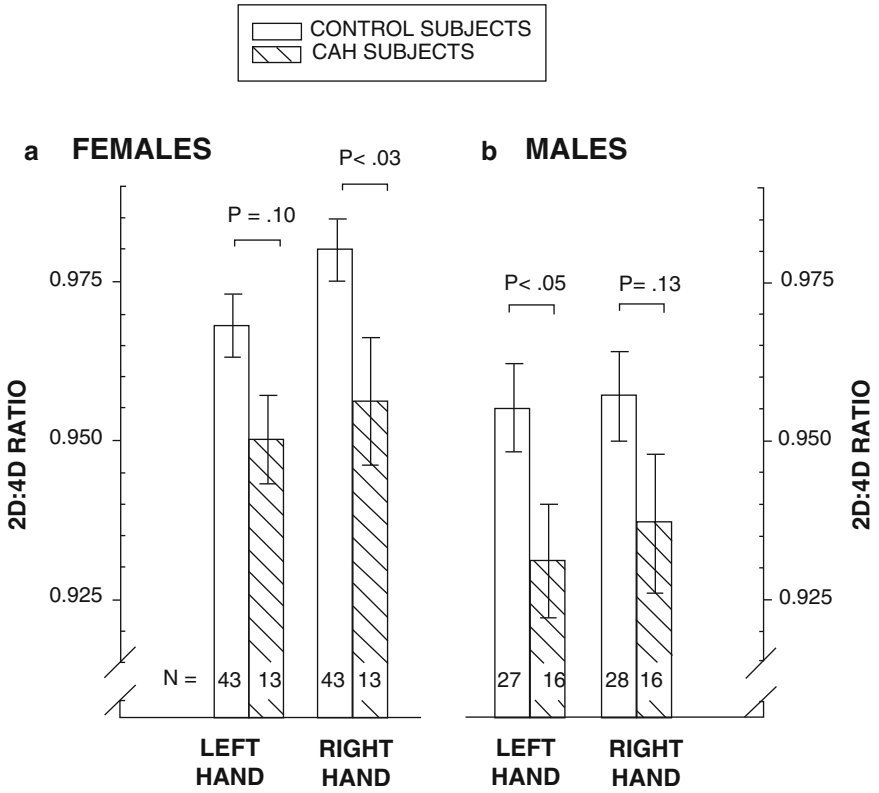

Fig.146.5 Ratios of the length of the index finger to the ring finger (2D-to-4D ratio) in females and males. Figure illustrating finger ratios in CAH individuals and controls. (**a**) Mean finger-length ratios of females with CAH and control females for both the *left* and *right* hands. Females with CAH have a significantly smaller 2D:4D on the *right* hand than do female controls. (**b**) Mean finger-length ratios of males with CAH and male controls for both the *left* and *right* hands. Males with CAH have a significantly smaller 2D:4D on the *left* hand compared with male controls. *Error bars* represent standard errors of the means; all *P* values are two-tailed (Reprinted from Brown et al. (2002), Copyright (2002), with the kind permission of Elsevier)

Males with CAH (aged 5–21 years) and male controls (aged 9–34) were also studied. Interestingly, in males affected by CAH, the 2D-to-4D ratio was smaller on both the left and the right hands compared to unaffected male controls. However, this did not reach statistical significance on the right hand. In addition, to adjust for a putative genetic influence, six male relatives without CAH were recruited to act as a further control group for six of the males with CAH. When the related unaffected males were compared to their male relatives with CAH, the latter displayed smaller 2D-to-4D ratios on both the left and right hands. The significance was far higher than when the males with CAH were compared with unrelated male controls. Hence, individuals with CAH demonstrate smaller 2D-to-4D ratios than controls, and this supports the hypothesis that intrauterine androgens affect the 2D-to-4D ratios. However, in adults, the correlation between sex and the right-hand 2D-to-4D ratio is quite low, with an approximately 60% overlap between males and females in a homogeneous population. Moreover, in a mixed-race population, race accounts for more variation in the 2D-to-4D ratio than sex. Populations of African descendents have lower 2D-to-4D ratios at all ages, but considerable differences have also been reported among ethnic groups usually considered to be racially comparable (McIntyre 2006).

146.11 Clitoral Size

Newborn girls with classic CAH present with virilized external genitalia, including varying degrees of clitoral hypertrophy, 'scrotalization' of the labial skin, and different degrees of posterior fusion of the labiae majorae, thus forming a common urogenital sinus of varying length. Genital surgery is usually performed to create female-looking genitalia. A number of different procedures have been used for surgery of clitoral hypertrophy. Historically, clitoral amputation was commonly performed, but due to the increased awareness of the importance of the clitoris for sexuality in females, more sophisticated techniques have been developed. Nowadays, a great deal of effort is made to provide a satisfactory cosmetic result without surrendering sensation and vascularity of the clitoris by modern methods of genital surgery, which include sparing as much as possible of the dorsal nerves.

Nordenskjöld et al. reported on 62 adult women with CAH, 62% of whom had had some kind of clitoroplasty performed (Nordenskjöld et al. 2008). The length of the clitoris was correlated with the surgical intervention and, unless amputated, it was longer than a normal-sized clitoris. In those not operated upon, the mean length was 28.8 mm (range 10–50 mm), which is considerably longer than normal (normal-sized clitoris, 16 ± 4.3 mm). A normal-sized clitoris was found in 17 women (six not operated upon). In eight women, the clitoris was small (defined as <11.5 mm) (four amputated, one not operated upon). In 36 women, the clitoris was larger than normal (defined as >20.5 mm) and 17 of them had had no clitoral surgery performed.

146.12 Testicular Adrenal Rest Tumors

The adrenals and testicles are developed in close vicinity during fetal life, and adrenal cells are present in normal testicles. Due to the increased ACTH levels in CAH, these cells can be stimulated and grow so as to result in benign testicular tumors typically located in the rete testis, causing obstruction of the seminiferous ducts and impaired fertility. Previously, testicular adrenal rest tumors were considered rare in CAH; however, new data have changed that perception. Stikkelbroeck et al. demonstrated one or more testicular tumors in 16 (94%) of the 17 males with CAH, examined by ultrasonography (Stikkelbroeck et al. 2001). In only six males (35%) were the tumors palpable. These findings are in agreement with our own experience.

146.13 Application to Other Areas of Health and Disease

Individuals with CAH demonstrate many special features which have to be accounted for when comparing with controls. For example, adult males and females affected by CAH are, on the average, considerably shorter than age- and sex-matched controls, which makes many comparisons incorrect if not adjusted for the difference in height. Moreover, in diseases with high or low androgen exposure, especially in females, this could render approximations of BMI as a measurement of obesity incorrect as the proportion of muscle mass is being under- or overestimated. DXA measurements using special software for body composition are therefore a more satisfactory technique. However, it is not just the present or the total lifetime exposure to androgens that is of importance. In fact, the intrauterine androgen exposure may be even more important as it affects the development of the brain and results in a more masculinized behavior. The change in behavior and interests may be of importance for future selection of work and leisure activities affecting muscle-mass development.

An indirect method of assessing intrauterine androgen exposure is to measure the 2D-to-4D ratio. Disorders of increased androgen exposure during fetal life include, apart from CAH, androgen-producing tumors in the mother, androgen intake by the mother, and girls with male co-twins. Disorders of decreased androgen exposure during fetal life include Turner syndrome (in which exposure to androgens and estrogen is exceptionally low as a result of undifferentiated gonads), complete androgen insensitivity syndrome (CAIS, 46 XY karyotype; testicles are developed but do not descend and testosterone levels are normal to high, but the phenotype is female due to malfunctioning androgen receptors), etc. Some of the anthropometric and other features of CAH could also be due to long-term exposure to supraphysiological doses of glucocorticoids. Long-term exposure to supraphysiological doses of glucocorticoids is also seen in Addison's disease, pituitary insufficiency, in some patients with bronchial asthma, in patients with rheumatologic, hematologic, nephrologic, dermatologic, and neurologic diseases, along with patients after different kinds of organ transplantation. Endogenous exposure to glucocorticoids can be seen in Cushing's syndrome.

146.14 Guidelines

In CAH growth, both height and weight measurements are the most powerful tools we have for assessing the effect of treatment at follow-up during childhood and adolescence.

We recommend that weight and height be measured at every visit, which should occur every 3 months to yearly, depending on the age of the patient and the severity of CAH.

As in many other conditions, BMI is not the optimal tool for estimating body fat. Waist circumference and the waist-to-hip ratio are better techniques for estimating, at least, central obesity. DXA measurement of body composition with adjustments for height constitutes a more advanced method which is quite in widespread use. However, if not available, bioelectrical impedance analysis or skinfold thickness measurements could be alternatives.

In adults, a waist and hip circumference measurement should be done yearly, and, we believe, a DXA scan for body composition, if available, should be done at least every 5 years, and usually bone mineral density is measured at the same time. If DXA measurements of body composition are not available, alternative methods might be used, such as skinfold thickness or, preferably, bioelectrical impedance analysis. The results of these anthropometric measurements should be used primarily to adjust the glucocorticoid dose, and also for implementing lifestyle changes.

The ratio of the length of the index finger to the ring finger can be used as an estimate of intrauterine androgen exposure, although mainly at the group level.

Summary Points

- Individuals affected by CAH are exposed to high intrauterine levels of androgens, that is, male hormones. There is a good genotype-to-phenotype correlation. Females are born with different degrees of virilization of the external genitalia (ambiguous genitalia) depending on the severity of the disease with, among other things, clitoral hyperplasia, and both males and females require glucocorticoid supplementation in most cases for survival.
- Increased androgen levels during childhood lead to increased growth and also to accelerated bone age and therefore compromised final height.
- Supraphysiological glucocorticoid doses may lead to short stature in adulthood, obesity, insulin resistance, high liver function test level, osteoporosis, and fractures.

- Many patients with CAH will demonstrate central obesity and other indices of increased body fat mass, but at least women aged ≥30 years with CAH will also demonstrate increased muscle mass. Waist-to-hip ratio and DXA measurements with body- composition assessments are good techniques for estimating fat and muscle mass.
- Measuring the second-to-fourth finger ratio may be a way to estimate prenatal androgen exposure. The ratio is usually decreased in both males and females with CAH compared to the general population.

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Chapter 147
Changes in Anthropometric Measures in Systemic Lupus Erythematosus

Chi Chiu Mok

Abstract Systemic lupus erythematosus is a chronic multi-systemic autoimmune disease that predominantly affects women of reproductive age. Despite the emergence of novel therapeutics, the main stay of systemic lupus erythematosus treatment remains systemic glucocorticoids. High-dose or long-term glucocorticoid administration is associated with bone demineralization and a profound change in body composition. Chronic use of glucocorticoids in children and adolescents retards growth velocity and leads to short adult body height. Although elevation of proinflammatory cytokines as a result of disease activity, imbalanced nutrition, lack of physical activity due to musculoskeletal complications, avoidance of sunshine and hormonal disturbances may contribute to a loss of lean body mass and bone mineral content, the chief mechanism for a change in fat distribution, abdominal obesity, loss of muscle mass and growth retardation in patients with systemic lupus erythematosus is glucocorticoid therapy. This chapter summarizes data on measurement of fat and lean body mass in patients with systemic lupus erythematosus and its relationship with bone mineral density.

Abbreviations

Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ATPIII	Adult Treatment Panel III
BMI	Body mass index
DXA	Dual energy X-ray absorptiometry
HDL	High density lipoprotein
hsCRP	High sensitivity C-reactive protein
IGF-1	Insulin growth factor 1
IL-6	Interleukin-6
NCEP	National Cholesterol Education Program
SLE	Systemic lupus erythematosus
TNF-α	Tumor necrosis factor α

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_147,

147.1 Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that mainly affects women of reproductive age. The disease may affect multiple organs and systems, with new clinical features developing at different time points of the disease course, which is characterized by periods of exacerbation and remission. The clinical manifestations of SLE are heterogeneous and no two patients are exactly alike. A recent cluster analysis (To et al. 2009) of the clinical features of 1082 SLE patients who were observed longitudinally for 8 years identified three patterns of clinical manifestations – predominant musculoskeletal and dermatological features (best prognosis), predominant and serious renal disease associated with higher mortality and heterogeneous clinical manifestations involving multiple systems.

Because of the clinical and immunological heterogeneity of the disease, the course and prognosis of SLE is largely unpredictable. Although certain environmental factors such as medications, ultraviolet light, hormonal changes and administration of exogenous estrogens have been implicated for triggering disease flares, no identifiable causes can be found in the majority of cases (Mok and Lau 2003). Patients with major organ involvement, recurrent disease relapses and refractory disease manifestations are associated with a poorer prognosis. There is still no cure for this chronic, disabling and potentially fatal disease, although newer medications are able to reduce the risk of disease flares with lower incidence of toxicities.

Management of SLE depends on the nature, severity and reversibility of organ manifestations, and their underlying pathology. Mild manifestations of SLE such as arthritis and dermatological disease usually respond to topical corticosteroids, sun-screening and antimalarials. Systemic glucocorticoids and more aggressive immunosuppressive treatment are indicated for major organ manifestations such as glomerulonephritis and neuropsychiatric disease. Despite the emergence and availability of newer immunosuppressive and biological agents such as mycophenolate mofetil, tacrolimus, rituximab, belimumab and abatacept (Mok 2010), glucocorticoid-based regimens remain the mainstay of treatment for SLE, both for initial and maintenance therapy.

However, the use of glucocorticoids is associated with a number of short-term and long-term adverse effects, some of which are related to the dosage and duration of administration. Long-term use of glucocorticoids is a major cause of organ damage in SLE. According to one observational study, the cumulative prednisolone dose was significantly associated with the development of osteoporotic fractures, symptomatic coronary artery disease and cataract in patients with SLE (Zonana-Nacach et al. 2000). In addition to chronic glucocorticoid therapy, renal insufficiency, premature menopause, avoidance of sun exposure, disabling arthritis and myopathy, the use of other medications such as anticoagulants and anticonvulsants also contribute to low bone mass and increased risk of fragility fractures in SLE patients (Lee and Ramsey-Goldman 2005). Other well recognized side effects of glucocorticoids are increase susceptibility to infections, reduction of growth velocity in children, proximal myopathy, impaired glucose tolerance, hypertension, hyperlipidemia, mood disorders and avascular bone necrosis.

147.2 Glucocorticoids and Body Composition

Glucocorticoid therapy induces the classical cushingoid body phenotype which comprises central obesity, prominence of dorsal, temporal, and supraclavicular fat pads and moon face and thin limbs. The pathophysiology is not fully understood, but lipid mobilization in the adipose tissues with redistribution of fat in the abdominal viscera appears to be the main mechanism (Bjorntorp 1997).

Lipid mobilization depends on both lipolysis and re-esterification of free fatty acids in the adipose tissues. In the presence of insulin, glucocorticoids inhibit catecholamine-induced lipolysis but promote the lipolytic effect of growth hormone (Ottosson et al. 2000). Moreover, glucocorticoids reduce re-esterification in adipose tissues by inhibiting glucose transport, leading to an increase in circulating free fatty acids (Divertie et al. 1991). The density of glucocorticoid receptor seems to be higher in intra-abdominal (visceral) than in subcutaneous adipose tissues (Rebuffe-Scrive et al. 1985) and this may explain the regionally specific effects of glucocorticoids, depending on the degree of perturbation on lipid accumulation and mobilization in various body sites. Adipose tissue biopsies from patients with Cushing's syndrome showed enlargement of abdominal fat cells with low lipolytic but high lipoprotein-lipase activity, which may explain the accumulation of fat in the abdomen after glucocorticoid exposure (Rebuffe-Scrive et al. 1988).

Besides inducing a centripetal body fat redistribution, glucocorticoids also lead to an increase in body weight (and hence body mass index) because of their stimulatory effect on appetite. In some individuals, particularly children, more generalized instead of central obesity develops after glucocorticoid treatment (Yanovski and Cutler 1994). Moreover, glucocorticoids increase protein catabolism which results in loss of proximal muscle mass. Thus, the use of high-dose or long-term glucocorticoids is the main cause for the reduction of bone mineral density and change in body composition observed in patients with SLE.

Long-term glucocorticoid treatment alters the pulsatility and secretion of growth hormone by increasing the somatostatin inhibitor tone (Simon 2007). Glucocorticoids also decrease the expression of growth hormone receptors on hepatocytes, leading to lower insulin growth factor-1 (IGF-1) mRNA levels (Mehls et al. 1993). In vitro studies have also shown that glucocorticoids may exert direct inhibitory effects on the growth plates by inhibiting chrondrocyte proliferation and transcription of the growth hormone receptor, resulting in decreasing production of IGF-1 (Jux et al. 1998). Administration of glucocorticoids in children and adolescents may lead to retardation of growth velocity and short adult height. The severity of growth retardation depends on the age at the time glucocorticoid treatment, severity of the underlying diseases and duration and dose of glucocorticoids received (Shamir et al. 2007).

147.3 Anthropometry and Body Composition in SLE

In addition to the untoward effects of chronic glucocorticoid administration, disease-specific factors may also contribute to a change in anthropometric measures and body composition in patients with SLE. Though uncommon, chronic active arthritis similar to that of rheumatoid arthritis is a problem in a subset of SLE patients. Chronic arthritis leading to joint deformity and disuse atrophy may lead to a loss in lean body mass. The levels of cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 are elevated in patients with active SLE compared to normal controls (Gomez et al. 2004; Chun et al. 2007). There is evidence that elevated TNF-α levels is linked to the loss in fat-free mass in disease states such as rheumatoid arthritis (Walsmith et al. 2004). IL-6 stimulates formation and activity of the oesteoclasts and is unfavorable for bone mineral density (Manolagas 1995). Moreover, TNF-α and IL-6 may also contribute to growth retardation and hence short adult height in children by inhibiting IGF-1 transcription via the growth hormone receptors and/or chrondrocyte proliferation in the growth plates (Shamir et al. 2007). On the other hand, insufficient physical activity due to chronic joint problem, imbalanced nutrition, lack of outdoor activity to avoid sunshine and hormonal disturbances as a result of active SLE and its treatment may also result in a change of fat and lean body mass and loss of bone mineral content.

Table 147.1 Summary of studies on body composition in patients with systemic lupus erythematosus

	Kipen et al. (1998)	Kipen et al. (1999)	Lilleby et al. (2007)	Mok et al. (2008)
Study design	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal
Number of patients	82	28	68	29
Ethnicity	Mainly Whites	Mainly Whites	93% Whites	All Chinese
Age, years	41	34.4	26.2	39.7
Sex	All women	All women	75% women	83% women
Disease duration, years	7.1	6.8	10.4	6.7
Organ damage	39%	25%	–	–
Glucocorticoid exposure	70%	64%	93%	52%
Cumulative prednisone dose, grams	12.8	9.6	17.0	–
Menopause	37%	–	–	29%
Chronic smoking	–	43%	19%	3%
Body weight, kg	64	–	66.4	53.7
Body height, m	1.6	–	1.65	1.57
Body mass index, kg/m^2	24	24.53	23.8	21.8
Fat mass, kg	24.3	23.82	23.25	14.81
Fat-free mass, kg	39.96	41.04	–	–
Lean mass, kg	–	–	39.71	35.77
% total body fat	–	–	35.3%	27.6
Total BMD, g/cm^2	1.12	1.144	–	1.055
Total BMC, kg	–	–	–	1.874

BMD bone mineral density; *BMC* bone mineral content

Besides measuring bone mineral density, the dual energy X-ray absorptiometry (DXA) scan enables precise measurement of body composition in terms of fat-free and fat body mass by passing photons of two levels of energy through the body (two-compartment model) (Deurenberg-Yap et al. 2001). Fat-free body mass can further be broken down into lean soft tissue mass and bone mineral content (three-compartment model). A number of cross-sectional and longitudinal studies have demonstrated the substantial effect of glucocorticoids on body composition in patients with various medical diseases including SLE (Azcue et al. 1997; Formica et al. 1997; Kipen et al. 1998). In most of these studies, an increase in fat body mass but a reduction in lean body mass and bone mineral content was reported.

There are much fewer studies which specifically target body composition in patients with SLE (Table 147.1). Kipen et al. (1998) performed a cross-sectional DXA study on the body composition of 82 predominantly Caucasian female SLE patients, 30 of whom were post-menopausal, with a median duration of menopause of 8.5 years. The median age of these patients was 41 years and the median SLE duration was 7.1 years. Seventy percent of these patients had been exposed to glucocorticoids at some stage of their disease but only 39% patients had damage scores as measured by the SLE damage index, indicating that this sample of patients had relatively mild disease manifestations. The median cumulative dose of corticosteroids received by the patients was 12.8 g and the median body mass index was 24 kg/m^2. There were no control subjects in this study. Using univariate linear regression analysis, it was demonstrated that a reduced fat-free mass was significantly associated with higher damage scores, a history of exposure to corticosteroids and increasing age. In a stepwise multiple linear regression model, fat-free body mass was significantly associated with total body, lumbar spine and femoral neck bone mineral density. Thus, older SLE patients with more serious disease that warrants systemic glucocorticoid treatment and more organ complications are more prone to a loss in fat-free mass and bone mineral density.

Twenty-eight SLE patients who participated in this study were followed longitudinally for serial changes in body composition and bone mineral density (Kipen et al. 1999). The mean age of this

cohort of patients was 34.4 years and the mean follow-up duration was 3.2 years. Seventeen (61%) patients were exposed to corticosteroids during the observation period and the mean daily dose of prednisolone was 12.0 mg. Over the 3-year follow-up period, a significant increase in body mass index and fat-free body mass was observed in these patients. In patients who were exposed to corticosteroids, only the increase in fat-free mass was statistically significant. A stepwise linear regression analysis showed that disease activity of SLE was associated with an increase in body mass index and fat body mass. In contrast, exercise was associated with an increase in fat-free mass. Older age at baseline and smoking were unfavorable factors for the change in whole body bone mineral density.

Lilleby et al. (2007) studied the body composition and lipid and lipoprotein levels in 68 childhood-onset patients with SLE and compared those with 68 age- and gender-matched healthy controls. The mean age of the SLE patients was 26.2 years and the mean SLE duration was 10.4 years. The mean body mass index was 23.8 kg/m^2. Corticosteroids were used in 93% of these patients and the mean duration of corticosteroid use was 36 months. This cross-sectional case-control study demonstrated that SLE patients had significantly higher percentage total body fat but lower lean body mass than healthy controls. The cumulative dose of corticosteroids was found to be independently associated with the percentage total body fat in a multivariate regression model. Disease activity score of SLE, physical activity and dietary intake was not associated with body fat. Compared to controls, patients with SLE had lower high density lipoprotein (HDL) cholesterol and apolipoprotein A1 (apo A1) levels, but a higher mean apo B/apo A1 ratio.

Recently, we also studied the serial changes in body composition and bone mineral density over 6 months in 29 SLE patients who were treated with high-dose glucocorticoids for various disease manifestations (Mok et al. 2008). The mean age of this cohort of patients was 39.7 years. Eight-three percent of these patients were women and 29% of them were postmenopausal. The mean duration of SLE was 80.1 months. Fourteen patients (48%) were glucocorticoid-naive. The mean maximum daily dose of prednisolone administered was 32.9 mg and the mean cumulative prednisolone dose in 6 months was 2.7 g. Except for calcium supplement and vitamin D, none of these patients had ever received bisphosphonates or other anti-osteoporotic medications.

After 6 months' glucocorticoid treatment, a significant drop in bone mineral content of the trunk (–5.0 ± 2.2%; $p = 0.04$) and the whole body (–1.2 ± 0.4%; $p = 0.002$) compared to baseline was observed in our cohort of patients. Moreover, the bone mineral density of the hip (–1.7 ± 0.6%; $p = 0.006$) and the whole body (–0.7 ± 0.3%; $p = 0.01$) also dropped significantly. The fat mass of the trunk (+14.5 ± 4.1%; $p = 0.001$) and the limbs (+10.0 ± 3.2%; $p = 0.004$) of the patients increased significantly, which was associated with a non-significant drop in lean mass of the trunk (–3.3 ± 1.8%; $p = 0.08$) and limbs (–0.8 ± 2.4%; $p = 0.75$) (Figs. 147.1 and 147.2). The fat content (% fat) of the trunk and whole body also increased significantly from baseline to month 6. The changes in whole body bone mineral content correlated significantly with age and changes in total fat body mass but not with lean mass, sex, body mass index, smoking, cumulative prednisolone dose or changes in bone mineral density. In this prospective study, it was demonstrated that in patients with SLE, high-dose glucocorticoid treatment led to an early and rapid drop in bone mass, which was more serious in older patients and correlated with an increase in body fat. Table 147.2 summarizes the essential findings of these studies.

147.4 Abdominal Obesity and Metabolic Syndrome in SLE

Patients with SLE are prone to premature atherosclerosis. This is caused in part by an increased prevalence of traditional vascular risk factors and other disease- or treatment- related factors such as antiphospholipid antibodies, chronic glucocorticoid therapy and elevation of inflammatory markers

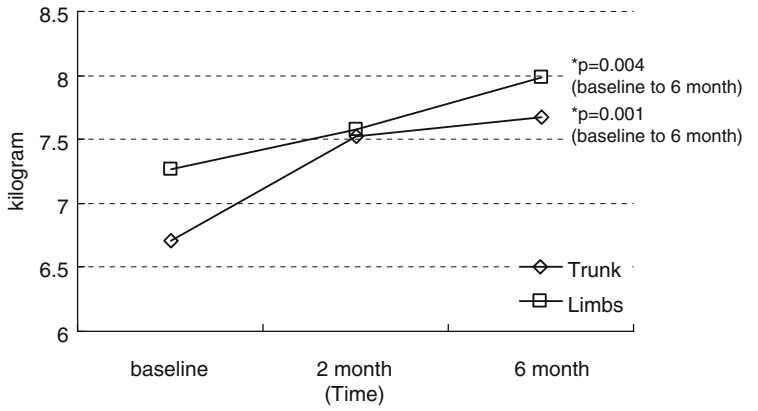

Fig. 147.1 Changes in fat mass of the trunk and limbs in SLE patients receiving high-dose glucocorticoids

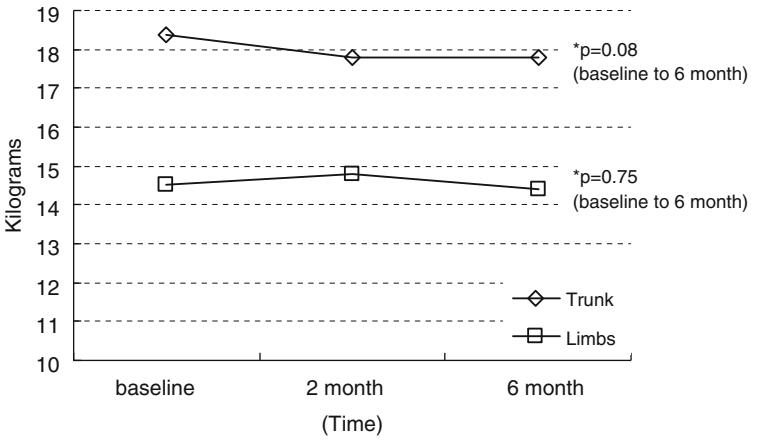

Fig. 147.2 Changes in lean mass of the trunk and limbs in SLE patients receiving high-dose glucocorticoids

Table 147.2 Summary of the findings in studies involving body composition in systemic lupus erythematosus

	Study design	Study duration	Findings
Lilleby et al. (2007)	Case-control	–	SLE patients had significantly higher body fat content but lower lean body mass than age-matched healthy controls. In SLE patients, the cumulative glucocorticoid dose was independently associated with body fat content
Kipen et al. (1999)	Longitudinal	3.2 years	Significant increase in body mass index and fat-free body mass in SLE patients was noted. There was also increase in fat body mass, but the change was not significant. Disease activity of SLE was associated with an increase in body mass index and fat mass. Physical exercise was associated with an increase in fat-free mass. Older age at baseline and smoking were unfavorable factors for a drop in whole body bone mineral density
Mok et al. (2008)	Longitudinal	6 months	Significant drop in bone mineral content (total body, trunk) and bone mineral density (total body and hip) after high-dose glucocorticoid treatment was demonstrated. Body fat mass and fat content also increased significantly. Drop in total body bone mineral content correlated with increasing age and increase in fat mass

SLE systemic lupus erythematosus

and cytokines such as high sensitivity C-reactive protein (hsCRP), homocysteine, IL-6 and TNFα (Mok 2006). The metabolic syndrome is a constellation of risk factors that increase the risk for type II diabetes mellitus and cardiovascular and cerebrovascular diseases. These risk factors include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure and insulin resistance (Grundy et al. 2005). A number of case control studies have reported an increased prevalence of the metabolic syndrome in SLE patients of different ethnic backgrounds (Chung et al. 2007; Bultink et al. 2008; Negron et al. 2008; Sabio et al. 2008; Bellomio et al. 2009; Vadacca et al. 2009; Mok et al. 2010) (Table 147.3).

The interplay among disease activity, treatment, obesity, metabolic syndrome and atherosclerosis is complex and intriguing. Disease complications such as renal impairment and glucocorticoid treatment lead to increased prevalence of impaired glucose tolerance, hypertension, dyslipidemia and visceral obesity, which in turn increases the incidence of metabolic syndrome in SLE patients. On the other hand, as a result of active SLE proinflammatory cytokines such as TNFα and IL-6 reduce the activity of insulin, inhibit insulin receptor autophosphorylation and signal transduction, thereby promoting insulin resistance and leading to hyperglycemia, compensatory hyperinsulinemia and dyslipidemia (Pereira et al. 2009). In patients with visceral obesity, hypertrophic adipocytes and the accumulation of macrophages in abdominal fat may be a source of production of proinflammatory cytokines that aggravate the degree of insulin resistance (Sidiropoulos et al. 2008).

Abdominal obesity, defined as a waist circumference of >102 cm in men and >88 cm in women by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), is one of the criteria for the diagnosis of the metabolic syndrome (Grundy et al. 2005). In Asians, the criterion for abdominal obesity is modified to >90 cm in men and >80 cm in women (Heng et al. 2006). In various case-control studies, an increase in waist circumference or proportion of patients meeting the central obesity criteria of the metabolic syndrome is demonstrated in patients with SLE. This is summarized in Table 147.3. Central obesity predisposes individuals to the metabolic syndrome and increases the risk of cardiovascular diseases. Thus, screening for central obesity and the metabolic syndrome may help identify a subset of patients in whom more rigorous control of vascular risk factors is warranted.

147.5 Summary and Clinical Implications

The take-home messages of this article are summarized in Table 147.4. There are very few case-control or prospective studies in the literature regarding body composition in patients with SLE. Although chronic arthritis and elevation of cytokines as a result of disease activity may contribute to a loss of lean body mass, the chronic use of systemic glucocorticoids is the main cause for a change in body composition in patients with SLE. Glucocorticoid use leads to a redistribution of body fat to the trunk and an overall increase in fat body mass. Central obesity is associated with insulin resistance and predisposes individuals to the metabolic syndrome. Although the increase in body weight may be beneficial for bone mineral density in the long-run because of its stimulatory effect on osteogenesis as a result of the corresponding increase in mechanical stress mediated by mass gravitational load on the skeleton, the overall effect of glucocorticoids on bone mineral density is negative. Glucocorticoids inhibit osteoblastogenesis, increase apoptosis of osteoblasts and suppress the activity of the osteoblasts, leading to a decrease in bone formation. Glucocorticoids also contribute to osteoporosis by prolonging the life span of the osteoclasts and hence enhancing bone resorption, reducing gastrointestinal absorption of calcium, increasing renal excretion of calcium and suppressing sex hormone production (Mazziotti et al. 2006). Patients with SLE have an early and rapid loss

Table 147.3 Summary of studies on central obesity and metabolic syndrome in systemic lupus erythematosus

Authors, year	Number of patients	Ethnicity	Mean age (years)	Sex	Waist circumference, cm	BMI, kg/m^2	Prevalence of the metabolic syndrome
Chung et al. (2007)	102	67% Whites	42	91% women	48% with high waist circumference	28 (24.1–33.2)	29.4%
Bultink et al. (2008)	141	70% Whites	39	All women	Not stated	25 ± 6	16%
Negron et al. (2008)	204	Hispanic	43.6	96.1% women	91% with high waist circumference	31.4 ± 6.5	38.2%
Sabio et al. (2008)	160	Spanish	30.9	89% women	86.3±13.5; 36% with high waist circumference	25.9 ± 5.3	20%
Bellomio et al. (2009)	147	Argentinian	37.2	89% women	49% with high waist circumference	Not stated	28.6%
Vadacca et al. (2009)	50	Whites	Not stated	All women	79 (64–118)	24.2	28%
Mok et al. (2010)	123	Chinese	47.9	93% women	37% with high waist circumference	17% with BMI ≥27 kg/m^2	16.3%

Values were expressed as mean ± standard deviation; brackets contain the upper and lower range of values
BMI body mass index

Table 147.4 Take-home messages

1.	Chronic glucocorticoid therapy leads to an increase in total body fat in patients with systemic lupus erythematosus
2.	High-dose glucocortioid contributes to an early and rapid drop in total bone mass despite an increase in fat mass in systemic lupus erythematosus
3.	Chronic glucocorticoid therapy is associated with catabolism of the skeletal muscles and a loss in lean body mass
4.	Chronic glucocorticoid therapy in childhood patients with systemic lupus erythematosus contributes to growth retardation and short adult height
5.	Bisphosphonates, calcium supplement and vitamin D should be routinely prescribed in patients with systemic lupus erythematosus receiving glucocorticoid therapy. The use of glucocorticoids should be judicious, with the adoption of lowest possible dose and duration of therapy that is adequate for the control of disease activity. Early institution of glucocorticoid-sparing agents should be considered
6.	Patients on chronic glucocorticoid therapy should be advised on a well-balanced diet and encouraged to perform weight-bearing exercises
7.	Systemic lupus erythematosus patients should be regularly screened for abdominal obesity and metabolic syndrome. More rigorous control of vascular risk factors is warranted in these patients
8.	Recombinant growth hormone treatment may be considered in selected children with systemic lupus erythematosus who receive long-term glucocorticoids

of total bone mass after treatment with high-dose glucocorticoids despite a significant increase in total fat mass and body mass index (Mok et al. 2008). Therefore, bisphosphonates should be routinely prescribed to SLE patients who are about to receive glucocorticoid therapy in order to alleviate the loss in bone mineral density. More vigorous preventive strategies are warranted in older patients receiving high-dose glucocorticoids and in those patients with early and more profound gain in body fat after glucocorticoid treatment. Central obesity and the metabolic syndrome should be screened so that more aggressive control of traditional vascular risk factors is warranted.

In addition to a deleterious effect on bone mineral density, the chronic use of glucocorticoids is also associated with an increase in protein catabolism in the skeletal muscles. This leads to a loss in lean body mass which is demonstrated in case-control studies (Kaji et al. 2006; Foster et al. 2004). SLE patients on chronic glucocorticoid therapy should be encouraged to perform weight-bearing exercises to strengthen their muscles and help improve their bone mineral density. The use of glucocorticoids in SLE patients should be judicious, with the adoption of the lowest possible dose that is adequate for the control of disease activity. Baseline and interval monitoring of bone mineral density should be undertaken during the course of glucocorticoid therapy. Glucocorticoid-sparing immunosuppressive agents should be considered early in the course of treatment to allow tapering of glucocorticoids.

Long-term glucocorticoid treatment in childhood and adolescence is associated with stunted growth and short adult height. In addition to the above measures, recombinant human growth hormone treatment may be considered in selected patients, in close collaboration with endocrinologists and pediatricians (Simon 2007).

147.6 Future Perspectives and Research Agenda

As emphasized in this review, the number of studies is too small to provide a clear view on the predisposing factors for a deleterious change of body composition in patients with SLE. Prospective studies involving larger cohorts of patients are needed in the future. Perhaps the changes in various parameters of body composition can be studied as a secondary end-point in multicenter randomized controlled trials of newer biological agents for the treatment of SLE. Moreover, the inter-relationship

Table 147.5 Research agenda

1. Prospective studies with larger cohorts of risk factors for deleterious changes in body composition in patients with systemic lupus erythematosus
2. Relationship among cytokines, hormones, lipid profile, body composition, central obesity and the metabolic syndrome in systemic lupus erythematosus
3. Interventional studies on the change in lean and fat body mass in patients with systemic lupus erythematosus e.g. exercise, hormonal therapy
4. Recombinant growth hormone therapy in high-risk pediatric patients with systemic lupus erythematosus receiving chronic glucocorticoid treatment
5. Newer glucocorticoid receptor agonists with fewer adverse effects on bone metabolism

among cytokines, hormones, lipid profile, change in body composition, central obesity and the metabolic syndrome in SLE patients has to be studied in more details. Interventional studies, such as the effect of exercise and hormonal replacement therapy on the change in lean and fat mass, quality of life, psychological well being and bone mineral density in patients with SLE receiving stable doses of gluccocorticoids, should be considered as one of main topics in future research agenda. Recombinant growth hormone therapy in children receiving long-term glucocorticoid for their SLE and who are at risk of short stature should be further explored. Finally, glucocorticoid receptor agonists with fewer side effects related to lipid and bone metabolism should be developed (Table 147.5).

Summary Points

- Elevation of cytokines due to disease activity, chronic arthritis leading to disuse atrophy, lack of physical activity, hormonal disturbances, avoidance of sunshine and imbalanced nutrition may contribute to a loss of lean body mass and bone demineralization in patients with SLE.
- The main cause for a profound change in body composition and low bone mineral density in SLE patients is chronic glucocorticoid treatment.
- Long-term glucocorticoid therapy leads to fat redistribution, increase in fat body mass, loss in muscle and lean body mass and reduction in bone mineral content.
- Central obesity and insulin resistance predisposes SLE patients to the metabolic syndrome and increased risk of atherosclerosis and cardiovascular complications.
- Glucocorticoid treatment in children and adolescents retards growth velocity and leads to short body height.
- Calcium, vitamin D and bisphosphonates should be routinely prescribed to patients with SLE who receive glucocorticoids. Abdominal obesity and the metabolic syndrome should be regularly screened, and more rigorous control of vascular risk factors is warranted. Recombinant human growth hormone may be considered in selected children who receive chronic glucocorticoid treatment.

Key Facts About Systemic Lupus Erythematosus

- Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease of unknown etiology that predominantly affects women of the childbearing age.
- SLE is clinically and immunologically heterogeneous.
- The main stay of treatment of SLE is systemic glucocorticoids, particularly for major and serious organ manifestations.

- Active disease with persistent elevation of cytokines, long-term use of glucocorticoids and disease-related complications such as renal disease predispose SLE patients to central obesity, insulin resistance and increased prevalence of traditional vascular risk factors, which in turn contributes to accelerated atherosclerosis and increased risk of cardiovascular complications.
- Chronic elevation of proinflammatory cytokines, the presence of the antiphospholipid antibodies and chronic renal insufficiency also increases the risk of premature atherosclerosis and vascular thrombosis in patients with SLE.

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Chapter 148
Anthropometric Measurement-Based Estimates of Body Water in Children on Peritoneal Dialysis

B.Z. Morgenstern

Abstract Total body water (TBW) is a critical body component in healthy children and those with disease, particularly those with kidney failure. There are gold standard methods to measure TBW directly, but they are expensive and cumbersome. Some require exposure to ionizing radiation. The ability to accurately and precisely estimate TBW from anthropometric data offers an opportunity to be more cognizant of TBW. Such estimates have been published and updated over the past 50 years, and are reviewed. They each perform well in the subjects in which they were developed, but do not seem to work as well when applied to different populations. An aggregate approach may be the most precise way to estimate TBW based upon anthropometric measures.

Estimating TBW, accepted to also be the volume of distribution of urea, in patients on dialysis is also emphasized. The measure of dialysis adequacy, *Kt*/*V* requires the ability to estimate or measure *V*, which is essentially TBW. For patients on peritoneal dialysis, *V* must be estimated to determine *Kt*/*V*. TBW estimating formulas developed in healthy children do not perform well at all in children on peritoneal dialysis. Formulas to estimate TBW in children on PD have been developed. They have been validated in a separate cohort of children. Still, these formulas are not precise in children who are at the extremes of hydration or degree of body fat. The ideal approach to estimate TBW in children on PD is yet to be determined.

Abbreviations

BIA	Bioimpedance analysis
BSA	Body surface area
CKD	Chronic kidney disease
D_{FFM}	Density of fat free mass
DEXA	Dual energy X-ray absorptometry
DXA	Dual X-ray absorptometry
HD	Hemodialysis
Ht	Height
Kt/*V*	Clearance × time/volume of distribution: a number used to dialysis treatment adequacy
PD	Peritoneal Dialysis

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_148,

TBW Total body water
Wt Weight

148.1 Introduction

Many chapters of this text have already established the importance of an understanding of body compartments in the greater understanding of human physiology, pathophysiology and in therapeutics. An ability to either measure or rapidly estimate with reasonable accuracy total body water (TBW) can have practical applications relating to parenteral fluid therapy (Winters 1973) or dialysis (AJKD 2006; Wells 2008). Previous chapters have described the various methods currently available to directly measure TBW (El-Bishti 1981, 1996; Davies 1997; Thomas 1998). These include the measurement of distribution of 'heavy' water (either D_2O or H_2O^{18}), bioimpedance analysis (BIA), and estimates from anthropometrically determined fat mass. The accepted 'gold standard' for measurement of TBW is the use of heavy water. Although not difficult to perform and free from radiation exposure, studies using heavy water are time consuming and costly. BIA is an accepted method, but there are some important caveats to performing studies in this manner, and sizable variations in the results are seen when compared with the heavy water (Thomas 1998). Given the logistical hurdles associated with the application of precise techniques, it is not surprising that estimates of TBW based upon simple and reliable body measures have been sought.

148.2 Key Facts Regarding Total Body Water Estimates in Children (Table 148.1)

148.3 TBW Estimates in Healthy Children

Estimates of TBW in children based upon body size have been published many times over the past half-century (Edelman 1952; Mellits 1970; Morgenstern 2002; Chumlea 2005; Wells 2005; Sen 2009). The degree of precision seems to decrease over time, likely due to secular trends in fatness seen over the same time period (Wells 2005). These prediction equations, as one might predict, are age and sex dependent. They tend to include basic measures only, specifically height and weight, and do not usually include anthropometric measures used to estimate fat mass. Not surprisingly, they tend to be most inaccurate at extremes of obesity, where the weight of the fat mass, which contains less water, obscures the estimates of TBW. As discussed in other chapters, sex differences become more pronounced after puberty, when lean body mass in males tends to increase more rapidly than in females and fat mass increases more rapidly in females.

Table 148.1 Key facts regarding estimates of total body water in healthy children based upon anthropometric measures

TBW can be estimated for populations of healthy children based upon simple anthropometric measures.
TBW estimates relative to body size have changed over the past three decades, likely due to a secular increase in adiposity.
TBW is most accurately estimated by using an aggregate value based upon multiple estimating formulas.
TBW linearly relates to body surface area via the anthropometric parameter height × weight.

Key facts regarding estimates of total body water in healthy children based upon anthropometric measures

Until the end of the twentieth century, the most widely accepted estimating equations for TBW were those of Mellits and Cheek (Mellits 1970). These are linear equations developed from studies of normal, healthy, and non-obese children and young adults. The equations are:

$$\text{Boys,} \quad \text{ht} < 132.7\ \text{cm} = -1.927 + (0.465 \cdot\ \text{wt}) + (0.045 \cdot\ \text{ht})$$
$$\text{Boys,} \quad \text{ht} > 132.7\ \text{cm} = -21.993 + (0.406 \cdot\ \text{wt}) + (0.209 \cdot\ \text{ht})$$
$$\text{Girls,} \quad \text{ht} > 110.8\ \text{cm} = 0.076 + (0.507 \cdot\ \text{wt}) + (0.013 \cdot\ \text{ht})$$
$$\text{Girls,} \quad \text{ht} > 110.8\ \text{cm} = -10.313 + (0.252 \cdot\ \text{wt}) + (0.154 \cdot\ \text{ht})$$

It can be seen that the breakpoints (where the slope of the relationships between height, weight, and TBW changed) differed for boys and girls (by 21.9 cm of height). There is no clear age dependence in the data, but the breakpoints can be viewed as a surrogate for age.

The original data of Mellits and Cheek were based upon studies performed on 236 children. Morgenstern et al. (2002), identified an additional 101 children who had TBW measures reported in the literature, including 71 infants. They reanalyzed the pooled TBW results and developed a series of estimates which were again age and sex based. Their equations were:

$$\text{Infants} \quad 0-3\ \text{month}\,(n=71)\text{TBW} = 0.887 \cdot\ (\text{Wt})^{0.83}$$
$$\text{Children} \quad 3\ \text{months to}\ 13\ \text{years}\,(n=167):$$
$$\text{TBW} = 0.0846 \cdot\ 0.95^{[\text{if female}]} \cdot\ (\text{Ht} \cdot\ \text{Wt})^{0.65}$$
$$\text{Children} > 13\ \text{years}\,(n=99):$$
$$\text{TBW} = 0.0758 \cdot\ 0.84^{[\text{if female}]} \cdot\ (\text{Ht} \cdot\ \text{Wt})^{0.69}$$

Not surprisingly, these equations fit better for TBW estimates in infants, but did not otherwise perform better than the equations of Mellits and Cheek (Morgenstern 2002). It should be noted that sex was not reported in 45% of the infants identified in their literature search, but, statistically, it did not impact the precision of the estimate when included in their model. Likewise, length also had no statistical impact on TBW in infants.

Subsequently, three additional reports have been published that assess the accuracy of anthropometric-based estimates of TBW. The most recent report of Sen et al. (2009) (Fig. 148.1) demonstrated that the estimates based upon the equations published by Morgenstern were more precise than those published by Mellits and Cheeks in a population of South Asian children. It is possible that the two prediction equation sets (those of Mellits and those of Morgenstern) worked well because both of those data sets were based upon measures in children from the 1970s and 1980s. Children in that era may have had the same degree of adiposity as children from South Asia have currently.

Two papers from more Western populations (as compared with the South Asian population in Sen's paper), where the secular increase in adiposity is more pronounced, did not demonstrate very precise performance by either set of prediction equations (Chumlea 2005; Wells 2005). The Chumlea study subjects were from southwestern Ohio in USA (the Fels study), whereas those of Wells were from Cambridge in the UK.

Chumlea (Chumlea 2005) developed the following series of estimating equations:

$$\text{Boys}: \text{TBW} = -25.87 + 0.23\,(\text{stature}) + 0.37\,(\text{weight})$$
$$\text{Girls}: \text{TBW} = -14.77 + 0.18\,(\text{stature}) + 0.25\,(\text{weight})$$

In their cross-validation analysis, these equations yielded a pure error mean of 3.6 liters for boys. In these children, the Morgenstern equations led to a pure error of 8.15 L, whereas the equation of Mellits yielded a pure error of 4.73 L. In girls, the Chumlea's model's pure error was 2.43 L, Morgenstern's was 5.76 L, and Mellits 2.87 L. The authors do not mention whether they evaluated a (ht × wt) parameter in their modeling.

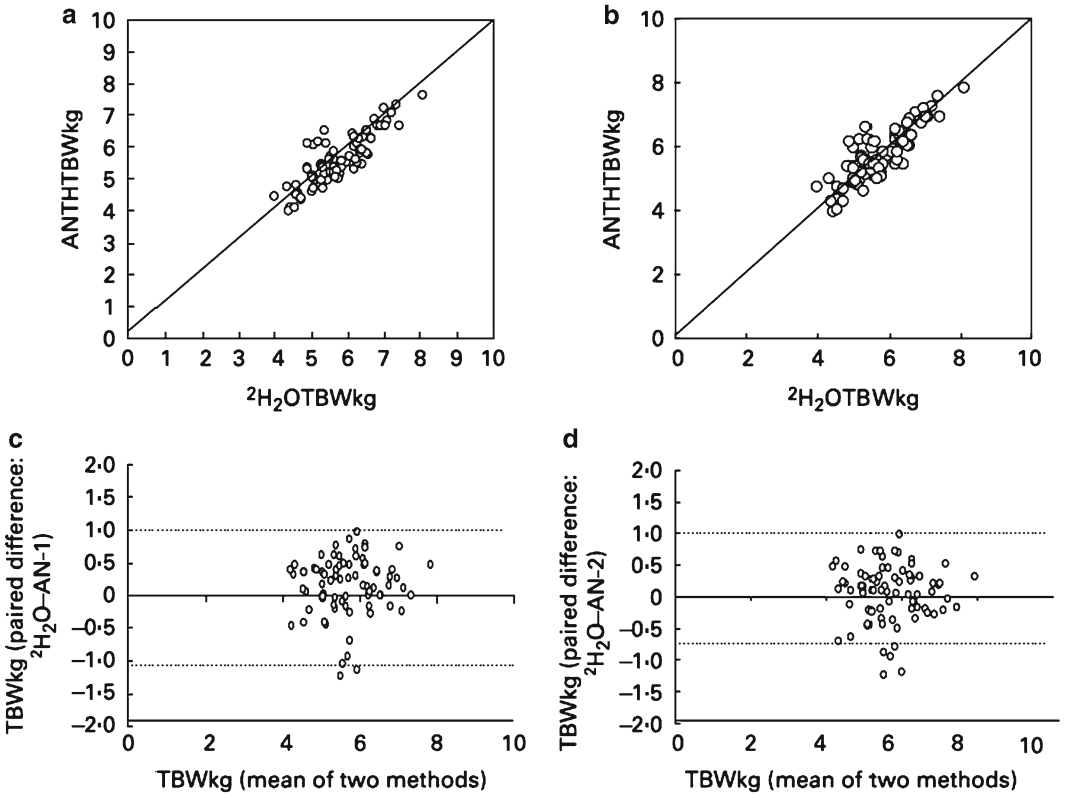

Fig. 148.1 Comparison of two TBW-estimating formulas. (**a** and **b**) TBWkg: Individual data points comparing values derived by the reference method (Deuterium water (D_2O)) with the anthropometric estimating equations plotted along the 'line of identity'. ANTHTBWkg = TBW in kg derived by the Mellits and Cheek equations on the left graph and the Morgenstern and Mahoney on the right graph. $2H_2O$TBWkg = TBW measured by D_2O. (**c** and **d**) Bland–Altman plots of the difference in each participant between TBW derived by D_2O and the estimating formula plotted against average of the TBW by D_2O and each estimating formula. D_2O – Mellits and Cheek (graph on *left*): mean difference = 0.15, SD = 0.44, $p = 0.005$, D_2O – Morgenstern and Mahoney (graph on *right*): mean difference = 0.05, SD = 0.45, $p = 0.372$ (Adapted from Sen (2009). With permission)

Wells et al. (2005) reported on TBW measures on 672 subjects from 1990 to 2003. They evaluated the equations of Mellits and Morgenstern (but not those of Chumlea, as the papers appeared within months of each other) and an older prediction equation reported by Friis-Hansen (1957a, b). They also found that no equations performed well, again presumably due to increased adiposity in the study population. Average differences were 11.5% for Friis-Hansen, 4.0% for Mellits, and 7.0% for Morgenstern. Errors >15% were seen in 40% of subjects for Friis-Hansen, 14% for Mellits, and in 17% for Morgenstern. The overestimation was approximately twice as high in infancy. The Friis-Hansen and Mellits equations showed greater bias in girls.

Wells et al. reported their own prediction equations (Wells 2005), the difference between males and females being that females have, on average, 470 mL less TBW than boys of equal size and age. Again, the authors do not report on any effort to evaluate the (ht × wt) parameter:

$$\text{Boys}: \ln\text{TBW} = -2.952 + (0.551 \cdot \ln(\text{wt})) + (0.796 \cdot \ln(\text{ht}) + (0.008 \cdot \text{age(years)})$$

$$\text{Girls}: \ln\text{TBW} = -2.952 + (0.551 \cdot \ln(\text{wt})) + (0.796 \cdot \ln)\text{ht}) - 0.047 + (0.008 \cdot \text{age(years)})$$

One paper, from Quiterio et al. (2009), has compared two of the more contemporary prediction models presented above. The authors evaluated these models in 188 adolescent athletes. They not only compared the prediction equations of Wells and Morgenstern, but also evaluated prediction equations based on DXA, bioimpedance spectroscopy, and bioimpedance analysis. Using equations of Wells and Morgenstern, they observed large biases, wide limits of agreement, and significant trend lines, which made both estimate equations less valid than the other methods in predicting TBW in adolescent athletes.

The equations developed by Morgenstern overestimated TBW in the athletes. Quiterio et al. agreed with Wells (Wells 2005) that prediction equations derived in children from earlier generations systematically overestimate TBW measurements in contemporary infants and children, since children have become heavier and fatter, which altered the relation between anthropometry and TBW. They also postulated that the overestimation of TBW values from equations of Morgenstern might be related to the fact that the athletes were taller and heavier than the subjects evaluated by Morgenstern.

By contrast, using the Wells equations significantly underestimated TBW values. Quiterio et al. did not expect this result, as the athletes were heavier and taller than the nonathletes studied by Wells. The authors hypothesized that because the prediction equations used were developed in nonathletic children and adolescents, who were presumably normally hydrated, they may have had a different fat-free mass density (D_{FFM}) than the athletes they studied. They demonstrated that there is a significant association between D_{FFM} and the mean errors between non-reference methods and deuterium dilution values, for almost all methods.

They concluded that TBW estimates compared to a gold standard method were most accurately predicted using TBW calculated from the specific constants of fat-free mass hydration using DXA measures of fat-free mass. Bioimpedance analysis and bioimpedance spectroscopy were found to be valid and nonbiased, but revealed wide limits of agreement and therefore poor accuracy. Unfortunately, the 'best' predictor, DXA, requires exposure to ionizing radiation, which limits its ability to be used repetitively.

With regard to the ability to predict TBW based upon simple anthropometric measures, the issue remains unresolved. A meta-analysis combining all the data on TBW published after 1990 might be beneficial. As a part of that analysis, an assessment of the utility of a (Ht × Wt) parameter would be critical. Morgenstern (Morgenstern 2002, 2006) (Fig. 148.2) demonstrated a strong linear relationship between log-transformed TBW and log-transformed (Ht × Wt). Many estimates of body surface area, especially that of Mosteller (Mosteller 1987; Modha 2009), contain some variation on the parameter (Ht × Wt). There is some compelling logic that TBW might be more tightly associated with body surface area than height or weight independently, irrespective of the impact of other variables, such as adiposity and D_{FFM}.

Perhaps the ultimate solution to developing reasonable estimates of TBW in healthy children will be to take the approach advocated by Wells (Wells 2009) and use the 'wisdom of crowds'. In their elegant studies on 196 children, the standard error of the estimates was smallest with the lowest mean bias (0.11 L), when they used an aggregate prediction model composed of 12 different equations. This aggregate approach may be the optimal way to arrive at reasonably precise estimates for individual subjects (Fig. 148.3).

148.4 TBW Estimates in Children on Peritoneal Dialysis

The estimate of TBW in patients with chronic kidney disease (CKD) is an example wherein a special population serves as an exemplar of the greater whole. Patients with CKD are assumed to have disorders of hydration, but these can result in either excess or reduced levels of hydration. Even more specifically, patients on dialysis may manifest greater extremes of over- or under-hydration. In addition,

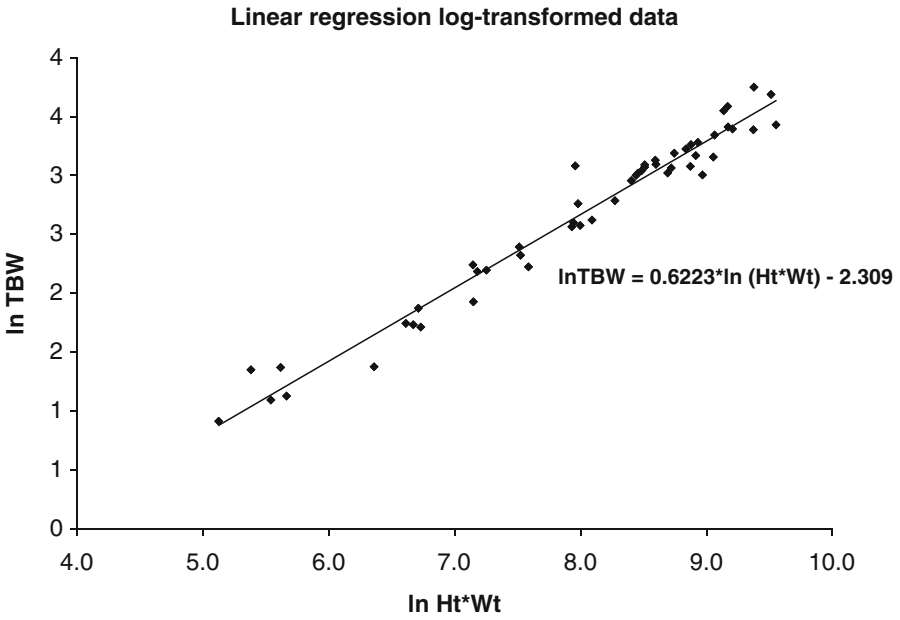

Fig. 148.2 Linear regression of log-transformed TBW versus the Height × Weight (Ht*Wt) parameter in children on peritoneal dialysis. Data not previously published, but used to develop formulas in (Morgenstern 2006)

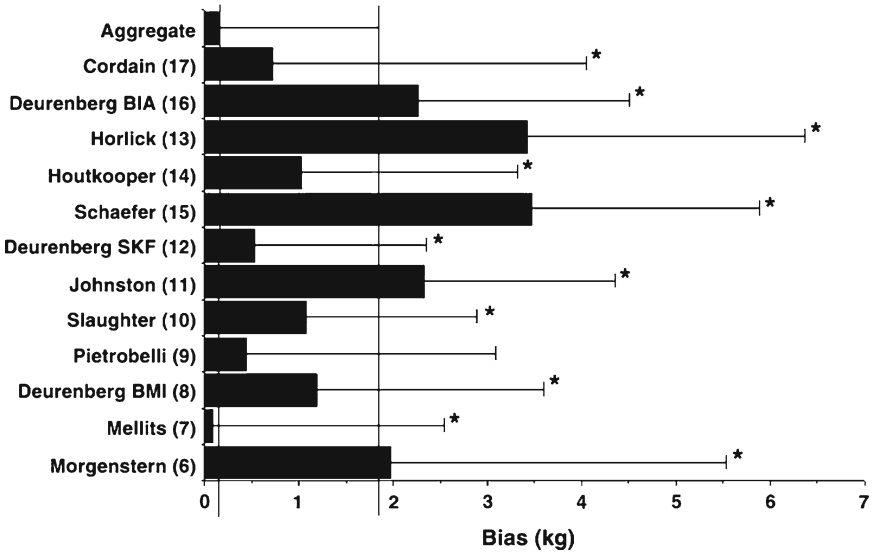

Fig. 148.3 Bias in fat-free mass or fat-mass estimates in 196 children. Mean (+SD) bias in fat-free mass or fat mass in 196 children, calculated as the predicted value minus the measured value. The bias in fat-free mass has the opposite sign of that in fat mass. The graph compares 12 individual predictions with the aggregate average of those 12 predictions. The vertical lines represent the mean bias and the mean bias +1 SD, for the aggregate prediction. All mean biases were expressed as positive values. *Asterisks* denote bias that is significantly greater than the aggregate bias. *BIA* bioelectrical impedance analysis; *SKF* skinfold thickness (Adapted from Wells (2009). With permission)

Table 148.2 Key facts regarding peritoneal dialysis (PD)

- PD is the commonest form of dialysis used on children with end-stage kidney disease.
- PD is uses the principles of diffusion and convection to remove water and solutes across the peritoneal membrane.
- PD requires the placement of a soft catheter into the peritoneal cavity and the use of balanced electrolyte solutions. Water is removed from patients by using hypertonic solutions.
- The optimal volume of fluid to place into the peritoneal cavity of a child is one that is estimated using the child's surface area.
- Dosing of dialysis modalities (hemodialysis and PD) is based upon the concept of the removal of urea from total body water. The expression is *Kt*/*V*, where K is the clearance of urea, t is the time of dialysis and *V* is the volume of distribution of urea, which is accepted to be total body water.
- Computer modeling to determine *Kt*/*V* in hemodialysis generates a value for *V* and for the urea generation rate. In PD, calculation of *Kt*/*V* requires a robust estimate of V, hence the importance of accurately estimating total body water in patients on PD.

Key facts regarding peritoneal dialysis for those unfamiliar with this treatment modality

dialysis dose is commonly measured by urea removal, reported as *Kt*/*V*, where *K* is the clearance of urea in mL/min, *t* is the time of the treatment, and *V* is the volume of distribution of urea. Urea is generally accepted to distribute in TBW; hence, it is critical to correctly estimate TBW in order to measure urea removal. Adequacy of a dialysis therapy is based upon achieving a target *Kt*/*V* (AJKD 2006) (Table 148.2).

There are two forms of maintenance dialysis: hemodialysis (HD) and peritoneal dialysis (PD). Hemodialysis is a very efficient process and leads to the simultaneous and relatively rapid removal of both urea and water. Classical urea kinetic modeling will solve for both *V* and the urea generation rate. Newer, simplified versions of kinetic modeling require that an estimate of *V* be performed (Dumler 2004). Some measurement techniques developed for HD can report a *Kt*/*V* result without the need to measure or estimate *V* separately (Sternby 1998). For PD patients, on the other hand, measurement of *Kt*/*V* requires a measurement or an estimate of *V*, which is, as noted above, TBW.

Efforts to estimate TBW in PD patients (the *V* of the expression, *Kt*/*V*) have been ongoing for over a decade. The importance of this measure has been highlighted (Tzamaloukas 1996; Morgenstern 2001). There continues to be some controversy as to the optimal formula to use to estimate TBW in adults on PD. The National Kidney Foundation KDOQI™ Guidelines for Peritoneal Dialysis in adults recommend the use of TBW estimates from either the formulas or Watson or Hume (AJKD 2006). When evaluated in adults on PD, these estimating formulas did not perform well, but were more accurate than a simple estimate of 0.58 × wt (Woodrow 2003).

Direct measurement of TBW in children with CKD and on dialysis has been performed with bioimpedance analysis (Bradbury 1995, 1996; Wuhl 1996). In patients on PD, however, controversy exists as to whether or not the dialysate in the abdominal cavity impacts the impedance measures (Rallison 1993; Aufricht 1995). Limits of agreement between directly measured TBW and that estimated by bioimpedance analysis in children with CKD and particularly those on dialysis are still quite wide.

There are somewhat more data available for the TBW estimates in children on PD. The KDOQI™ Guidelines for PD in children recommend the formulas developed by Morgenstern et al. (2006). These formulas were developed from direct measures of TBW in children using D_2O or H_2O.[18] A total of 64 children aged 1 month to 23 years on maintenance PD in either Germany or the USA was studied. The same statistical analysis that was applied to the healthy children reevaluated by Morgenstern (Morgenstern 2002) was used on these data. A tight linear correlation existed between the log-transformed TBW and log-transformed (ht × wt): $r^2 = 0.96$, $p < 0.0001$. When back transformed, the following estimating equation was identified:

$$\mathrm{TBW} = 0.11 \cdot \left(\mathrm{HtWt}\right)^{0.61}$$

Somewhat greater precision, not surprisingly, was found when sex-specific equations were generated, and an additional weight factor was added:

$$\text{Boys}: \text{TBW} = 0.10 \cdot \left(\text{HtWt}\right)^{0.68} - 0.37 \cdot \text{ weight}$$

$$\text{Girls}: \text{TBW} = 0.14 \cdot \left(\text{HtWt}\right)^{0.64} - 0.35 \cdot \text{ weight}$$

In a validation cohort, TBW was predicted with a mean difference of 0.001 (±2.5, SD) L. The prediction was weakest in children who were at extremes of hydration status. A preliminary version of these formulas (Morgenstern 2001) was validated by Mendley (Mendley 2005) in 14 children on PD. Of the TBW estimates, including formulas based on bioimpedance analysis, the formulas of Morgenstern in children on PD (Morgenstern 2006) had the smallest root mean squared error, and the least skewing. Interestingly, DEXA-derived values based on an age-adjusted hydration constant yielded results closest to measured TBW.

The relationship between body surface area and TBW could be explored in this model, since TBW and BSA are both dependent on (ht × wt). This led to the following simple linear equations being derived, using the Mosteller (Mosteller 1987) BSA equation:

$$\text{Boys}: \text{TBW} = 20.75 \cdot \text{ BSA} - 3.88$$

$$\text{Girls}: \text{TBW} = 16.96 \cdot \text{ BSA} - 1.57$$

Even more than for TBW estimates based upon anthropometric measures for healthy children, the need for accurate and precise estimates in children on PD is critical. The formulas of Morgenstern still have fairly large limits of agreement in individual children, even though they apply well to a population. Additional components to these estimating equations will need to be developed to improve their performance. These additional components, especially for the children on PD, will need not only to account for adiposity, but will also need to include a measure of the degree of over- or underhydration.

148.5 Applications to Other Areas of Health and Disease

As noted earlier in this chapter, there are a number of uses for precise yet simple estimates of total body water. These areas specifically include the provision of parenteral fluid therapies to healthy children, for example, when they are to undergo surgery, and to ill children, especially those with dehydration, a major cause of morbidity and mortality. The evaluation of the pharmacokinetics of medications is also dependent on assessment of TBW.

In the areas of kinesiology and performance, especially as they relate to body composition and optimizing muscle output in competitive sports, it is equally important to understand TBW and to be able to use TBW estimates to determine changes in lean body mass.

Summary Points

- Estimation of TBW in healthy children has implications related to medication dosing and fluid therapies.
- TBW can be reasonably estimated for populations of healthy children based upon simple anthropometric measures.
- TBW estimates relative to body size have changed over the past three decades, likely due to a secular increase in adiposity.

- TBW is likely most accurately estimated by using an aggregate value based upon multiple estimating formulas.
- TBW may linearly relate to body surface area via the anthropometric parameter height × weight.
- TBW in children on peritoneal dialysis directly impacts measures of delivered dialysis dose.
- TBW in children on peritoneal dialysis can be estimated from anthropometric measures using formulas that differ slightly from those that apply to healthy children.
- In children on PD, a linear relationship still exists between height × weight, TBW, and body surface area.

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Chapter 149
Anthropometry and Body Composition in Chronic Kidney Disease Patients not on Dialysis

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Abstract Chronic Kidney Disease (CKD), characterized by complex metabolic derangements is burdened by changes in nutritional status during the entire course of the disease. Overt malnutrition is usually observed in the late stages of CKD, but a decrease of body cell mass and other changes in body composition, for instance over-hydration, may occur early, even with no evidence of weight loss. The effects of alteration in nutritional status and body composition on clinical outcome are critical; protein-energy wasting by itself can worsen renal function and prognosis, being also strictly related to cardiovascular risk. On the other hand, some studies, but not all, have indicated that in CKD patients not yet on dialysis there is an inverse relationship between higher body mass index and some hard outcomes, such as mortality and cardiovascular events. In addition, body mass index seems to be a predictor of the onset of CKD in the general population; a possible association with waist circumference or waist-to-hip ratio has been described, as well. Thus, a challenge for nutritionists and nephrologists is to identify early changes of nutritional status in CKD patients in order to improve the patient's prognosis. International guidelines advise to assess nutritional status on a regular basis, but indications for CKD patients not yet on dialysis have been much less defined than those for dialysis patients. In addition, assessment of nutritional status in CKD requires multiple measurements and different techniques should be used concurrently. Anthropometry represents a first level assessment tool with some limitations because of the possible influence of an over-hydration state; although not very sensitive in detecting minor changes in body composition, it remains useful if associated with other nutritional tools. Among these, bioimpedance analysis (BIA) should be considered because it is very easy to perform at the bedside and can detect changes of body fluids in the early stages of CKD, such as blunted over-hydration in absence of clinically detectable edema. Thus, anthropometry and BIA should be used concurrently in the evaluation of nutritional status in CKD patients.

Abbreviations

BCM	Body cell mass
BIA	Bioimpedance analysis
BMI	Body mass index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_149,

CARI	Caring for Australian with Renal Impairment
CKD	Chronic kidney disease
CORR	Canadian Organ Replacement Registry
CT	Computed tomography
DXA	Dual X-ray absorptiometry
eGFR	Estimated GFR
ESRD	End stage renal disease
EURO-BPGL	European Best Practice Guidelines
FM	Fat mass
FFM	Free-fat mass
SFT	Skinfold thickness
GFR	Glomerular filtration rate
GH	Growth hormone
HR	Heart rate
KDIGO	Kidney Disease: Improving Global Outcomes
K/DOQI	Kidney/Disease Outcome Quality Initiative
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
PhA	Phase angle
PNAA	Prompt neutron activation analysis
PTH	Parathyroid hormone
R	Resistance
SGA	Subjective global assessment
TBW	Total body water
Xc	Reactance
WC	Waist circumference
WHO	World Health Organization
WHP	Waist-to-hip ratio

149.1 Introduction

149.1.1 Classification of Chronic Kidney Disease

The current classification of severity for chronic kidney disease (CKD) is mainly based on functional criteria referring to both a marker of renal function (glomerular filtration rate = GFR) and a marker of kidney damage (proteinuria), thus overcoming the cause of disease; such CKD staging system incorporates all the old, vague definitions of kidney diseases such as *chronic renal failure*, *chronic renal insufficiency*, *pre-dialysis, and pre-end-stage renal disease* (Eckardt et al. 2009). CKD stages 1 and 2 define conditions of kidney damage (as revealed by proteinuria) with normal GFR (≥90 mL/min/1.73 m^2) or slightly reduced GFR (89–60 mL/min/1.73 m^2), whereas CKD stages 3, 4, and 5 describe conditions of moderate-to-severe reduction of GFR (respectively, 59–30, 29–15, and <15 mL/min/1.73 m^2), independently of proteinuria; stage CKD-5D refers to CKD-5 patients with end-stage renal disease (ESRD) requiring dialysis treatment, while the suffix 'T' is used for all CKD stages in kidney-transplant recipients. Such a classification based on the severity of disease has the major advantage to allow a better definition of patient's prognosis. Nonetheless, the question whether additional factors associated with prognosis, such as body weight, should be included in the classification of CKD remains to be addressed.

Table 149.1 Key points of Chronic Kidney Disease – CKD

1. The primary function of the kidney is to maintain the body electrolytes and water balance and to eliminate the waste products of protein catabolism.
2. Additional major functions of the kidney are the regulation of acid–alkali balance and the production/activation of several hormones (erythropoietin; renin; and vitamin D).
3. Chronic kidney disease is characterized by a progressive and definitive decline of all renal functions, irrespectively of the underlying disease.
4. As a consequence of renal function impairment, hypertension, anemia, electrolyte disturbance, metabolic derangement, and body water imbalance are common clinical features in CKD.
5. Changes of body composition (water, free-fat mass, etc.) occur early during CKD and the onset of malnutrition is not unusual, mainly in advanced CKD.
6. Severe loss of renal functions is incompatible with life and needs renal functional replacement with either dialysis or transplantation.

This table points out the key factors of chronic kidney disease, including major renal functions and consequence of renal function loss
CKD chronic kidney disease

Table 149.2 Key points of nutritional nomenclature in CKD

1. Different terms are commonly used for the same nutritional condition or the same term is used for different nutritional conditions in CKD.
2. On behalf of the International Society of Renal Nutrition and Metabolism, an expert panel reviewed basic terminology related to nutritional problems in CKD.
3. Malnutrition was considered as a confusing and ambiguous term because it may indicate both undernutrition and overnutrition.
4. The terms protein–energy wasting and cachexia were recommended.
5. Protein–energy wasting was defined as the state of decreased body stores of protein and energy fuels (that is, body protein and fat masses), often associated with diminished functional capacity related to metabolic stresses due to CKD and refers to very different degrees of nutritional depletion.
6. Cachexia refers to a very severe form of protein–energy wasting, often associated with profound psychological, metabolic, and immunological disorders, which develops as a serious complication of CKD and carries a very poor prognosis; and almost no therapies for its treatment are approved.

This table points out the complex issue of nutritional nomenclature in CKD and describes which terms have to be considered ambiguous or should be recommended according to international experts (Fouque et al. 2008)
CKD chronic kidney disease

149.1.2 Metabolic and Nutritional Derangements in Chronic Kidney Disease

Metabolic and nutritional abnormalities represent major features of uremic syndrome. Retention of excretory products and metabolic wastes due to loss of renal function induces the accumulation of toxic metabolites, which, in turn, generate changes in both cellular metabolism and volume and/or electrolyte composition of body fluids. Moreover, severe kidney disease is associated with abnormalities of various hormones which are directly related to the loss of renal parenchyma and contribute to the derangement of several metabolic pathways. In addition, the decrease of lean body mass due to a net protein catabolism, and eventually associated with weight loss, may occur in renal patients even when they are clinically stable and without metabolic acidosis. Also, complex alterations of carbohydrate metabolism take place early in CKD, leading to insulin resistance independently of the presence of diabetes. Furthermore, dyslipoproteinemia and dyslipidemia can also arise in the initial phases of CKD. Altogether, these major metabolic changes occurring in early and advanced stages of the disease may substantially affect body composition and nutritional status.

Table 149.3 Causes of metabolic and nutritional derangements in CKD

- Anorexia
  - Uremia (i.e., *wasting toxins*)
  - Depression
  - Gastrointestinal intolerance
- Hyper-catabolism
  - Increase of catabolic hormones (*PTH and glucagon*)
  - Resistance to anabolic hormones (*insulin and GH*)
  - Acidosis
  - Inflammation
  - Medications (i.e., *steroids*)
  - Chronic diseases (*diabetes, heart, and lung*)
- Acute illness
  - Infections
  - Surgery
  - Hospitalizations

This table describes the major causes of either reduced nutrient intakes or enhanced nutrient requirements which produce the metabolic and nutritional derangements observed in CKD patients not yet on dialysis
CKD chronic kidney disease; *PTH* parathyroid hormone; *GH* growth hormone

The impairment of both body composition and nutritional status actually starts early during the course of CKD, and renal failure by itself is a strong and independent risk factor for protein–energy wasting (Garg et al. 2001). As a matter of fact, there is a spontaneous, progressive reduction of both protein and energy intakes and almost half of the patients are not compliant with prescribed diets and do not consume the needed minimum amount of nutrients, mainly of energy; on the other hand, during CKD, an increase in nutrient requirements occurs due to specific catabolic factors related to uremia, such as metabolic acidosis and inflammation (Table 149.3). This negative nutrient balance may cause nutritional changes during the entire course of CKD with an apparent protein–energy wasting, especially in CKD-5 and CKD-5D, whereas blunted nutritional abnormalities already occur in the early stages of the disease. As protein–energy wasting by itself affects renal function, impairing renal plasma flow, GFR, and tubular excretion capabilities (for sodium, acids, water, etc.), the identification of initial abnormalities in nutritional status is one of the major objectives of a nutritional approach to CKD patients.

149.2 Changes of Anthropometry and Body Composition in Chronic Kidney Disease

149.2.1 Body Weight Changes in Chronic Kidney Disease

A decrease in body weight is expected in CKD patients due to the fact that the complex metabolic abnormalities in such disease lead to reduced lean body mass (see earlier). On the other hand, the mean body weight of the general population has been rapidly growing in the last decades, likely affecting both the onset and progression of CKD (see below). The question is how and to what extent the behavior of body weight in the 'real life' of CKD patients is influenced by these conflicting factors. In the USA, patients starting dialysis showed a rise of body mass index (BMI) from 25.7 to

Table 149.4 Clinical characteristics of prevalent CKD patients

Age, years	66.4 ± 13.7	(range: 19 ÷ 103)
Sex,		
Male	800	(57%)
Female	596	(43%)
Diabetes,		
yes	392	(28%)
No	1,004	(72%)
eGFR, ml/min	31.5 ± 14.7	(range: 4 ÷ 77)

This table describes BMI (kg/m^2) characteristics of a cohort of 1,396 prevalent CKD patients not yet on dialysis followed in a tertiary care nephrology system (TABLE study database). Data are reported as mean ± SD, prevalence, and ranges. The *p* value represents the significance for the *t*-test

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate

Table 149.5 BMI values in prevalent CKD patients

All population	27.2 ± 4.6	(range: 16 ÷ 47)
Sex,		
Male	26.9 ± 5.3	$p = 0.007$
Female	27.6 ± 3.9	
Diabetes,		
yes	28.6 ± 5.1	$p < 0.0001$
No	26.6 ± 4.2	
CKD,		
stage 2	26.8 ± 4.9	p = NS (0.485)
stage 3	27.3 ± 4.8	
stage 4	27.3 ± 4.3	
stage 5	26.6 ± 5.2	

27.5 kg/m^2, observed over an 8-year period (from 1994 to 2002) and a further increase is expected in the future. In Europe, the average BMI was 25.3 kg/m^2 in a cohort of incident dialysis patients, and more than half of patient starting dialysis are expected to be overweight or obese (Zoccali 2009). Observations on BMI and BMI changes in early to advanced CKD prior to dialysis are scarce. In a single-center cohort of 521 mild/moderate CKD US Veterans (males: 68 years; black 21%; eGFR 37 mL/min/1.73 m^2), 50% of the subjects were overweight/obese (BMI >28 kg/m^2) (Kovesdy et al. 2007). A subgroup of participants to the 'AIRC' and 'CHS' studies (carried out in the USA), affected by mild CKD (*n*, 1,669; 70 years; eGFR, 51 mL/min/1.73m^2), had a mean BMI of 27.2 kg/m^2 (for both males and females) and 65% of patients were overweight/obese (Elsayed et al. 2008b). In Asiatic CKD patients, the BMI was lower in a younger (59 years) cohort of mild CKD (eGFR, 54 mL/min/1.73m^2) patients from Japan, the mean BMI being 24.1 kg/m^2, with slight lower values in females (Sawara et al. 2009). In addition, a group of patients in Taiwan, similar for age and CKD stage, had a BMI of 24.7 kg/m^2, both for males and females (Lin et al. 2007). Indeed, it is well known that, in Asian populations, the cutoff points for overweight and obesity correspond to BMI values lower than in Caucasians. To give additional information, we analyzed BMI data from a cohort of Italian patients with moderate to advanced CKD followed up in tertiary care facilities (Table 149.4) (De Nicola et al. 2006). Similarly to a US CKD population, we found a mean BMI of 27.2 kg/m^2, with higher values in females and diabetic patients (Table 149.5). Interestingly, no differences were detected in the course of the disease, the BMI being similar from stages 2 to stage 5. According to the World Health Organization (WHO) classification, two out of three patients (65%) were overweight/obese (Fig. 149.1). Overall, it seems that the burden of overweight/obesity in CKD population is increasing similarly worldwide.

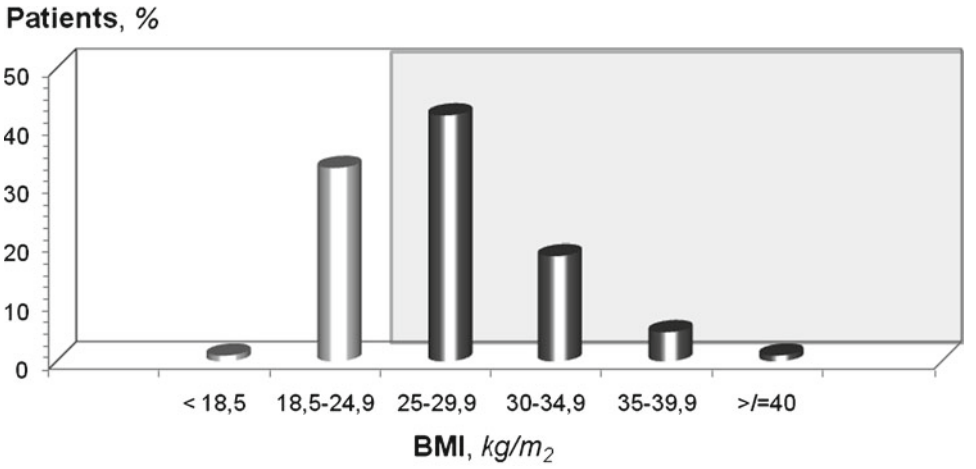

Fig. 149.1 Prevalence of BMI in CKD patients. This figure describes the distribution of groups of BMI in a cohort of 1,396 prevalent CKD patients not yet on dialysis followed in a tertiary care nephrology system (TABLE study database). The *gray* background indicates the area of overweight/obesity according to the WHO classification and the black columns represent the percentage of overweight/obese CKD patients. *BMI* body mass index; *CKD* chronic kidney disease

149.2.2 Body Water Changes in Chronic Kidney Disease

Since the management of water and inorganic ions is mainly accomplished by the kidney, an inadequate homeostasis of body water and electrolytes appears as soon as renal function declines. Because water and electrolyte abnormalities may lead to significant changes of body composition and fatal outcomes, underlying mechanisms should be evaluated and such disturbances have to be ascertained and early corrected. For instance, in CKD, the capability of the kidney to appropriately excrete dietary sodium is impaired due to decreased glomerular filtration. Although, in surviving nephrons, the fractional sodium reabsorption decreases in order to maintain sodium balance, the overall sodium excretion drops and net sodium retention occurs. Such a condition raises serum osmotic pressure, stimulates thirst, increases fluid intake, and rapidly causes water overload. As a consequence, a mild-to-moderate expansion of extracellular volume is expected to occur in the early phases of CKD as well. Of note, even in advanced CKD patients (stages 4–5), edema is not always apparent, except when nephrotic syndrome or heart failure is present. Such water overload in CKD is isotonic and, differently from edema, can lead to hypertension and heart failure.

149.3 Clinical and Prognostic Significance of Anthropometry in Chronic Kidney Disease

149.3.1 Anthropometry and the Onset of Chronic Kidney Disease

In the past decade, several studies have investigated the relationships between obesity and the onset of CKD using simple anthropometric measures as proxy variables of excess body fat or abdominal fat. BMI, waist circumference (WC), and waist-to-hip ratio (WHR) have all been reported to be

proper markers of obesity for assessing the risk for CKD. In 2004, two papers indicated that the onset of ESRD is related to initial body mass index. Data from the Framingham Offspring Study showed that, taking into account a mean follow-up period of 18.5 years, each increase of one standard deviation in BMI augmented the risk for the onset of kidney disease by 23%, whereas in the study carried out in Okinawa the odds ratio for men and women combined was 1.29 before and 1.11 after adjustment for systolic blood pressure and proteinuria (Fox et al. 2004); the risk increased for a BMI >21 kg/m^2 in men (but not in women) (Iseki et al. 2004). Similarly, in a large cohort of individuals living in northern California, BMI remained a strong independent predictor of CKD even after adjustment for a number of factors, including age, gender, race, proteinuria, etc., with the adjusted risk clearly increasing in both overweight and obese individuals (Hsu et al. 2006). The relationship between BMI and the onset of CKD was partially confirmed later by Yamagata and co-workers, who observed a 6% greater risk only in overweight/obese females (not in men) (Yamagata et al. 2007). Similarly, a weak effect was observed in a study on Austrian adults showing that an increase in one unit of BMI was associated with a 4% higher risk (Obermayr et al. 2008). Finally, the combined effects of blood pressure and excess body weight were recently evaluated in a large cohort of individuals in Norway, with ESRD or CKD-related death as principal composite outcome: BMI was not associated with the risk of kidney disease in participants with baseline blood pressure less than 120/80 mmHg and increases substantially if prehypertension is present only in obese individuals (Munkhaugen et al. 2009). The steepest increase in risk was observed in the individuals with a BMI >30 kg/m^2. Altogether, available data have indicated that the onset of CKD is associated with a number of risk factors. A relationship with BMI exists in univariate analyses and, in most cases, also in multivariate analyses. An exception is the paper by Foster and co-workers (Foster et al. 2008), discussing that the increased odds of developing CKD due to BMI does not persist after adjustments for cardiovascular risk factors. Indeed, it should be noted that hypertension, and possibly diabetes, may be considered as covariates and also as obesity-linked pathogenetic factors leading to a decrease in renal function. None of the aforementioned studies reported data on fat distribution. On this topic, interesting results have been obtained by some recent papers investigating the association of anthropometric markers of visceral fat, such as WC or WHR, with the onset of CKD. Elsayed and co-workers examined pooled data from the 'ARIC' study and the 'CHS' study (Elsayed et al. 2008a). Whereas in univariate analysis WHR and BMI were associated with the risk of developing CKD, in multivariable analyses the risk of CKD rose by 22% for each increase in one standard deviation of WHR but no relationship with BMI (or WC) emerged. On the contrary, in a cohort of Iranian adults after a follow-up of 7 years, both BMI and WC, but not WHR, predicted the onset of CKD (Noori et al. 2009), but baseline WC was a better predictor of CKD than BMI. Indeed, the role that abdominal fat may play in the decrease of renal function is also indirectly confirmed by the fact that several epidemiological studies have observed a significant association between metabolic syndrome (often characterized by abdominal obesity) and CKD, which could be even more significant in obese individuals (Sawara 2009).

149.3.2 Anthropometry and Outcomes in Chronic Kidney Disease

It is well known that there is an apparently paradoxical inverse association between mortality and higher BMI in dialysis patients, which indeed is observed in other chronic diseases and in the coeval general population too. In such patients, underweight is also associated with worse prognosis (Mafra 2008). Less information is available on the effects of excess body fat on mortality or morbidity in CKD patients not yet on dialysis. In a review published in 2009 eight studies were listed that had

examined the association between BMI and different outcomes (Kovesdy and Kalantar-Zadeh 2009). Four studies found an inverse relationship with poor outcomes (first of all mortality), but the other four studies did not. Papers differed with respect to experimental protocol, patients' characteristics, and statistical analysis. For instance, in the paper by Weiner and co-workers, around half of the 1,678 individuals with reduced GFR reached the composite endpoint (myocardial infarction, stroke, and all-cause mortality) during a median follow-up of 108 months and no association with BMI emerged (Weiner 2008); no information was given about the number of subjects who started dialysis. On the contrary, Obermayr and co-workers observed that BMI seems to reduce the risk of cardiovascular death in CKD patients with proteinuria, whereas the opposite was true in those without proteinuria (Obermayr et al. 2009). With respect to measures of body-fat distribution, data from two community surveys were pooled by Elsayed and co-workers and examined to assess the relationship between adiposity measures and cardiac events in CKD patients not yet on dialysis (Elsayed et al. 2008b). In multivariable statistical analyses, after a mean follow-up period of 9.3 years, WHR (but not WC or BMI) was observed to be associated with a higher incidence of cardiac events (myocardial infarction and fatal coronary heart disease).

149.3.3 Anthropometry in CKD and application to other areas of health and disease

An increase in the prevalence of overweight and obesity has been observed in most countries, with negative effects on the risk for non-communicable chronic diseases. It is time now to consider that excess body fat also increases the risk for developing CKD, with resulting complex relationships between body fat, inflammation, cardiovascular risk factors, and proteinuria. Programs for the prevention/therapy of overweight and obesity on a community or individual level should take into consideration and evaluate their possible, positive impact on renal disease. This is even more imperative since CKD has been recognized as an independent risk factor for the development of cardiovascular diseases in the general population; indeed, according to the Task Force on Cardiovascular Disease in CKD of the American Heart Association, patients with CKD have to be considered in the 'highest risk group' for subsequent development of cardiovascular events (Sarnak et al. 2003).

149.4 Anthropometry and Nutritional Guidelines for Chronic Kidney Disease

A number of guidelines have been formulated concerning nutritional approaches to CKD patients. Although they mostly focus on dialysis patients, it is of interest to summarize essential indications given on the assessment of body composition and especially on anthropometry and bioimpedance analysis (BIA) (Table 149.6). In general, techniques should be chosen to detect initial changes in muscle mass and body water in the clinical setting, and to acquire information that can be included in a panel of data related to nutritional status.

1. *European Best Practice Guidelines* (EURO-BPGL)
   The European Guideline Steering Committee stated that either anthropometry or other techniques for assessing body composition (such as BIA or dual X-ray absorptiometry) can be used for the diagnosis of malnutrition in dialysis patients (opinion evidence) (Fouque et al. 2007), but no

Table 149.6 Guidelines for nutritional status in CKD

Parameter	Guideline	CKD patients	Dialysis patients
Anthropometry	EBPG 2007	No recommendations	It should be assessed immediately after dialysis (opinion).
Body mass index	EBPG 2007	No recommendations	It should be maintained at a value >23 (evidence level).
MAC, MAMC, and SFT	EBPG 2007	No recommendations	They should be performed by the same operator on the non-fistula arm (evidence level).
Technical investigation	EBPG 2007	No recommendations	Can be recommended for routine follow-up: BIA every 3 months; DXA at dialysis start and every 1 year (opinion)
	K/DOQI 2000	No recommendations	Precision and accuracy of fat mass estimates by DXA are approximately 2–3% in hemodialysis and 3% in peritoneal dialysis patients.
			It is recommended that focus be placed on the direct BIA impedance parameters (R, Xc, and PhA) rather than on regression estimates of edema-free lean body mass or other body compartments (opinion).

This table summarizes the suggestions from international guidelines for the evaluation of the major nutritional parameters in either CKD patients not yet on dialysis or dialysis patients
CKD chronic kidney disease; *EBPG* European Best Practice Guidelines; *MAC* mid-arm circumference; *MAMC* mid-arm muscle circumference; *SFT* skinfold thickness; *BIA* bioimpedance analysis; *DXA* dual X-ray absorptiometry; *K/DOQI* Kidney/Disease Outcome Quality Initiative; *R* resistance; *Xc* reactance; *PhA* phase angle

suggestion was given for CKD patients not yet on dialysis. Dialysis patients should maintain a BMI > 23.0 kg/m^2. Mid-arm anthropometry and four sites' skinfold thickness should be considered as measurements relevant for overall nutritional assessment (Fouque et al. 2007). In particular, mid-arm circumference (MAC) and mid-arm muscle circumference (MAMC) can be used to assess muscle mass. BIA allows estimation of body fluid compartments, which may then be used to make inferences about body composition.

2. *K/DOQI* (Kidney/Disease Outcome Quality Initiative)
According to K/DOQI guidelines, nutritional status in dialysis patients should be assessed by a combination of valid, complementary measures rather than a single measure (K/DOQI 2000). As a matter of fact, there is no single measure which provides a comprehensive indication of metabolic-nutritional status and under-/overnutrition may be identified with greater sensitivity and specificity using a combination of tools. BMI values may be misinterpreted in the CKD population because of fluid overload. MAC and skinfold thickness are recommended as part of the nutritional assessment in CKD. In addition, K/DOQI guidelines describe BIA as an attractive tool for nutritional assessment of individuals undergoing chronic dialysis because it is relatively inexpensive to perform, noninvasive, and painless, requires minimal operator training, and provides data that can be correlated with several aspects of body composition.

3. *United Kingdom Guidelines*
The United Kingdom guidelines give a few indications with respect to the determination of body composition. Only in guideline 4.1 C-NUTR: Nutritional Screening, is it stated that all patients in CKD stages 4–5 should undergo regular nutritional screening (good practice) (No author 2007). A number of potential measures of nutritional state, including serum creatinine, serum cholesterol, serum albumin, subjective global assessment, BMI, lean body mass, and handgrip strength, predict a worse patient survival. Therefore, because there is not a single 'gold standard' measure

for nutritional state in CKD patients, a panel of measurements should be used for assessing different metabolic and nutritional aspects of the disease (No author 2007).

4. *Pediatric guidelines*
   The CARI guidelines (Caring for Australian with Renal Impairment) provide indications only for pediatric CKD patients. Height, weight, head circumference, skinfold thickness, and serum albumin are markers of nutritional status commonly used in children with renal diseases. Nutritional assessment and counseling is mandatory in the management of children with CKD and ESRD, although it is hard to find consistent data to support such statement.

   K/DOQI states that valid measures of protein and energy nutritional status in children treated with maintenance dialysis include dietary interview/diary, nutritional counseling, serum albumin, height and weight, estimated dry weight, weight/height index, mid-arm circumference and muscle circumference or area, skinfold thickness, head circumference in children aged 3 years or less, and standard deviation score for height (K/DOQI 2009).

   According to the British Renal Association, supine length or standing height and weight should be monitored at each clinic visit. Head circumference should be measured at each visit before 2 years of age and 6 monthly up to 5 years of age. All children should undergo dietary assessment by a pediatric renal dietitian at least every 3 months. The best parameter for assessing treatment adequacy in children is the growth rate.

5. *Other guidelines*
   No information is presented on anthropometric measures in CKD patients by KDIGO (Kidney Disease: Improving Global Outcomes), Canadian Organ Replacement Registry (CORR), and Australian guidelines (CARI).

149.5 Anthropometry and Body Composition Measurements in Chronic Kidney Disease

149.5.1 Anthropometry and Assessment of Body Composition in Chronic Kidney Disease

Assessing and monitoring body composition, as well as protein and energy balance, is fundamental to effectively tackle undernutrition and overnutrition in CKD, both of which are common in such patients. In this perspective, anthropometric methods may be an important clinical tool in individuals with CKD since they help evaluate nutritional status, a modifiable factor that can influence morbidity and mortality. The most common anthropometric variables considered are body weight, height, skinfold thickness, mid-arm anthropometry, and WC. They have several advantages (measurement is simple, safe, noninvasive, and not expensive) but also some limitations in CKD patients, mainly because of the possible occurrence of abnormalities in body hydration. From a practical point of view, the interpretation of body weight/BMI values is sometimes difficult since sudden variations in weight can be determined just by changes in body water. Derived estimates of lean body mass should also be considered with attention and prudence because, for instance, a decrease in body cell mass could be masked by an increase in extracellular body water.

Few studies in CKD patients have compared anthropometry with other techniques for assessing body composition, in some cases including together patients before and after entering dialysis. In a study on individuals not yet on dialysis, body fat assessed by skinfold thickness was significantly higher compared to body fat as measured by DXA (Avesani et al. 2004), whereas a good agreement

between skinfold thickness and bioimpedance analysis was observed in non-obese, but not in obese patients (Barreto Silva et al. 2008). With respect to body fat distribution, in a cross-sectional study on 122 CKD patients not yet on dialysis, WC strongly correlated with visceral fat (but also with subcutaneous fat, actually) measured using computed tomography (CT), the linear regression being quite similar in the two genders, with a correlation coefficient of 0.75 in men and 0.81 in women (Sanches et al. 2008); indeed, it was not possible to assess whether this relationship differed in CKD patients compared to healthy individuals because there was no control group. Interestingly, the strength of the correlation between WC and blood lipids or insulin resistance was similar to that observed for CT-derived measures of visceral fat. A similar association between WC and visceral fat was also observed by Sawara et al. (2009). Recently, changes in visceral fat (assessed by CT) were compared to those of WC in patients not yet on dialysis after a follow-up of 12 months (Velludo et al. 2009); the authors concluded that the variations in WC did not accurately reflect variations in visceral fat, but, actually, some very extreme outliers were included in the statistical analysis. Finally, to establish specific criteria for the risk of metabolic syndrome, 217 CKD outpatients were studied in a cross-sectional study using anthropometric measures, CT (for measuring visceral fat), and a number of biochemical variables (Sawara et al. 2009); with respect to WC, the authors proposed cutoff values of 84 cm in males and 83 cm in females that defined high risk of metabolic syndrome.

149.5.2 Anthropometric Measurements and New Techniques in Chronic Kidney Disease

Keeping in mind that the nutritional management of CKD patients is a difficult and complex task, anthropometric measurement may be utilized in such population for either assessing protein–energy wasting or cachexia or defining some relationships between body composition and metabolic abnormalities and/or cardiovascular risk factors. With respect to undernutrition, the usefulness of anthropometry is also demonstrated by the fact that subjective global assessment (SGA), which is a clinical technique widely used in CKD patients, assesses nutritional status considering not only features of the history but also muscle wasting and subcutaneous fat loss (evaluated by physical examination). Actually, the assessment of nutritional status in CKD patients involves the evaluation of visceral proteins and/or somatic stores and requires that a number of different tools are used concurrently. Data on anthropometric measures, for instance, BMI, but also skinfold thickness and mid-arm anthropometry, are reported in many papers and are usually in agreement with those obtained with other techniques. Basic nutritional assessment includes anthropometry, subjective global assessment (SGA), biochemical variables (albumin), and assessment of nutrient intakes. Anthropometry (body weight, body mass index, mid-arm circumference, and mid-arm muscle circumference) represents the first-level assessment tool for somatic protein stores (essentially muscle mass) and body fat (Pupin et al. 2004), but, to the best of our knowledge, no specific reference values for anthropometric variables exist for CKD patients. The estimation of body fat using skinfold thickness could be, at least in theory, of particular interest in patients with edema, who exhibit an increased weight and BMI due to a pathological increase in extracellular body water. From a very different perspective, the association between indices of fatness and cardiovascular risk factors has been evaluated by a number of cross-sectional studies, but often as a secondary endpoint of the protocol. For instance, Madero et al. (2007) in 1,772 subjects in the advanced stages of CKD, but not yet on dialysis, observed that greater BMI quartiles were associated with a greater prevalence of diabetes, higher blood pressure, and LDL-cholesterol, and lower HDL-cholesterol. In another study on CKD patients not yet on dialysis, the correlation between WC and blood lipids or insulin resistance appears to be similar to that observed for CT visceral fat (Sanches et al. 2008). In addition, BMI, truncal fat, or visceral fat

have been found to be associated with inflammatory markers, while a complex relationship between obesity, metabolic syndrome, and CKD has also been described (Kwan et al. 2007). Last but not least, overweight and obesity are a known risk factor for proteinuria (Iseki et al. 2004; Madero et al. 2007; Foster et al. 2008).

149.5.3 Bioimpedance Analysis in Chronic Kidney Disease

Anthropometry represents a relevant part of the assessment of body composition but does not distinguish between body protein, minerals, and water. Therefore, it is reasonable to use anthropometry concurrently with tools that allow easy and reliable measures and/or estimates of body water and possibly body cell mass. Bioimpedance analysis (BIA) is a simple, safe, noninvasive technique measuring the electrical properties of the body (resistance = R; reactance = Xc), which are used to derive measures of body compartments with respect to fluids (total body water = TBW; extracellular water = ECW) and soft tissues (fat mass = FM; fat-free mass = FFM). Phase angle (PhA) is another BIA parameter, corresponding to the Xc/R ratio, which has been found to be related to body cell mass, total body proteins and muscle mass, and the ICW/TBW ratio (Chertow 1999). Also, reference values for BIA in healthy populations have been provided for both adults (percentiles) and children (vectors) (De Palo et al. 2000; Di Iorio et al. 2000). BIA has attracted the interest of nephrologists as a simple tool to assess the body composition in CKD patients since it is a bedside method that provides information on both hydration status and body composition. As a matter of fact, it has been utilized in CKD patients to identify a threshold for apparent edema and compared with deuterium oxide dilution and dual-energy X-ray absorptiometry to obtain estimates of TBW and FFM, respectively (Piccoli et al. 1994). Derived values for FFM, FM, and TBW can be obtained in CKD patients using predictive formulas that include BIA values. Alternatively, R and Xc as raw measures have been used to obtain a qualitative information on a patient's hydration status (BIA vector analysis) (Piccoli et al. 1994). Interestingly, the reduction of phase angle has been considered to reflect an increase in the ratio between extracellular water and intracellular water or a decrease in body cell mass (BCM); in addition, phase angle has been discovered to be an independent predictor of survival in various pathologic conditions and also in dialysis patients (Maggiore et al. 1996). On the other hand, a limitation of BIA accuracy for the evaluation of body composition in CKD is represented by the hydration status; since estimation of lean and fat mass can be inaccurate due to overhydration, BIA should be performed in patients at near-free edema status.

149.5.4 Early Changes in Bioelectrical Estimates of Body Composition in Chronic Kidney Disease

Although several observation on BIA have been reported in dialysis patients, few and conflicting results on BIA are available in early stages of CKD. Bellizzi et al. (2006) studied consecutive, incident, CKD patients who had a CKD stage ranging from 3 to 5 without clinically detectable edema; other major clinical conditions that should affect body composition were also considered as exclusion criteria. A further strength of that paper was the presence of a consistent healthy control group (Bellizzi et al. 2006).

Table 149.7 BIA in CKD patients

	Males			Females		
	Patients	*Controls*	*p*	*Patients*	*Controls*	*p*
Resistance, ohm	465 ± 81	492 ± 64	<0.01	550 ± 80	574 ± 63	<0.05
Reactance, ohm	39 ± 9	53 ± 9	<0.01	43 ± 11	59 ± 9	<0.01
Phase angle, degrees	4.8 ± 1.0	6.2 ± 0.9	<0.01	4.5 ± 1.0	5.8 ± 0.8	<0.05
TBW, L	41.8 ± 7.3	40.1 ± 5.1	<0.05	30.0 ± 4.7	29.0 ± 3.4	=0.06
BCM, kg	26.0 ± 4.3	27.9 ± 3.4	<0.01	15.3 ± 2.5	16.4 ± 2.1	<0.01

This table lists the gender-related BIA characteristics (raw measures and derived estimates) in a cohort of incident CKD patients not yet on dialysis as compared with a cohort of healthy control subjects. Data are reported as mean ± SD. The *p* value represents the significance for the *t*-test

BIA bioimpedance analysis; *CKD* chronic kidney disease; *TBW* total body water; *BCM* body cell mass

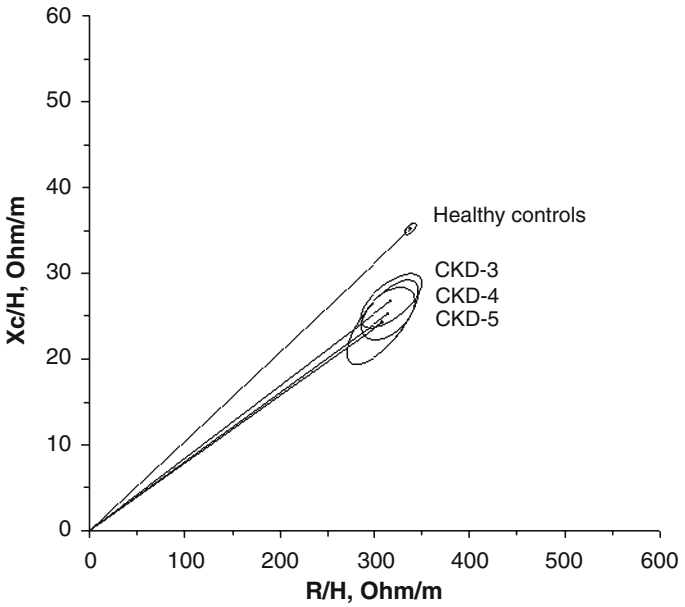

Fig. 149.2 R/Xc graph in CKD patients according to disease stage. This figure shows the R/Xc graph, representing both vectors and confidence ellipses for groups of CKD patients on stages 3–5 (not yet on dialysis) as compared with healthy controls. Compared to controls, vectors for CKD groups were shorter and more downsloping, indicating overhydration in CKD; no difference emerged in the mean impedance vector between the CKD groups (Hotelling's *t*-test). *CKD* chronic kidney disease; *R/Xc* resistance/reactance; *Xc/H* reactance/height; *R/H* resistance height

CKD patients showed overt abnormalities of measured BIA variables, that is, lower R, Xc, and phase angle, and derived measures of body composition (Table 149.7). Definite differences emerged in mean impedance vector analysis in both male and female CKD patients as compared to control subjects: vectors were similarly shorter and downsloping in all CKD stages, suggesting the presence of overhydration since the early stages of CKD, even in absence of edema (Fig. 149.2). Additionally, bioimpedance index (height^2/R), which is considered a variable directly related to TBW, was higher in CKD, with 27% of men and 20% of women being above the 90th percentile derived in healthy subjects. Also, the differences in BIA-derived TBW were similar to those observed for R index: TBW increased in CKD patients (+4%) to an extent which was similar in the different stages of disease. On the contrary, BIA-derived BCM was reduced in CKD (around 7%). Interestingly, phase

angle, which reflects the distribution between ICW and TBW, was markedly lower (-22%) in each of the CKD stages than in controls; the occurrence of short mean impedance vectors associated with a lower phase angle further confirms the presence of fluid overload (Maggiore et al. 1996). Overall, the study indicated that CKD patients suffer of complex changes of body composition starting in the early stages of the disease; in particular, overhydration occurs in patients with mild-to-moderate CKD, even in the absence of clinically detectable edema, whereas body cell mass tends to decrease. Thus, bearing in mind that guidelines pointed out the need for sensitive measures of nutritional status in early CKD stages to prevent the onset of protein–energy wasting, BIA could represent an attractive tool to discover initial abnormalities of body composition in such patients.

149.5.5 Anthropometry in Chronic Kidney Disease: Overall Considerations

The use of anthropometric variables in dialyzed patients as also in CKD patients not yet on dialysis has already yielded interesting information on the changes in nutritional status due to undernutrition or overnutrition. From a practical point of view, fewer indications are available on the use of anthropometric variables in the single patients, and this is even truer for CKD patients not yet on dialysis. Anthropometry should be used in basic nutritional assessment in combination with a panel of other variables exploring biochemical and functional areas. Data obtained in patients with large shifts of body water or edema should be interpreted with caution. Bedside techniques, such as BIA, that assess body fluid compartments, should be utilized concurrently with anthropometry to allow an appropriate evaluation of changes in nutritional status and body hydration. Finally, the use of anthropometry and BIA in monitoring nutritional status during the entire course of CKD should be better evaluated in the future.

Summary Points

- Most CKD patients are overweight or obese.
- Emerging studies show an association between protein–energy malnutrition and mortality in CKD patients not yet on dialysis.
- In CKD patients some, but not all, studies indicate that there is an inverse relationship between body mass index and some outcomes, such as mortality and cardiovascular events.
- Body mass index seems to be a predictor of the onset of CKD; a possible association with waist circumference or waist-to-hip ratio has been described as well.
- International guidelines do not produce very clear indications about the evaluation of nutritional status in CKD patients not yet on dialysis.
- Some anthropometric measures such as body mass index, arm circumference, mid-arm muscle circumference, and some skinfolds may be useful in the evaluation of early abnormalities of nutritional status in CKD patients not yet on dialysis.
- Anthropometric variables should be used together with other tools for a multidimensional evaluation of nutritional status in CKD patients not yet on dialysis.
- In most cases, bioelectrical impedance analysis could be a valuable technique for evaluating body fluids in CKD patients.
- The use of anthropometry or bioelectrical impedance analysis for monitoring changes in nutritional status of CKD patients with time is still not well defined.

Acknowledgment We are in debt to the TABLE study group (Prof. G. Conte, Prof. L. De Nicola, and Prof. R. Minutolo; Nephrology Division, Department of Gerontology, Geriatrics and Metabolic Diseases, Second University of Naples, Naples, Italy) for providing us the database of CKD outpatients in the Italian tertiary nephrology care system which we used to obtain information on prevalence of overweight/obesity in chronic kidney disease.

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Chapter 150
Obesity, Leptins, Hypogonadism and Waist–Hip Ratio in men: An Interplay

J. Elizabeth, C. Rakshita, and S. Ramkumar

Abstract Adipose tissue and androgens have a reciprocal link in obese men. Hypogonadism is a nonspecific term for decreased testicular function. It is diagnosed by the low serum testosterone levels and low serum gonadotropin levels due to various etiologies. A deficiency of Testosterone is associated with decreased libido, male erectile dysfunction, excessive sweating and symptoms associated with aging like lack of energy, fatigue, central adiposity, reduced strength, cognitive decline and depression (Davidson et al. 1983; Yesavage et al. 1985). Many of the symptoms are seen in men with increasing age and are not specific in all cases of hypogonadism. Obesity predicts increased mortality due to the link with co morbidities such as diabetes mellitus, cardiovascular disease, the Metabolic Syndrome and Obstructive sleep apnoea (Poirier et al. 2006). Anthropometric measurements like Body Mass Index (BMI), Waist Hip Ratio (WHR) and Waist Circumference (WC) and Waist to Height Ratio (WHtR) have been used as tools to assess obesity and hence the cardiovascular risk status in individuals with hypogonadism.

The Waist Hip Ratio (WHR) measurement is considered a good indicator of abdominal obesity which predisposes to serious health risks. The WHO recommends these measurements as a universal criterion for the detection of obesity. WHR which is a better measure of abdominal fat accumulation has been implicated as a more sensitive predictor of cardiovascular risk than BMI (Cambien et al. 1980; Yusuf et al. 2005). There is a fundamental relationship between energy balance and reproductive function in the mammalian species wherein population growth is controlled during times of scarcity. Recent epidemiological studies have shown that Androgens play an important role in the pathogenesis of Metabolic Syndrome in men. Conversely hypogonadism can develop in established metabolic syndrome (Laaksonen et al. 2005). Studies have shown that Androgen therapy has been found to reduce visceral abdominal obesity which is the main target in the treatment of obesity in hypogonadal men (Schroeder et al. 2004).

The WHR is not recommended to be used as a lone indicator of cardiovascular disease in an obese individual as it was thought earlier. Recent studies have shown Waist Circumference to be a better tool to assess the cardiovascular risk than WHR.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_150,

Abbreviations

BMI	Body mass index
BMR	Basal metabolic rate
CAD	Coronary artery disease
CRF	Corticotropin releasing factor
FFM	Fat free mass
FM	Fat mass
FSH	Follicle stimulating hormone
GLP 1	Glucagon like peptide-1
GnRH	Gonadotropin releasing hormone
hCG	Human chorionic gonadotropin
IHH	Idiopathic hypogonadotropic hypogonadism
kDa	Kilo Dalton
LEP	Leptin gene
LEPR	Leptin receptor
LH	Luteinising hormone
MRI	Magnetic resonance imaging
MSH	Melanocyte stimulating hormone
NPY	Neuropeptide Y
PCSK 1	Protein convertase subilisin/kexin type 1
SHBG	Serum hormone binding globulin
WC	Waist circumference
WHR	Waist hip ratio
WHtR	Waist to height ratio

150.1 Introduction

The obesity epidemic is spreading worldwide in genetically predisposed populations who have a high caloric diet and a sedentary lifestyle (Cambien et al. 1980). There is a known evolutionary relationship between energy balance and reproduction in humans, which ensures population control.

Numerous advances in the study of obesity have given us a better understanding but definitive answers remain elusive. Identification of the *ob* gene and transcription factors that regulate adipocyte differentiation, proliferation, and metabolism has produced significant advances in the understanding of the pathophysiology of adipose tissues. The most important concerns in relation to obesity are the associated comorbidities, such as cardiovascular disease, diabetes mellitus, and metabolic syndrome.

Leptin, the adipocyte hormone, has a direct relationship to BMI and WHR, which are considered to be good indicators of the degree of obesity. Leptin has been shown to play a pivotal role in regulation of fertility, and various researchers have studied its relationship with testosterone levels. The most proven relationship between testosterone and leptin is that a deficiency of androgen was associated with obesity and raised serum leptin levels in hypogonadal men. Altered secretory rhythm resulting in very high levels of leptin as a result of obesity will have deleterious effects on the steroidogenic cell and, hence, the synthesis of testosterone. The regulation of testosterone is primarily by pituitary LH. On the contrary, FSH facilitates Leydig cell maturation. Testosterone also maintains the sensitivity of the pituitary to the hypothalamic-releasing factor GnRH. In addition, it acts on the

hypothalamus to slow down the GnRH formation, thus decreasing pulsatile LH release. Under physiologic conditions, the LH response to feedback from testosterone is unique; however, a prolonged elevated plasma LH level as seen in hypogonadism reduces the pituitary's sensitivity to the negative feedback control by the androgen.

Usually, hypogonadism indicates gonadal failure associated with androgen deficiency. There are two types of hypogonadism, hypergonadotropic and the hypogonadotropic. Hyper-gonadotropic hypogonadism or primary gonadal failure results when the gonads do not produce sufficient androgen to suppress LH and FSH by a negative feedback mechanism. Reduced androgen levels and increased levels of LH and FSH characterize this condition.

Hypogonadotropic hypogonadism is a deficiency or absence of gonadal function secondary to lack of gonadal stimulating hormones, LH and FSH. It is characterized by low levels of androgens and low to normal levels of LH and FSH.

Leptin is a 16 kDa cytokine produced by the adipocytes that circulate in plasma at concentrations that parallel the amount of fat reserves. Generally, obese humans show high levels of leptin.

Obesity is known to have a reciprocal link with testosterone levels and total and free testosterone decrease in proportion to its severity. Major pathogenic factors leading to this reduction of testosterone levels in obesity are:

(a) Reduced binding capacity of SHBG (in spite of which the low androgens clearly indicate a failure in production);
(b) Decreased LH pulse amplitude; and
(c) Excessive increase of estrogen or hyperestrogenemia.

Obesity itself is one of the several conditions which can lead to a reduced SHBG level. This results in a low normal or below normal range of total testosterone, wherein the free or bioavailable testosterone is however within normal limits. These changes are reversible with weight loss, suggesting that they are consequences of obesity. Body weight, as is generally known, is regulated by numerous complex afferent metabolic and hormonal signals to the brain. Abnormal production or action of the afferent messengers may lead to a gain in weight. Subsequent increase in leptin levels reflects the body's attempt to counterbalance the increased body fat stores.

150.2 WHR in Hypogonadism

Studies have shown inverse correlations between testosterone levels and BMI, WC, WHR, amount of visceral fat, and serum leptin levels. In 16 different studies, inconsistent and conflicting results were provided on the relation of testosterone and CAD. WHR is measured by the circumference of the waist at its smallest point, divided by the circumference of their hips at the widest point. A waist-to-hip ratio of greater than 0.9 for men and 0.85 for women indicates increased health risks.

Although WHR has been strongly recommended as a cardiovascular risk predictor, it has also been critically commented upon for not representing the accretion of abdominal fat, if the WC is also increased. In the Asian population, the WHtR has already been suggested as a common measure of central obesity with the cutoff level being 0.5 for both sexes. Among the ways to understand the effect of testosterone is to observe the effects of induced hypogonadism. This condition is induced medically or surgically in patients with metastatic prostate cancer. In such cases, induction of hypogonadism results in increased insulin resistance and increased body fat mass.

Besides energy storage, adipose tissue can also synthesize and release substances that can act on distant targets in an endocrine fashion or act locally in a paracrine or autocrine fashion (Griffin et al.). Excess adipose tissue can compound the hypogonadal state as the enzyme aromatase is found in abundance. This enzyme converts testosterone to estradiol (Cohen 2001). Evidence suggests that testicular interstitial function can be impaired due to either an altered fat metabolism or an excess of fat-derived hormonal products (Markku et al. 2006).

There have been interventional studies to establish the relationship between energy balance and androgens in obese men, but they have been inconclusive. It is seen that metabolic syndrome, which is a combination of obesity, hypertension, dyslipidemia, impaired glucose regulation, and insulin resistance, is seen in hypogonadal men. The altered lipid metabolism may be attributed to these integrating signals, primarily leptin, one of the messengers released by the adipocyte.

150.3 Role of Leptin in Abdominal Obesity

The relationship of adipose tissue mass, fat metabolism, and energy balance to reproduction was illuminated by the discovery of the genes encoding leptin, an adipocyte satiety factor, and its receptor. Leptin is a highly conserved 167-amino-acid cytokine-like protein produced mainly, but not exclusively, by adipose tissue; a mutant gene was first isolated from the very obese ob/ob mouse by positional cloning. Soon thereafter, the leptin receptor was cloned, which is a member of the gp family of cytokine receptors and the mutation identified in the obese db/db mouse.

Animal models that exhibit hypogonadotropic hypogonadism have also demonstrated the important role of leptin in reproduction. This was further substantiated by the correction of infertility on administration of recombinant leptin. This protein may play a triggering role as a hormonal determinant of energy balance in addition to the role played by catecholamines, insulin, glucagon, and thyroid hormones. Leptin was found to be the satiety factor, inhibiting food intake and increasing energy expenditure. It acts as a communication between the adipocyte and the hypothalamus (Styne et al. 2008).

Leptin has been implicated to play a crucial role in regulation of body weight, more specifically the body fat stores. Almost all studies have reported a strong relationship between leptin and body weight, expressed as BMI.

BMI and WHR were the only easily measurable indices and are considered as the most precise measure of short-term longitudinal changes in the body fat, although BMI does not discriminate between fat and fat-free mass.

Leptin and its receptor are the important components of the homeostatic system regulating body fat. The signaling by leptin of the hypothalamus involves the modulation of many other molecules, such as NPY, MSH, GLP-1, and CRF. Autoradiography and in situ hybridization techniques have helped in identifying leptin receptor sites in the ventromedial and arcuate nuclei of the hypothalamus and the choroid plexus (Widjaja et al. 1997).

Studies on leptin receptors and genes have demonstrated the role of mutations of these components in obesity (Wilding et al. 1997). Such receptor polymorphisms are seen in humans as well (Chen et al. 1996). The expression of leptin mRNA in the adipocyte also correlates significantly with BMI (Oksanen et al. 1998). Studies have shown correlations between leptin and BMI, and waist and hip circumferences, thus indicating that leptin levels may be associated with the fat depots. These suggest that human obesity is associated with insensitivity to leptin. This could be due to a problem with the transport at the blood–brain barrier, as described by the saturable binding model (Considine et al. 1996).

Generally, obese humans show high levels of leptin. It may be the 'lipostat' factor, which governs the energy balance through a negative feedback originating in the adipocyte and acting on the

hypothalamus. There are evidences of leptin levels being very low in some obese people, indicating an abnormal secretion from the adipocyte stores themselves (Caro et al. 1996).

Higher leptin mRNA levels may be found in subcutaneous than in omental adipocytes (Montague et al. 1997). This indicates that leptin plays a role in the adipose tissue distribution in the human body (Friedman 1997).

In obese males, androgen levels decline in proportion to the degree of obesity. In vitro studies have shown that leptin inhibits hCG-stimulated testosterone secretion at the concentrations found in obese men (Montague et al. 1997). Increased leptin concentrations not leading to weight loss may be because of the defects in other systems regulating body weight. It is thus clear that an increased leptin level is a mere reflection of the attempt made by the human body to reduce the increased fat stores (Caprio et al. 1999). Even if the leptin receptor is functional in obese men, it is apparent that it does not alter their food intake or their BMR in response to a high serum leptin concentration.

Recent studies (Piji et al. 1996; Rolf et al. 2002) have shown that when the expected fall in testosterone levels with aging was prevented by exogenous testosterone replacement in hypogonadal men, the age-related increase in BMI and leptin did not occur.

A significant correlation was found between leptin and most anthropometric parameters, such as BMI, hip circumference, FFM, and FM in kilogram and as a percentage (Rolf et al. 2002).

However, few studies on the effect of testosterone replacement in cases of IHH and Klinefelter's syndrome concluded that mean plasma leptin levels were not influenced by testosterone (Vaan Gaal et al. 1999). Another study reported that there was no correlation between leptin and testosterone in middle-aged normoglycemic men (Kilciler et al. 2002). The reason for these conflicting results is still unclear, but considering the complexity of the factors affecting leptin secretion and the heterogeneity of the population studied, the varied etiology of the hypogonadal cases may be the contributing factor. The primary cause of the inverse correlation between testosterone and leptin could be ascribed to the action of the androgen at the adipocyte level.

A short-term replacement with testosterone may not alter the BMI and WHR, probably because of the anabolic effects of testosterone and conversion of fat into fat-free mass. In support of this, Snyder et al. (2000) have shown that a minimum of 6 months of replacement with testosterone was required to cause a 5.8% increase in fat-free body mass. Evidence suggests that a 6-month testosterone replacement leads to a 16% reduction in fat mass (Pugeat et al. 1991).

In our study of testosterone and leptin levels in 20 hypogondal men, prior to and after exogenous testosterone, the pre-treatment values of testosterone in subjects were found to be significantly lesser than that in the control group. The leptin values too were significantly lower in controls in comparison to the untreated hypogonadal men. The lipid profile showed varied significances. The total cholesterol and low-density lipids showed a significant difference ($p < 0.001$) between pre-treatment subjects and controls. Both total cholesterol and low-density lipids were significantly higher in the hypogonadal men when compared to controls.

High-density lipids showed significant difference between pre-treatment subjects and controls ($p < 0.01$). The study group of untreated hypogonadal men had a significantly reduced level of high-density lipids. Triglycerides and very low-density lipids did not show a significant difference between the subjects pre-treatment and controls ($p > 0.05$). The serum triglyceride levels and very low-density lipid levels did not differ in the hypogonadal men and the controls.

The post-treatment levels of testosterone had improved significantly with reduction in leptin levels in hypogonadal men. These differences were statistically significant ($p < 0.05$).

The total cholesterol and low-density lipids pre- and post-treatment showed significant reduction in levels ($p < 0.001$). (Tables 150.1 and 150.2).

Table 150.1 Mean, standard deviation, *t*-value, and significance levels of testosterone and leptin in Controls and Study Group (pre-treatment) (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

Variable	Group	Mean	SD	*t*-value	DF	*p*-Value
Testosterone	Study Group	0.50	0.61	11.595	38	$p < 0.001$
	Controls	5.95	2.01			
Leptin	Study Group	40.25	37.05	3.658	38	$p < 0.01$
	Controls	8.80	10.30			

The subjects in the study group had lower levels of testosterone and higher levels of leptin in comparison with the controls prior to treatment. The difference was found to be statistically significant.

Table 150.2 Mean, standard deviation, *t*-value, and significance levels of testosterone and leptin in post-treatment Study Group and Controls (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

Variable	Group	Mean	SD	*t*-Value	DF	*p*-Value
Testosterone	Study group	6.00	5.53	0.038	38	NS
	Controls	5.95	2.01			
Leptin	Study group	19.95	19.20	2.288	38	$p < 0.05$
	Controls	8.80	10.30			

The testosterone levels increased while the leptin levels decreased after treatment in the study population. The difference in leptin levels following treatment was found to be statistically significant.

On the other hand, high-density lipids showed a highly significant increase in levels following treatment with testosterone ($p < 0.001$). Triglycerides and very low density lipids showed no significant differences in the study group following exogenous replacement with testosterone.

The testosterone levels in the post-treatment state and controls showed no significant differences. This was because of the normal levels of testosterone, which matched the controls that were achieved post-treatment.

The leptin levels showed a significant difference post-treatment and ($p < 0.05$). This indicates that leptin levels did not match that of the controls in the post treatment of subjects (Figs. 150.1–150.3).

150.4 Waist Circumference, the Newer Measurement

Numerous epidemiological studies have established a close relationship between obesity and low serum testosterone levels in healthy men. In men with hypogonadal values of testosterone, testosterone administration has been shown to improve body composition, decrease fat mass, and increase the lean body mass. (Rita et al. 2007).

Body mass index has been recommended by the WHO as a universal criterion to determine obesity. Waist circumference and waist/hip ratio have been used as markers of abdominal obesity. However, few studies consider that WHR predicts cardiovascular risk better than BMI (Figs. 150.4–150.6).

Waist circumference, on the other hand, has been promoted by some studies and two different criteria have been proposed based on population studies (92–102 cm for men and 80–88 cm for women). The WC has also correlated well with MRI of visceral fat assessed. This measure has not escaped controversy due to the fact that it does not take into account the height and, hence, the waist-to-height ratio (WHtR) was proposed by some others as a better predictor of cardiovascular risk.

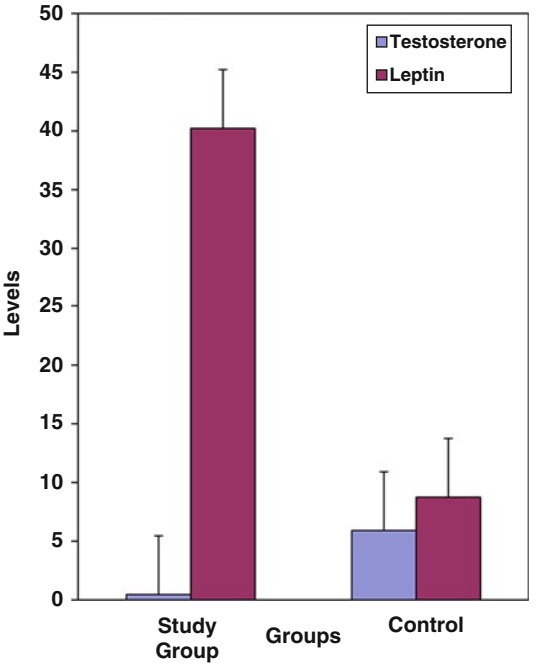

Fig. 150.1 Mean and Standard deviation of testosterone and leptin levels in control group and study group prior to treatment. In comparison to the controls, the study group had lower testosterone and higher leptin levels. (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

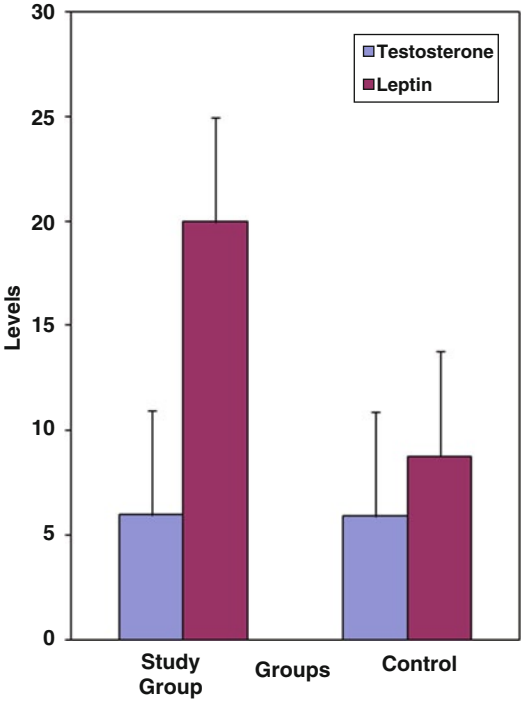

Fig. 150.2 Mean and Standard Deviation of testosterone and leptin levels in the study and control groups following treatment. The levels of testosterone had improved while leptin levels also showed a reduction post-treatment in the study group. (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

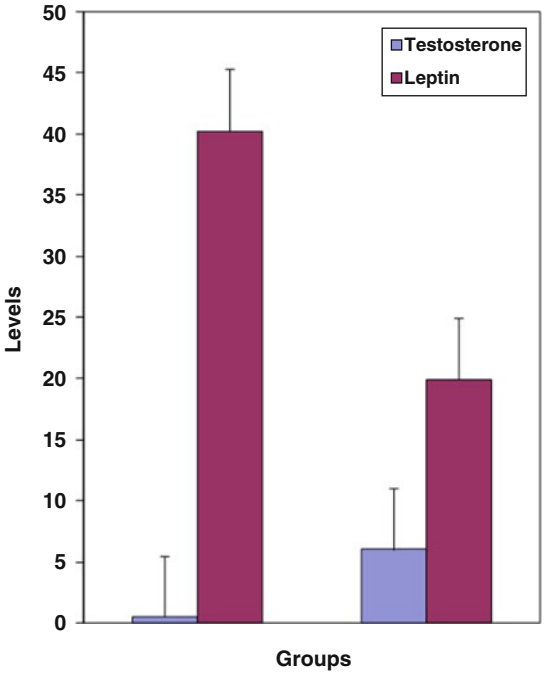

Fig. 150.3 Mean and standard deviation of testosterone and leptin in the study group – Pre- and Post treatment. This figure shows the effect of exogenous testosterone administration on testosterone and leptin levels in the study group (hypogonadal men). The testosterone levels had improved significantly, while the leptin levels showed reduction after exogenous testosterone administration (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

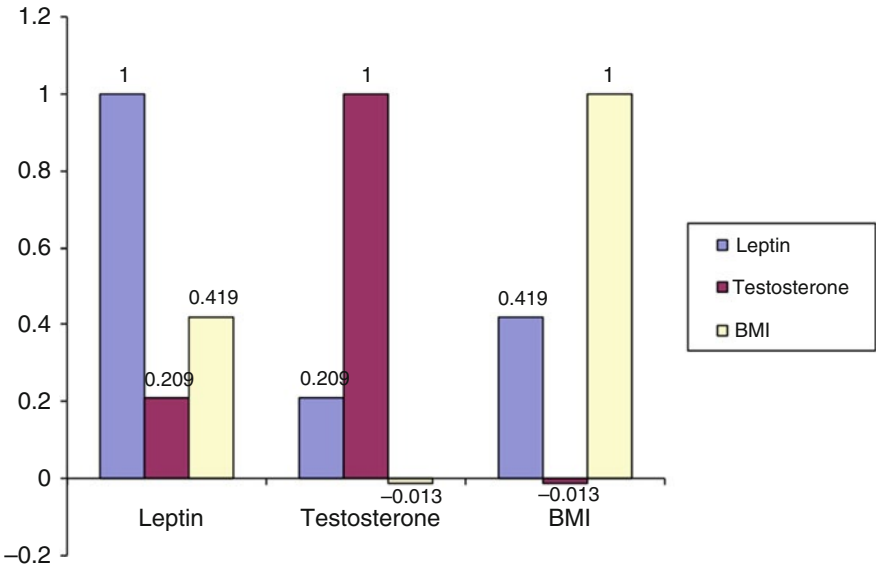

Fig. 150.4 Pearson correlation between leptin, testosterone levels, and BMI prior to treatment in the study group. A direct relationship exists between BMI and leptin levels while BMI and testosterone levels vary inversely. (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

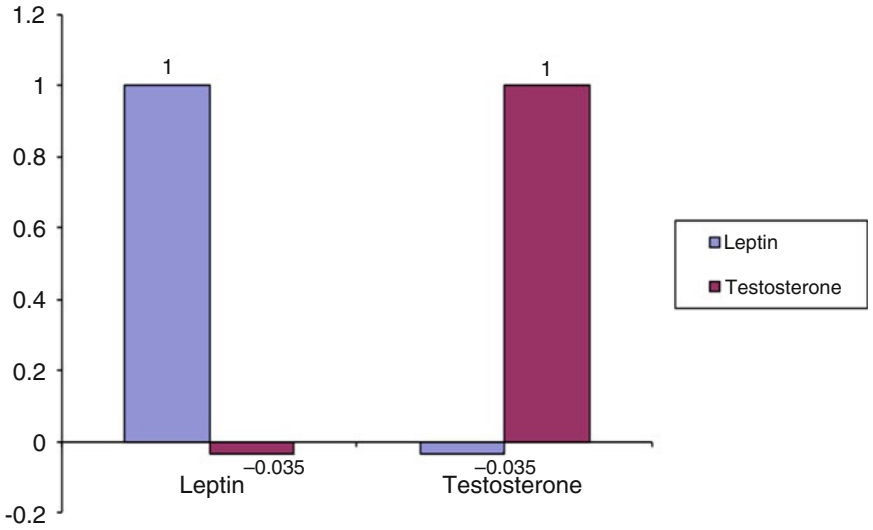

Fig. 150.5 Pearson correlation between leptin and testosterone levels post-treatment in the study group. This figure explains the relationship between serum leptin and testosterone levels on the study group following administration of exogenous testosterone. Leptin and testosterone levels in serum are inversely (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

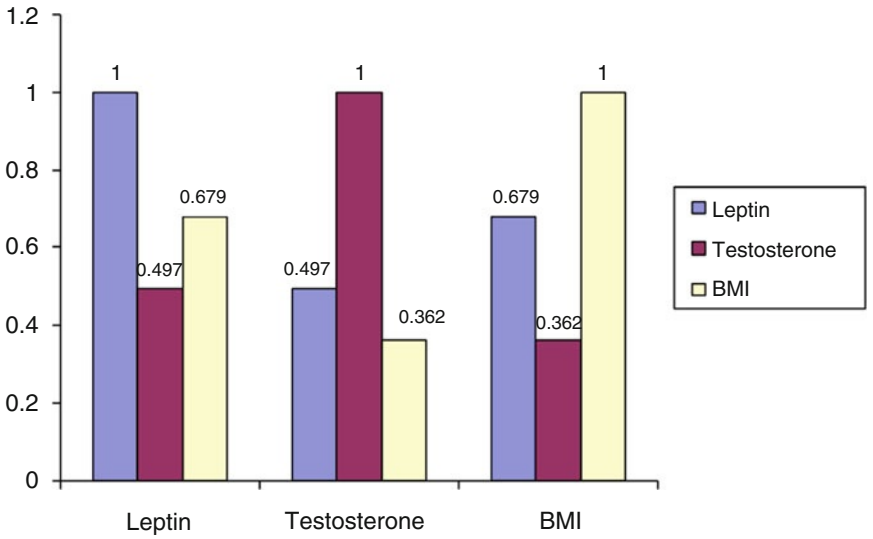

Fig. 150.6 Pearson Correlation between leptin and testosterone levels with BMI in the control group. This figure explains the relationship between serum leptin and testosterone levels and BMI in the control group. BMI and leptin levels show a positive correlation, while leptin and testosterone levels are inversely related. (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

Table 150.3 Mean, standard deviation, *t*-value, and significance levels of testosterone and leptin from pre-treatment and post treatment – Study Group (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

Variable	Mean	SD	*t*-Value	DF	*p*-Value
Testosterone pre-treatment	0.50	0.61	4.373	19	$p < 0.001$
Testosterone post-treatment	6.00	5.53			
Leptin pre-treatment	40.25	37.05	2.576	19	$p < 0.05$
Leptin post-treatment	19.95	19.02			

WHtR has advantages over BMI as it is easier to calculate and understand for the ordinary man as the formula is simpler and the measurement taking is less cumbersome. WC, on the other hand, is more likely to vary with diet and physical activity than the BMI because a replacement of fat by muscle mass might lead to little change in BMI but to clear changes in WC and WHtR. The WHR is not only more complicated to assess, but it also has been shown to be a far weaker predictor of cardiovascular risk factors.

Testosterone treatment may improve body composition, but studies have not sufficiently proven whether it is a significant weight change or change in adipose tissue depots.

A reduction in fat mass was seen with androgen therapy in ancillary data obtained from 32 older men, indicating a reduction in total and abdominal fat (Table 150.3).

150.5 Metabolic Syndrome, Hypogonadism, and WHR – Role of Exogenous Testosterone

Hypogonadism can result in a decreased lean body mass, decreased bone mineral density, and an increased body fat distribution. Baseline androgen levels have been shown to be inversely related with metabolic syndrome, and manifestations, such as higher plasma fasting glucose, increased waist circumference, hypertension, and dyslipidemia, have been seen in such men (Carr et al. 2004). There have been longitudinal and population-based cohorts, which showed that metabolic syndrome can predict the development of hypogonadism (Schroeder et al. 2004).

There is a cause–effect relationship between low serum testosterone levels and visceral obesity, leading to one contributing to the other. This leads us to the fact that obesity is a state of androgen deficiency which is relative.

Waist circumference has been proven to be a more important component of prediction of cardiovascular risk than total fat mass, which is measured by BMI (Yusuf et al. 2005). Visceral abdominal fat has been shown to be an independent predictor of cardiovascular disease.

Therefore, treating visceral abdominal obesity is the main target in the correction of metabolic syndrome. Androgen therapy has been advocated in order to reduce WHR and, hence, visceral abdominal obesity in men. Various studies on testosterone replacement in older men (Katznelson et al. 1996) and hypogonadal men (Rodriguez et al. 2007) have shown a reduction in visceral abdominal obesity.

Therefore, WC appears to be a better indicator of cardiovascular risk than BMI. Moreover, WC is more sensitive to diet and training than BMI because increase of muscle mass might lead to little change in BMI but to clear changes in WC. WHR is not only more complicated to assess, but it also has been shown to be a far weaker predictor of cardiovascular risk factors (Table 150.4).

Table 150.4 Pearson correlations in Study Group pre-treatment (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

	Leptin	Testosterone	BMI
Leptin	1.000	0.209	0.419
Testosterone	0.209	1.000	–0.013
BMI	0.419	–0.013	1.000

This table shows the Pearson correlation coefficients between leptin, testosterone, and BMI of individuals in the study group prior to treatment. Leptin levels are higher in individuals with a higher BMI, that is, obese individuals, while BMI and testosterone seem inversely related.

Table 150.5 Pearson correlations in the Study Group post-treatment (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

	Leptin	Testosterone
Leptin	1.000	–0.035
Testosterone	–0.035	1.000

The table shows the correlation between serum testosterone and leptin levels in the study group following the administration of testosterone. The two parameters are inversely related

Table 150.6 Pearson correlations in the Control Group (The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. Elizabeth et al. 2008)

	Leptin	Testosterone	BMI
Leptin	1.000	0.497 (*)	0.679 (**)
Testosterone	0.497(*)	1.000	0.362
BMI	0.679 (**)	0.362	1.000

This table explains the relationship of serum leptin and testosterone levels with BMI of individuals in the control group
*Correlation is significant at the 0.05 level (two-tailed)
**Correlation is significant at the 0.01 level (two-tailed)

150.6 Application to Other Areas of Disease

As mentioned earlier, short-term testosterone replacement can help in reducing leptin levels in hypogonadal subjects and can further decrease the waist/hip ratio. This has a direct effect on the risk of acute coronary syndromes in the individual (Tables 150.5 and 150.6).

Leptin, on binding to neuropeptide Y (NPY) neurons in the Arcuate nucleus, reduces the activity of these neurons. Satiety is brought about by leptin signals to the brain, indicating that the body has had enough to eat. A homozygous mutation for the leptin gene, which results in severe obesity, leads to a constant desire for food. This condition may be treated by the administration of recombinant human leptin.

Both these concepts require further study before they can be used in clinical practice.

150.7 Conclusion

In hypogonadism, low testosterone levels, raised leptin levels, and anthropometric changes are all associated with each other and are components of the predisposing factors that lead to obesity, which is the cornerstone in the development of metabolic syndrome. WHR was a good predictor of visceral abdominal obesity but it has been recently proven beyond doubt that WC is a better measure of the same.

Summary Points

- The waist–hip ratio (WHR) measurements are considered as a good indicator of visceral abdominal obesity, which predisposes to serious cardiovascular health risks.
- Leptin has a major role in body fat distribution.
- WHR and WC, which are better measures of abdominal fat accumulation, have been implicated as more sensitive predictors of cardiovascular risk than BMI.
- Androgens play an important role in the pathogenesis of metabolic syndrome in men and, conversely, hypogonadism can develop in established metabolic syndrome.
- Androgen therapy has been found to reduce visceral abdominal obesity, which is the main target in the treatment of obesity in hypogonadal men.

Key Points

Table 150.7 Significance of various anthropometric indicators

Anthropometric measurement	Significance
Body Mass Index(BMI)	Commonly used measure of obesity but does not differentiate fat from fat-free mass
Waist–Hip Ratio (WHR)	Commonly used to measure visceral abdominal obesity but is considered as a poor predictor of cardiovascular risk
Waist-to-Height Ratio (WHtR)	Used as a measure of obesity, considered a better measure of cardiovascular risk than BMI
Waist Circumference (WC)	Considered as the most reliable predictor of visceral abdominal obesity and thus of cardiovascular disease

This table lists the various anthropometric indicators and their significance in estimating the risks of obesity

Table 150.8 Key points: leptin – a brief summary

1. *Leptin, a cytokine-like protein* is one of the key factors influencing adipose tissue accumulation and distribution in the body.
2. *Leptin receptor sites* are present in the *Ventromedial and Arcuate nuclei* of the hypothalamus and the *choroid plexus* in the brain.
3. Leptin plays a triggering role as a hormonal determinant of energy balance, in addition to other hormones.
4. Leptin functions as the *satiety factor* – it acts as a communication between the adipocyte and the hypothalamus.
5. Leptin *levels in blood parallel the fat reserves* in the body.

This table outlines role of leptin in the body

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Chapter 151
Usage of Anthropometry to Determine Etiological and Risk Factors in Deep-Tissue Injury

Amit Gefen

Abstract Pressure ulcers, also termed pressure sores, bedsores or decubitus, are a serious complication which is typical of patients with impaired motosensory capacities, and of those confined to a wheelchair or bed for long periods. There is medical evidence associating severe pressure ulcers with life-threatening conditions including sepsis, osteomyelitis, myocardial infarcts, renal failure and multiple organ system failure. The American National Pressure Ulcer Advisory Panel recently defined a *deep tissue injury* (DTI) as a particularly severe type of pressure ulcer which onsets internally, in skeletal muscle tissue overlying weight-bearing bony prominences. A DTI spreads subdermally and often develops to a full-thickness pressure ulcer, i.e. it evolves into an open wound that extends from skin to bone. This chapter is focused on anthropometric features that increase internal mechanical loading in skeletal muscle tissue adjacent to weight-bearing bony prominences, and therefore, increase the risk for DTI. The ischial tuberosities in the pelvis are being considered herein as the main example for this interaction. Specifically, this chapter reviews the effects of whole-body anthropometric measures, such as the bodyweight and body mass index, as well as effects of internal anthropometric characteristics, e.g. the thickness of the gluteus muscles that envelop the ischial tuberosities, or the curvature of the ischial tuberosities, on the internal mechanical conditions in adjacent skeletal muscle tissue, and on the consequent risk for DTI.

Abbreviations

BMI	Body mass index
CII	Compression intensity index
DTI	Deep tissue injury
FE	Finite element
IT	Ischial tuberosities
MRI	Magnetic resonance imaging
NPUAP	National Pressure Ulcer Advisory Panel (U.S.)
PU	Pressure ulcers
SCI	Spinal cord injury

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_151,

151.1 Introduction

Pressure ulcers (PUs), also termed pressure sores, bedsores, or decubitus, are a serious complication which is typical of patients with impaired motosensory capacities and of those confined to a wheelchair or bed for long periods. There is medical evidence associating severe PU with life-threatening conditions, including sepsis, osteomyelitis, myocardial infarcts, renal failure, and multiple organ system failure (Agam and Gefen 2007). The American National Pressure Ulcer Advisory Panel (NPUAP) recently defined a *deep-tissue injury* (DTI) as a particularly severe type of PU which onsets and spreads subdermally (Black 2009). A DTI often develops to a full-thickness PU, that is, it evolves into an open PU that extends from skin to bone. Treatment is typically surgical and combined with aggressive medications to prevent or treat infections. A DTI is currently described by the NPUAP as a "purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue." This clinical manifestation of DTI is the outcome of sustained mechanical deformations in soft tissues, which are warped between loaded bony prominences of the body, for example, the ischial tuberosities (IT) or sacrum, and a supporting surface, such as a mattress or a wheelchair cushion (Fig. 151.1).

Elevated tissue deformations that occur over critical time periods lead to cell death and tissue necrosis via the following mechanisms: (1) collapse or crush of cell membranes or intracellular structures, for example, cytoskeletons (Slomka et al. 2009), (2) hindered diffusion of metabolites in the deformed, denser extracellular space (Gefen et al. 2008), (3) obstruction to blood flow at the geometrically distorted capillaries and possible capillary occlusion by clots, which leads to ischemia (Linder-Ganz and Gefen 2007), (4) oxidative damage from free radicals that are flushed into the tissue when capillaries reopen, for example, if the body posture has been changed after a period of ischemia (Tsuji et al. 2005); such reperfusion events cause both direct cell death by free radicals reacting with intracellular chemical compounds and increased permeability of capillaries that leads to edema, which in turn increases localized tissue and cellular deformations, and (5) impaired lymphatic flow, which, similarly to the dysfunction of the capillary bed, allows for more edema to build up and exacerbates mechanical loading conditions at the tissue and cellular levels (Pieper 2007) (Table 151.1).

Clearly, all the damage pathways listed above are either directly or indirectly caused by mechanical deformations in soft tissues. Skeletal muscle tissue is especially susceptible to these deformation damage pathways since for many anatomical locations, and for the clinically relevant supported body postures (e.g., recumbency and sitting), muscles directly overlie bony prominences, for example, the gluteus muscles which pad the IT during sitting. Indeed, soft tissues around the IT are one of the most frequent anatomical locations for PU and DTI, particularly in patients who use a wheelchair (Gefen 2007a). Not only that muscle tissue at these locations is subjected to high deformations as the weight-bearing IT bones sag into the viscoelastic muscle tissue while sitting or lying (Fig. 151.1), muscle is also rich with capillaries and is a metabolically more demanding tissue compared with adipose tissue, fascia, or skin. These factors, altogether, make skeletal muscle tissue highly susceptible to deformation damage. Accordingly, this chapter is focused on anthropometric features that increase internal mechanical loading in skeletal-muscle tissue adjacent to weight-bearing bony prominences, and, therefore, increase the risk for DTI. The IT is being considered herein as the main example for this interaction. Specifically, this chapter reviews the effects of whole-body anthropometric measures, such as the bodyweight and body mass index (BMI), as well as effects of internal anthropometric characteristics, for example, the thickness of the gluteus muscles that envelop the ITs, or the curvature of the ITs, on the internal mechanical conditions in adjacent skeletal muscle tissue and on the consequent risk for DTI.

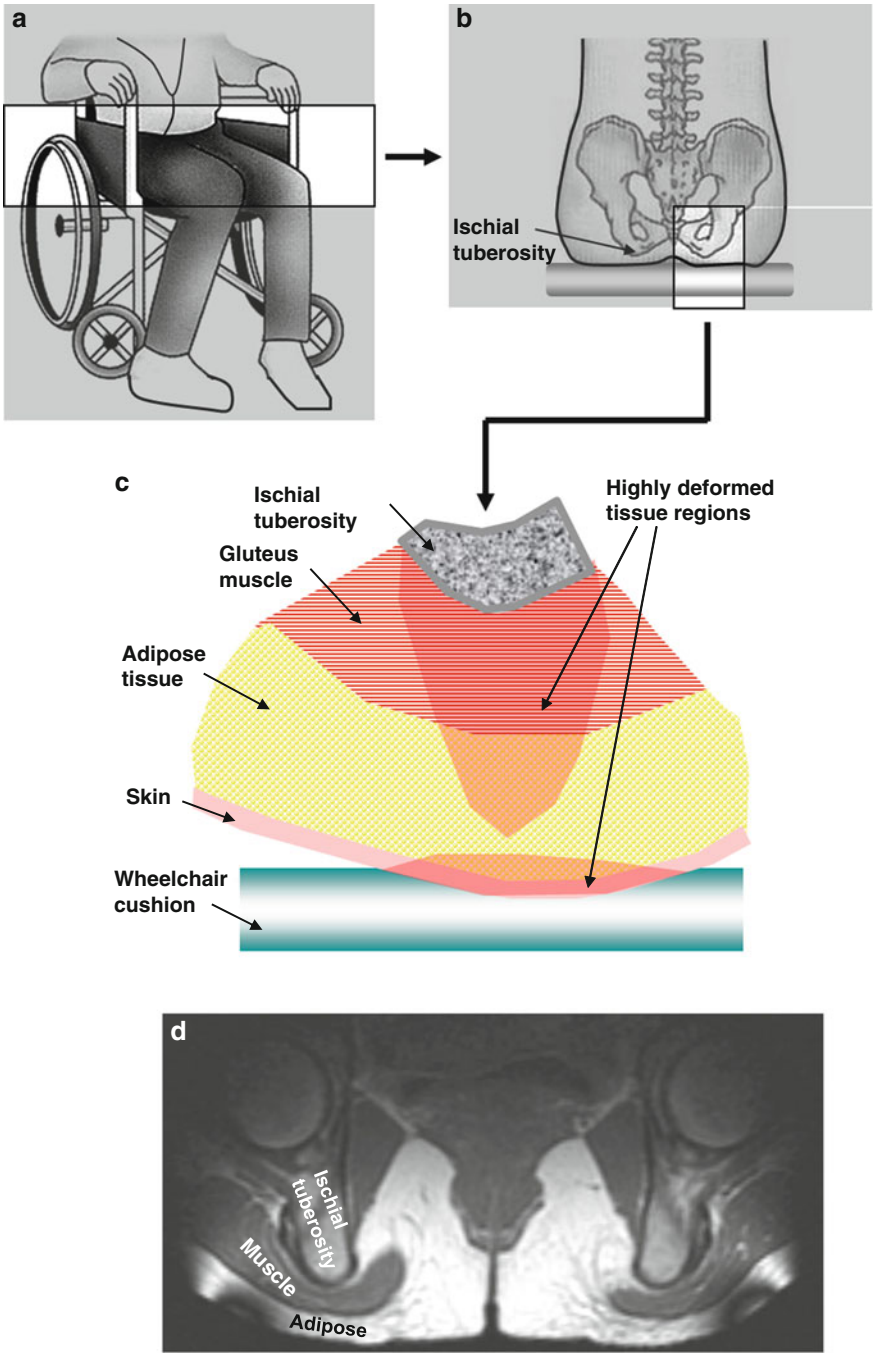


Fig. 151.1 A deep-tissue injury is formed in skeletal muscle due to sustained tissue deformations. For example, in individuals confined to a wheelchair (**a**), the soft tissues of the buttocks are being deformed between the ischial tuberosities and the wheelchair cushion (**b**), which induces elevated tissue deformations, particularly in gluteus muscle tissue adjacent to the ischial tuberosities, as shown schematically in (**c**) and in a magnetic resonance image of the buttocks of a sitting female in (**d**). Internal deformations that occur in weight-bearing soft tissues under bony prominences can be clearly demonstrated by means of weight-bearing magnetic resonance imaging (MRI), as shown in the bottom frame for the muscle and adipose tissues that are deformed under the ischial tuberosities of the buttocks during sitting in an Open-MRI system

Table 151.1 Key facts of anthropometry usage in deep-tissue injury

1. Obesity and reduced gluteal muscle thickness associated with disuse atrophy are anthropometric features that biomechanically increase the risk for DTI.
2. Flattened ischial tuberosities are associated with a faster occurring, more severe DTI.
3. New clinical risk-assessment tools designed to identify patients at risk for a DTI should screen for these anthropometric changes, for example, by employing imaging modalities to measure these internal bone and muscle changes, which are particularly characteristic of the population of patients with spinal cord injuries.

This table summarizes the key facts of anthropometric usage in deep-tissue injury (DTI). It specifically lists obesity, reduced thickness of the glutei muscles, and flattened ischial tuberosities as anthropometric characteristics that make patients more prone to DTI, and who should be screened for in DTI risk assessments

151.2 Bodyweight and Body Mass Index

Using the weight categories of the World Health Organization (underweight denoting BMI < 18.5, obese as BMI > 30), epidemiological studies report higher prevalence of PU and DTI in patients with both abnormally low and abnormally high bodyweights (VanGilder et al. 2009). Surgical patients who are morbidly obese (BMI > 40) were identified in up-to-date nursing literature to be especially vulnerable to DTI (Baugh et al. 2007), which apparently puts an end to the myth that obese patients are more protected from PU, because they have 'more padding'. The understanding that obesity is actually a serious risk factor for DTI is already implemented in practice, in the Waterloo risk assessment tool, which is commonly used in the UK for evaluating the individual's risk for developing a PU. Based on expert views and clinical experience (but still lacking sufficient basic-science foundations), the Waterloo risk assessment tool assigns more risk scores to patients having BMI > 30 and to those with BMI < 20 kg/m^2 (http://www.judy-waterlow.co.uk/). Biomechanical theory can provide the missing theoretical foundations for this clinical practice, as follows.

An analytical biomechanical approach, employing the contact mechanics theory, was used by Gefen (2008). Based on calculations of muscle-tissue distortion in a simplified model of a spherical-shaped bony prominence that sags into an elastic muscle layer (Fig. 151.2a), a compression intensity index (CII) was defined as

$$\mathrm{CII} = \frac{\mathrm{BW}}{\sqrt{R \cdot t}} \tag{151.1}$$

where BW is the bodyweight in kilogram, R is the radius of curvature of the weight-bearing bony prominence in millimeter, and t is the thickness of skeletal muscle tissue overlying that bony prominence, also in millimeter. The higher the CII is, the more intense the localized loading in the soft tissues will be. The CII is particularly useful for understanding the long-term effects of obesity on internal loading in muscle tissue. Obesity involves loss of lean muscle mass and thickness due to a sedentary lifestyle, by a process called muscle-disuse atrophy. As obesity worsens, the BW increases, whereas the muscle thickness t decreases. The decrease in t over time is accelerated if there are neuromuscular impairments, such as after a spinal cord injury (SCI) (Berry et al. 2008). The increase in BW and the decrease in t both act to increase the CII, but, for lower muscle thicknesses t, a rise in BW will have a more substantial adverse effect, as depicted in the plot in Fig. 151.2b for anthropometric dimensions representative of the IT bone and the biological variability in thicknesses of the gluteus muscles of the buttocks. It is shown in these plotted biomechanical model predictions that morbidly obese subjects, with BMI of 60, develop at least 1.5-times higher loads in skeletal muscle under the IT compared to subjects with a normal BMI of 25. It is further shown in Fig. 151.2b that

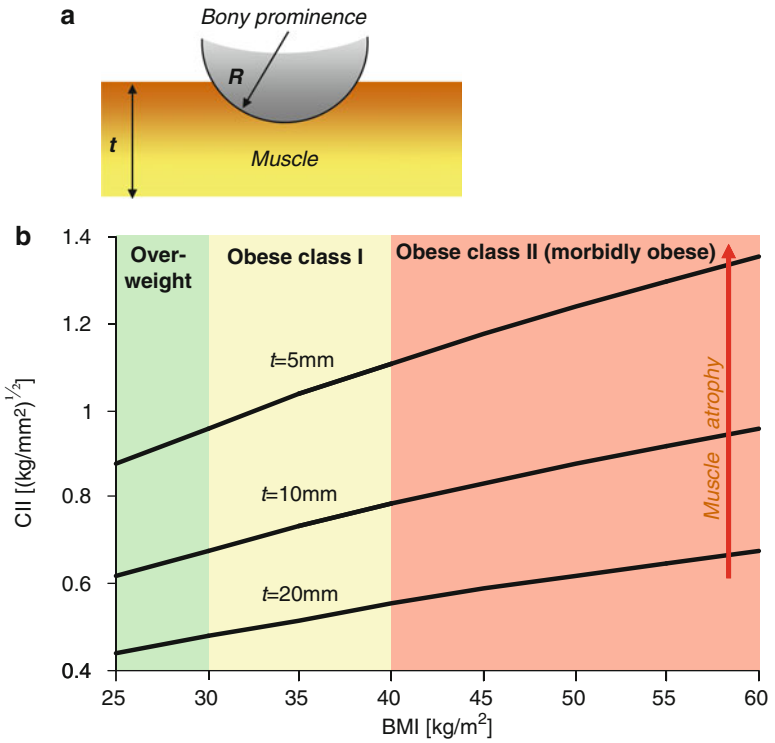
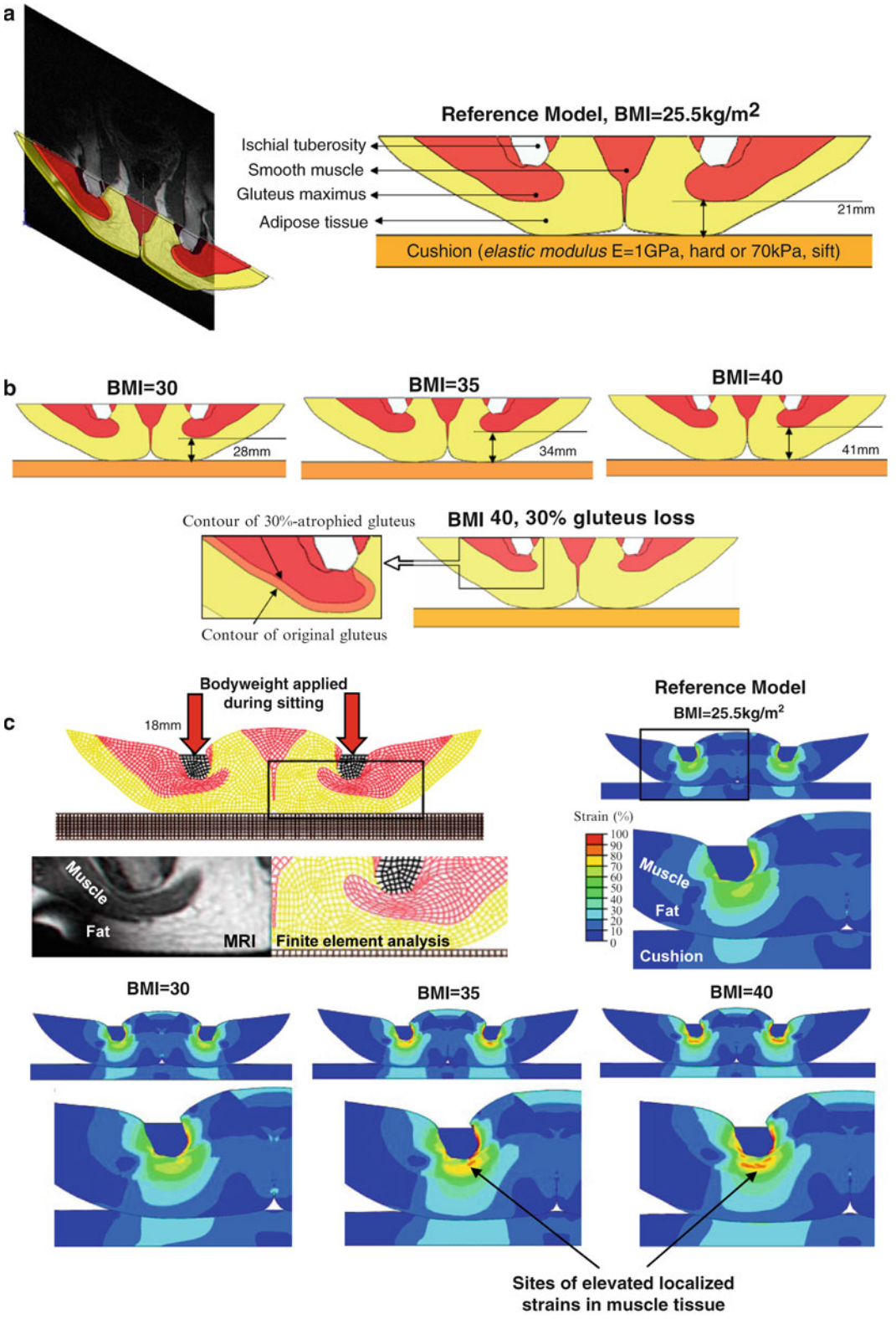


Fig. 151.2 The compression intensity index (CII) for evaluating the effect of the body mass index (BMI) on internal loading in skeletal muscle tissue deformed under a weight-bearing bony prominence. (**a**) The biomechanical model used to formulate the CII. (**b**) Curves of rise in CII with an increase in BMI for muscle tissue thicknesses *t* of 20, 10, and 5 mm, the last two values being representative of gluteal muscle atrophy (Gefen 2008). The body height was taken as 1.75 m for all calculations shown in this figure, and the bony prominence was assumed to be the ischial tuberosity, with radius of curvature of 20 mm (Gefen 2008). The categories of obesity (used in the horizontal axis) are those of the World Health Organization

these internal muscle loads can rise by as much as threefold from non-obese to morbidly obese conditions if a disuse muscle atrophy, reducing muscle thickness to 25% of its original thickness, also occurs. This extent of decrease in muscle thickness is expected in patients with neuromuscular impairments. For example, magnetic resonance imaging (MRI) studies of thickness of the gluteus muscles under the IT in patients one year post-SCI showed that their muscle thickness was 6 ± 1 mm, whereas the thickness of controls was 21 ± 2 mm (Linder-Ganz et al. 2008).

More complex modeling to study the effects of obesity on internal tissue loading in the buttocks, which considered a more anatomically realistic buttock structure, was conducted by Elsner and Gefen (2008). In their work, mechanical strain (relative tissue deformation) and stress (force per unit area of tissue) magnitudes and distributions were determined in the gluteus muscles and enveloping fat of the seated buttocks, using finite element (FE) modeling. Elsner and Gefen (2008) specifically studied the internal loading in coronal slices through the seated buttocks in five cases: a 'reference model' representing BMI = 25.5 kg/m^2 (non-obese), BMI = 30 kg/m^2 (grade-I obesity), BMI = 35 kg/m^2 (grade-II obesity), BMI = 40 kg/m^2 (grade-III morbid obesity), and BMI = 40 kg/m^2 also involving 30%-atrophied glutei (Fig. 151.3). Their reference model was developed from a non-weight-bearing MRI scan of the


a
Reference Model, BMI=25.5kg/m2
Ischial tuberosity
Smooth muscle
Gluteus maximus
Adipose tissue
21mm
Cushion (elastic modulus E=1GPa, hard or 70kPa, sift)
b
BMI=30
28mm
BMI=35
34mm
BMI=40
41mm
Contour of 30%-atrophied gluteus
BMI 40, 30% gluteus loss
Contour of original gluteus
c
Bodyweight applied during sitting
18mm
Muscle
Fat
MRI
Finite element analysis
Reference Model
BMI=25.5kg/m2
Strain (%)
100
90
80
70
60
50
40
30
20
10
0
Muscle
Fat
Cushion
BMI=30
BMI=35
BMI=40
Sites of elevated localized strains in muscle tissue

buttocks of a non-obese male, who was sitting on a rubber tire so that his soft tissues of the buttocks were mostly unloaded (Fig. 151.3a). Contours of bones and soft tissues were detected and segmented from the MRI to form the geometry of the reference model, using solid modeling software (Fig. 151.3a). The reference model was then modified, using the solid modeling software, to virtually form the anthropometric changes in the buttocks that are associated with increasing levels of obesity (Fig. 151.3b). The increase in volume of adipose tissue in the buttocks was estimated by employing an empirical relation between BMI and percentage body fat (Jackson et al. 2002):

$$\text{Body fat}(\%) = 3.76\text{BMI} - 0.04\text{BMI}^2 - 47.80 \tag{151.2}$$

In order to construct the variant BMI models shown in Fig. 151.3b, so that they together represent the biomechanical outcomes of a process of gradually gaining weight, the superficial border of fat tissue in the reference model was stretched out uniformly, until the percent increase in body fat predicted by eq. 2 was accomplished for each BMI level. The additional model, built to represent a combination of obesity and disuse muscle atrophy (Fig. 151.3b, bottom), was identical to the BMI = 40 kg/m^2 model in all aspects but the volume of skeletal muscle tissue, which was reduced by 30%, which is a reasonable muscle loss expected in the chronic phase of SCI (Weaver et al. 2007; Linder-Ganz et al. 2008). The reference model and all the model variants in Elsner and Gefen (2008) were solved by simulating the vertical sagging of the IT toward the sitting surface during weight-bearing sitting.

Consistent with the mathematical modeling used to develop the CII ((151.1), Fig. 151.2), the study of Elsner and Gefen found that mechanical strains and stresses in skeletal-muscle tissue of the buttocks increase with the extent of obesity (Fig. 151.3c). The trends for peak strain and stress measures in skeletal muscle of the seated buttocks are shown in Fig. 151.4, as a function of the BMI. It is evident from these data that peak compression and shear strains in muscle tissue increase by approximately 7% for each five BMI units added above a BMI of 25 kg/m^2. The peak tensile strains in muscle tissue increase even more rapidly, by about 16% for each five BMI units added. Peak compression stresses in muscle tissue increase by approximately 4 kPa for each five BMI units added, whereas tensile and shear stresses increase more moderately, by about 2 kPa for this extent of rise in BMI. The increase in BMI at the obese levels results in not only an increase in peak muscle strains and stresses but also a dispersion of the concentrated peak strain region in muscle tissue under the IT into several such regions (Fig. 151.3c). Disuse atrophy in the gluteus muscles, on top of obesity, escalated the intensity of mechanical loads in muscle tissue under the IT, particularly for tensile stresses (which were 1.3-times higher for atrophied muscles) and shear stresses (1.2-times higher), and also increased the region in muscle tissue that is subjected to concentrated loads (Elsner and Gefen 2008).

Fig. 151.3 The biomechanical model of Elsner and Gefen (2008) for studying the effects of obesity on internal tissue loading in the buttocks. (**a**) The 'reference model' geometry, representing a coronal slice through the seated buttocks of a person with a normal body mass index (*BMI*); the model geometry was built from an MRI scan of a sitting male (*left frame*). (**b**) Variant model geometries, representing increasing degrees of obesity (*top row*) and obesity combined with a disuse muscle atrophy (*bottom*). (**c**) Magnitudes and distributions of internal mechanical compressive strains in skeletal muscle and fat tissues of each of the BMI models, obtained from computer analyses of tissue deformations, which are compared to tissue deformations seen in the weight-bearing MRI scan for validation (*top left frame*). Sites of elevated localized mechanical strains in muscle tissue, identified as such by the computer models of Elsner and Gefen (2008), are marked in yellow and red colors in the color-coded maps in (**c**). Internal strains in muscle tissue maximize directly under the ischial tuberosities and fade away medially and laterally to these bones. The intensity of muscle-tissue strains and the number of sites of elevated strains in muscle increase with the level of the body mass index (BMI)

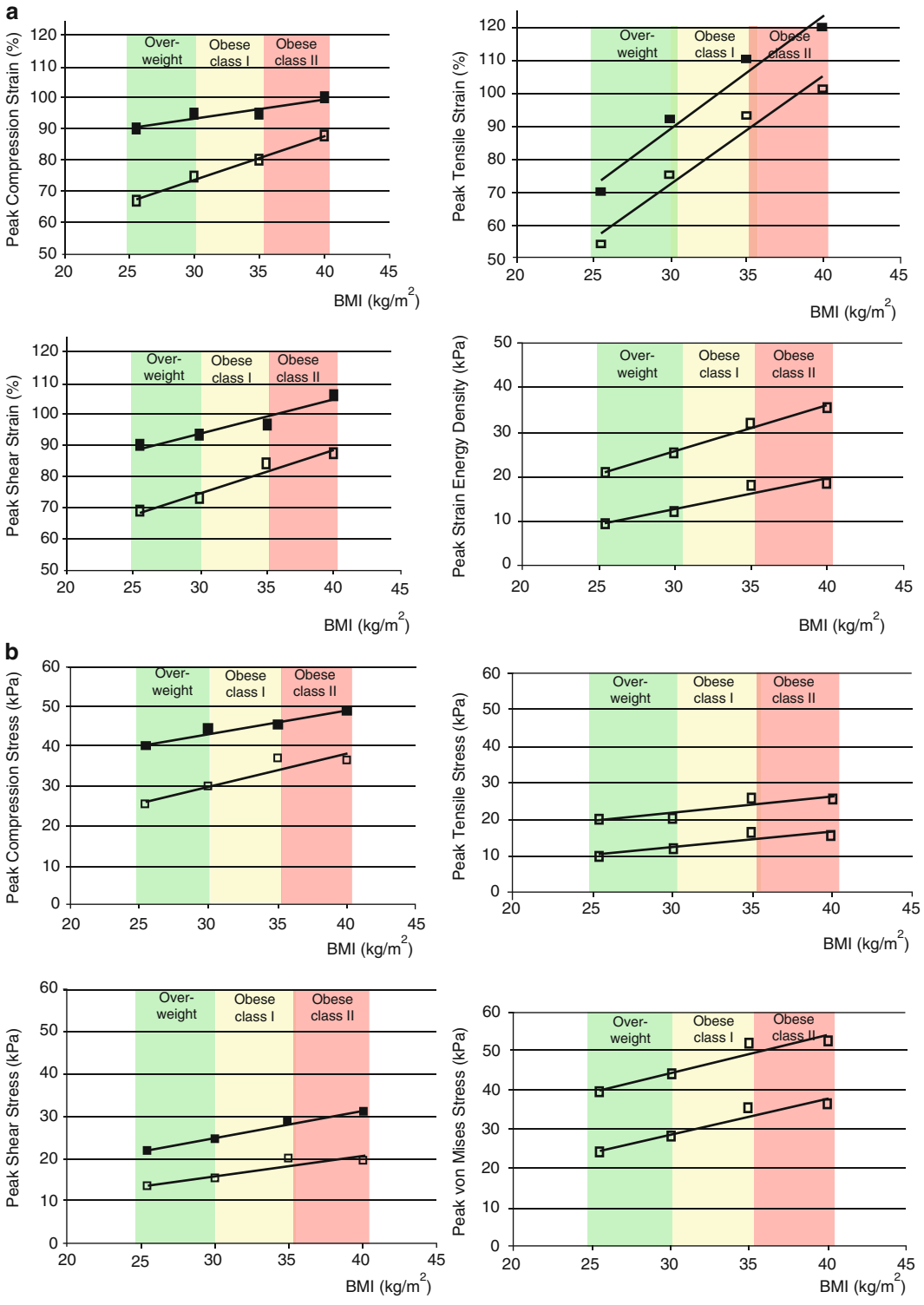


Fig. 151.4 The rise predicted in (**a**) mechanical strain measures in gluteal muscle tissue and (**b**) mechanical stress measures in muscle for increasing levels of body mass index (*BMI*) in the obesity categories, based on the biomechanical modeling study of Elsner and Gefen (2008), for sitting on a hard surface (■) and on an elastic cushion (□). Internal tissue strains and stresses in the gluteus are consistently higher for sitting on a hard surface compared to sitting on an elastic cushion, regardless of the level of the body mass index (*BMI*). The categories of obesity are those of the World Health Organization

The FE analyses of Elsner and Gefen (2008), representing growing extents of obesity (Fig. 151.3), clearly show a trend of increase in all the geometrical distortion and loading measures for the internal soft tissues, with the BMI level (Fig. 151.4). Measurements of seat-interface pressures generally report that the highest pressures occur in thin individuals, not in overweight ones (Kernozek et al. 2002), but epidemiological studies indicate that, among individuals with SCI, obesity is common (Weaver et al. 2007). Moreover, recent case-series reports state that obesity could be a risk factor for DTI (Baugh et al. 2007; Gallagher 2005). These seemingly contradicting indications can be settled if it is recalled that interface pressures of the seated buttocks are not a reliable predictor of subdermal tissue loads (Gefen and Levine 2007). The study of Elsner and Gefen (2008) supports this, because it demonstrated that seat-interface pressures at the different BMI levels changed only slightly, by no more than 10%, despite a 1.5-times increase (on average) in strains and stresses at skeletal muscle tissue when the BMI was increased from 25 to 40 kg/m^2 (Fig. 151.4).

In subjects with SCI, the progressive increase in bodyweight and BMI post-injury (Weaver et al. 2007) is physiologically coupled with a process of loss of muscle mass (Linder-Ganz et al. 2008). A recent study comparing BMI-matched groups of subjects with SCI and controls (BMI was approximately 24 kg/m^2 in the two groups) concluded that the total lean tissue mass in SCI was 8.9 kg lower (Jones et al. 2003), which clearly demonstrates that muscle–fat ratios can be substantially different between SCI and controls, despite similar BMI values. In this regard, Elsner and Gefen (2008) showed that inducing some muscle atrophy (30%) on their BMI = 40 kg/m^2 FE model resulted in a substantial increase in all measures reflecting geometrical distortion and internal loading of muscle tissue with respect to the no-atrophy condition. This increase was not only in peak strain and stress values, but also in the size of the affected tissue regions, which is unsurprising considering the reduced muscle thickness subjected to elevated loading by the IT in disuse atrophy coupled with obesity. This result of Elsner and Gefen (2008) highlights that obesity and muscle atrophy, which are both typical of the chronic phase of SCI, contribute together to the state of elevated tissue loads, which consequently increases the likelihood of DTI. Since physical exercise is well known to counteract both obesity and muscle atrophy in individuals with SCI, a practical interpretation of this could be that exercise is highly recommended for the SCI population, wherever possible.

Although there is an association between BMI and adiposity, BMI is a poor evaluator of adiposity or of the lean tissue mass on an individual basis (Kuk and Ross 2007). This is particularly true for subjects with SCI, for whom there are no specific measures of obesity. Hence, one topic that requires further research is the development of specific anthropometric measures for the SCI population, particularly for characterizing obesity and loss of muscle mass and thickness. For example, surface anthropometry, such as skinfold measurements, has been suggested to evaluate adiposity better than BMI (Nevill et al. 2006), and this has to be tested specifically for the SCI population. Another topic that warrants future research is the effect of the other side of the extreme in the BMI range, namely, underweight conditions, on the risk for DTI. This question has not yet been investigated at all, from an anthropometrical or biomechanical point of view. However, there are medical reports that malnourished patients face higher risk for PU (Russell 2000), and indeed, the Waterloo risk assessment tool, which is in practical clinical use, already assigns greater risk scores to patients with BMI < 20 kg/m^2 (http://www.judy-waterlow.co.uk/). From anthropometrical and biomechanical aspects, underweight conditions impose a problem of counteracting the effects of bodyweight and tissue cushioning in the seated buttocks, which is analogous to the questions related to obesity discussed in detail earlier. Future research work should therefore look into effects of underweight and thinning of fat and muscle tissues and their potential role in influencing the risk for DTI.

151.3 Thickness of the Musculature Under Loaded Bony Prominences

Linder-Ganz et al. (2008) used Open MRI to compare anthropometric characteristics of internal hard- and soft-tissue structures in the seated buttocks between subjects with SCI, 1–35 years post-injury, and controls (six subjects were included in each group). The authors found significant differences between the groups (Table 151.2); specifically, gluteus muscle thicknesses under the IT were approximately 2.3-times higher in the controls ($p < 0.01$, Table 151.2), indicating the extent of atrophy in the muscles of the subjects with SCI. The loss of muscle mass induced an average of 36% less ($p < 0.01$) overall soft-tissue thickness under the ischial tuberosities in the SCI group (muscle and adipose tissues taken together for this calculation). This is despite the fact that the fat thickness in the SCI group was slightly higher (but not statistically significantly higher), and also that the mean bodyweight in the SCI group was 8% higher than that of the control group (Table 151.2). From the muscle thickness data of the SCI group, it could be generally seen that the decrease in their gluteal thickness (and also, in their overall soft tissue thickness) under the ischial tuberosities became more prominent with the time post SCI (Linder-Ganz et al. 2008, 2009). These measurements were consistent with numerous previous literature that overall reports loss of muscle mass in the chronic phase of SCI (Castro et al. 1999; Giangregorio and McCartney 2006), but Linder-Ganz et al. (2008) were the first to quantify this loss specifically for the gluteus muscles in a sitting posture, which is relevant to sitting-acquired DTI.

In order to study potential effects of these group differences on the risk for DTI in the SCI population, Linder-Ganz and Gefen (2009) later developed an FE-based algorithm for simulating DTI onset and progression in muscle tissue overlying the IT, based on experimental data from their previous animal studies, including a muscle cell-death injury threshold and an injury-stiffening damage law for muscle tissue (Fig. 151.5). Their computational simulations successfully reproduced clinically reported 'crater' shapes of DTI in muscles (Fig. 151.5) that progress to full-thickness muscle injury and then spread to more superficial tissues, until eventually penetrating the skin. The shapes of the simulated DTI obtained in the study of Linder-Ganz and Gefen (2009), as shown in Fig. 151.5,

Table 151.2 Comparisons of anthropometric characteristics relevant to deep-tissue injury between spinal cord injury patients and controls

Parameter	Controls	SCI
Bodyweight (kg)	70.5 ± 15.7	76.3 ± 8.9
Radius of curvature of the ischial tuberosities^{+} (mm)	12 ± 2	19 ± 4*
Distance between the ischial tuberosities (horizontal) (cm)	122 ± 15	125 ± 10
Thickness of the gluteus muscle under the ischial tuberosities^{+} (cm)	21 ± 3	9 ± 10*
Thickness of the adipose tissue under the ischial tuberosities^{+} (cm)	12 ± 4	13 ± 8
Overall soft-tissue thickness (muscle + fat) under the ischial tuberosity^{+} (cm)	33 ± 5	21 ± 12*

(+) Left and right body sides averaged per each subject. *$p < 0.01$ in an unpaired, two-tailed t-test.
This table specifies the mean values ± standard deviations of the internal anatomy of the buttocks of subjects with spinal cord injury (SCI), 1–35 years post the injury, and those of controls (each group included six subjects). All data were measured from Open MRI scans of the participating subjects when they were sitting on a rubber tire in the MRI, with their soft tissues being unloaded under the ischial tuberosities (Linder-Ganz et al. 2008, 2009)

Fig. 151.5 (continued) simulations, the DTI first appears after 15 min of continuous sitting and is increasing monotonically in size to about 10% of the total gluteus muscle volume, until approximately 75 min, where it quickly escalates to occupy 53% and 74% of the muscle volume at 90 and 110 min, respectively. It was assumed in these simulations that the glutei muscles are 70% atrophied (that is, 70% of the normal muscle mass was lost), that the radius of curvature of the ischial tuberosities is 11 mm, and that the buttock is seated on a cushion with stiffness of 100 kPa

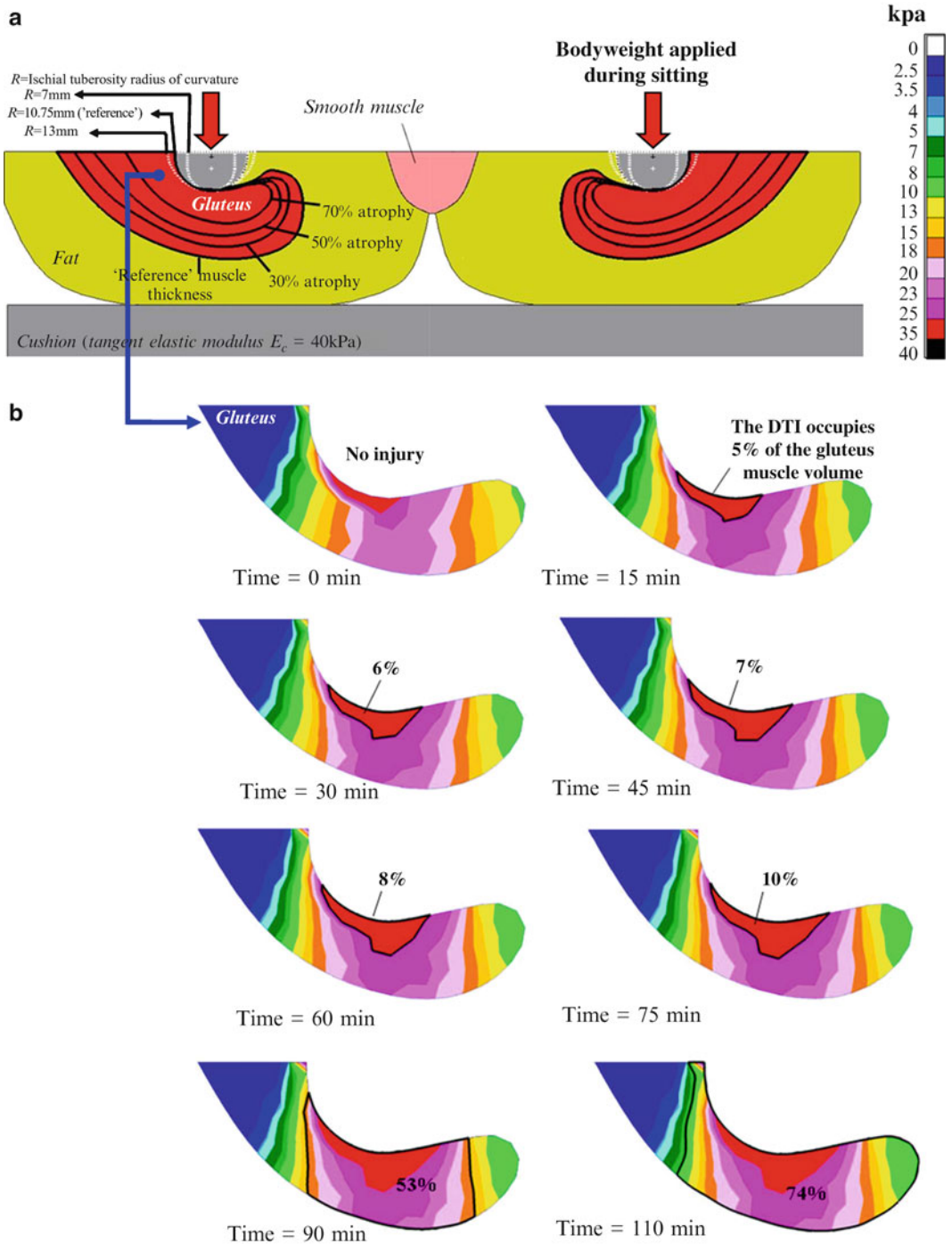


Fig. 151.5 Computer simulations of a deep-tissue injury (*DTI*) occurring in a severely atrophied gluteus muscle as a result of prolonged sitting with no relief of the bodyweight loads. (**a**) The biomechanical model, which included a time-dependent cell-death injury threshold for skeletal muscle and was able to represent different degrees of muscle atrophy (Linder-Ganz and Gefen 2009). (**b**) The resulted distributions of internal mechanical stresses in the gluteus at different time points over a total simulated time of 110 min are depicted using a color scale, and the computer-predicted boundaries of the DTI are marked at each time point (equal to or over 15 min) using *solid lines*. In this set of

markedly resemble DTI shapes in humans, which were recently characterized by means of computed tomography and ultrasound imaging (Ohura et al. 2007). The biomechanical FE modeling analyses of Linder-Ganz and Gefen (2009) have identified the level of muscular atrophy as being the most important predictor of the rate and final extent of the DTI (Fig. 151.5), with a thinner muscle predicting a faster injury, which results in a larger percentage of non-viable muscle tissue. Moreover, some simulations of severe muscle atrophy levels, particularly those representing loss of over 50% of the gluteal muscle mass, showed concurrent DTI-onset events at multiple sites that fused with time to form a larger wound. The final extent of tissue damage over a long time, over 90 min, grew exponentially with the degree of loss of muscle thickness.

151.4 Sharpness of Loaded Bony Prominences

In their Open MRI study, Linder-Ganz et al. (2008) compared the radius of curvature of the IT bones, which were scanned during sitting, between their groups of subjects with SCI and controls ($n = 6$ in each group). Interestingly, the IT radii of curvature were approximately 1.6-times higher in the paraplegics compared with controls ($p < 0.01$, Table 151.2), indicating significant changes in bone structure in addition to the soft-tissue changes discussed earlier, due to the chronic sitting in the SCI group. Similarly to the muscle-thickness data, the IT curvature data from the SCI group also generally indicated that changes in IT shape became more pronounced with the time post-SCI.

Linder-Ganz and Gefen (2009) further studied the effect of the surface curvature of the IT, the 'IT sharpness', on the predicted prognosis of DTI, using FE computer simulations employing the model in Fig. 151.5. They reported that the resulting data were more difficult to interpret than those pertaining to the effect of the muscle thickness under the IT. Specifically, an IT bone with a larger radius, namely, a 'flattened' IT, eventually resulted in a wider damage region in the muscle post 90 minutes, despite the fact that more 'sharp' IT bones induce higher peak mechanical stress values during sitting (Linder-Ganz and Gefen 2009). Injury rate analyses of Linder-Ganz and Gefen (2009) further showed that a flattened IT produced the damage faster than a sharp IT. This is consistent with the previously reported results of Gefen (2007b), who employed a simpler, analytical modeling approach that indicated an increase in the extent of injury for larger IT radii at long times, over 2 h. To summarize this point, although a sharper weight-bearing IT appears to induce higher localized mechanical stresses in muscle tissue overlying the IT during sitting, these stress concentrations are confined to a relatively small area adjacent to the bones (Linder-Ganz and Gefen 2009). Accordingly, if a DTI develops under sharp IT, it will occupy a relatively small volume of muscle tissue (less than 10% of the total volume), at least during the first hour after the DTI onsets (Fig. 151.5). However, flattened IT bones load a larger part of the glutei muscles when they bear the bodyweight, and if muscle stresses exceed critical levels (specified in Linder-Ganz and Gefen 2009), for example, if the muscle is atrophied and thin, and/or if a rigid support is used, the size of the resulting DTI is eventually greater (Linder-Ganz and Gefen 2009). The fact that larger muscle-tissue volumes are affected by a flattened IT and become necrotic activates a positive feedback that spreads the injury faster, as the large necrotic-tissue volumes become stiffer, and, therefore, produce significant inhomogeneities in the tissue material, which accelerate the injury spiral (Linder-Ganz and Gefen 2004; Gefen et al. 2005). The more detrimental effect of a flattened IT with respect to a sharp IT, as found in the Linder-Ganz and Gefen (2009) study, is highly relevant to the clinical setting, considering that individuals with SCI tend to have flattened IT shapes compared with controls (Table 151.2), likely owing to bone loss and shape adaptation. Individuals with SCI whose ITs are flattened might therefore become more prone to massive DTI, in the sense that if the DTI onsets, it will spread faster and will eventually

occupy a larger percentage of volume of their muscle tissues. Taken together, the findings of Linder-Ganz and Gefen (2009) indicate that loss of muscle mass per se is a major risk factor for DTI in patients who are chairfast (and likely, also in those who are bedfast), but IT bone loss and shape adaptation of the IT, which were both previously observed experimentally in subjects with SCI (Linder-Ganz et al. 2008), are associated with faster occurring, more severe DTI. Accordingly, both muscle atrophy and hard-tissue changes appear to contribute to the higher susceptibility of SCI patients to DTI.

151.5 Applications to Other Areas of Health and Disease

Many believe that PU and DTI are a problem restricted to the elderly population and particularly to patients at the end of their life. While elderly, especially bedfast or chairfast elderly, are indeed at high risk, there are many other populations of young individuals, who are at high risk. These include individuals with SCI, those with a serious neurological or neuromuscular disease (such as multiple sclerosis or amyotrophic lateral sclerosis), patients who are admitted for orthopedic or cardiovascular surgeries, and even pediatric patients who cannot move freely or who are connected to tubing for long periods (e.g., for ventilation or intravenous drug administration). With an ever-growing elderly population, the impact of PU and DTI on human society is expected to escalate quickly over the next few years, and this necessitates development of screening measures to identify patients who are at the greatest risk, so that attention of the medical staff can be prioritized to giving them preventive care. The quickest, most economical means for such screening, which could become available through nearly all nurses in clinical settings, are classic anthropometric measures, such as BMI and adiposity. More complex anthropometric measures, requiring some imaging technology, for example, ultrasound, could also be employed in the screening process where possible, to identify, for instance, patients with either thin musculature or irregularly sharp/flat IT. New risk-assessment procedures that are specific to DTI should therefore include such anthropometric measures and weigh them in the calculation of risk scores in order to lower the prevalence of DTI in the large number of susceptible populations. Finally, much of the contents of this chapter were focused on overweight and obesity as anthropometric measures which indicate a greater risk for DTI. Bariatric medicine, the branch in medicine that deals with obesity and its complications, is a relatively young field of medical expertise, which is growing day by the day, corresponding to the rise in sizes of populations of obese individuals in Western countries. In this chapter, it has been well demonstrated that bariatric patients are especially susceptible to DTI because of the high mechanical loads that are developed internally in their soft tissues at weight-bearing postures, such as sitting. Hence, the data presented in this chapter are important to several branches in medicine where PU and DTI are relevant, including rehabilitation, gerontology, neurology, and bariatrics.

151.6 Practical Methods and Techniques

Though BMI is a relatively simple anthropometric measure to record in large population studies of DTI, internal anthropometric data, for example, thicknesses of the glutei muscles and radii of curvature of the IT, are more complicated to obtain. In the present chapter, these internal anthropometric data were derived from MRI scans, which provide high accuracy but might not be economical in large population studies or as a clinical routine to conduct risk assessments for DTI. However, if measurements of

thickness of the glutei muscles and radius of curvature of the IT are obtained by means of ultrasound, they can be integrated into large population studies at reasonable costs. Ultrasound measurements of muscle thickness and bone curvature can also be included in new cost-effective risk-assessment scales for DTI, in facilities such as nursing homes, community clinics, small hospitals, and rehabilitation centers where, even in the future, it may appear either impractical or too expensive to conduct MRI scans. The potential for employing ultrasound scans in DTI risk assessments is discussed in detail in Gefen (2008).

Summary Points

- Deep-tissue injury is a serious category of pressure ulcers. A DTI onsets in skeletal muscle tissue overlying load-bearing bony prominences and then progresses subdermally until skin breakdown occurs.
- This chapter reviewed some key anthropometric characteristics that raise the risk for development of DTI by increasing the internal mechanical loads transferred to gluteal skeletal-muscle tissue of the seated buttocks via the IT, which were used herein as an example to study the bone–muscle interactions.
- The specific anthropometric characteristics referred to in this chapter were the bodyweight and BMI, and, internally, the thickness of the glutei muscles and the curvature of the IT.
- It was shown that obesity (defined as BMI ≥ 30 kg/m^2) and disuse atrophy (loss of over 30% of the gluteal muscle volume or reduction exceeding 50% in thickness under the IT), which are typical of the chronic phase of spinal cord injuries, each contributes to the state of elevated muscle loads.
- When obesity and muscle atrophy coexist, internal loads in muscle tissue under the IT escalate substantially. Hence, obesity and reduced gluteal muscle-tissue thickness are anthropometric features that biomechanically increase the risk for a DTI.
- Loss of bone tissue mass, which is also known to occur during the years after an SCI, affects the shape and curvature of the IT, and gradually flattens them. Flattened ITs were associated herein with a faster occurring, more severe DTI.
- The anthropometric information presented in this chapter is important to several branches in medicine where PU and DTI are relevant, including rehabilitation, gerontology, neurology, and bariatrics.
- In particular, the present anthropometric information is useful for formulating risk-assessment scales, in order to screen patients admitted to hospitals, rehabilitation centers, or nursing homes and identifying the ones most susceptible to DTI, so that the occurrence of these dreadful wounds can be minimized.

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Chapter 152
Anthropometry in the Assessment of HIV-Related Lipodystrophy

Giovanni Guaraldi, Stentarelli Chiara, Stefano Zona, and Bruno Bagni

Abstract Infection with HIV causes a spectrum of clinical problems. Abnormalities in body composition have been reported in 40–50% of ambulatory HIV-infected patients.

Progressive, involuntary weight loss is an AIDS-related metabolic disorder called "wasting syndrome". Its etiology in untreated HIV infection, is multifactorial. This condition is still common in developing countries while is much more rarely seen in industrialized countries.

Indeed, in the late 1990s, reports of unusual changes in body fat distribution named "Lipodystrophy" began to appear in HIV patients. This syndrome includes peripheral fat loss (lipoatrophy; LA), central fat accumulation (lipohypertrophy; LH) separately present or in combination in the same individual (mixed forms). In this clinical condition, abnormal fat accumulation is observed in intra-abdominal region, as well as in subcutaneous area of the cervical, retroauricolar, dorsal and pubic region. Abnormal fat loss is observed from the arms and legs, face, and buttocks. The driving force behind lipoatrophy is undoubtedly the cumulative exposure to thymidine analogue (TA) drugs. Risk factors for fat accumulation, on the contrary, are still obscure.

The absence of a clear-cut definition unavoidably has led to uncertainty about changes in prevalence and incidence of lipodystrophy over time. The absence of a precise definition of lipodystrophy suggested the need for regulatory consideration for its anthropometric measurement and the choice of objective treatment goals.

Objective lipodystrophy (LD) measurement tools analysed refer to general anthropometry evaluation (BMI, Waist girth and waist to hip ratio), as well as to radiological evaluation for lipoatrophy or fat accumulation (Ultrasound, Dual Energy X-ray absorptiometry, abdomen and limb Computed Tomography or Magnetic Resonance). Given that lipoatrophy and fat accumulation may coexist in the same individual, radiological tools for measuring both these changes are needed for the assessment of the same individual analysing at the same time the degree of lipoatrophy in the limbs and fat accumulation in the visceral area: lipoatrophy is measured with Dual Energy X-ray absorptiometry (DXA); fat accumulation is usually measured with lumbar computed tomography (CT) or with Magnetic resonance Imaging (MRI). Several studies have investigated changes in body composition that occur in HIV-infected individuals.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_152,

There are also some relevant clinical implications of body fat changes in HIV: morphological changes induced by HIV-related lipodystrophy profoundly affect body image and influence health-related quality of life. Additionally, HIV infection and elevated VAT are significantly associated, linking HIV and VAT to inflammatory events and to an increased cardiovascular risk.

Abbreviations

AIDS	Acquired immunedeficiency syndrome
ART	Active antiretroviral therapy
BIA	Bio-impedentiometry
BMI	Body mass index
CRP	C-reactive protein
CAC	Coronary calcium score
CI	Confidence Interval
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DXA	Dual Energy X-ray absorptiometry
FRAM	Fat Redistribution and Metabolic Change in HIV Infection
LA	Lipoatrophy
LD	Lipodystrophy
LH	Lipohypertrophy
MRI	Magnetic resonance imaging
OR	Odds ratio
PI	Protease inhibitor
SAT	Subcutaneous fat mass
SKF	Skin fold assessment
TA	Thymidine analogue
VAT	Visceral adipose tissue
WC	Waist circumference
W/H	Waist to hip ratio

Infection with HIV causes a spectrum of clinical problems beginning at the time of seroconversion and terminating with AIDS and death. It is now recognized that it may take 10 years or more for AIDS to develop after seroconversion.

The progression of HIV infection is a result of a decline in immune competence that occurs due to increased replication of HIV, clinically evident with constitutional symptoms including malaise, fevers, night sweats, weight loss, and diarrhea.

Progressive, involuntary weight loss reflects the adverse effect of HIV on nutritional status.

The etiology of weight loss and wasting in untreated HIV infection is multifactorial and may include decreased dietary intake, malabsorption, opportunistic infection or malignancy, or an increased expenditure of energy (Coodley et al. 1994).

This AIDS-related metabolic disorder is called ‘wasting syndrome’ and is characterized by a decrease in lean body mass, fat body mass, and intracellular water volume, as assessed with bioimpedentiometry.

HIV-associated wasting is clinically defined as a patient meeting one of the following (Wanke et al. 2002): loss of 10% of body weight in 1 year, loss of 5% of body weight in 6 months (between two study visits), and a decrease in BMI to <20 kg/m^2.

This condition is still common in developing countries where antiretroviral treatment is limited, though it is much more rarely seen in industrialized countries, where a decrease in viral load in response to the introduction of antiretroviral therapy often corresponds to a complete or partial resolution of constitutional symptoms and weight recovery.

In the late 1990s, reports of unusual changes in body fat distribution named 'lipodystrophy' began to appear in HIV patients, mitigating the enormous enthusiasm about improvement of survival and quality of life provided by highly active antiretroviral therapy (ART), which had just become available at that time. This syndrome includes peripheral fat loss (lipoatrophy; LA), central fat accumulation (lipohypertrophy; LH) separately present or in combination in the same individual (mixed forms), usually, but not invariably, associated with alterations of lipid metabolism, and derangement of insulin sensitivity and diabetes mellitus (Carr et al. 1998).

In this clinical condition, abnormal fat accumulation is observed in the intra-abdominal region, (Engelson et al. 1999; Miller et al. 1998) (Fig. 152.2–152.3), as well as in the subcutaneous area of the cervical, retroauricolar, dorsal, and pubic regions (Lo et al. 1998). Abnormal fat loss is observed from the arms and legs, face, and buttocks (Carr et al. 1998; Bacchetti et al. 2005; Lichtenstein et al. 2003) (Fig. 152.4–152.6).

Abnormalities in body composition have been reported in 40–50% of ambulatory HIV-infected patients (Lichtenstein et al. 2001); the proportion is greater in those receiving combination antiretroviral therapy. Prevalence rates vary widely, from 11% to 83%, in cross-sectional studies (Carr et al. 1999). Lipoatrophy rates may be even higher, depending on the characteristics of the cohort (sex, age, and possibly race), the type and duration of antiretroviral therapies, the criteria for changes in body composition, and the comparison population.

The absence of a clear-cut definition has led unavoidably to uncertainty about changes in prevalence and incidence of lipodystrophy over time (Carter et al. 2001).

The contributing factors are CD4+ lymphocyte cell count, HIV clinical stage, race, sex, exercise level, and age at the start of antiretroviral therapy (Lichtenstein et al. 2001), but the driving force is undoubtedly the cumulative exposure to thymidine analog (TA) drugs. These drugs, in particular, stavudine and to a lesser extent zidovudine, antagonize mitochondrial DNA polymerase function resulting in apoptosis of fat cells. Risk factors for fat accumulation, on the contrary, are still obscure and are not directly related to the use of any antiretroviral drugs.

Earlier detection and treatment of HIV infection (Kitahata et al. 2009), as well as the use of antiretroviral drugs with less deleterious effects on body fat, make it reasonable to hypothesize a decrease in prevalence of lipodystrophy in the coming years.

Decreasing thymidine analog (TA) use, the leading risk factor for LA development and, moreover, the availability of new drugs and drug classes that allow treatment scenarios where a TA-based backboneparadigms is over, as well as the effort for earlier detection and treatment of HIV infection (Kitahata et al. 2009), reasonably lead to the same hypothesis.

Few epidemiological data exist to verify this so far. A Swiss HIV Cohort Study recently reported a reduced likelihood, by life-table Kaplan–Meier analysis, of lipodystrophy development in patients who started ART between 2003 and 2006 compared with those who started ART between 2000 and 2002, coinciding with decreased rates of TA use, mainly stavudine. Unluckily, the study did not provide any objective assessment of body fat changes (Nguyen et al. 2008).

In the same time period, epidemiological data from the southern hemisphere demonstrated an opposite trend toward an emerging epidemic of lipodystrophy in those countries. In a study from Rwanda, lipodystrophy was observed in 34% of subjects, with prevalence increasing to 69.6% in those receiving ART for 72 weeks. Peripheral LA combined with abdominal LH was observed in

72% of lipodystrophy subjects (Mutimura et al. 2007). In a more recent case-control study from Senegal, the prevalence of moderate–severe lipodystrophy was 31.1%, with 13.3%, 14.5%, and 3.3% for LA, LH, and mixed forms, respectively. The overall prevalence of lipodystrophy was 65.0% and stavudine was the only independent risk factor (Mercier et al. 2009). In both these studies, lipodystrophy was only clinically assessed, and body fat changes not unexpectedly coexisted with abnormalities of glucose and lipid metabolism.

The absence of a precise definition of lipodystrophy suggested the need for regulatory consideration for its anthropometric measurement and the choice of objective treatment goals.

Objective LD measurement tools analyzed refer to general anthropometry evaluation (BMI, waist girth, and waist-to-hip ratio), as well as to radiological evaluation for lipoatrophy or fat accumulation (ultrasound, DEXA, and abdomen and limb CT or MRI).

The body mass index (BMI) is a crude index (kg/m^2) of overall body fatness, and it is commonly used in large-scale epidemiological surveys and clinical settings to classify individuals as obese, overweight, or underweight (respectively, BMI >30; >25; <18.5) (Joy et al. 2008).

This index has limited value in evaluating LD, given that most HIV-infected patients have BMI within the normal range but may have a significant alteration of body fat component, with a characteristic body fat redistribution pattern from periphery to central accumulation.

Waist-to-hip ratio (W/H) is commonly used as an indirect measure of lower- and upper-body fat distribution. Given that most HIV patients with LD may have severe fat loss in the buttock region, this index appears to be less reliable than waist circumference (WC) to assess intra-abdominal (visceral) fat deposition and appears to be less influenced by age, gender, height, and degree of overall adiposity. WC is highly related to MRI and CT measures of visceral fat in men and women and to cardiovascular risk factors.

The skinfold assessment (SKF) is a measure of the thickness of the two layers of skin and the underlying subcutaneous fat. This measurement is considered not useful in the assessment of patients with LD, because, in this clinical condition, it does not appear to have any reliable relationship between subcutaneous fat and total body fat; for this reason, the sum of several SKFs cannot be used to estimate total body fat. For the same reason, bioimpedentiometry (BIA) (a function of resistance and reactance to current flow through the body) is of limited use in LD evaluation.

152.1 Radiological Tools for Assessing Lipodystrophy

Given that lipoatrophy and fat accumulation may coexist in the same individual, radiological tools for measuring both these changes are needed for the assessment of the same individual, analyzing at the same time the degree of lipoatrophy in the limbs and fat accumulation in the visceral area. For both these measurements, there are no defined cutoff values and results are best considered in longitudinal evaluation using each patient as control for themselves (Mallon et al. 2003; Dube et al. 2007; Martin et al. 2004).

1. Lipoatrophy is measured with dual energy X-ray absorptiometry (DXA), which is based on the attenuation of two different X-ray energies as they pass through tissues having different densities and chemical compositions. DXA estimates of whole-body composition are based on a three-component tissue model (fat mass/bone mineral density/bone-free lean mass) (Smith et al, 2003; Podzamczer et al, 2007; Mallal et al, 2000; Delpierre et al, 2007).
   DXA of the limbs measures the total fat mass of the limbs or the ratio of the limbs' fat mass over the total limb mass as surrogate markers for lipoatrophy.
2. Fat accumulation is usually measured with lumbar computed tomography (CT) or with magnetic resonance imaging (MRI). CT is a radiographic method that measures the differences in the

attenuation (or the weakening) of X-ray beams as they pass through the participant. It allows for separate recognition of bone, adipose tissue, and lean tissue. It is usually limited to regional assessment. MRI creates a computer-generated image from radiofrequency signals emitted by hydrogen nuclei. CT and MRI measure body composition at the tissue level and are the preferred methods for separating total adipose tissue into its subcutaneous and visceral components.

Fat accumulation is measured in the abdominal area using the fourth lumbar vertebra as the anatomic reference. The absolute value of visceral adipose tissue or the ratio of VAT over the sum of subcutaneous fat mass (SAT) and the VAT (total fat mass – TAT) is used as a surrogate for fat accumulation (Andrade et al. 2002; Bacchetti et al. 2005; Saint-Marc et al. 2000).

Several studies have investigated changes in body composition that occur in HIV-infected individuals. The Fat Redistribution and Metabolic Change in HIV Infection (FRAM 2006) study compared fat distribution between HIV-infected individuals and HIV-negative controls and revealed a greater degree of fat loss in peripheral and most central depots among HIV-infected men and women when compared with controls (Bacchetti et al. 2005).

Peripheral lipoatrophy can be considered a consistent finding among HIV-infected men and women with metabolic abnormalities.

Importantly, the FRAM study and several recent studies have shown that peripheral lipoatrophy is not linked to central lipohypertrophy in most HIV-infected individuals (Bacchetti et al. 2005, 2006; Mulligan et al. 2006). Weight itself may influence the amount of adipose tissue present, however, and there may be differences in VAT, SAT, and regional body adipose measurements within specific anthropometric categories.

Relative increases in VAT are most pronounced among male and female HIV-infected subjects in the normal weight and overweight categories.

Gender differences in abdominal SAT accumulation are observed, with preservation of SAT among HIV-infected women relative to control subjects (Joy et al. 2008).

With HAART initiation, HIV-infected patients often demonstrate increases in weight and trunk and limb fat over the first 16–24 weeks of therapy (Mallon et al. 2003; Gallant et al. 2004). Subsequently, whereas amounts of trunk fat generally stabilize, limb fat frequently decreases progressively over time, which is most closely correlated with stavudine exposure (Mallon et al. 2003; Gallant et al. 2004). Mallon, for example, reported a 13.6% decrease per year in limb fat after the initial 24 weeks of stavudine containing HAART over 96 weeks among 40 HIV-infected men initiating therapy (Mallon et al. 2003). The stability of these body composition changes after prolonged HAART is unknown. In addition, the extent to which body composition changes occur as a result of aging or HIV infection per se is unknown.

A forum for collaborative HIV-related lipodystrophy research [http://www.hivforum.org/storage/hivforum/documents/Liporegfinal.pdf] was held at the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV on October 27, 2004, in Washington, DC. The main goals of this document were to review the types of lipodystrophy and recommend methods of objective and subjective measurement so as to be able to advocate entry criteria for clinical trials, based on the type of lipodystrophy. These recommendations identify surrogate markers for different LD phenotypes:

152.2 Facial Lipoatrophy

Up to now, there is neither a standardized available tool to measure facial-pad thickness nor clear facial reference points that could be of use in the clinical setting. The severity of facial lipoatrophy has been established using a photo-comparison grading scale. It should be stressed that the buccal

fat pad has a minor role in facial appearance and does not have a concrete area in superficial anatomy. For this reason, ultrasound evaluation of the cheek is a controversial endpoint in plastic facial-reconstruction surgery.

Entry into a clinical trial should be decided by the patient and the physician, based on subjective determination of the presence of facial lipoatrophy not caused by HIV wasting.

Effectiveness of treatment should be based on (1) objective measurements of fat restoration, for example, by ultrasound and photograph and (2) subjective determination of satisfactory improvement on the part of the patient and the physician.

152.3 Peripheral Lipoatrophy

Entry into a clinical trial should be decided by both the patient and the physician, most likely based on a subjective determination of peripheral fat loss and, if possible, an objective DEXA measurement indicating less than 8 kg of peripheral limb fat or a 25% loss of limb fat compared to population normal values (although normal values are not available for all population types).

Effectiveness of treatment should be based on objective DEXA measurements. The percentage of increased fat that will indicate effectiveness of a treatment will depend on the baseline value.

152.4 Visceral Adiposity

Entry into a clinical trial should be based on objective waist circumference and waist-to-hip ratio measurements and, to a lesser extent, on patient and physician selection depending on a subjective determination of increased truncal fat.

Early trials should recruit subjects with body mass indices in the overweight or obesity range.

Effectiveness of treatment should be based on CT scans at the L4–L5 level (a direct measure of visceral adipose tissue [VAT] and the preferred measurement), DEXA scans (a measure of truncal fat, i.e., VAT plus subcutaneous abdominal fat), and objective anthropometry, such as waist-to-hip ratio. Induction of satisfactory efficacy after at least 3 months of treatment and durability of efficacy after at least six additional months of treatment should be demonstrated. Inclusion of quality-of-life outcomes assessed by validated instruments is strongly recommended. All studies should be placebo controlled.

152.5 Clinical Implications of Body Fat Changes in HIV

Morphological changes induced by HIV-related lipodystrophy profoundly affect body image and influence health-related quality of life. Additionally, HIV infection, elevated VAT, and elevated C-reactive protein (CRP) are significantly associated, linking HIV and VAT to inflammatory events.

The adipocyte has shifted from being a passive storage cell for triglycerides to a secretory organ of adipokines, such as leptin, adiponectin, and inflammatory factors, such as tumor necrosis factor alpha. The role of lipodystrophy and central adiposity and visceral adipose tissue, in particular, VAT, in cardiovascular (CV) and diabetes mellitus (DM) risk, has been recognized independently and through the metabolic syndrome (Balkau et al. 2007).

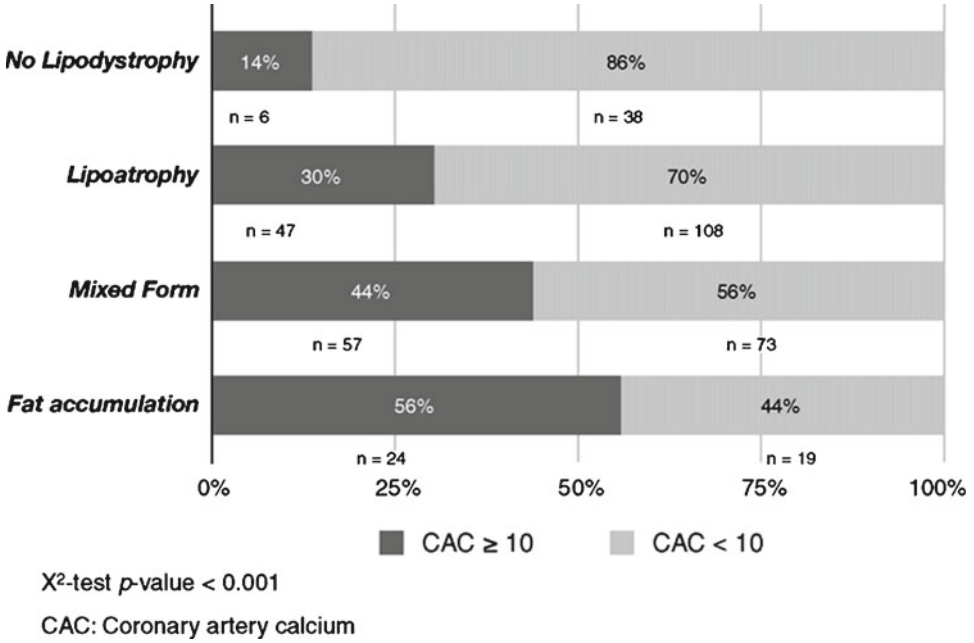

Fig. 152.1 Prevalence of coronary artery calcium score >10 in different phenotypes of lipodystrophy and in its absence

There is widespread concern that the metabolic and morphological abnormalities in HIV-infected patients lead to an increased risk of cardiovascular disease. Some observational studies suggest an increased risk of cardiovascular disease among HIV-infected patients compared with the general population.

The extent of the increased risk of cardiovascular disease in this population and its association with factors related to HIV infection, antiretroviral therapy, and its metabolic consequences are topics of intense investigation. In the recent years, cardiology taught us that a combination of blood serum biomarkers of atherosclerosis and inflammations and vascular markers may constitute a better way to identify people vulnerable to cardiovascular disease. Silent plaque imaging assessed with coronary calcium score (CAC) may be able to globally define a patient's CVD event risk by virtue of its strong association with total coronary atherosclerotic disease burden. CAC score is the strongest predictor of subsequent CVD and, recently, it has been shown that slowing the coronary artery calcification process will translate into a reduced risk of events (as previously demonstrated with regression of luminal stenosis in angiographic trials).

The contribution of chronic HIV infection, ART use, and LD to the presence of subclinical atherosclerosis as evaluated by coronary artery calcium (CAC) imaging was assessed in an observational cross-sectional study of 372 HIV-infected patients receiving ART attending Modena's University cardiometabolic clinic. Presence of CAC defined as a score >10 was found in 134 patients (36%) with a median CAC score of 50 (range 10; 1,243). Lipoatrophy alone (OR 3.82, 95% CI: 1.11; 13.1), fat accumulation alone (OR 7.65, 95% CI: 1.71; 37.17), and mixed lipodystrophy phenotypes (OR 4.36, 95% CI: 1.26; 15.01) were strongly associated with presence of CAC after adjusting for age, sex, hypertension, and cumulative exposure to ART (Fig. 152.1) (Guaraldi et al. 2009).

The prospective extension of this study analyzing predictors of progression of CAC in 132 patients who underwent two sequential CT scans (median follow-up time 333 days) showed that probability of CAC progression in the follow-up period was independently related with any single year of age

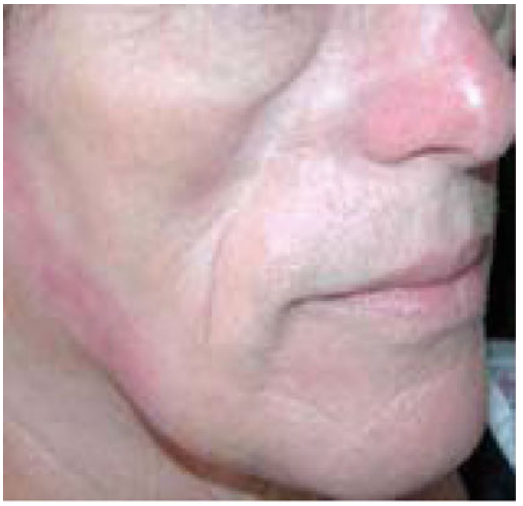

Fig. 152.2 Physical manifestations of lipoatrophy: subcutaneous fat loss in the face

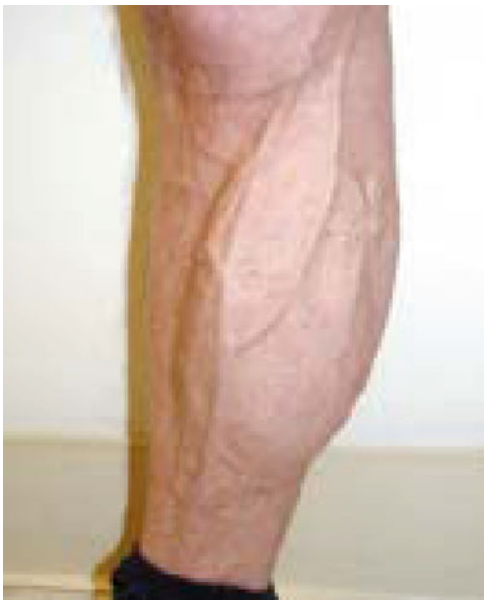

Fig. 152.3 Physical manifestations of lipoatrophy: subcutaneous fat loss in the limbs

increase, any 10 mg of increase of LDL cholesterol, any 50 cells increase of CD4 lymphocytes, and any 10 cm^3 of VAT (Fig. 152.1).

These findings may have important implications for the management of HIV-infected patients receiving long-term ART therapy and demonstrating features of LD. Such patients may be at increased risk for the development of atherosclerotic coronary artery disease and consideration should be given to switch choice of ART; furthermore, these patients may be targeted to undergo early and aggressive cardiovascular disease risk-modification strategies.

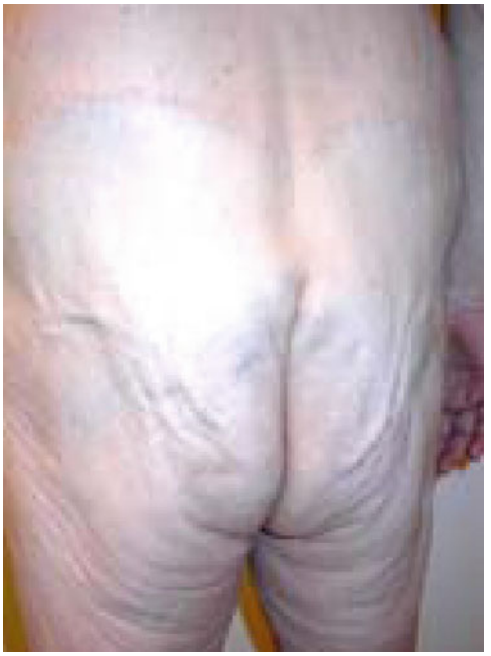

Fig. 152.4 Physical manifestations of lipoatrophy: subcutaneous fat loss in the buttocks

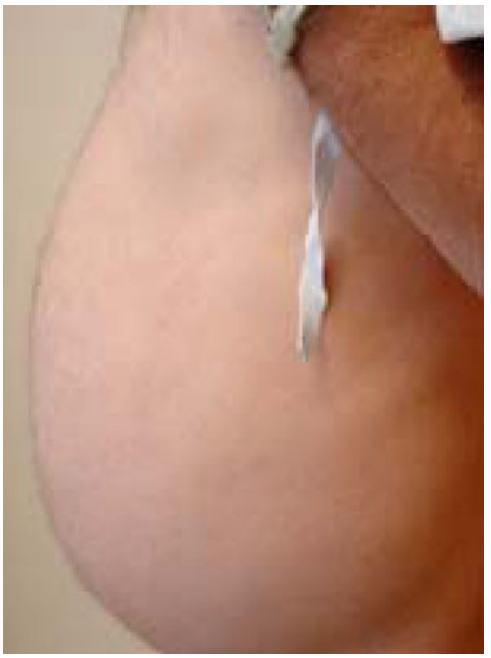

Fig. 152.5 Physical manifestations of lipohypertrophy: this accumulation of adipose tissue is clearly distinguishable from the lipoatrophy

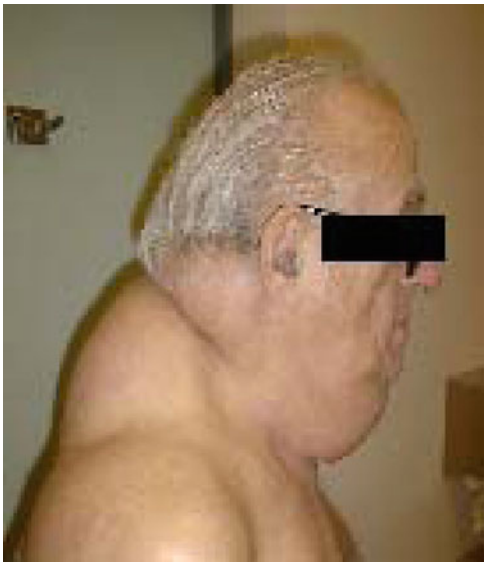

Fig. 152.6 'Buffalo hump'

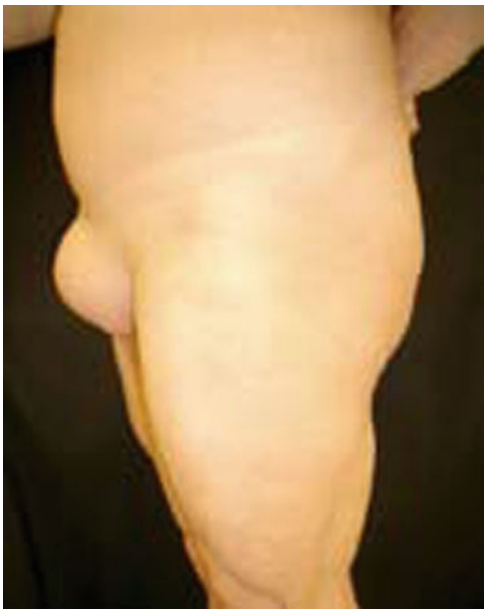

Fig. 152.7 'Pubic lipoma'

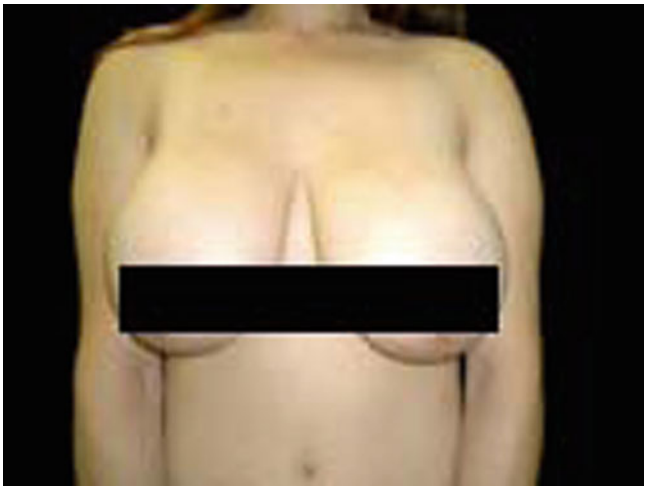

Fig. 152.8 Breast hypertrophy

Summary Points

- Manifestations of HIV-related body fat distribution are 'wasting syndrome' and lipodystrophy. Progressive weight loss is an AIDS-related metabolic disorder called 'wasting syndrome:' this condition is actually more rarely observed in industrialized countries. The lipodystrophy syndrome includes peripheral fat loss (lipoatrophy; LA) and central fat accumulation (lipohypertrophy; LH) present separately or in combination in the same individual (mixed forms), and this is considered to be a side effect of antiretroviral therapy.
- *Objective lipodystrophy (LD) measurement tools*: They refer to general anthropometry evaluation (BMI, waist girth, and waist-to-hip ratio), as well as to radiological evaluation for lipoatrophy or fat accumulation (ultrasound, dual energy X-ray absorptiometry, and abdomen and limb computed tomography or magnetic resonance).

  WC is highly related to magnetic resonance imaging and computed tomography measures of visceral fat in men and women and to cardiovascular risk factors.
- *Lipoatrophy*: Lipoatrophy is measured with dual energy X-ray absorptiometry (DXA); DXA of the limbs measures the total fat mass of the limbs or the ratio of the limbs fat mass over the total limb mass as surrogate markers for lipoatrophy.
- *Fat accumulation*: Fat accumulation is usually measured with lumbar computed tomography (CT) or with magnetic resonance imaging (MRI). CT is a radiographic method that measures the differences in the attenuation (or the weakening) of X-ray beams as they pass through the participant. It allows for separate recognition of bone, adipose tissue, and lean tissue.
- Several studies have investigated changes in body composition that occur in HIV-infected individuals.

  The Fat Redistribution and Metabolic Change in HIV Infection (FRAM 2006) study compared fat distribution between HIV-infected individuals and HIV-negative controls and revealed a greater degree of fat loss in peripheral and most central depots among HIV-infected men and women when compared with controls.

  Importantly, the FRAM study and several recent studies have shown that peripheral lipoatrophy is not linked to central lipohypertrophy in most HIV-infected individuals.

  Relative increases in VAT are most pronounced among male and female HIV-infected subjects in the normal weight and overweight categories.

- Recommended entry criteria for clinical trials are based on the type of lipodystrophy. These recommendations identify surrogate markers for different LD phenotypes: for example, an objective DEXA measurement for peripheral lipoatrophy indicates less than 8 kg of peripheral limb fat or a 25% loss of limb fat compared to population normal values.

Key Points

- HIV is an infection that results in an impaired immune system. AIDS is the end stage of HIV and wasting is a major prognostic marker from mortality in this disease.
- Lipodystrophy is a fat-redistribution syndrome characterized by thinning in extremities but increased fat in the trunk. This is a side effect of antiretroviral therapy against HIV infection.
- Why is the use of anthropometric technique so relevant in HIV infection?
- Because body changes are strongly linked to mortality;
- Because studying anthropometric alterations can give insight into the knowledge of drug toxicities; and
- Because body fat changes profoundly affect body image and consequently health-related quality of life.

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Chapter 153
Use of Anthropometry in Monitoring the Nutritional and Health Status of Persons Living with HIV/AIDS

Selby Nichols, Nequesha Dalrymple, and Marlon Francis

Abstract Approximately 33 million persons are living with HIV/AIDS globally. Majority of these persons living with HIV/AIDS (PLWHA) reside in low and middle income countries where there is a scarcity of resources to deal with the magnitude of the problems associated with this HIV/AIDS pandemic. Weight loss is common feature of HIV/AIDS. In fact, the extent of this weight loss is a reasonable predictor of the morbidity and mortality among PLWHA. Malnutrition in PLWHA results from several factors. Among these are changes in metabolism resulting in increased utilization of nutrients, mal-absorption of nutrients associated with the frequent diarrheas and reduced dietary intakes due to nausea and vomiting, inability to swallow, and reduced access to nutritious foods. Malnutrition and HIV/AIDS act in a synergistic manner to accelerate and perpetuate the deleterious effect of the latter. HIV/AIDS is associated with deficiencies of zinc, vitamins B, C, E, proteins and calories. Consequently, PLWHA tend to exhibit clinical symptoms that are relatively similar to those associated with macro and micronutrient deficiencies. More recently, HIV/AIDS has been associated with unhealthy lipid profiles, especially among those on Highly Active Anti-Retroviral Therapy (HAART). While nutritional status cannot be measured directly, there are several anthropometric measures that can provide useful information on aspects of the nutritional status of PLWHA. To ensure accuracy of the data generated, anthropometric measures of nutritional status in PLWHA should be highly sensitive, specific and have good predictive values. They should also be simple to use, relatively inexpensive, acceptable to PLWHA, non-invasive, easy to interpret by all categories of workers in the health care system and applicable to all stages of the life cycle from infancy to adulthood. Among the anthropometric measures fulfilling these criteria are weight, height, weight-for-age (WA), weight-for-height (WH), body mass index (BMI), mid upper arm circumference (MUAC), skinfold thickness (SF), waist circumference (WC) and waist-hip ratio (WHR). Studies suggest that several of these anthropometric measures are associated levels of immune function (e.g., CD4+, CD8+ cells counts), blood proteins levels, and anaemia. Moreover, excess weight loss is predictive of both the morbidity and mortality among PLWHA. Anthropometric indices therefore provide useful tools for monitoring and evaluating the patho-physiological changes among PLWHA. While anthropometry allow us to monitor and evaluate changes in the nutritional status of PLWHA, its greatest benefit can only be realized as part of a comprehensive monitoring strategy that includes clinical assessment and biochemical tests.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_153,

Abbreviations

AMA	Arm muscle area
BMI	Body mass index
CDC	Center for Disease Control
HAART	Highly Active Anti-Retroviral Therapy
MUAC	Mid upper arm circumference
PEM	Protein Energy Malnutrition
PLWHA	Persons living with HIV/AIDS
SF	Skinfold thickness
TSF	Triceps skinfold
WC	Waist circumference
WHR	Waist-to-hip ratio
WA	Weight-for-age
WH	Weight-for-height
π	3.14

153.1 Introduction

Globally, it is estimated that there are 32.8 million persons living with HIV/AIDS (PLWHA). Additionally, nearly 15 million children have lost one or both parents to the epidemic (Worldwide HIV & AIDS Statistics Commentary 2009). Moreover, majority of PLWHA reside in developing and emerging economies where there is a paucity of resources for effective management of the epidemic. While sub-Saharan Africa accounts for approximately two-thirds of PLWHA and Asia a further 20%, Latin America and the Caribbean represent regions that have experienced high rates of new infections. The impact of HIV/AIDS is felt at all levels of the society from individuals to communities and, by extension, the nation. In fact, the increasing prevalence of the epidemic among women of reproductive age and the working class has serious implications for the economies of the countries concerned. Thus, the potential socioeconomic impact of HIV/AIDS has tremendous consequences for national development, especially among developing countries (Dixon et al. 2002).

Studies in Africa have shown that HIV/AIDS can have devastating effects on a country's pool of skilled workers (Ilinigumugabo 1996; Gentilini and Chieze 1990). In the case of countries such as Mozambique and Kenya, HIV/AIDS has depleted the pool of skilled workers, such as teachers, engineers, and nurses (Gentilini and Chieze 1990). These workers usually represent key sectors of the economy that are crucial to infrastructural and human development. In turn, this can lead to a scarcity of resources needed to comprehensively manage existing cases and reduce the numbers of new infections in the population (Fig. 153.1). It is estimated that it will cost some 2.69 US$ each day to effectively treat this disease (Koenig et al. 2008; Keiser et al. 2001). This will pose a serious problem for many of the countries with the highest burden of infections, as majority of their citizens exist on less than US$ 1 per day (Bachmann and Booysen 2003). Improved nutrition remains the last bastion of hope for prolonging the quality of life and minimizing the symptoms among PLWHA even when they are on HAART (Mangili et al. 2006).

One of the hallmarks of HIV/AIDS is the weight loss that accompanies disease progression (Siddiqui et al. 2009). This is usually an indication of nutritional inadequacies and requires proper clinical management to prevent progression to severe malnutrition. Malnutrition in turn can lead to

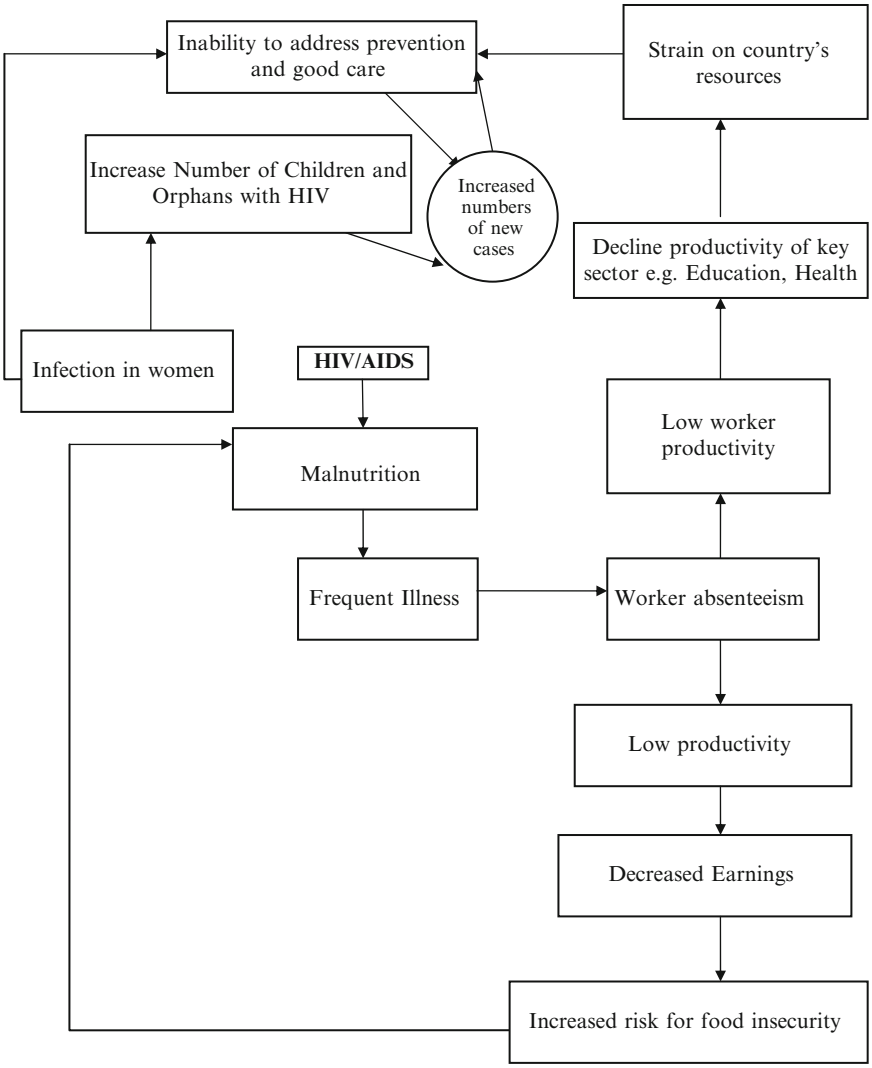

Fig. 153.1 Impact of HIV/AIDS on Society. It presents a scenario for the socio-demographic impact of HIV/AIDS leading to malnutrition and food insecurity

impaired immune function. The synergistic effects between nutrition and immune function are well known (Oguntibeju et al. 2007). HIV/AIDS also has major physiological effects on the immune system that are independent of the effects produced by the malnutrition associated with the disease. The links between malnutrition, infection, health, and development place HIV/AIDS at the center of a chain of events that have tremendous socioeconomic consequences. In this chapter, we review the pathophysiological issues in HIV/AIDS that have implications for the nutritional status of individuals. We also review the role of anthropometry in monitoring and evaluating changes in the nutritional status of PLWHA. Additionally, we will propose a framework for the use of anthropometry in the regular monitoring and evaluation of PLWHA. Finally, we present suggestions for increasing the use of anthropometry at all levels of the healthcare system.

153.2 Nutrition and HIV/AIDS

The nutritional issues in HIV/AIDS are primarily due to changes in metabolism that influence nutrient utilization, malabsorption-associated opportunistic infections, and reduction in dietary intakes resulting from a combination of factors that reduce the ability to acquire foods (Oguntibeju et al. 2007). HIV infection is accompanied by a myriad of metabolic changes. It is also associated with the production of several cytokines, such as gamma interferon, macrophage inflammatory factors, and tumor necrosis factor alpha, by $CD8^+$ cells in an attempt to rid the body of the invading virus (Migueles and Connors 2002). These cytokines modify metabolic function resulting in a hyper-catabolic state, thereby increasing the demand for nutrients (Crocker 1989). In particular, evidence suggests that there is a greater demand for energy and protein (Charlin et al. 2002; Sattler et al. 2008). This increases the risk of developing protein energy malnutrition (PEM) among PLWHA. Micronutrient deficiencies, especially deficiencies in zinc, selenium, and vitamins A, C, and E, are common in HIV/AIDS (Lanzillotti and Tang 2005). Moreover, increasing the serum level of these nutrients improves control of viral replication (Jones et al. 2006). Figure 153.2 shows the impact of HIV/AIDS with implications for nutrition.

More recently, HIV/AIDS has been shown to result in unfavorable lipid profiles (Ogunro et al. 2008). This increases the risk of cardiovascular ailments among PLWHA (Farrugia et al. 2009). HIV/AIDS also affects several organs and systems in a manner that impacts directly on nutrition (i.e., the ability to feed and effectively utilize nutrients). Systems affected include the nervous, gastrointestinal, immune, skeletal, and pulmonary systems (Timbo and Tollefson 1994). Figure 153.3 shows the impact of HIV/AIDS on body organs and systems, with implications for nutrient availability and utilization.

153.3 Wasting Syndrome and HIV/AIDS

Weight loss is characteristics of HIV/AIDS. In this respect, HIV/AIDS shares a common characteristic with PEM, cancers, and anorexia nervosa through the pathophysiological and etiological process leading to rapid weight loss (Colecraft 2008; Hoyt and Staats 1991; Kotler 1995). This similarity in weight loss suggests that anthropometric techniques for monitoring changes in nutritional status in these diseases may be applicable for monitoring nutritional status among PLWHA. Weight loss in HIV/AIDS >10% (indicative of the wasting syndrome) is associated with an increase in the risk of death. On the other hand, the increased use of antiretroviral therapy and aggressive treatments to increase weight and prolong survival has made overweight and obesity an issue that must be addressed in PLWHA. Furthermore, HAART can independently increase the risk of cardiovascular disease by its ability to increase serum lipid levels (Adeyemi 2007; Martínez et al. 2009). The clinical effects of HIV/AIDS on PLWHA go beyond issues of weight loss and nutritional status. In fact, HIV/AIDS is associated with conditions, such as diarrhea, anemia, and impaired immune status, to name a few. Table 153.1 shows the effect of HIV/AIDS on organs/systems that have important consequences for nutrition.

153.4 Use of Anthropometry in HIV/AIDS

Anthropometric measures can be used to indicate changes in the progression of HIV/AIDS (Justman et al. 2008). For anthropometric measures to be efficacious in monitoring changes in nutritional status among PLWHA, they should be sensitive, specific, easy to use, relatively cheap, and provide data that are easy to interpret by all levels of the healthcare team. They should also correlate with

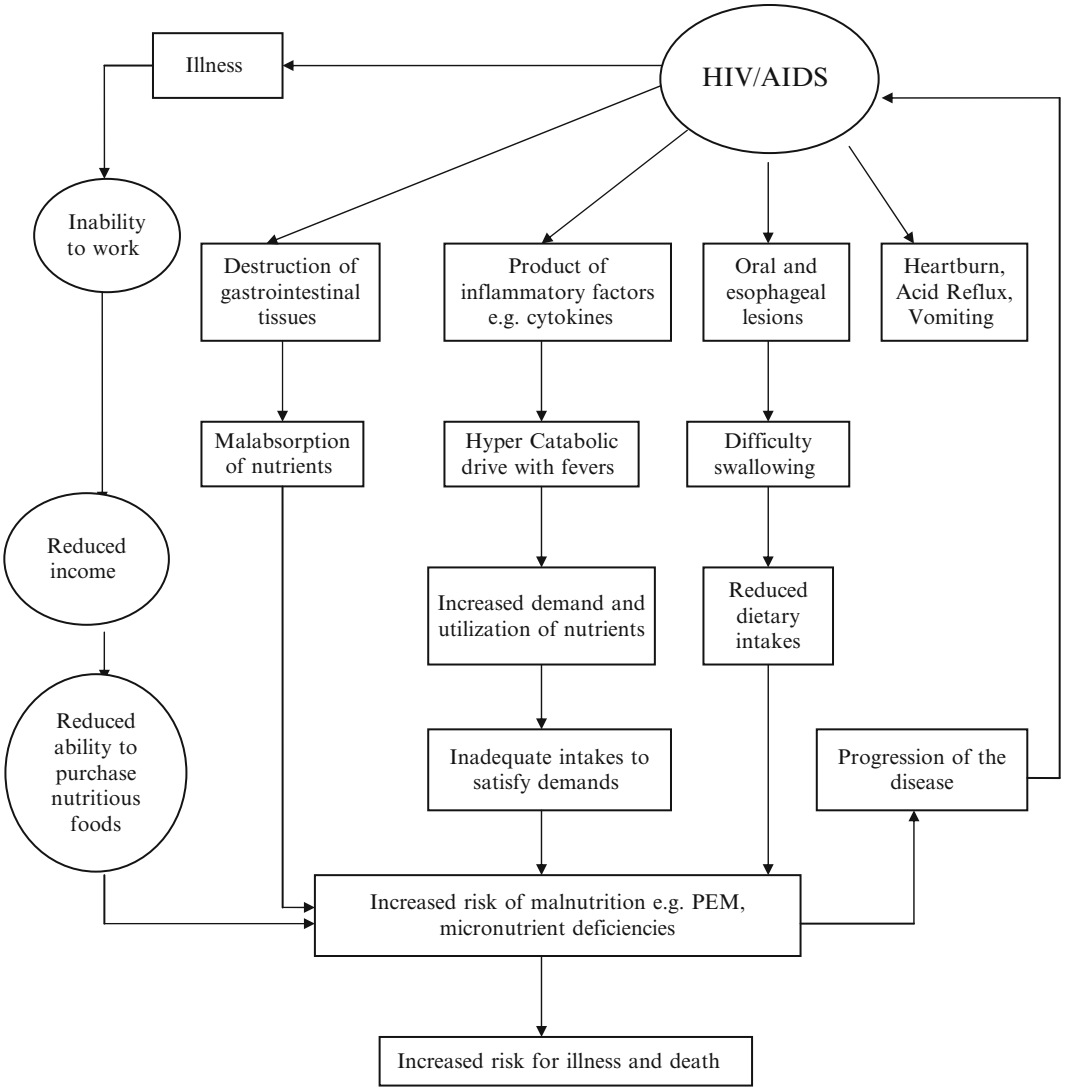

Fig. 153.2 Pathophysiology of HIV/AIDS with Implications for Nutritional Status. It shows the impact of HIV/AIDS on organs and body systems that increases the risk for illness and death

pathological changes in HIV/AIDS, should be easily accepted by PLWHA, capable of providing consistent results in field and clinical situations, and should be applicable to all stages of the life cycle (i.e. infancy to adulthood). Anthropometry provides us with a wide range of indicators of body composition and nutritional status. In this section, we review the main indicators which are of importance in monitoring and evaluating changes in body habitus associated with HIV/AIDS. Nutritional status cannot be measured directly and anthropometry is simply a proxy for this state. Other proxies include clinical assessment and biochemical markers. Consequently, it is important to interpret the information that anthropometry offers in a manner that reflects the context of the measurement. In addition, more than one indicator should be used to provide evidence of changes in the nutritional status of individuals. In fact, anthropometry should be grounded in a comprehensive plan for the monitoring and evaluation of individuals. Figure 153.4 shows a framework for incorporating anthropometry in the monitoring and evaluation of PLWHA.

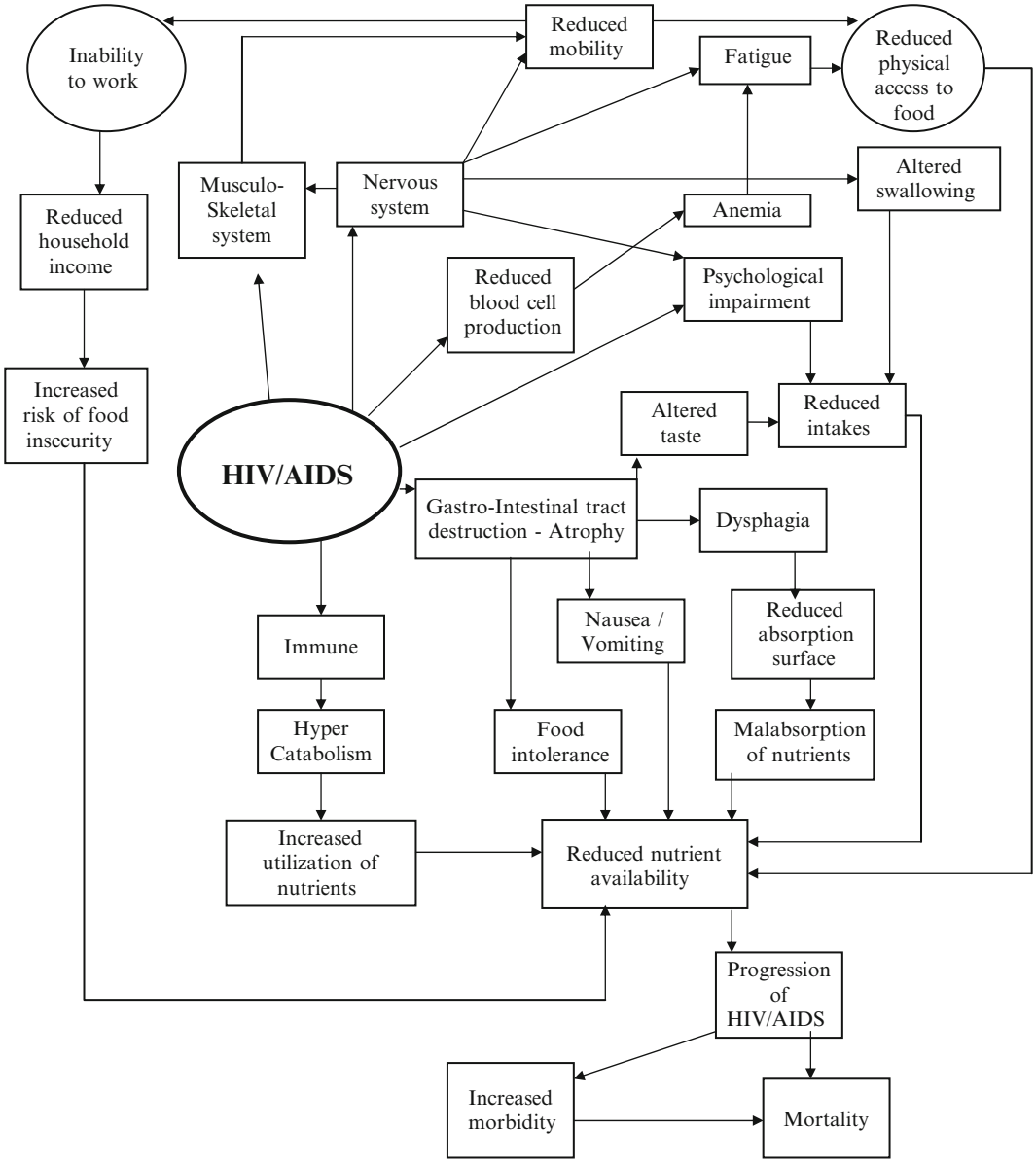

Fig. 153.3 Impact of HIV/AIDS on Body Organ Systems and Nutrient Availability. It shows the manner in which HIV/AIDS impacts on the availability of nutrients in the body

153.5 Height/Length

Height is a good index of the nutritional status of individuals and populations. Severe height deficit (stunting) is a useful indicator of chronic malnutrition.

Requirements: Recumbent length board, knee-height calipers, and stadiometer.

Applicability: Children and adults.

Table 153.1 Impact of HIV/AID on key organ systems in the body

Reference	Study design, objective and method	Organ/system affected with implications for nutrition	Findings
Stebbing et al. (2010)	The purpose of this study was to document patient, virologic, and tumor characteristics and clinical outcomes among HIV-positive patients. A total of 19 patients of ages 35–69 years with primary adenocarcinoma and/or squamous cell carcinoma of the esophagus was identified	Upper gastrointestinal	Prior esophageal disease (reflux, peptic ulcers, and achalasia) was reported in almost half of all patients. Primary esophageal carcinoma was associated with moderate immunosuppression and lifestyle habits including tobacco and alcohol use
Roc et al. (2007)	This study sought to examine whether lactate, a marker of inflammation and anaerobic glycolysis, and lipid, an indicator of cell membrane turnover resulting from oxidative stress, could serve as surrogate biomarkers within the lenticular nuclei of HIV-positive patients with different degrees of neurocognitive impairment. Ten seronegative controls and 45 HIV-positive patients with different degrees of neurocognitive impairment participated in this study. In vivo two-dimensional chemical-shift-imaging magnetic resonance spectroscopy analysis of *N*-acetyl aspartate:creatine, choline:creatine, lactate:creatine, and (lipid + lactate): creatine ratios were determined.	Brain	The lactate-to-creatine ratio was significantly greater in HIV-positive patients with moderate-to-severe impairment compared with seronegative controls. The (lipid + lactate):creatine ratio was significantly elevated within each HIV-positive subgroup compared with seronegative controls (0.01± 0.01 vs. 0.13 ± 0.03 and greater).
Chhagan and Kauchali (2006)	The purpose of this study was to describe the profile of comorbidities in children admitted with diarrhea to an urban hospital with high human immunodeficiency virus (HIV) prevalence in South Africa and to examine the contribution of comorbidities to inpatient mortality. Data from a retrospective random sample of 319 children were extracted and analyzed from a total of 1,145 children hospitalized for diarrhea in 2001	Lower gastrointestinal	Overall, 68% of the diarrheal admissions were classified as HIV infected and 61% were classified as malnourished. Mortality was higher among HIV-infected than among uninfected children [crude odds ratio (OR), 6.0; 95% CI 2.1–17.0].
Dolan et al (2006)	The objective of the study was to investigate change in bone mineral density (BMD) over time in HIV-infected women in comparison with healthy control subjects similar in age, race, and body mass index (BMI). BMD was measured by dual-energy X-ray absorptiometry in 100 HIV-infected females and 100 healthy controls similar in age (41 ± 1 vs. 41 ± 1 year, $p = 0.57$)	Bone	HIV-infected subjects had lower BMD at the lumbar spine (1.01 ± 0.01 vs. 1.07 ± 0.01 g/cm(2), $p = 0.001$), hip (0.94 ± 0.01 vs 0.98 ± 0.01 g/cm(2), $p = 0.02$), and femoral neck (0.83 ± 0.01 vs. 0.87 ± 0.01 g/cm(2), $p = 0.02$). Forty-one percent of the HIV-infected women demonstrated osteopenia at the hip, femoral neck, or spine, and 7% demonstrated osteoporosis. BMD in the HIV-infected subjects remained lower than that in control subjects over 24 months of follow-up ($p = 0.001$ for the spine, $p = 0.04$ for the hip, and $p = 0.02$ for the femoral neck)

(continued)

Table 153.1 (continued)

Reference	Study design, objective and method	Organ/system affected with implications for nutrition	Findings
Adediran and Durosinmi (2006)	The aim of this study was to evaluate the importance of peripheral blood and bone marrow changes in a population of adult Nigerians managed for symptomatic HIV infection. Peripheral blood cell counts and bone-marrow cytology of serologically confirmed HIV/AIDS patients 21–51 years were studied	Blood	Nearly two-thirds (68%) of the data were evaluable. None of the patients had conventional antiretroviral therapy. Lymphopenia (lymphocytes < 2× 10(9)/l) was seen in 64.4% of the patients; 50% and over 40% of the patients had moderate–severe anemia and neutropenia, respectively
Masiá et al. (2010)	Endothelial dysfunction was evaluated in HIV-infected patients with and without lipodystrophy in a prospective study. Endothelial function was measured through flow-mediated dilatation (FMD) of the brachial artery. Inflammation, endothelial activation, and coagulation associated with adipose tissue and endothelial dysfunction were evaluated by measuring interleukin 6 (IL-6), plasminogen activator inhibitor 1 (PAI-1), adiponectin, and vascular cell adhesion molecule 1	Cardiovascular	FMD was significantly lower in patients with lipodystrophy than in those without lipodystrophy (median [IQR] 3.1% [0.4–8.9] versus 6.3% [3.3–10.7]; $p = 0.004$). Lipodystrophy was associated with significantly higher plasma levels of IL-6 and PAI-1 and lower levels of adiponectin; severe lipodystrophy was associated with higher concentrations of vascular cell adhesion molecule 1. Lipodystrophy was an independent predictor of endothelial dysfunction (odds ratio 5.22, 95% confidence interval 1.76–15.46; $p = 0.003$)
George et al. (2010)	The objective of this study was to determine the correlation between kidney function and the risk of cardiovascular events (CVEs) among the HIV-infected persons. A nested, matched, case-control study design was employed in this investigation of 315 HIV-infected patients (63 patients who had CVEs and 252 controls). Estimated glomerular filtration rate (eGFR) and proteinuria were the primary exposures of interest	Kidney	Mean eGFR was significantly lower in the patients compared with controls by both estimation methods (68.4 vs. 103.2 ml/min per 1.73 m, $p < 0.001$ and 69.0 vs. 103.1 ml/min per 1.73 m, $p < 0.001$). The prevalence of proteinuria in HIV-positive participants was approximately twice that of controls (51 vs. 25%, $p < 0.001$, respectively)
Pierre et al. (2004)	This study sought to document the frequency of clinical conditions, opportunistic and co-infections among children with HIV/AIDS. A total of 110 HIV-infected children 0.9–17.5 years from several clinics in Jamaica was monitored over a one-year period and clinico-pathologic characteristics were recorded	Multi-systemic	The most common symptoms were lymphadenopathy (29.7–42.8%), dermatitis (19.8% of children mildly symptomatic), persistent or recurrent upper-respiratory-tract infections (19.8% of children mildly symptomatic), bacterial sepsis (34.6% of children moderately symptomatic), recurrent diarrhea (21.2%) of children mildly symptomatic and wasting (30.0% of children severely symptomatic), and encephalopathy (26, 27.9%). Pulmonary tuberculosis (7.5%) and *Pneumocystis* (*jiroveci*) *carinii* pneumonia (5.4%) were the most frequent opportunistic infections

Table shows the effect of HIV/AIDS on organs/systems which have important consequences for nutrition and food security. Values shown are a combination of absolute change, mean ± standard deviation, percent change, and odds ratio

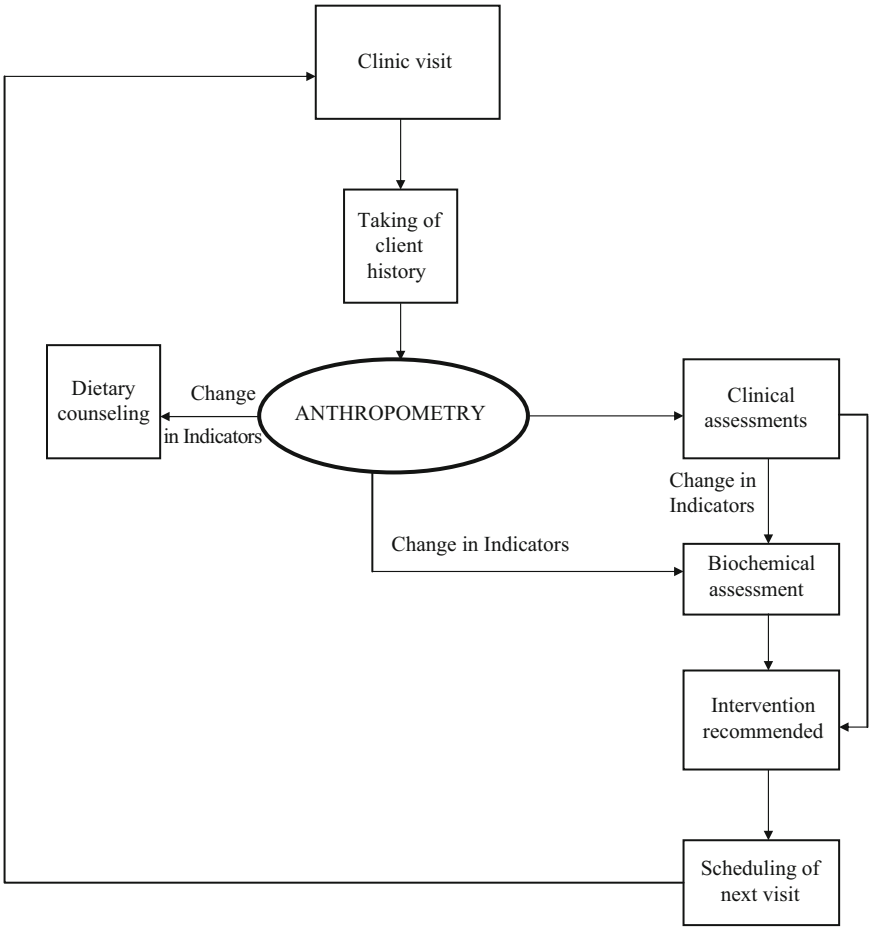

Fig. 153.4 Framework for Anthropometry in the Monitoring and Evaluation of PLWHA. It presents a contextual framework for the role of anthropometry in the monitoring and evaluation of the health status of PLWHA

153.5.1 Clinical Correlations in PLWHA

Studies have suggested that while there may be little differences between HIV-infected and HIV-uninfected children at birth, the former are significantly shorter at ages 8–10 years. Height is also predictive of the risk of developing anemia among HIV-infected children. Severe height deficits are associated with chronic diarrhea and final percentage CD_4^+ cells (Arpadi et al. 2009; Shet et al. 2009).

153.5.2 Practical Methods

The methods used to assess height in PLWHA depend primarily on their age and overall health status. For children who are unable to stand, height should be measured using a recumbent length board. Several brands are available commercially. They can also be manufactured on demand to

meet the needs of users. The effective use of this device requires two trained individuals to take accurate measurements. One person is required to hold the child's head against the board with the head in the Frankfort plane while the other individual presses the bottom of the heel against the sliding board and adjusts the latter until there is no change in height. Height should be measured to the nearest 0.1 cm (Gibson 1990). The averages of three such measurements should be recorded as the final height. Interpretation of height requires persons to be familiar with a relevant reference population. The CDC height chart represents one of the most popular reference growth charts and may be used in situations where there are no population-specific reference standards (Mei et al. 2008). The use of these charts requires that the age of the child be accurately known. This can be problematic in countries where majority of children are delivered outside of a clinic setting. In such circumstances, it might be appropriate to use other chemical markers of age as well as information from family or relatives. Using this age, we plot a vertical line on the reference height chart and note the values for the 97th, 95th, 50th, 5th, and 3rd percentiles. Children whose height falls below the 5th percentile may be experiencing severe height defects. Similarity of growth in the reference standard to the true growth projections of the population being measured is crucial to the eventual interpretation of the data. For HIV-infected adults and children who can stand unassisted, a stadiometer should be used to measure height. Measurement should be taken to the nearest 0.1 cm. Individuals should be positioned with their heads in the Frankfort plane with both heels pressed against the vertical part of the stadiometer. Height should be measured using the headboard or similar device at the top of the head. An average of three such measurements should be used as the mean height. Data can then be interpreted using the CDC or appropriate standard, as outlined earlier. For persons who are bedridden or have spinal deformations, height may be estimated from limb measurements. Knee height may be measured using a knee-height caliper. For knee-height measurements, the knee is bent at a 90° angle with the subject supine left. The immovable blade of the caliper is placed under the heel and its sliding end is placed against the elevated thigh 5-cm proximal to the patella and above the condyles of the femur (Gibson 1990). The caliper can also be positioned with the person in a sitting position. This measure can be done using the right or left leg. We recommend the average of at least two measurements for knee-height measurements. Stature may then be calculated using established equations. Again, the utility of the calculated height depends on the similarity of the reference population to the population being measured (e.g., age, health status, ethnicity, and gender). Many of the algorithms used to estimate stature from these equations require that the age of the person being measured be known. Given the neurological impairment that may be associated with HIV/AIDS, it is important to record age from a verifiable and accurate source. When the proper technique is used, height can be measured with great accuracy.

153.6 Weight

Weight loss is an important feature of HIV/AIDS. The loss of weight and its concomitant effect on lean body mass is a good predictor of the progression of HIV/AIDS. More recently, with the introduction of HAART, there have been concerns about excess weight gain in persons with HIV/AIDS and its impact on health. The measurement of weight is therefore an important variable in the monitoring and evaluation of the health of PLWHA.

Requirement: Infant balance beams and electronic foot scale (preferably one that operates on strain-gauge technology).

Applicability: Children and adults.

153.6.1 Clinical Correlations in PLWHA

HIV-infected children are known to have weight-for-age and weight-for-height values that are significantly lower than their non-infected counterparts (Guillén et al. 2007). Among infected children, lower weight is associated with increased risk for diarrhea, respiratory illness, poorer nutritional status, lower CD4+ cell count, and increased risk for anemia. In fact, weight loss in excess of 10% of body weight is a strong predictor of mortality resulting from HIV/AIDS, while losses of 2–5% are associated with increased risk for morbidities. This includes the risk of anemia, opportunistic infections, and increased use of antiretroviral medications. HIV-infected persons on HAART are at an increased risk for being overweight as well as having an altered fat distribution. Overweight in PLWHA has been linked to the development of serum lipid profiles highlighted by high levels of cholesterol and triglycerides, thereby increasing the risk of cardiovascular diseases (Sodjinou et al. 2008).

153.6.2 Practical Methods

Weight can be measured accurately under standardized conditions. We recommend the use of beam balances and electronic scales. As a general principle, persons should be weighed with minimal clothing and without shoes. Persons should also void their bladders prior to taking their weights. As far as possible, weight should be taken at the same time of day at the different visits. This can be difficult in a typical clinical setting. For adult persons who cannot stand, a bed scale or similar device may be used in the clinical setting. When weighing infants and children, the beam balance or suitable electronic scale should be used. For interpretation of weight among children, suitable weight-for-age and weight-for-height reference standards should be used to establish suitable cutoff points. Again, a relevant standard may be used when there are no population-specific reference data. The important cutoff points are the 97th, 95th, 50th, 5th, and 3rd percentiles of the relevant growth chart. HIV infants and children below the 5th percentile weight-for-age and weight-for-height reference standard are at increased risk for wasting and accelerated progression of HIV/AIDS. Children above the 97th percentile of the weight-for-age and weight-for-height reference standard are at increased risk for being overweight. The reading and interpretation of these charts require trained personnel. Where children are approaching the 3rd percentile, we recommend weekly visits or, if possible, clinic-based interventions. Again, the interpretation of these charts is dependent on the similarities in growth between the population being measured and the reference population. We also recommend continuous charting of the growth record of HIV-positive children. Where the continuous growth curve appears to be flattening or has a negative slope, suitable interventions should be instituted immediately. This may range from nutrition counseling to hospitalization. Among adult PLWHA, unexplained weight loss of >5% in 1 month or >10% in 6 months is indicative of severe risk of undernutrition, which may facilitate the progression of the disease. This change can be calculated as

$$\text{Percentage change in weight } (\%) = \frac{\text{New weight} - \text{weight last visit} \times 100}{\text{Weight at last visit 1}}$$

If the visits were months apart, divide the percentage calculated above by the number of months to calculate an average monthly weight loss. If possible, information on the period of most rapid weight loss should be collected. PLWHA who are >120% of their ideal body weight are considered overweight and should have their serum lipids monitored regularly, especially when they are receiving HAART.

Table 153.2 Anthropometry of persons with (PLWHA) and without (CONTROL) (Burgin et al. 2008)

Variable	PLWHA $n = 36$	CONTROLS $n = 37$	p value
Weight (kg)	63.7 ± 14.0	72.9 ± 12.5	0.004
Height (cm)	167.9 ± 9.3	168.0 ± 8.9	0.93
Waist circumference (cm)	80.3 ± 9.9	83.5 ± 11.3	0.20
Hip circumference (cm)	95.9 ± 12.6	101.4 ± 14.6	0.10
Waist/hip	84.2 ± 8.1	82.7 ± 6.1	0.38
Upper mid-arm circumference (cm)	27.2 ± 4.3	36.7 ± 6.4	0.001
Triceps skinfold (mm)	26.2 ± 8.6	28.9 ± 7.6	0.16
Arm muscle area (cm^2)	22.0 ± 10.08	34.5 ± 17.0	< 0.001
Arm fat area (cm^2)	30.8 ± 13.7	40.1± 16.0	0.01
Perception of weight			
Underweight	15 (41.7)	0	$p < 0.001$
Normal weight	19 (52.8)	28 (75.0)	
Overweight	2 (5.6)	9 (25.0)	
Changes in weight in the past 3 months (%)	22 (60.0)	18 (49.0)	0.34
BMI (kg/m^2)	22.6 ± 4.9	25.8 ± 4.0	0.003
<18 Underweight	2 (5.6)	1 (2.7)	
18–24.9 Normal weight	28 (77.8)	15 (40.5)	
25.0–29.9 Overweight	3 (8.3)	14 (37.8)	
30^+ Obese	3 (8.3)	7 (18.9)	0.004

153.6.2.1 Body Mass Index (BMI)

Body mass index (BMI) is a measure of body habitus, which takes weight and height into consideration. It is calculated as Weight (kg)/height $(m)^2$ or Weight (lb) * 704.5/height $(in.)^2$. BMI has become popular as an index of overweight and obesity. Persons with BMI 25–29.9 are considered overweight and those with BMI 30 and above as obese. Adults with BMI <18 are considered at increased risk for undernutrition. Studies suggest that low BMI in PLWHA is associated with increased risk of anemia, low $CD4^+$ count, and increased risk for diarrhea and opportunistic infections (Villamor et al. 2005). The CDC has several reference charts for BMI of persons 2–20 years, which may be used in assessing the BMI of HIV-positive children and adolescents. The use of BMI in assessing nutritional status must be interpreted with caution as BMI may not accurately reflect body composition (Nichols and Cadogan 2009). As with the weight and height charts, persons below the 5th percentile of the reference chart may be at increased risk for becoming underweight, while those above the 95th percentile are at increased risk for overweight and obesity. Table 153.2 shows a comparison of anthropometry between persons with and without HIV/AIDS. These results suggest that PLWHA are at increased risk for wasting, as suggested by their lower weights and BMI.

153.7 Body Circumferences

Common circumferences that are measured in PLWHA include head circumference (HC), mid-upper-arm circumference (MUAC), waist circumference (WC), and hip circumference (H).

153.7.1 Head Circumference

Requirements: Non-stretchable measuring tape
Applicability: Infants and children <5 years

153.7.1.1 Clinical Correlations in PLWHA

Head circumference (HC) in infants is closely associated with brain and neurological development. Humans have a significant brain growth and development spurt during the first 2 years of life. During this phase, the brain is particularly sensitive to factors that impact on its development. Research conducted over the past few decades have suggested that early malnutrition can result in reduced cognitive development (Kar et al. 2008). Infants who are HIV positive have lower HC than their non-infected counterparts (Mac Millan et al. 2001; Llorente et al. 2003). Given the high risk of undernutrition in infants living with HIV/AIDS, HC measurements represent a good opportunity to assist in timely interventions that may be protective against subsequent poor cognitive development.

153.7.1.2 Practical Methods

Head circumference is measured at the widest circumference of the head. Measurements should be taken to the nearest 0.1 cm. The interpretation of the resulting data requires a reference standard against which it can be compared. The CDC head circumference reference charts for males and female are the most popular in use. The risk for impaired neurological and cognitive development increases with measurements that are below the 5th percentile for the particular age. These charts encompass ages 0–36 months.

153.7.2 Waist and Hip Circumference

Requirements: Non-stretchable measuring tape
Applicability: Children and adults

153.7.2.1 Clinical Correlations in PLWHA

Abdominal fat is an independent predictor of morbidity and mortality among adults (Kuk et al. 2006). Research has shown that waist and hip circumferences are strongly associated with abdominal visceral adiposity among adults (Onat et al. 2004). Waist circumference above 102 cm in males and 88 cm in females is associated with an increased risk for developing diabetes mellitus, high blood pressure, and elevated serum lipids (Grundy et al. 2005; Carroll et al. 2000). This is especially important for persons on HAART which has been shown to increase the risk of overweight and obesity and alter fat patterning of the body in a manner that increases their risk for developing cardiovascular disease (Mutimura et al. 2007; Shevitz and Knox 2001). It has been recommended that the waist-to-hip ratio among adults should be less than 0.9 in males and 0.8 in females (Gibson 1990). Low waist and hip circumference are also indicative of weight changes in PLWHA. In fact, low waist

and hip circumferences among adult PLWHA are associated with an increased risk of diarrhea, opportunistic infections, and reduced immune function (Burgin et al. 2008).

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153.7.2.2 Practical Methods

Waist circumference is taken midway between the last rib and the iliac crest (top of the hip bone). Clients should be measured with this area exposed. Where it is culturally inappropriate or the PLWHA may be self-conscious of their physical appearance in this area, measurements should be taken with minimal clothing over this area. The midpoint should be marked using a marker whose writing can be easily erased after measurement. The non-stretchable measuring tape should be placed over this point and the measurement taken. It is important that the tape be placed horizontally over the area to be measured (Lohmann et al. 1988). Also, subjects should breathe normally. The average of three measurements over the area while the subject is exhaling should be used as the measure of waist circumference. Hip circumference should be measured with the person standing with their feet together. Measurement should be taken at the maximum circumference of the buttocks. Again, the average of three measurements should be taken in a manner similar to the measurement of hip circumference. All measurements should be taken to the nearest 0.1 cm or 1/8 in.

153.7.3 Mid-Upper-Arm Circumference (MUAC)

Requirements: Non-stretchable measuring tape
Applicability: Children and adults.

153.7.3.1 Clinical Correlations in PLWHA

In both children and adults, mid-upper-arm circumference is a useful indicator of adipose tissue and muscle reserves. MUAC can be used in conjunction with triceps skinfold to estimate arm muscle area (AMA). AMA is also a useful indicator of lean body mass. Using the following equations, corrected AMA can be calculated for males and females:

$$\text{Corrected AMA} = \left[\text{MUAC} - (\pi \times \text{TSF})\right]^2 \div (4 \times \pi)$$

where TSF=triceps skinfold (cm), π = 3.14 and MUAC = mid-upper-arm circumference (cm). From this value, we must subtract 6.5 for females and 10 for males (Heymsfield 1982). Values below 32 cm^2 in males and 18 cm^2 in females are indicative of depleted reserves (Merck Manual Professional 2009). Lower corrected AMA is associated with reduced CD4+ cell count among PLWHA. Other studies have shown increases in infections and anemia with reduced MUAC (Burgin et al. 2008). Furthermore, MUAC is highly correlated with weight, BMI, WC, hip circumference, and peripheral energy stores as indexed by arm fat area among PLWHA (Table 153.3).

Table 153.3 Correlation coefficient of anthropometric variables by infection status and gender (Burgin 2008)

	Female controls $n = 19$	Female PLWHA $n = 19$	Male controls $n = 18$	Male PLWHA $n = 17$
	CAMA	CAMA	CAMA	CAMA
	MUAC	MUAC	MUAC	MUAC
Weight (kg)	$r = 0.75$	$r = 0.78$	$r = 0.61$	$r = 0.61$
	$r = 0.85$	$r = 0.91$	$r = 0.79$	$r = 0.60$
	($p < 0.001$)	($p < 0.001$)	($p = 0.008$)	($p = 0.009$)
	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p = 0.01$)
Body mass index (kg/m^2)	$r = 0.39$	$r = 0.76$	$r = 0.48$	$r = 0.85$
	$r = 0.55$	$r = 0.87$	$r = 0.76$	$r = 0.75$
	($p = 0.10$)	($p < 0.001$)	($p = 0.04$)	($p = 0.002$)
	($p = 0.016$)	($p < 0.001$)	($p < 0.001$)	($p = 0.002$)
Waist circumference (cm)	$r = 0.71$	$r = 0.84$	$r = 0.65$	$r = 0.64$
	$r = 0.92$	$r = 0.91$	$r = 0.83$	$r = 0.58$
	($p = 0.001$)	($p < 0.001$)	($p = 0.003$)	($p = 0.005$)
	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p = 0.014$)
Hip circumference (cm)	$r = 0.69$	$r = 0.73$	$r = 0.37$	$r = 0.40$
	$r = 0.92$	$r = 0.84$	$r = 0.63$	$r = 0.60$
	($p = 0.001$)	($p < 0.001$)	($p = 0.13$)	($p = 0.11$)
	($p < 0.001$)	($p < 0.001$)	($p = 0.005$)	($p = 0.01$)
Triceps skinfold (cm)	$r = 0.60$	$r = 0.22$	$r = 0.27$	$r = –0.47$
	$r = 0.88$	$r = 0.77$	$r = 0.64$	$r = 0.21$
	($p = 0.007$)	($p = 0.31$)	($p = 0.27$)	($p = 0.06$)
	($p < 0.001$)	($p < 0.001$)	($p = 0.004$)	($p = 0.42$)
Arm fat area (cm^2)	$r = 0.73$	$r = 0.53$	$r = 0.59$	$r = –0.08$
	$r = 0.94$	$r = 0.92$	$r = 0.87$	$r = 0.59$
	($p < 0.001$)	($p = 0.02$)	($p = 0.01$)	($p = 0.76$)
	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p = 0.013$)

CAMA Corrected arm muscle area (cm^2); *MUAC* Mid-upper-arm circumference (cm)

153.7.3.2 Practical Methods

To determine the position of the midpoint of the upper arm, the upper arm is positioned parallel to the body. The forearm is then placed palm down over the mid body with the elbow bent at a 90° angle. Either the left or right arm could be used. The upper mid-arm is located midway between the acromion and olecranon processes. This point should be marked. The MUAC should be measured at the level of the established midpoint using a non-stretchable tape. This tape should be perpendicular to the humerus and should not compress the skin and underlying tissue during measurements. An average of three measurements should be used as the MUAC. Overall, circumferential measurements, when not conducted properly, result in tremendous errors. It is therefore necessary to conduct regular training sessions to ensure that measurements are taken accurately.

153.8 Skinfold Measurement

Requirements: Skinfold caliper and non-stretchable measuring tape.
Applicability: All age groups.

153.8.1 Clinical Correlation in PLWHA

Skinfold measurement provides an indirect way of estimating adiposity. When used in conjunction with certain body circumference measures, as outlined earlier, it is possible to estimate body adiposity and lean body mass. Both these measures are important for PLWHA as they index body compartments which are important sources of energy and protein. Triceps and subscapular skinfold are two of the more common skinfold measurements taken. Studies have shown that skinfold thickness is lower in PLWHA compared to non-infected persons. Furthermore, infected persons experiencing the wasting syndrome associated with HIV/AIDS show significant reduction in their triceps skinfold thicknesses (Burgin et al. 2008).

153.8.2 Practical Methods

153.8.2.1 Triceps Skinfold

The triceps skinfold is taken on the posterior midline at the site established for MUAC, as described earlier. After establishing the midpoint of the upper arm, the arm should hang loosely with the palm facing forward. The person taking the measurement should stand behind the client. The skinfold should be grasped about 1 cm posterior to the midpoint with the thumb and index finger of the left hand. The caliper should be placed over the midpoint perpendicular to the humerus. The average of three such measurements should be taken as the triceps skinfold (Gibson 1990).

153.8.2.2 Subscapular Skinfold

The individual to be measured must stand erect with shoulders and arms relaxed at their side. The inferior angle (or triangle portion) of the right scapula should then be located and marked. A fold of the skin and subcutaneous adipose tissue directly below (1.0 cm) and medial to the inferior angle should then be grasped. The skinfold would then form a line about 45° below the horizontal, extending diagonally toward the right elbow. The jaws of the caliper should then be placed perpendicular to the length of the fold about 2.0 cm lateral to the fingers, with the top jaw of the caliper on the mark over the inferior angle of the scapula. The skinfold thickness is measured to the nearest 0.1 mm, while the fingers continue to hold the skinfold (Lohmann et al. 1988).

153.8.2.3 Suprailiac Skinfold

The right hip area should be exposed for this measurement. The iliac crest should be marked. The left thumb should be placed on the intersecting marks and the skinfold should be picked up with the thumb and fingers. The skinfold should slope downward and forward at a 45° angle extending toward the pubic symphysis. The caliper should be placed perpendicular to the skinfold about 2.0 cm medial to the fingers and the skinfold is measured to the nearest 0.1 mm (Lohmann et al. 1988).

153.8.2.4 Abdominal Skinfold

The abdominal skinfold is measured at a site 3 cm to the side of the midpoint of the umbilicus and 1 cm below it. The skinfold is horizontal and should be measured on the right side of the body while the subject relaxes the abdominal wall as much as possible. In order for skinfold measurements to generate information that can be of use in monitoring aspects of the nutritional status of PLWHA, it is necessary to associate them with well-established indices of nutritional status. For example, skinfold measurements can be used to generate information on body composition. This can be done by converting skinfold thickness into body density by using well-established equations, such as those developed by Durnim and Womersley. Body density can be converted to percentage body fat by using Siri's equation (i.e. 490/d – 450, where d is the calculated body density). Other equations that use skinfold measurements allow the direct estimation of percentage body fat (Lee et al. 2003). Overall, anthropometry can be used to monitor and evaluate several adverse clinical outcomes among PLWHA. Table 153.4 shows a summary of clinical outcome in PLWHA for which anthropometry can provide useful monitoring and evaluation data.

Table 153.4 HIV and change in anthropometry

Reference	Study design, objective, and method	Age	Results
Miller et al. (1993)	Prospective study of 89 children born to HIV-infected mothers following from 1986 to 1991. Children were compared using length, weight, and weight for height percentiles and *Z*-scores. Triceps skinfold and arm muscle circumference percentiles were also determined	0–4 years	HIV-infected children had significantly higher rates of decrease in triceps skinfold (–1.09 +0.30 vs. –0.20 +1.06) and smaller rates of increase in arm muscle mass (0.26 + 0.30 vs. 2.30 + 0.71) than seroreveters
Bailey et al. (1996)	Prospective cohort of 258 children born to HIV-positive mothers. These children were followed from birth to 20 months, and anthropometric measures such as length, height, and weight were measured	0–20 months	Height-for-age *Z*-scores were lower in HIV-infected children compared to seroreverters at 6 months
Brown et al. (2006)	Prospective 4-year follow-up of HIV-infected and HIV-uninfected men to determine the pattern of BMI, waist circumference, hip circumference, and waist-to-hip ratio		Increased BMI in HIV seronegative compared to HIV infected (0.12 ± 0.04 kg/m^2 vs. 0 kg/m^2; $p < 0.01$); increased waist circumference in HIV seronegative compared to HIV infected (0.49 ± 0.07 cm/year vs. 0.18 ± 0.06 cm/year; $p < 0.01$); increased hip circumference in HIV on HAART compared to HIV seronegative (0.51 ± 0.14 cm/year vs. 0.63 ± 0.18 cm/year; $p = 0.03$); increased waist-to-hip ratio in HIV on HAART compared to HIV seronegative (0.005 ± 0.001 vs. 0.0003 ± 0.001; $p < 0.01$)

(continued)

Table 153.4 (continued)

Reference	Study design, objective, and method	Age	Results
Webb et al. (2009)	Prospective cohort. This study investigated the predictors of growth among 1,078 HIV infected women. Length for age and weight for length Z-scores were monitored among their newborns or the first 2 years of life	0–2 years	After controlling for mother's age, education and CD4+ count, and infant's sex and weight at birth, HIV-positive children had significantly lower mean, length for age *Z*-scores at 6 months (–0.23), 12 months (–0.38), and 24 months (–0.63) than their uninfected counterparts. Similarly, they had lower weight for length *Z*-scores at 6 months (–0.38), 12 months (–0.35), and 24 months (–0.69)
Justman et al. (2008)	Prospective cohort. This study described the longitudinal pattern of body mass index (BMI), waist–hip ratio, and waist and hip circumference among 942 HIV-infected women and 266 uninfected women over a four-year period	41 years	Mean BMI at each visit was significantly lower in HIV-infected men compared to HIV-uninfected men (range = –1.29 kg/m^2 to –4.33 kg/m^2). Over the duration of the study, mean BMI in HIV-uninfected men increased by 2.49 kg/m^2 or 8.2%. Waist-to-hip ratio for HIV-infected women increased from 0.016 to 0.032 ($p = 0.024$)
			HIV-uninfected women had significant increase in waist circumference (+4.1 cm or 4.4%) and hip circumference (3.76 or 3.5%)

Table shows the impact of HIV/AIDS on commonly used anthropometric measures. Values shown are a combination of absolute change, mean ± standard deviation, percent change, and changes in *Z*-scores. These findings suggest that anthropometric measures may be useful for monitoring and evaluating disease progression among PLWHA

153.9 Applications to Other Areas of Health and Disease

The similarity of the pattern of weight loss seen in HIV/AIDS to that seen in other diseases, such as cancer, anorexia nervosa, and severe protein–energy malnutrition, suggests that anthropometric measurements for monitoring and evaluating nutritional status among PLWHA may be useful for monitoring and evaluating persons with these conditions and vice versa.

Summary Points

- Approximately 33 million persons globally are living with HIV and AIDS.
- Majority of persons living with HIV/AIDS reside in developing countries.
- Persons living with HIV/AIDS are at increased risk of malnutrition and food insecurity, as a result of increased nutrition utilization, malabsorption of nutrients, and inability to acquire food, as the disease progresses.
- Anthropometric measurements, such as weight, height, body circumferences, and skinfold thickness, are good proxies for gauging the nutritional status of individuals.
- Anthropometric measurements are associated with the morbidity and mortality among PLWHA.

- Anthropometric measurements are easy to take; they are also relatively cheap, reliable, and noninvasive.
- Anthropometry should be a component part of any comprehensive strategy for monitoring and evaluating PLWHA.

Key Facts on the Role of Nutrition and Anthropometry in Monitoring the Nutritional Status of Plwha

- HIV/AIDS is associated with changes in metabolic physiology that influence the metabolism, absorption, and ability of infected persons to acquire foods.
- PLWHA are at increased risk for food insecurity and malnutrition.
- HIV/AIDS increases the risk for illness and death.
- HIV/AIDS is most prevalent in the 15–44-year age group – a group that forms a large portion of the productive workforce in many developing countries.
- The link between nutrition, health, and development is well established.
- Indices of nutritional status of individuals and populations can provide a useful proxy for future development of nations.
- Anthropometric measures provide us with useful proxies to the nutritional status of individuals.
- Anthropometric measures, such as weight, height, waist circumference, and mid-upper-arm circumference, are associated with morbidity, mortality, and clinical and biochemical parameters among PLWHA.
- Anthropometric measures can provide valuable information that would allow timely intervention to prevent and mitigate poor health outcome among PLWHA.

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Chapter 154
Antropometry in HIV Patients: Effects of Recombinant Human Growth Hormone

Livio Luzi, Ileana Terruzzi, and Stefano Benedini

Abstract Patients with HIV infection treated with protease inhibitors (PIs) drugs for a long period have a prolonged life expectancy and an improvement of quality of life. Often, HIV-patients on PIs develop a syndrome characterized by peripheral lipoatrophy, truncal fat accumulation, hyperlipemia and insulin resistance.

In HIV-1 patients undergoing antiretroviral treatment, lipodystrophy is associated with peripheral fat wasting and central adiposity, dyslipidemia, insulin resistance, and increased intramuscular fat accumulation.

In HIV lipodystrophy fat distribution changes are heterogeneous and can include reduced subcutaneous fat and increased visceral fat. In literature there are evidences showing overnight growth hormone (GH) secretion and pulse amplitude reduction in patients with HIV lipodystrophy, in response to standard GH stimulation test.

Excess accumulation of visceral fat with increasing of intra-abdominal adiposity (central obesity) is also a typical feature of patients with GH deficiency. Recombinant human growth hormone (rhGH) can be a useful treatment to diminish excess visceral fat. Up to day there are evidences that GH therapy in HIV-infected patients with syndromes of central fat accumulation show a significant decrease of body fat.

In this chapter, we discuss the anthropometry of lipodystrophy in HIV patients and the indication of rhGH treatment in HIV-related lipodystrophy.

Abbreviations

Apo B	Apolipoprotein B
11ß-HSD1	11beta-hydroxysteroid dehydrogenase type 1
BMD	Bone mineral density
CT	Computer tomography
DEXA	Dual-energy x-ray absorptiometry
FFA	Free fatty acids

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_154,

GC	Glucocorticoid
GH	Growth hormone
GHD	GH-deficient
GHBP	GH-binding protein
GHR	GH receptor
GHRH	Growth hormone releasing hormone
GLUT4	Glucose transporter 4
GR	Glucocorticoid receptor
Grb2	Growth receptor binding protein 2
HAART	Highly active antiretroviral therapy
HDL-C	High Density Lipoprotein-Cholesterol
HIV	Immunodeficiency virus
HMG CoA	3-Hydroxy-3-methylglutaryl coenzyme A
IDL	Intermediate density Lipoprotein
IGF-I	Insulin-like growth factor I
IGFBP-3	Insulin-like growth factor -binding protein 3
JAK	Janus Activated Kinase
Lp (a)	Lipoprotein (a)
LPL	Lipoprotein lipase
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemotactic protein-1
MRI	Magnetic resonance imaging
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
PIs	Protease inhibitors (drugs)
Pl3K	Phosphatidylinositol 3-kinase
rhGH	Recombinant human growth hormone
Shc	Src (it is short form for sarcoma) homology domain containing
SOCS	Suppressor of cytokine signaling
SOS	Son of sevenless
STATs	Signal transducer and activator of transcription factors
TC	Total cholesterol
TG	Triglycerides
TNFα	Tumor necrosis factor-α
VLDL	Very Low Density Lipoprotein

154.1 Introduction

In adulthood, a reduction in GH production causes a particular syndrome, characterized by an alteration of body composition which includes increased total visceral fat, decreased muscle mass, and bone density (Ho et al. 1996). All symptoms are improved by GH replacement (Carroll et al. 1998). The dose of GH recommended in the adult is much lower than that used in pediatric practice; consequently, hormone side effects are proportionally lesser.

In the last years, protease inhibitor (PI) therapy improved survival and quality of life of HIV-infected patients. These patients often develop a syndrome characterized by peripheral lipoatrophy, trunk fat accumulation, and metabolic alterations. The causes of this syndrome are still not completely defined. Both the infection with human immunodeficiency virus-1 (HIV-1) per se and the combination of HIV with different anti-retroviral drugs seem to play a role in the pathogenesis of the

lipodystrophic syndrome. Insulin resistance leads to an alteration of lipid metabolism resulting in a metabolic picture similar to the one of patients affected by the metabolic syndrome (Carr et al. 1998). In fact, in HIV-lipodystrophy, the intramuscular fat accumulation contributes to development of insulin resistance. Additional metabolic alterations are hypertriglyceridemia, reduction of high-density lipoprotein (HDL) cholesterol, glucose intolerance, and hyperuricemia. The most relevant hormone alterations in these patients are: increased levels of insulin, C-peptide, prolactin, erythropoietin, and tumor necrosis factor-α (TNFα) (Haugaaer et al. 2006b). An abnormal circadian cortisol pattern was also described.

A defect of growth hormone (GH) secretion following a combined arginine/GH-releasing hormone (GHRH) stimulation (Koutkia et al. 2005) was demonstrated. In adulthood, a defective GH secretion is associated with abnormal fat distribution, and GH administration normalizes the pattern of fat deposition. A beneficial effect of growth hormone (GH) administration (clinically justified when an absolute or a relative GH secretory defect is assessed by GHRH/arginine test) was recently suggested by our group (Luzi et al. 2003).

A low-dose GH treatment improves body fat distribution and is devoid of major metabolic side effects once drug administration is discontinued. The question, which is still open, is the duration of the effect of the GH treatment. Previous work suggested a reversal of the effect on fat distribution after cessation of GH treatment. For this reason, even in the light of the results of previous studies (Esposito et al. 2006), a temporary low-dose GH treatment (for example, 6 months, Luzi et al. 2005) combined with a program of physical activity (to be performed continuously both during the treatment and the wash-out periods) could be recommended in HIV patients with lipodystrophy. Physical exercise is known to be a powerful physiological stimulus for GH release in humans per se (Thomas et al. 2003) and can be a lifestyle intervention to maintain the effects of recombinant GH in patients with HIV lipodystrophy for a longer time after discontinuation of the GH treatment.

In this chapter, we suggest the possible use of recombinant human growth hormone for the treatment of HIV-associated adipose-tissue redistribution syndrome and the anthropometric changes in body composition before and after GH therapy.

154.2 Growth Hormone Action

Growth hormone (GH) has been known for a long time to have a role in the promotion of postnatal somatic growth in children and adolescents, and to have “important metabolic action” both fat and lean body mass in adult. Nonetheless, the cellular and molecular bases for these effects of GH are not completely understood. A summary of the mechanisms by which GH affects cellular function is provided in this section.

The start of GH signaling pathway is mediated by the GH receptor (GHR), and it is characterized by a first step which is the formation of a trimer complex with one molecule of ligand and two molecules of receptors. Two specific sites (sites 1 and 2) on a single GH molecule are responsible for this interaction.

The mature human GHR is a 620-amino-acids molecule. A soluble form of the GHR, known as the GH-binding protein (GHBP), derives by a simple proteolytic cleavage of the extracellular domain of the GH receptor.

Receptor dimerization appears to be crucial for signal transduction, since bringing the two GHRs in close proximity increases the affinity of each GHR for JAK2 and its consequent GH-dependent activation. JAK2 is a member of the Janus kinase family of cytoplasmic tyrosine kinases characterized by the presence of an N-terminal domain believed to be important for both GHR-induced phosphorylation and other cytoplasmic signal molecules’ activation. The downstream signaling

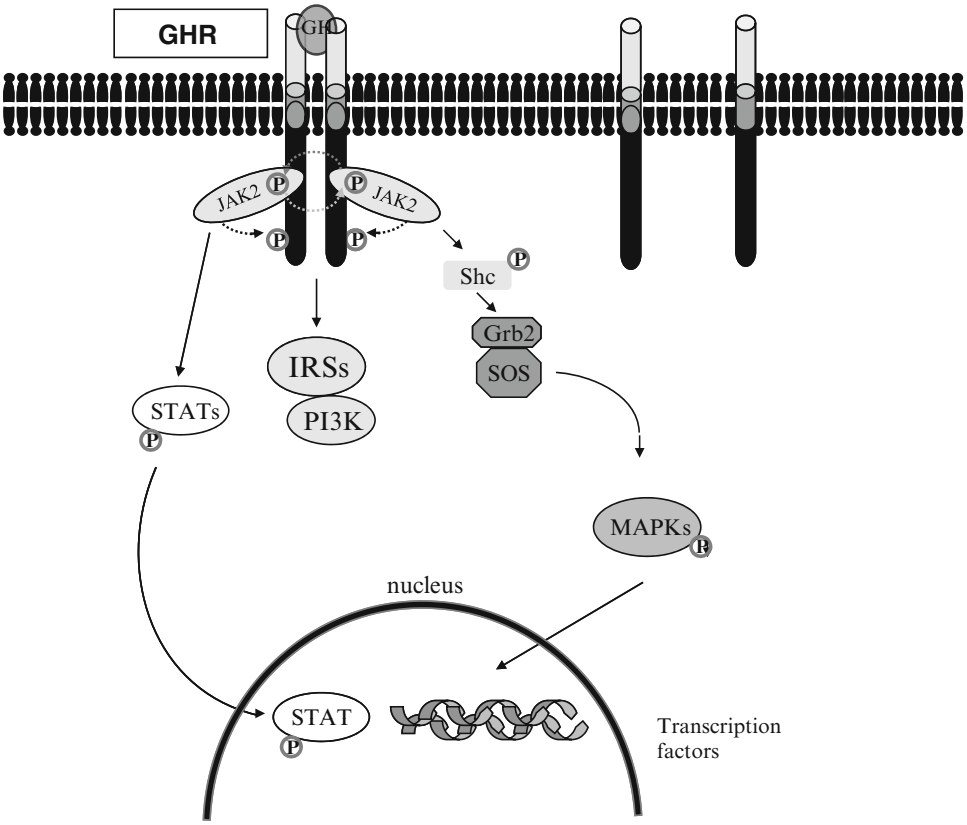

Fig. 154.1 Intracellular Mechanism of Growth Hormone Action. Intracellular mechanism of growth hormone (*GH*) action. *GHR* growth hormone receptor; *Grb2* growth receptor binding protein 2; *IRS* insulin receptor substrate; *JAK2* Janus-activated kinase 2; *MAPK* mitogen-activated protein kinase; *MEK* MAPK kinase; *Pl3K* phosphatidylinositol 3-kinase; *Shc* Src homology domain containing protein; *SOS* son of sevenless; *STATs* signal transducer and activator of transcription factors

pathway recruited and activated by the GHR–JAK2 complex includes signal transducers and activators of transcription (Stat) factors. STATs are a family of cytoplasmic proteins that directly bind the phosphorylated tyrosine residues on the GHR in a GH-dependent manner, allowing them to be phosphorylated and activated by JAKs. GH is able to modulate this pathway by activating the binding of the protein Shc to phosphorylated residues in both JAK2 and GHR. Phosphorylated Shc sequentially activates growth factor receptor bound 2 (Grb2) and son of sevenless (SOS), which can then activate MAPK (see Fig. 154.1).

Growth hormone is not only a regulator of somatic growth, but it also exerts relevant effects on body composition through effects on adipose-tissue kinetics of accumulation and reduction of triglyceride deposition acting on lipoprotein lipase activity. LPL induces the uptake of FFA derived from the complete hydrolysis of the triglyceride. The GH-induced suppression of LPL activity inhibits the hydrolysis of triacylglycerols in chylomicrons and very low density lipoproteins for the provision of free fatty acids for tissue utilization or storage.

The hormone is also necessary for the regulation of the metabolism of mature adipocyte. Growth hormone enhancement of the lipolytic activity of adipose tissue in combination with a reduction of triglycerides' accumulation via inhibition of lipoprotein lipase activity appears to be the major mechanism by which GH administration results in a reduction of total fat mass.

Summarizing growth hormone actions, GH exerts profound effects on whole-body- and district-body composition through a combination of anabolic and lipolytic actions playing a central role in human metabolic homeostasis (Benedini et al. 2008).

154.3 Anthropometric Feature of HIV: Lipodystrophy

Lipodystrophy was originally described as a condition characterized by regional or generalized loss of subcutaneous fat. Lipodystrophies are rare disorders characterized by the selective loss of adipose tissue in certain body regions, coupled with accumulation of fat in other body districts. Adipose tissue is a key player in metabolic homeostasis through its role as an energy depot and an endocrine organ.

In humans, the distribution of fat is regulated by many factors, including genetics, sex, age, environmental factors (such as diet, exercise, and drugs), and illness. Anthropometrical measurements, in particular, waist–hip ratio and the body mass index (squared body weight in kilograms divided by height in meters), correlate well with total body fat in simple obesity and are good measures of central adiposity.

Localized fatty changes may occur in some illnesses, such as the development of dorsocervical fat accumulations and peripheral subcutaneous fat atrophy in hypercortisolism.

Lipoatrophy is primarily subcutaneous fat loss. Fat deposition in patients with HIV occurs in the visceral depot (intra-abdominally), breasts, and dorsocervical area of the neck. Some patients have fat deposits in the form of lipomas. The term 'HIV-associated adipose redistribution syndrome' has been used to define a distinct subset of general lipodystrophy that is primarily characterized by the abnormal accumulation of visceral adipose tissue, with or without comorbid lipoatrophy and metabolic abnormalities, such as dyslipidemia or insulin resistance (Cofrancesco et al. 2009).

In particular, the term 'lipodystrophy syndrome in association with HIV' was introduced to describe a complex medical condition including the apparent abnormal fat redistribution and metabolic disturbances seen in HIV patients receiving protease inhibitor therapy. After the first description, several papers correlated lipodystrophy with HIV (Carr et al. 1998). The mechanisms of HIV lipodystrophy are unknown and may relate either to specific drug effects of protease inhibitors and nucleoside reverse transcriptase inhibitors (Kravcik 2000) or to an interaction between pharmacological and non-pharmacological factors. Furthermore, it is still unknown whether HIV-related lipodystrophy represents a single syndrome or several distinct clinical conditions. Among the NRTIs, stavudine leads to an earlier onset of clinically apparent fat wasting compared with zidovudine. Fat wasting associated with NRTI use may be a manifestation of mitochondrial toxicity, which may be exacerbated by PI use. For all the above reasons, lipodystrophy will be considered to have several features, which can either be isolated or occur in various combinations among them. Features of lipodystrophies may be hypertrophic, atrophic, and metabolic manifestations. Hypertrophic changes consist of excess fat deposition, most commonly around the abdominal region, and also in the neck, in the supraclavicular fossae, or in the subcutaneous tissues of the posterior neck, between the scapulae. Fat deposition may also take the form of bilateral symmetrical lipomatosis or breast enlargement. Atrophic changes consist of subcutaneous fat atrophy in the legs, buttocks, arms, and nasolabial and malar fat pads (Fig. 154.2). Often, veins are prominent in the limbs, but varicosities are absent. The cosmetically disfiguring changes that occur with lipodystrophy may have a significant impact on quality of life and relational/social activities. Dyslipidemia was reported in HIV-infected individuals on and off drug therapy (Carr et al. 1998). PI therapy of HIV-infected individuals was associated with increased total cholesterol, non-HDL-C, triglyceride, IDL, and VLDL cholesterol. The increased VLDL levels were due to increased concentrations of large VLDL particles,

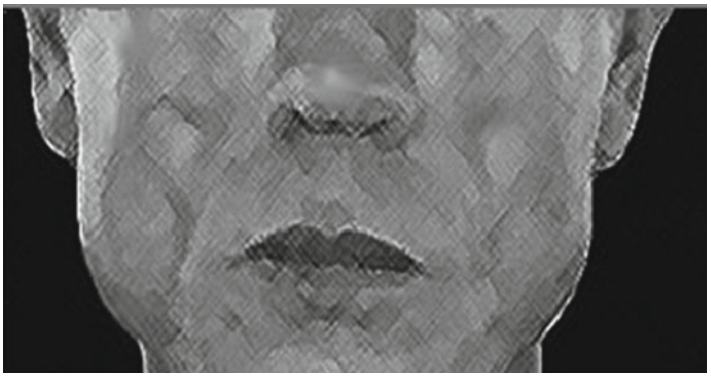

Fig. 154.2 Fat atrophy in nasolabial folds and malar fat pads. This figure represents a clear example of atrophy of the face in an HIV patient

which include chylomicron remnants. Furthermore, the individuals receiving PI therapy were shown to have altered flow-mediated vasodilation of the brachial artery, indicative of endothelial dysfunction (Hoffmann et al. 2005). The fact that the dyslipidemia in these individuals was significantly predictive of the endothelial dysfunction suggests that this dysfunction is mediated by the PI-related dyslipidemia. Of interest, a unique and unexplained aspect of the HIV/PIs-associated dyslipidemia is the significant increase observed in Lp(a). Lp(a) levels are thought to be largely genetically determined and generally not suitable for therapeutic intervention, and administration of PIs was associated with an increase in plasma levels of Lp(a) in case of subjects who had elevated pretreatment plasma Lp(a) levels. Therefore, this category of patients could be at high risk of premature atherosclerosis. Also, as described below, other studies suggest that HIV-associated dyslipidemia is due to increased synthesis, not to decreased breakdown of triglycerides.

The prevalence of HIV lipodystrophy is variable, but, in the patients treated with PIs, the prevalence varied between 5% and 83% and may increase with duration of use of such a drug (Kravcik 2000).

Often, patients receiving PIs who developed LD had higher triglyceride, cholesterol, insulin, and C-peptide levels and greater insulin resistance than patients taking PI but without lipodystrophy (Carr et al. 1998). It is not clear if these altered metabolic factors are secondary to the lipodystrophy, or are somehow involved in its pathogenesis.

Both the lack of a formal definition and uncertainty about the pathogenesis and possible long-term consequences lead to a continuing discussion about appropriate guidelines for the assessment and management of HIV lipodystrophy syndrome and its metabolic abnormalities. The diagnosis relies principally on the occurrence of apparent clinical signs and the patient reporting them. A standardized data collection form may assist in diagnosis. This appears sufficient for the routine clinical assessment, especially when the body habitus changes develop rather rapidly and severely. However, for clinical investigations, especially in epidemiological studies, more reliable measurements are required.

Unfortunately, no diagnostic protocol demonstrated sufficient sensitivity, specificity, or predictive value to definitively diagnose the HIV lipodystrophy syndrome by comparison with results obtained from a ‘normal’ (not lipodystrophic) population (Hoffmann et al. 2005).

In fact, a standardized measure of the localized manifestations of fat accumulation is not available (Kravcik 2000). Several techniques are suitable for measuring regional fat distribution. These include dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI). DEXA is a noninvasive radiological method that allows for direct measurement of

lean mass, fat mass, and bone mineral mass. CT and MRI should only be considered in routine clinical practice for selected patients because limitations of these methods include most notably their cost, availability, and radiation exposure (CT). Interestingly, a refined evaluation of content of tryglicerides in some organs (in this case muscle) can be performed using 1H MR spectroscopy. This method was recently applied in patients affected by HIV lipodystrophy (Luzi et al. 2003), although many authors have used 1H MR spectroscopy during recent years for evaluation of intramyocellular triglycerides' concentration in several clinical conditions. High-resolution, T1-weighted images of the right calf are obtained before spectroscopic acquisition to localize the voxel of interest for the 1H spectroscopy study. Voxel shimming is executed to optimize the homogeneity of the magnetic field within the specific volume of interest. Two 1H spectra are collected from a $15 \times 15 \times 15$ mm^3 volume within the soleus and tibialis anterior muscles. A PRESS pulse sequence (repetition time = 2,000 ms and echo time = 60 ms) is used, and 128 averages were accumulated for each spectrum, with a final acquisition time of 4.5 min. The water signal is suppressed during the acquisition, since it would dominate the other metabolite's peak. A third 1H spectrum of a triglyceride solution inside a glass sphere, positioned within the extremity coil next to the calf, is also obtained during the same session in order to have an external standard acquired in the same conditions as the subject's spectra. Postprocessing of the data, executed with the Sage/IDL software, consists of high-pass filtering, spectra apodization, zerofilling, Fourier transformation, and phasing of the spectra. The integral of the area under the peak is calculated using a Marquardt fitting with Lorentzian functions of the peaks of interest. The integral of the methylene signal (CH_2) at 1.35 parts/million is used to calculate intramyocellular triglyceride content expressed in arbitrary units (AU) as the ratio to the integral of the peak of the external standard × 1,000 (Luzi et al. 2003).

This useful method for evaluation of triglycerides in the skeletal muscle can be used as an index of insulin resistance; in fact, the intramyocellular lipid concentration inversely correlates with insulin sensitivity.

Probably, the retroviral infection, in combination with HAART (including both NRTIs and PIs), is responsible for the metabolic defect, which is associated with abnormal fat distribution. Recent publications point to a selective impairment of GLUT4 activity by PI drugs, and genetic manipulation of GLUT4 expression has shown a role of this protein in adipose tissue metabolism (Hruz 2006).

In summary, different human diseases (other than HIV) associated with lipodystrophy are characterized by major metabolic derangements, such as insulin resistance and dyslipidemias. In particular, the diagnosis of lipodystrophy can be very difficult using only anthropometric measures (waist: hip ratio, skinfold thickness, and weight and height); therefore, a radiological test can be very useful to assess the real body composition.

154.4 Previous Experience with GH Treatment and Potential Risks

Optimization of growth hormone (GH) replacement during childhood is likely to be a key factor for normal skeletal development in GH-deficient (GHD) children. In the past, GH replacement for childhood-onset growth hormone deficiency has been discontinued at completion of linear growth. However, GH replacement in GHD adolescents and adults is increasingly believed to have beneficial effects on a number of biological endpoints, including skeletal health. After epiphyseal closure, skeletal effects of GH replacement in GHD subjects include improvements to a perturbed bone remodeling cycle. The resulting beneficial effects on bone mineral density (BMD) may be crucial before the attainment of peak bone mass, which may not occur until the beginning of the fourth decade. Additional beneficial effects, including improvements in lean body mass, muscle strength,

exercise capacity, cardiac performance, and psychological well-being, will result in inevitable benefits to the young-adult skeleton (Mukherjee et al. 2003).

Growth hormone (GH) secretion from anterior pituitary is regulated by the hypothalamus and by the mediators of GH actions (Table 154.2). Factors including GH-releasing hormone (GHRH), somatostatin (SRIF), GH endogenous peptide with GH-releasing properties (ghrelin), and insulin-like growth factor (IGF-I) modulate GH secretion. The principal physiological regulatory mechanisms of GH secretion are neural endogenous rhythm, sleep, stress, physical exercise, and nutritional and metabolic signals. GH deficiency results from various hereditary or acquired causes, which may take place in isolation or in combination with other pituitary hormone deficiencies.

The use of recombinant human GH has expanded the narrow indication of treating children with severe GH deficiency (GHD) to include a broader target population of children with growth retardation and short stature and adults with hypopituitarism and severe GHD (Mauras et al. 2000). More recently, some authors speculated about use of recombinant human GH in obesity and in the metabolic syndrome (Shadid and Jensen 2003).

In subjects with hypothalamic–pituitary disease, the adult GH-deficiency syndrome (GHD) is typically characterized by changes in body composition, including a reduction in lean mass and bone mineral density (only in patients with GHD of childhood onset) and an increase in fat mass, with a preponderance of central adiposity and increased waist circumference. Muscle strength and exercise performance decline. An impaired sense of well-being and the alteration of other psychological complaints are common. The excess abdominal fat accumulates mainly in the viscera. In epidemiological studies, this abdominal fat distribution has been associated with a higher risk of mortality and morbidity due to cardiovascular disease. Using various methods, few studies have demonstrated decreased bone mass at several skeletal sites in patients with GHD when compared with healthy control subjects (Carroll et al. 1998).

GH and cardiovascular risk. There are many reports in the medical literature on the increased cardiovascular mortality rates associated with GHD, supporting the hypothesis that long-standing GH deficiency in adults predisposes to the development of premature atherosclerosis and hypercoagulability. Moreover, adults with GHD are likely to be insulin resistant. Using a hyperinsulinemic euglycemic clamp (40 mU/m^2·min), Johansson et al. (1995) found a lower glucose infusion requirement in 15 adults with GHD than in matched controls, demonstrating their reduced insulin sensitivity, which was associated with the central obesity and increased intra-abdominal adiposity typical of GHD. Most studies utilizing the hyperinsulinemic euglycemic clamp have confirmed the presence of insulin resistance in GHD (Carroll et al. 1998). Higher concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (ApoB) were observed in GHD patients compared with age- and sex-matched controls. High-density lipoprotein cholesterol (HDL-C) levels are lower and triglycerides (TG) levels are higher than in healthy controls.

Central adiposity, insulin resistance, diabetes mellitus, and hyperlipidemia are common in adults with hypopituitarism. The consensus statement of the Endocrine Society of Evaluation and Treatment of Adult Growth Hormone Deficiency in 2006 showed that there are benefits of GH therapy including improvements in body composition, exercise capacity, skeletal integrity, lipids, and quality of life. Although it has been suggested that GH treatment may reduce the increased vascular mortality associated with hypopituitarism, this has not yet been proved. It should be emphasized that long-term clinical-outcome studies on hard endpoints, such as fractures, clinical heart disease, cancer, and mortality are still lacking at present. The KIMS study demonstrated that GH replacement is associated with an improvement in central fat mass and mean reductions in serum total and LDL cholesterol, which may be compared to those achieved with HMG CoA reductase inhibitors. These beneficial effects are maintained for at least 2 years after the beginning of the therapy. In particular, there was a reduction in central adiposity, both in men and women, when the GH dose was adjusted

to achieve a serum IGF-I level between the median and the upper value of the age-related range of reference. The net effects of GH replacement on cardiovascular risk are likely to derive from the reduction of central adiposity and lipid metabolism combined with an improvement in insulin resistance (Monson 2003).

Thus, all the metabolic alterations of GHD are partially reverted by short-term rGH therapy (about 1 year) (Carroll et al. 1998), although its real impact on vascular damage and endothelial dysfunction is still unknown. Recent reports showed the improvement of metabolic picture and of flow-mediated vascular dilatation in patients treated with hrGH (Benedini et al. 2006). Surprisingly, Lp(a) seems to be increased after GH therapy in a population of men with abdominal obesity, but, regarding cardiovascular risk, the effects on total cholesterol, LDL, and Apo B are probably of more importance than the moderate increase observed in serum Lp (a) concentration.

The data reported so far are encouraging and indicate the beneficial cardiovascular effects of GH in the short term as one of the major factors supporting this treatment in hypopituitary GHD adults. Furthermore, consistent evidence derived from GHD studies suggests a physiological role for the GH/IGF-I axis in the control and regulation of several metabolic cardiovascular risk factors (Benedini et al. 2006).

GH deficiency during childhood is associated with severe growth retardation, resulting in marked impairment of adult height.

GH and tumors. There is increasing evidence that the growth hormone/insulin-like growth factor-I axis may provide a major link between these factors and the development of cancer through its influence on the regulation of normal cell proliferation, differentiation, and apoptosis (Jenkins et Bustin 2004).

The question of the impact of GH therapy on tumor growth has often been raised, particularly in reference to populations of children previously treated for childhood malignancies. Because interpretation of tumor recurrence data is complicated by biases introduced by the selection of children for GH therapy, careful matching of control populations is necessary. In a condition such as acromegaly (constantly high GH concentrations), there is little evidence that cancer risk is increased, and one possible explanation of this fact is that, in acromegaly, both IGF-1 and IGFBP-3 are high and, hence, the GH-binding protein is able to modulate negatively the role of IGF-1 in cell growth. Both single-center studies and large-multicenter surveillance studies have failed to show any increase in the incidence of de novo malignancies during GH replacement (Benedini et al. 2008). A recent updated analysis confirms that childhood cancer survivors treated with GH appear to have an elevated risk of developing a secondary solid tumor compared with survivors not treated. However, the elevation of risk resulting from GH use appears to decrease with increasing length of follow-up, and the overall risk remains small. This risk should be carefully weighed against the potential benefits of GH therapy in cancer survivors (Table 154.3).

GH and diabetes mellitus. Fasting glucose levels were shown to rise after the commencement of GH therapy in children, and there have been reports of development of diabetes mellitus during treatment. Data from the National Cooperative Growth Study (NCGS) (Blethen et al. 1996) and KIMS (Pharmacia International Growth Database) have not suggested an increase in the incidence of type 1 diabetes, but the KIGS database did demonstrate a higher than expected incidence of type 2 diabetes in a heterogeneous population including children treated with GH for short stature not due to GHD (Cutfield et al. 2000). this incidence in children and adolescents was, very small (34 cases per 100,000 yr of GH treatment), and it was postulated that the higher rates may indicate an acceleration of the disorder in predisposed individuals.

The diabetogenic effect of GH arises from the (direct or indirect) ability of GH to enhance endogenous glucose production and to inhibit cellular glucose uptake, thus raising plasma glucose concentrations (see Table 154.1).

Table 154.1 GH therapy: side effects

Arthralgia
Peripheral edema
Generalized edema
Pseudotumor cerebri
Myalgia
Carpal Tunnel Syndrome
Paraesthesia
Hyperglycemia

In this table are summarized the most common side effects of GH therapy

Insulin resistance and type 2 diabetes have been reported in a few patients in the early, large clinical trials (Svensson et al. 2002). Thus, with current treatment dose, there may be a moderate increase of the risk to develop diabetes mellitus. Careful monitoring of diabetic patients for changes in medication needs is appropriate.

154.5 GH Therapy in Lipodystrophy

Reduced secretion of GH is associated with excess total body fat in obese non-HIV- infected patients (Carroll et al. 1998; Benedini et al. 2006). However, GH dynamics have not previously been characterized in patients with HIV lipodystrophy in whom weight and total body fat are normal but visceral fat is increased in association with reduced subcutaneous fat. Our data demonstrate normal GH pulse frequency but significantly reduced mean GH concentrations, basal GH concentrations, and GH pulse amplitude (Luzi et al. 2005). In the past, many studies demonstrated a significant reduction in GH secretion in patients with HIV-related lipodystrophy (Koutkia et al. 2005; Luzi et al. 2005). Visceral adiposity seems to be the most significant predictor of reduced GH concentrations in this population.

In the past, many treatments were proposed to improve lipodystrophy (for example, drugs, such as metformin, that improve insulin sensitivity), but all had only minor beneficial effects on the metabolic picture (Saint-Marc and Touraine 1999).

In our recent study, we showed that low-dose GH treatment improves body fat distribution and is devoid of metabolic side effects (Luzi et al. 2005). Previous works suggest a reversal of positive effects on fat distribution after cessation of GH treatment. For this reason, even in the light of the results of previous studies, we foresee the possibility of proposing short periods of low-dose GH treatment (6 months in our experience) combined with a program of physical training (to be performed continuously both during the treatment and the wash-out periods) (Luzi et al. 2005). The quoted results may also be relevant for future studies aimed to assess the effect of low-dose GH treatment in clinical conditions (other than HIV lipodystrophy) characterized by visceral obesity. The known metabolic effects of higher doses of rhGH on glucose and lipid metabolism should always be taken into consideration (Luzi et al. 2003) (see previous section).

Approximately 20% of HIV-infected patients with lipodystrophy and increased visceral adiposity have inadequate GH response to GHRH/arginine using a stringent cutoff threshold of 3.3 ng/ml and, therefore, may be considered functionally GH deficient. Those patients may benefit from GH administration in terms of improving body composition and metabolic parameters, although further studies are necessary to test the efficacy of low-dose GH therapy. Use of a less stringent cutoff threshold may increase the number of patients failing the GH stimulation test but will decrease the specificity of the test. Additional studies are needed to optimally identify the cutoff for HIV patients with

reduced GH secretion and to assess, therefore, whether lipodystrophic patients might benefit from GH replacement (Koutkia et al. 2005).

Kotler et al. suggested that 4 mg of rhGH administered daily for 12 weeks significantly reduced visceral adipose tissue, trunk fat, dorsocervical fat, non-HDL cholesterol, and related cardiovascular risk parameters in carefully selected HIV patients with excess visceral adipose tissue. The optimal regimen to sustain these effects over time awaits determination (Kotler et al. 2004). With high-dose rhGH replacement, Lp (a) increases, glucose metabolism may become impaired, increasing the cardiovascular risk (in particular in males). High-dose GH therapy cannot be continued for more than a few months without incurring in the risk of cancer and impaired glucose tolerance or overt diabetes.

The presence of different sensitivity to GH of target tissues and of different GH response after GH administration in HIV-infected patients with and without lipodystrophy are yet presumed. In particular, IGF-I-producing tissues in lipodystrophic HIV-infected patients seem to be much more sensitive to injected GH than those in HIV-infected patients with wasting. In a interesting pilot study, Andersen and associates performed a 16-week open-label prospective study in six male patients with HIV-associated lipodystrophy syndrome using an s.c. low-dose hGH (0.7 mg/day). After treatment, the patients demonstrated significant increases in total and free plasma IGF-I, and a trend toward a favorable change in fat distribution was suggested. The low-dose hGH treatment was not associated with the side effects observed with the higher doses of hGH. Despite these results, the authors await placebo-controlled, randomized studies before extending the indication of hGH therapy in lipodystrophic HIV-infected patients (Benedini et al. 2008).

Also, GH administration in the absence of true GH deficiency did not show metabolic benefits in a study conducted in obese patients without HIV lipodystrophy (Shadid and Jensen 2003). By contrast, almost all studies reporting the effects of GH administration on glucose metabolism in obesity show trends toward worsening of insulin resistance. Thus, if visceral fat loss was truly achieved, the possible benefits (a primary incentive for GH administration) could be lost; however, any demonstrable effects on body composition were minimal, not necessarily attributable to the GH administration, and present only when isocaloric diets were given. Although GH administration attenuated nitrogen loss, this effect was lost after a few weeks, whereas it did not convincingly affect other parameters related to lean body mass. Troublesome non-metabolic side effects of GH treatment include fluid retention, arthralgia, and carpal tunnel syndrome (see Table 154.3).

Perhaps not surprisingly, GH returns to normal after weight reduction in obesity. This finding strongly suggests that low GH is a consequence, not a cause, of central obesity. Considering the high costs and the lack of a full knowledge of the long-term consequences of GH treatment of obesity, we argue against its use for this purpose, at present.

It is possible that the exogenous administration of GH can promote the deactivation of 11beta-hydroxysteroid dehydrogenase type 1 (11ß-HSD1), an important enzyme highly expressed in the visceral adipose tissue. This enzyme is able to decrease the autocrine generation of cortisol by cortisone in adipose tissue. Cortisol is well known to be able to interfere with normal fat distribution and cell proliferation (Benedini et al. 2008).

A low concentration of GH in the basal condition and after stimulation could be related to an high urinary cortisol level secondary to excessive activation of 11ß-HSD type 1. In fact, 11ß-HSD1 is highly expressed in human adipose tissue. It is conceivable that decreased 11ß-HSD1 activity represents a compensatory mechanism to the adverse metabolic profile in obesity. Although the effects of cortisol excess on adipose tissue mass are well recognized, as shown in patients with Cushing's syndrome, the impact of the autocrine generation of cortisol on fat mass regulation is less clear. Cortisol promotes adipocyte differentiation and inhibits preadipocyte proliferation, and it was previously shown that limiting cortisol availability to the glucocorticoid receptor (GR) through inhibition of 11ß-HSD1 inhibits adipocyte differentiation and promotes preadipocyte proliferation.

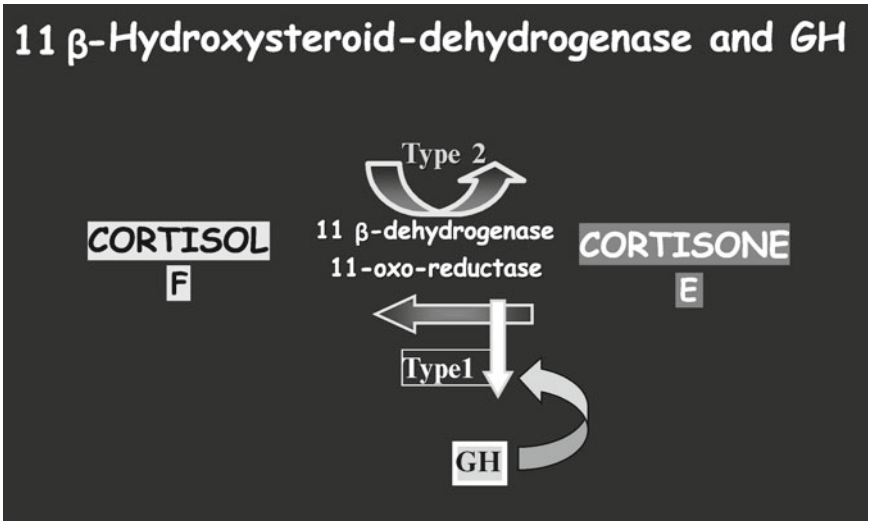

Fig. 154.3 11-Beta-hydroxysteroid dehydrogenase type 1 and GH. This figure explains the action of GH on 11-ß-HSD1 and the link between GH and steroid action

Therefore, it is possible that inhibition of 11ß-HSD1 by GH will decrease the autocrine generation of cortisol within adipose tissue, reduce adipocyte differentiation, and enhance preadipocyte proliferation. Once again, there is a delicate balance of actions between increasing and decreasing adipose tissue mass, and this may explain why GH did not alter absolute fat mass, despite inhibiting 11ß-HSD1 (see Fig. 154.3). In fact, a recent paper by Filipsson and colleagues showed the impact of different glucocorticoid regimens in patients with hypopituitarism (KIMS population) after 1 year of GH treatment (Filipsson et al. 2006). It is possible that increased tissue exposure to GC, as a result of increased 11ß HSD1 activity, which occurs in replaced ACTH-deficient and GHD subjects, promoted adipocyte differentiation and preadipocyte proliferation. A similar hormonal picture is present in HIV patients with lipodystrophy, who have relative hypercorticism and associate metabolic and nutritional alterations.

In summary, human growth hormone (hGH) was demonstrated to increase lean body mass in HIV wasting syndrome, but its long-term efficacy in patients with HIV-lipodystrophy is uncertain. Prospective studies documented hGH's role in reducing fat and increasing lean mass, especially in the trunk, without changing overall body weight significantly. The response is usually nearly complete by 12 weeks of therapy and reverses rapidly upon discontinuation (Hoffman et al. 2005).

154.6 Conclusions

Both nucleoside reverse transcriptase inhibitors (NRTIs) and the protease inhibitors (PIs) are considered causes of the lipodystrophic syndrome in HIV.

These drugs have significantly improved the survival and prognosis of HIV-infected individuals. However, side effects, such as lipodystrophy and metabolic disturbances, have appeared in past years (Carr et al. 1998).

Table 154.2 Key features of growth hormone

1. GH is a protein hormone of 190 amino acids that is synthesized and secreted by the acidophil cells of the anterior pituitary gland.
2. The pituitary gland is responsible for the production of eight hormones; GH secretion is largely regulated by the hypothalamus.
3. GH is a major participant in the control of several physiologic processes, including growth and metabolism.
4. The major role of growth hormone in stimulating body growth is to stimulate the liver and other tissues to secrete IGF-I.
5. IGF-I stimulates the proliferation of chondrocytes (bone growth), but also appears to be the key player in muscle growth and decreasing fat accumulation.
6. GH and IGF-1 stimulate amino-acid uptake and protein synthesis in muscle and other tissues and also stimulate lipolytic activity of adipose tissue in combination with a reduction of triglycerides' accumulation (inhibition of lipoprotein lipase activity).
7. GH exerts profound effects on whole-body- and district-body composition through a combination of anabolic and lipolytic actions.

This table lists the actions of growth hormone, including site of production, regulation, and the principal effects on body composition
IGF-I insulin-like growth factor I

Table 154.3 Absolute contraindications to recombinant human Growth Hormone (rhGH) therapy

Contraindication of GH therapy
• Active malignancy
• Benign intracranial hypertension
• Proliferative or preproliferative diabetic retinopathy
• Pregnancy after first trimester

This table lists the major contraindications for using recombinant human growth hormone in adult patients

Much remains to be learned about the HIV lipodystrophy syndrome. Although, morphologically, there are distinctive and recognizable markers of this metabolic pattern. There is compelling evidence that the NRTIs, particularly stavudine, play a facilitative, if not primary, role in its development. PI use appears to be responsible for the metabolic manifestations, but, again, the mechanism(s) responsible is(are) undefined for both drugs. Aside from the effect on quality of life, the short-term consequences of lipodystrophy are manageable. However, there is concern about the potential long-term risks, especially for atherosclerotic disease. At present, the metabolic complications are, to an extent, treatable with standard therapies or possibly with substitution for the PI component of therapy. Among other therapies, hGH and metformin may reduce lipodystrophy (Kravcik 2000).

Low value of GH in basal condition and after stimulation could be related to high value of plasma and urinary cortisol. In fact, the role of 11beta-hydroxysteroid dehydrogenase type 1 (11ß-HSD1) in the pathogenesis of human obesity and the regulation of adipose tissue mass is not fully explained. 11ß-HSD1 is highly expressed in human adipose tissue. It is plausible that decreased 11ß-HSD1 activity represents a compensatory mechanism to the adverse metabolic profile in obesity. Although the effects of cortisol excess on adipose tissue mass are well recognized, the impact of the autocrine generation of cortisol on fat-mass regulation is less clear. It is clear that there is a delicate balance of actions between increasing and decreasing adipose tissue mass; this may explain why GH did not alter absolute fat mass despite inhibiting 11ß-HSD1. Furthermore, the degree of inhibition mediated by IGF-I may not be sufficient to truly limit the availability of cortisol to the glucocorticoid receptor. Other factors that may explain the lack of effect of GH on fat mass in this study also need to be considered.

Although GH treatment may not represent an effective therapy in simple obesity because of its many complex actions and perhaps because of its lack of potency as an inhibitor of 11ß-HSD1, selective, potent inhibition of 11ß-HSD1 may represent a novel therapeutic strategy for insulin sensitization (Tomlinson et al. 2003). Patients with central obesity but with no evidence of hypopituitarism have relative GH deficiency and it is exciting to speculate that low-dose GH treatment in this group, by inhibiting cortisol generation within omental fat, may offer a novel therapeutic approach.

This important action on endocrine picture suggests that GH treatment could be an important support in HIV-related lipodystrophy. The question, which is still open, is the duration of the GH treatment. Previous work suggests the reversal of effects on fat distribution after cessation of GH treatment. For this reason, we foresee the possibility of proposing short periods of low-dose GH treatment combined with a program of physical training. Recent preliminary data show that two to three sessions of aerobic exercise performed for 3 months at 40–60% of VO_2 max improve insulin secretion and reduce TNF-α and MCP-1 in HIV-1-infected patients with lipodystrophy. The use of low-dose hGH showed favorable change in fat distribution (Luzi et al. 2005). Also, in adults with GH deficit after more than 6 months of GH therapy, lipid profile, insulin resistance, and flow-mediated dilatation improved (Benedini et al. 2006). A point that seems unclear is the real impact on cardiovascular risk secondary to elevation of Lp (a) after GH therapy. In fact, in patients with abnormal lipid profile, the positive impact on cardiovascular risk of GH treatment could be offset by the rise of Lp (a), particularly in males. Regarding the potential worsening of lipid profile in patients on GH therapy, many authors emphasized the positive effect on cardiovascular risk of this therapy in patients with GH deficit (Benedini et al. 2006). In HIV-related lipodystrophy, there is a lipid profile very similar to patients with GH deficit and the use of GH therapy could improve dyslipidemia and, consequently, cardiovascular risk. Some authors have suggested also the use of more physiologic strategy, which involves the use of growth-hormone-releasing hormone (GHRH) to augment growth hormone secretion, leading to a reduction of abdominal fat accumulation (Grinspoon 2006).

In conclusion, hrGH therapy is able to change the fat distributions, as stated in a recent paper by Haugaard et al. (2006a) and seems to improve also metabolic picture[3]. However, before suggesting hGH therapy in selected HAART-treated patients with HIV-related lipodystrophy, we would like to stress the importance of further studies (placebo-controlled, randomized studies) with the aim to better define the strategies to revert lipodystrophy and to minimize the side effects of GH therapy.

Summary Points

- The growth hormone exerts profound effects on whole-body- and district-body composition through a combination of anabolic and lipolytic actions playing a central role in human metabolic homeostasis.
- Different human diseases (other than HIV) associated with lipodystrophy are characterized by major metabolic derangements, such as insulin resistance and dyslipidemias.
- In the past, many treatments were proposed to improve lipodystrophy, but all of these had only partial beneficial effects on the metabolic picture.
- Even if GH/IGF-1 therapy does result in a small increase in cancer risk compared with untreated patients with GH deficiency, it is likely that the eventual risk will be the same as in the general population.
- Human growth hormone (hGH) was demonstrated to increase lean body mass in HIV wasting syndrome, but its role in patients with lipodystrophy is not very clear.

Key Points

- HIV-related lipodystrophy is associated with peripheral fat wasting and central adiposity, dyslipidemia, insulin resistance, and increased intramuscular fat accumulation.
- In literature, there are some pilot studies in patients having HIV with lipodystrophy showing that low-dose GH treatment improves body fat distribution and is devoid of metabolic side effects.
- hGH was demonstrated to stimulate redistribution of fat in HIV with lipodystrophy. However, before suggesting hGH therapy in selected HAART-treated patients with HIV-related lipodystrophy, the importance of further studies with the aim to better define the strategies to revert lipodystrophy and to minimize the side effects of GH therapy needs to be stressed.

- In HIV-infected patients with lipodystrophy, hrGH therapy is able to change the fat distributions and seems to also improve the metabolic picture.

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Chapter 155
Digital Three-Dimensional Photogrammetry: Craniofacial Applications to Facial Growth, Orthognathic and Reconstructive Surgery, and Morphometrics

Nada M. Souccar, Chung How Kau, and Seth M. Weinberg

Abstract Three-dimensional (3D) surface imaging systems have been extensively used in the past three decades by orthodontists and maxillofacial surgeons. The principal advantages of these devices are their quick image acquisition time, non-invasiveness and ease of application, which make them particularly suitable for children and patients with disabilities. In addition, they have been validated against anthropometry for precision, accuracy, bias and reproducibility. The generated models are easy to store and manipulate, making them a unique tool for diagnosis, treatment planning, surgical evaluation and longitudinal studies. Three-dimensional photogrammetry has multiple applications: The creation of average faces has been described and allows age, gender and racial comparison. Monitoring and quantitation of post-surgical changes in reconstructive surgery and orthognathic interventions is also possible using surface imaging. Moreover, it is a powerful morphometrics method used to identify phenotypic markers associated with genetic risk for a particular condition such as non-syndromic cleft lip and palate. Finally, a virtual face can be created by combining surface imaging with cone beam computed tomography.

Abbreviations

3D	Three dimensional
CL/P	Cleft lip with or without Palate
CT	Computed tomography
CBCT	Cone Beam Computed Tomography

155.1 Introduction

For centuries, the human face has inspired artists and challenged the medical profession. Over the past three decades, three-dimensional surface-imaging devices that allow a realistic capture of the craniofacial complex have been developed. This chapter will present some craniofacial applications of surface-image acquisition to facial growth, orthognathic and reconstructive surgery, and morphometrics.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_155,

Cranial dimensions were traditionally used in anthropometry to determine normal proportions in selected similar individuals. Distances and angles were measured directly on defined cranial and facial landmarks, generally using calipers (Farkas 1994). With the evolution of three-dimensional imaging technology, it is now possible to capture craniofacial surface images for diagnosis, treatment, and research purposes. This technology enables clinicians and researchers to study the soft tissue of the face in a faster and less invasive way than direct examinations. The acquired data are a collection of points, each defined by x, y and z coordinates and, therefore, represent a mathematical expression of the human face. If color and texture information are gathered at the same time, they will be added over the produced 3D model. It then becomes possible to define soft-tissue landmarks, measure distances, and compare proportions on this newly created geometrical model (Lane and Harrell 2008; Kau et al. 2007b).

155.2 Validation of Systems

Weinberg and Kolar (2005) define at least four equally important aspects of measurement error to evaluate 3D anthropometry: the magnitude of error associated with multiple observers/repeated measurements (precision), the degree of similarity between the device and conventional techniques (accuracy), the tendency of the device to systematically under- or overestimate values (bias), and the device's ability to capture data in a consistent manner (reproducibility). Studies have been conducted to validate various 3D surface morphometric systems:

Aldridge et al. (2005) identified facial landmarks on 3D images from a sample of 15 children and adults obtained with the 3-dMD system (3dMDface, Atlanta, GA) and tested precision, measurement error, and repeatability of image acquisition. They showed that the average error associated with landmarks placement was submillimeter. Precision was high (error below 1 mm) and repeatability exceeded 95% for most identified landmarks. Weinberg et al. (2006) compared the precision and accuracy of two structured light systems, the Genex FaceCam (Kensington, MD) and 3dMD systems, with anthropometrics. They used 18 mannequin heads with marked facial landmarks to measure 12 linear distances. The measurements were taken twice with each method to evaluate intra-observer reliability. They reported submillimeter-level accuracies and good precision, regardless of the employed method. In a publication by Wong et al. (2008), the 3dMD system was tested against direct anthropometry by taking linear measurements in 20 normal adults. Most measurements were found to be reliable (mean $r = 0.91$) and precise (high correlation between direct and digital values, $r = 0.88$). Computerized stereophotogrammetry (C3D), another type of structured light system, was extensively researched by a team of orthodontists and maxillofacial surgeons. Their findings indicate that the precision of facial landmark identification of 21 facial stone models of patients with cleft lip was within 1 mm (Ayoub et al. 2003). As a result, they validated the use of this device in infants, children, for surgical procedures, and orthodontic models. Laser light systems were also tested for validity. The accuracy of Minolta VI-900 scanners (Konica Minolta, Tokyo, Japan) was found to be 0.56 ± 0.25 mm and the error in computerized registration of left and right scans was 0.13 ± 0.18 mm (Kau et al. 2005).

Because of the ease of data acquisition, storage, manipulation, and image superimposition over different time points, 3D imaging is now widely used for various craniofacial applications such as:

1. Facial averages;
   1.1 Gender analysis
   1.2 Facial morphology in different populations;

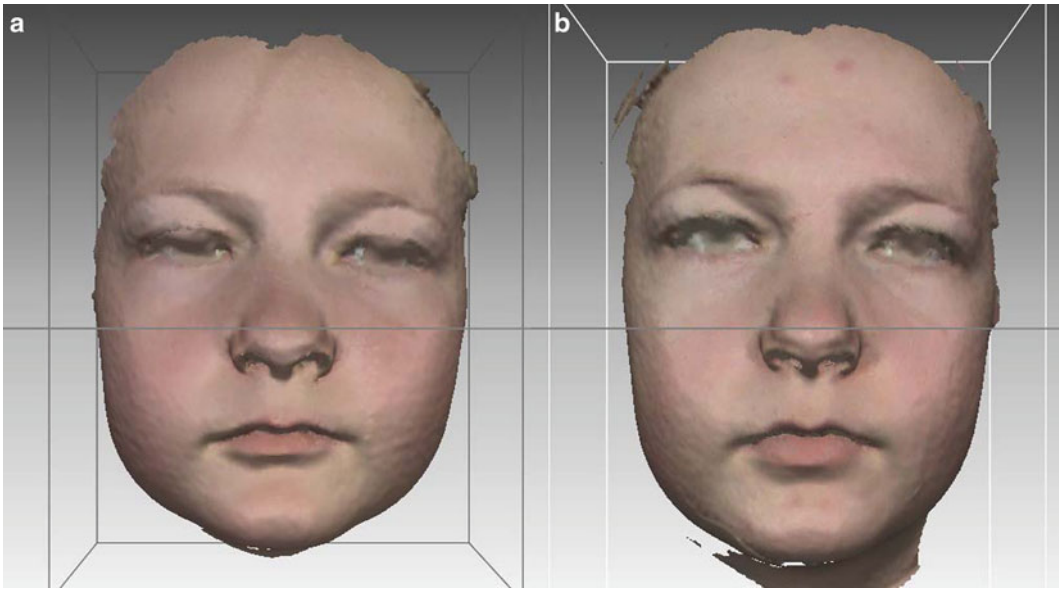

Fig. 155.1 Three-dimensional surface reconstruction of a female patient. Three-dimensional laser reconstruction of a female patient taken at two different time points. (**a**) Time 1: height = 145 cm, weight = 39.0 kg and (**b**) time 5: height = 155 cm, weight = 48.3 kg

2. Facial growth;
3. Orthognathic and reconstructive surgery;
4. Morphometrics; and
5. The virtual face.

155.2.1 Facial Averages

Our modern society emphasizes the importance of esthetics. However, the concept of beauty, although related to proportions and harmony, varies from population to population. Therefore, it is of prime importance to understand the characteristics of faces across diverse cohort groups and posit specific norms for each of them. Just as cephalometric averages vary according to age, gender, and ethnicities (Bishara et al. 1990), a targeted three-dimensional soft-tissue template would allow clinicians to treat a particular group to a particular norm, within the limits of biology and stability.

A three-dimensional construction of the average face can be done in the following sequence (Kau et al. 2006a):

1. Pre-aliging images by determining the principal axes of rotation (based on computing the tensor of inertia of each 3D image);
2. Manual positioning, when necessary, to improve the previous stage;
3. Applying best-fit alignment using inbuilt algorithms;
4. Averaging coordinates of the images normally to a facial template;
5. Point-cloud triangulation to obtain an average face;
6. Improving the average face by filling in small holes and removing possible mesh defects; and
7. Applying color texture (Fig. 155.1).

This process allows the comparison of intergroup average faces in addition to the analysis of an individual face against his/her corresponding gender/age group mean. Gender analysis, population comparisons, and growth studies are possible applications for this method.

155.2.1.1 Gender Analysis

Female and male morphologies are intrinsically different. One can visually determine that females present a rounder, thinner, and softer face than males who often have larger bones and overall facial dimensions. However, it would be much more interesting to be able to quantitate gender variation. In a study by Kau et al. (2006b), a set of left and right scans was taken from 80 healthy males and females (mean age 24.5 years) using two laser-scanning devices assembled as a stereopair (Minolta VI900, Osaka Japan). The resulting images were merged to form a composite 3D soft-tissue reconstruction of the face (a surface shell). Sex differences in facial morphology were then measured and visualized using shell-to-shell deviation color maps. The average difference between the male and female facial templates was 1.28 ± 1.02 mm. The areas of greatest deviation included supraorbital, zygomatic, and lower mandibular regions.

155.2.1.2 Comparisons Among Various Ethnic/Racial Groups

The three-dimensional face average is a unique tool to investigate morphologies and identify common features across populations. A series of studies conducted on subjects from five different countries (Wales, UK; Houston, TX, USA; Slovenia; and Egypt) illustrates this concept (Bo Ic et al. 2009; Seager et al. 2009; Gor et al. 2010; Kau et al. 2010). Two stereophotogrammetric systems were used: Minolta VI-900 and 3dMDface. The generated images were superimposed and a complex mathematical algorithm created one average composite female and one average composite male face per subgroup. Each obtained 3D shell was compared on the basis of gender to the other populations, in order to quantify facial similarities. The findings show that facial morphologic differences are greatest when very different populations are evaluated (Slovenia and Egypt for women, Houston and Egypt for men). Also, even though Europeans and Northern Americans show high concordance percentages, their differences are more concentrated in areas of the face that can be altered by orthodontic treatment. These results highlight the need to establish 3D norms inherent to each population. Since clinicians are relying more and more on soft-tissue appearance to decide treatment modalities, three-dimensional databases would allow them to have averages specific to each cohort group. Furthermore, being aware of the norms will help better understand the extreme variations of facial deformities.

155.2.2 Facial Growth

Growth and development of the human face have always been a major issue for the medical profession in general, and for orthodontists in particular. Dentofacial orthopedics is believed to enhance the differential growth of the jaws and correct unbalanced faces. Patients are unconsciously classified as ‘good’ or ‘poor’ growers, based on treatment outcomes. Progress has traditionally been measured by superimposing lateral cephalograms taken a few months apart on stable landmarks, such as the cranial base. Since radiographs are a two-dimensional representation of a three-dimensional reality

and because of the associated risk of harmful radiations, many researchers have found 3D-surface imaging a very attractive tool to understand soft-tissue changes and their underlying growth concepts. A mixed longitudinal and cross-sectional design by Ferrario et al. (1999a) used automated infrared photogrammetry to investigate soft-tissue growth in both genders and create three-dimensional facial soft-tissues normative data. Selected linear and angular measurements as well as ratios were calculated and averaged for age and sex. Their findings show that the soft tissue, particularly the middle third of the face, continues its growth in boys after age 13. The lower face grows continuously in both genders, boys being always larger than girls. A three-dimensional mesh-diagram analysis by the same group demonstrated that boys and girls have the same pattern of growth between ages 6 and 11. The pattern changes after adolescence, and males end up having a larger forehead, longer and more vertical nose, more inferior and posterior gonia, more inferior and prominent lips, and a larger mouth than female faces of corresponding age (Ferrario et al. 1999b). In a cross-sectional trial, Nute and Moss (2000) used a surface laser to acquire facial images of 132 five- to ten-year-old children and created average scans for each age and sex subgroup. The scans were superimposed on identified landmarks using the Procrustes method. This method proved to be useful to track changes in both genders at each age and changes of the same gender at different ages. A longitudinal study followed a cohort of 12-year-old children over 2 years. Researchers compared 3D laser surface reconstructions (Vivid VI900, Minolta, Tokyo, Japan) taken six months apart (Kau and Richmond 2008). Shells were superimposed according to the best-fit method. Using the appropriate software (Rapidform 2004, INUS technology, Seoul, Korea), the differences between the two facial reconstructions were automatically generated. The findings confirm that surface changes are more important and occur at a later time in boys than in girls. Growth occurs in a downward forward direction. The areas that grow the most are the nose, brows, lips, and vertical dimension of the face. Overall, in both genders, the eyes deepen and the cheeks become flatter (Fig. 155.2).

These analyses prove that 3D imaging is a successful method to monitor the effect of growth on the human face.

155.2.3 Orthognathic and Reconstructive Surgery

Orthognathic and facial reconstructive surgery treatment usually brings together a team of oral and maxillofacial specialists. One approach to monitor soft-tissue changes is to use color codes on facial-deviation maps to distinguish groups of normal adults and those with facial disproportion (Mc Cance et al. 1997). Another way is to superimpose 3D images on identified landmarks with a best-fit Procrustes method. This method was tested for pre- and post-surgical asymmetries' evaluations (Hajeer et al. 2004). Guest et al. (2001) demonstrated that the most sensible results in superimposition and comparison of two surfaces were achieved by the closest-point and the correspondence-by-sensitivity-to movement algorithms. However, average values for 3D maxillofacial morphologies were calculated and tested to evaluate post-surgical treatment effects in women (Terajima et al. 2009). By superimposing scans and measuring shell-to-shell deviation, Kau et al. (2007a) have shown that the greatest reduction in postoperative swelling occurred within the first month after single- and double-jaw orthognathic surgery, and the mean percentage of improvement was approximately 60–70%. Based on this timetable, Alves et al. (2009) conducted a prospective study to analyze facial surface after surgery. Three-dimensional surface images of 30 adults were taken pre- and post-operation and superimposed on the forehead, as it is not affected by the procedure. The color-coded millimetric map they developed was successful in tracking soft-tissue changes. Moreover, patients

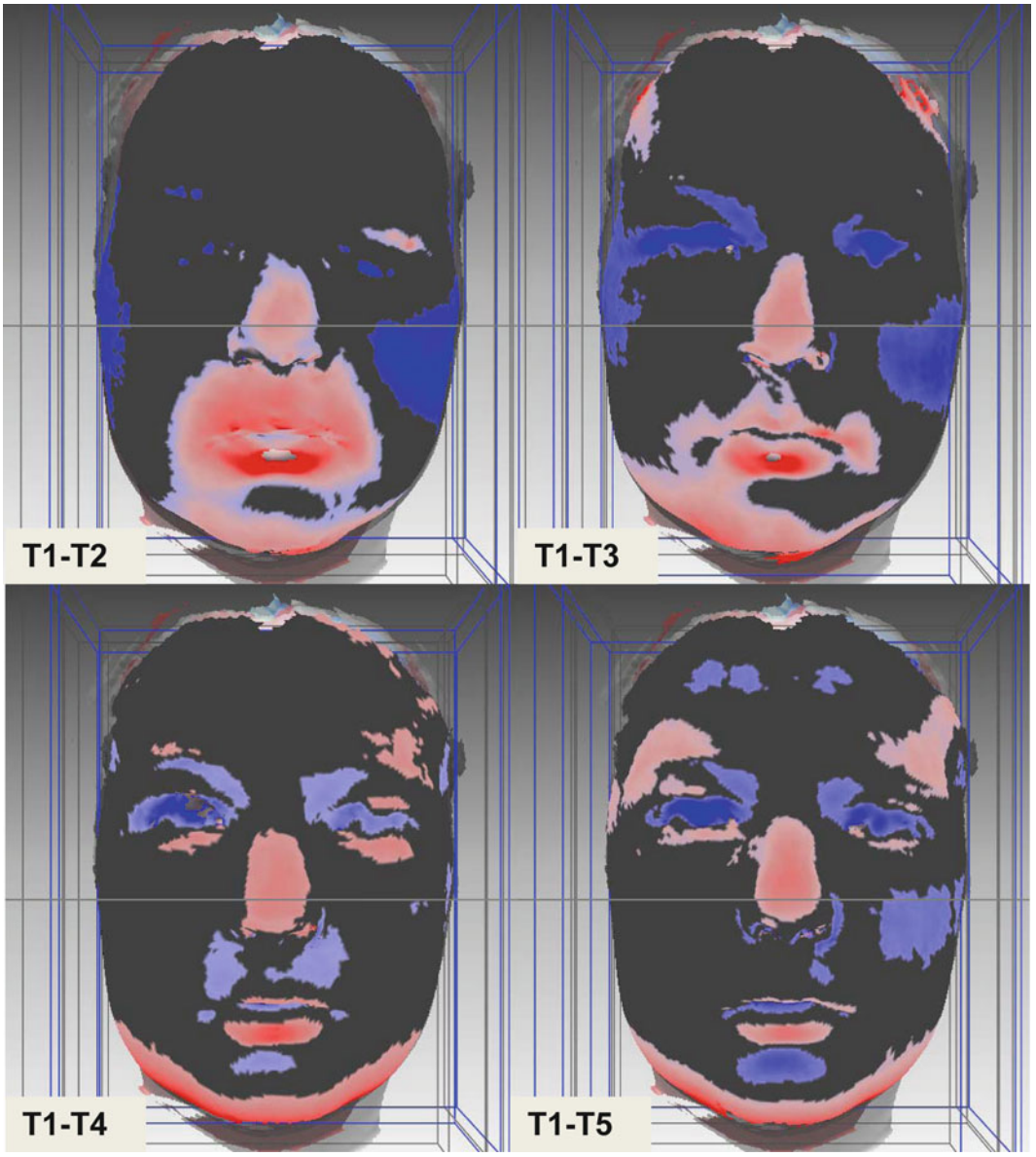

Fig. 155.2 Superimposition of two facial shells of a female patient obtained at four different time points to depict changes associated with orthodontic treatment and growth. The facial shells of the patient shown in Fig. 155.1 are superimposed to visualize the changes between T1 and four different time points (T2, T3, T4, and T5). Each time point is superimposed on the initial shell, obtained at T1. Red indicates positive changes (increase in prominence), blue indicates negative changes (retrusion), and black indicates similarities

with genetic syndromes requiring reconstructive surgery are excellent candidates for three-dimensional surface imaging. A review by Al-Omari et al. (2005) recommends the utilization of three-dimensional imaging for the diagnosis and evaluation of treatment outcome in cleft lip and palate patients. Additionally, the authors advocate the creation of a standardized method to assess cleft lip and palate affections, which will unify research protocols and allow a much more significant interpretation of results.

155.2.4 Morphometrics

Morphometrics aim at identifying phenotypic variations that could represent markers of genetic susceptibility. The combination of powerful statistical tools with three-dimensional surface acquisition allows investigators to precisely analyze the fine details of biological shape. One application is the investigation of morphometrics in non-syndromic cleft lip with or without palate (CL/P) patients. A meta-analysis of the cephalometric literature highlighted the following morphologic differences between unaffected parents of cleft lip and palate patients and controls: wider faces, interorbital and nasal cavity dimensions, narrower cranial vaults, longer cranial bases, and longer and more protrusive mandibles. The variations were subtle and gender specific (Weinberg et al. 2006). Recently, unaffected relatives of cleft lip and palate patients were compared to healthy controls (Weinberg et al. 2008). Using a selection of linear distance-based methods, the investigators observed a number of craniofacial differences between the two age- and sex-matched groups: increased upper and midfacial width, excess midface retrusion, increased lower facial height, and decreased upper facial height. Discriminant function analysis was able to correctly classify over 70% of female subjects and over 80% of male subjects, with facial width contributing most to group discrimination. Therefore, the assumption is that unaffected parents of CL/P patients present midface characteristics that differentiate them from the general population. If these traits are identified, they could serve as markers to classify 'at-risk' individuals. Therefore, morphometrics could assist genetic studies and improve recurrence risk estimation. A more recent study looked at face shape in unaffected parents with one or more cleft-affected children (Weinberg et al. 2009). Eighty parents were divided in two groups: 1. with a positive family history of cleft lip and palate, that is, an affected relative and 2. with a negative family history. A significant discrepancy was noted between unaffected parents and controls ($p < 0.01$). Parents with a positive family history of CL/P presented distinct midface retrusion, reduced upper facial height, increased lower facial height, and excess interorbital distance. In this group, it was also interesting to note that nasal dimensions were related to a specific gender pattern, with fathers having reduced and mothers having increased width.

These studies strongly indicate the need for the creation of a phenotype/genotype database to research morphologic characteristics and their associations with genetic disorders.

155.2.5 New Application: The Virtual Face

Surface imaging can be combined with hard-tissue imaging, such as the cone beam computed tomography (CBCT) to create a virtual patient. The idea is to start constructing the virtual face from the outside in, that is, from the soft tissue to the hard tissue. This concept is somewhat in opposition with the general idea of the face being a soft-tissue element resting on a hard-tissue structure. The major advantage is to capture the patient's natural head posture without any external aiding device. Consequently, by locking the CBCT inside the soft-tissue surface image, the CBCT can be reorientated, according to the patient's posture. The 3dMDvultus Software Platform allows the fusion of the 3dMD surface with three-dimensional hard-tissue imaging (CBCT, CT, or even dental models) (Fig. 155.3). In this complete reconstruction, it becomes possible to fully evaluate a patient and plan any treatment, including surgery. Surgical simulations are achievable and results can be anticipated. The software also permits surface distance and angle measurements with volume calculation. Volumetric analysis is critical for airway evaluation. Other applications include reconstructive surgery follow-up, such as in cleft lip and palate patients, aging changes, and non-surgical treat-

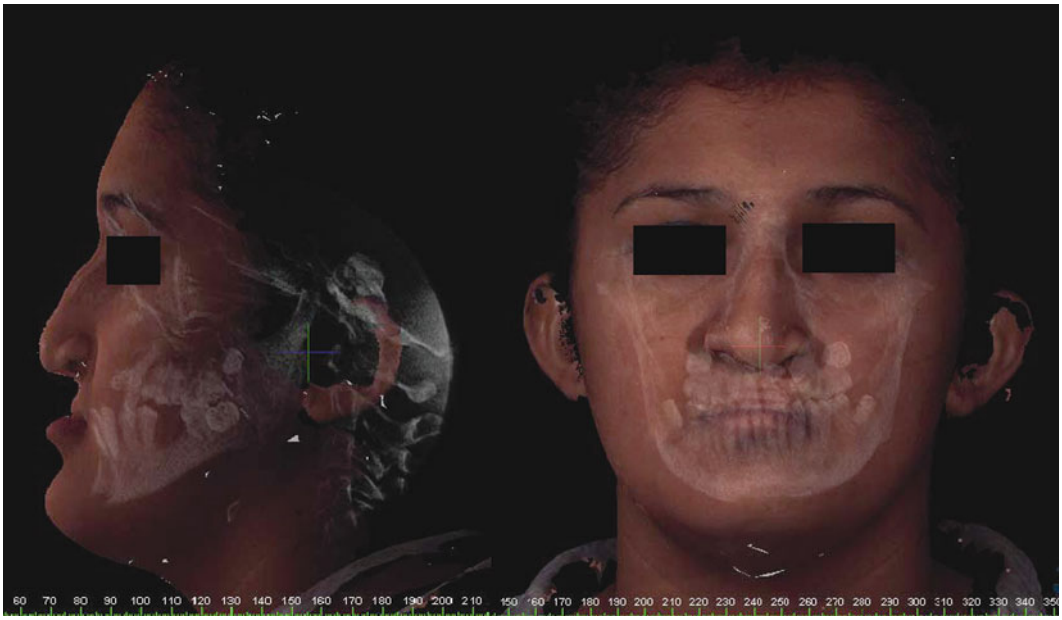

Fig. 155.3 The virtual face. Profile and Frontal view of a Cleft Lip and Palate patient. The 3dMDvultus Software Platform allows the fusion of the 3dMD surface with CBCT

ment evaluation. Prospective studies of facial development can also be conducted. Given all these features, we now have the tools to understand the mechanisms involved in craniofacial growth, development, dysmorphologies, and treatment. Research possibilities are therefore "virtually" endless.

Summary Points

- Surface-acquisition systems are noninvasive, inexpensive, and powerful tools to generate a three-dimensional model of the human face.
- They are particularly well suited for children and patients with facial deformities because of their quick acquisition and non-ionizing properties.
- The acquired data can be translated into a set of *x*, *y*, and *z* coordinates.
- Multiple quantitative comparisons between individuals at one or different time points render non-contact surface-imaging devices perfectly suited for research and clinical applications.
- Surface images can be superimposed to investigate the effects of growth and surgical treatment be used to track gender and ethnic differences.
- When used in morphometrics, 3D surface acquisition is a powerful tool to study subtle morphologic features that represent non-penetrant phenotype.
- The association of surface imaging with hard-tissue imaging, such as the CBCT, results in the creation of a virtual face. In addition to the above-mentioned applications, the virtual face can be the basis for future longitudinal craniofacial research.
- Comprehensive normative facial databases are needed and can be generated with surface imaging. Their purpose is to provide baseline reference dimensions for different ages, genders, and populations for direct morphologic comparisons and genetic studies and allow for inter-center research cooperation.

Key Facts on Cleft Lip and Palate

- Cleft lip with/without palate is the most common congenital craniofacial defect.
- It occurs in approximately 1 in 700 births.
- CL/P can be an isolated condition or be a part of an inherited disease or syndrome.
- Embryologically, the maxillary processes fuse with the frontonasal process at week 6. A failure of fusion results in a cleft lip.
- At week 8, the tongue is depressed and the palatal shelves migrate and fuse. Clefting of the palate results from the failure of the palatal shelves to fuse.
- Treatment of CL/P calls for a multidisciplinary approach: patients usually require multiple surgeries as well as extensive dental treatment to restore the lip, palate, and teeth, as needed. Patients also benefit from speech therapy and counseling.

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Part XXIII
Anthropometry in Ethnic Groups and Cultural and Geographical Diversity

Chapter 156
Anthropometry in Ethnic Groups and Cultural and Geographical Diversity

Auricular Anthropometry of Newborns: Ethnic Variations

Wee Bin Lian

Abstract The human ear is important not just for its aesthetic value and hearing ability, but also helps to confer normality to a newborn. Developmental abnormalities can result in abnormal ear shape and size. Descriptive examination must therefore be supplemented by objective anthropometric measurements, to aid a complete diagnosis profile. Ethnic and race variations are well known to have an impact on various anthropometric measurements. The ear is likely to be no different. However, comparisons of ear measurements in different ethnic groups have been difficult and rarely carried out. Differences in methodologies and definitions have also made comparisons of reported studies challenging. Nevertheless, just as gestation is an important consideration when making such measurements, so is the ethnicity of the baby. Ear length by convention is most often defined as the maximum length measured from the superior to the inferior aspect of the external ear. By and large, the Caucasian ear appears to have a marginal edge on the Asian ear, with the Israeli and Turkish babies registering the longest ears. The impact of even minor differences in ethnicity is further realized in seeing that even Chinese of different historical roots may have different measurements, with the Hong Kong Chinese ear being somewhat smaller than the Taiwanese and Singaporean Chinese ear. Also interestingly, the longest ear need not necessarily be the widest ear. Ear width is defined as the transverse distance from the palpable anterior base of the tragus through the external auditory canal to the margin of the helical rim at the widest point. For this, the Japanese ear is supreme. Another aspect would be the placement of the ear which changes as the child grows. The few studies that evaluated this aspect of the ear concurred that it was normal to have at least a third of the ear above the intercathial medial line across the eyes, with the Asian ear appearing to be somewhat higher placed than the Caucasian ear. Knowing the size, shape and position of the normal ear lends more weight to terms such as microtia (small ear), macrotia and low-set ears, allowing the practicing clinician to pinpoint abnormalities and effect investigations and interventions more accurately, reducing unneeded parental anxiety.

Abbreviations

EL	Ear length
EW	Ear width
IMCL	Intermedial canthial line

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_156,

156.1 Introduction

The human external ear, also known as the auricle, is embryologically derived from the pharyngeal arches, with the ear canal being derived from the branchial groove that joins the first pharyngeal pouch. Developmental defects of the 1st and 2nd arches or the groove would thus result in congenital malformations of the ear. Malformations of the pinna are relatively common conditions, reported to be in the range of 1 in 670 births, though external ear malformations and branchial sinuses and tags collectively are more common, with an incidence of 1 in 90 (Melnick et al. 1979). A whole range of ear abnormalities has been described, including abnormalities in size, shape and position (Table 156.1).

Ear development is also intrinsically related to the development of other organs being formed around the same embryological period. As such, abnormalities in the ear may herald a host of other significant abnormalities, which thus form the basis of the importance of dysmorphological examination of a newborn. The exclusion of any malformations or genetic syndromes is an integral part of the newborn screening process. It has become clear that the ear, besides being an aesthetic addition to the head, is an important organ not only for its function of hearing and equilibrium, but also as a diagnostic handle for dysmorphology and genetic disorders (Clark and Eteson 1991; Behrman et al. 2004; Jones 2006).

Table 156.1 Summary of types of ear malformation

Property	Abnormality	Description	Associated conditions
Size (Patil 2007)	Anotia/Agenesis	Absent ear (often with atretic ear canal)	Autosomal dominant (Gupta and Patton 1995), isoretinoin embryopathy (Clark and Eteson 1991), Treacher-Collins syndrome (Clark and Eteson 1991; Jones 2006), chromosomal anormalies, for example, trisomy 18
	Microtia	Small ears	Goldenhar syndrome (Clark and Eteson 1991), Hereditary autosomal dominant (Potter 1937), Down syndrome (Aase et al. 1973; Awwad et al. 1994; Thelander and Pryor 1966), rubella and other intrauterine infections
	Macrotia	Large ears	Hereditary (Rogers 1968), Fragile X syndrome (Butler et al. 1992; Hull and Hagerman 1993), Marfan syndrome (Jones 2006), De Lange type 2 (Verloes et al. 1996)
Shape	Cup-shaped	Small auricle cupped forward over the meatus	Pierre-Robin syndrome (Peterson and Schimke 1968), Autosomal dominant (Rogers 1968), Towns-Brocks syndrome (Jones 2006)
	Lop-shaped	Auricle lifting off the head at a greater angle	Autosomal dominant (Rogers 1968), Towns-Brocks syndrome (Jones 2006)
	Elfin	Pointed	Chromosomal anomaly (Golbus et al. 1973)
	Dysplastic	Abnormal shape	Trisomies 13–15, Treacher Collins (Clark and Eteson 1991; Jones 2006)
Position	Low set	Less than one-third of the ear length is above an arbitrary line drawn through both medial canthi of the eye	Noonan's syndrome (Sanchez-Casco 1983), Turner's syndrome (Horowitz et al. 1976), Down syndrome (Aase et al. 1973; Awwad et al. 1994; Thelander and Pryor 1966)
	Protruding	Ear sticks out/not flat against head	Foetal-alcohol syndrome (Jones 2006)

156.2 The Importance of Anthropometry in Newborn Assessment

Descriptions and anthropometric measurements of the ear are thus important to help establish norms for the purpose of comparison. Descriptions are important, especially in combination with visual cues but can sometimes be confusing, as there are many varied definitions as well as interpretations of definitions (Feingold and Bossert 1974; Saitta and Zackai et al. 2005; MedicineNet.com 2007; Patil 2007). Anthropometric measurements, on the other hand, using instruments, such as callipers, measuring tapes or specific purpose-built instruments, are systematised techniques which can provide quantitative values for qualitative descriptions. Using a combination of objective and subjective measures, it becomes possible to achieve some degree of consistency in dysmorphologic assessment.

156.3 Definitions

Ear length (EL) is usually defined as the maximum length measured from the superior to the inferior aspect of the external ear (Fig. 156.1). This definition has been employed by many authors across different ethnic populations (Sivan et al. 1983; Hall et al. 1989; Tateishi and Kaajii 1992; Chou et al. 2001; Fok et al. 2004; Agnihotri and Singh 2007; Lian et al. 2008), although, more specifically, Kalcioglu et al. (2006), described it as the length from the superaurale to the subaurale. Of particular significance was the landmark paper, by Farkas et al. (1992), who described EL as being the projective

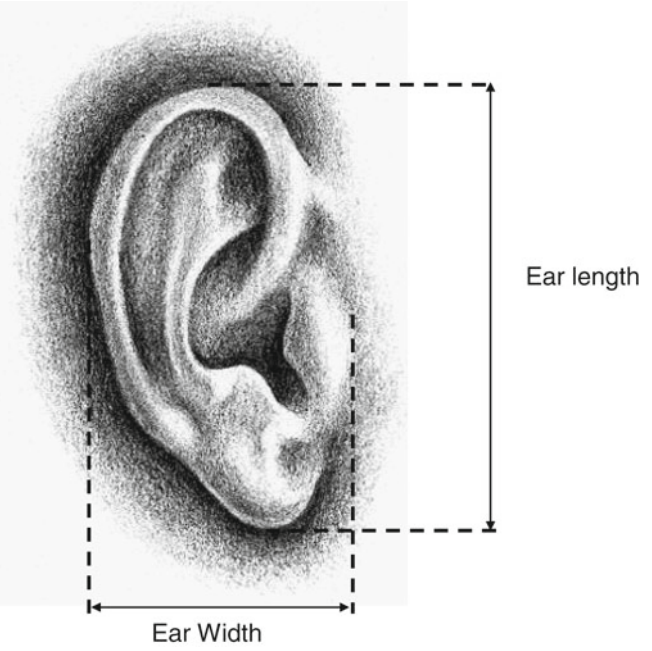

Fig. 156.1 Ear measurements. Ear length (*EL*) is usually defined as the maximum length measured from the superior to the inferior aspect of the external ear. Ear width (*EW*) is defined as the transverse distance from the palpable anterior base of the tragus through the external auditory canal to the margin of the helical rim at the widest point (Adapted from "Drawing the Ear" (www.artyfactory.com). With kind permission of John MacTaggart, art teacher from Glasgow, Scotland)

distance between the level of the highest point (superaurale) on the free margin of the auricle and the level of the lowest point (subaurale) on the free margin of the ear lobe. This was demonstrated in a schematic drawing, which, despite the similarly worded description, was different from that by Kalcioglu et al. (2006), who demonstrated a figure denoting a similar measurement as the other authors, using the maximal length measured between the most superior and inferior points. Such differences therefore need to be taken into account when comparing the results of the different studies.

Ear width (EW) is defined as the transverse distance from the palpable anterior base of the tragus through the external auditory canal to the margin of the helical rim at the widest point (Chou et al. 2001; Golalipour et al. 2003; Fok et al. 2004; Agnihotri and Singh 2007) (Fig. 156.1). This corresponds to the description and schematic drawing by Farkas et al. (1992). Kalcioglu et al. (2006), on the other hand, defined it as the distance from the tragus to the helix but denoted the posterior edge of the tragus to the helical rim in the accompanying figure. Minor differences may not make much difference in an older child or adult but would certainly make a difference amongst newborn infants. It is thus important to be aware of such differences when making comparisons, particularly amongst newborns.

156.4 Impact of Gestation and Age

In almost every newborn measurement, gestational age plays a significant role. Birth weight is classically linked to gestation, as is head circumference. Physical measurements, such as bone length and body proportions, are also related to gestation and therefore cannot be simply taken on their absolute values without information on gestation. This is important when making comparisons between studies. Shimizu et al. (1992) reported a linear relationship between foetal ear length and width and gestational age in an ultrasonographic study of 124 normal singleton pregnancies. The measurements quoted in this article generally have been based on measurements in term infants carried out soon after birth (Table 156.2). Also, as the baby grows, changes in facial structure and ear growth would have an impact on subsequent measurements (Farkas et al. 1992). Figure 156.2 (Fok et al. 2004) depicts the impact of gestation on ear length amongst Hong Kong Chinese populations. Figure 156.3 (Chou et al. 2001) also demonstrates the impact of age on the ear lengths amongst the Taiwanese Chinese babies and children. In this last study, an attempt had been made to compare the Caucasian ear and the Chinese ear in the older children, though no studies have thus far reported direct comparison across gestation in the newborn period.

It is well known that maturation and growth of the ear continues throughout the early years of a child's life, reaching mature size at between 7 and 13 years in the males and between 6 and 12 years in the females, with further growth toward maximal size in adulthood past 18 years (Farkas et al. 1992; Chou et al. 2001). As such, one wonders whether measurements at birth were different amongst the different ethnic groups and races, to have then become influenced by environmental and geographical changes, diminishing the differences as the child grows. The proportion of growth could also differ in different populations. A German study reported annual growth of 0.66 and 0.46 mm in boys and girls, respectively, and developed a nonlinear regression model only for EL, commenting that EW, conversely, was rather independent of age in both sexes (Pelz and Stein 1990). It was noted in the study by Farkas et al. (1992) that EW rapidly expands in early childhood and EL continues to expand beyond a year, despite reaching 75% of its adult size by 1 year. Consistent with that, Itoh et al. (2001) reported that rapid growth was observed until late teenage and significant growth

Table 156.2 Comparison of ear length (EL) of term infants amongst different ethnic populations

Author	Year	Country	Gestation (weeks)	Ethnicity (n)	Mean EL ± SD [Range] (cm)	Ear & time measured
Sivan et al.[a]	1983	Israel	Term	Caucasian males/ females[#] (48/39)	3.90 ± 0.30 [–]	Right ear[#]
Merlob et al.[a]	1984		27–41			36–60 h
Tateishi and Kajii[a]	1992	Japan	37–41, Term	Entire cohort (100)	3.5 ± 0.24 [2.8–4.0]	Left ear[#] 8–64 h (majority within 40 h)
				Japanese males (50)[#]	3.6 ± 0.25 [3.0–4.0]	
				Japanese females (50)[#]	3.5 ± 0.25 [2.8–4.0]	
Adeyemo et al.	1998	Nigeria	Term, AGA	Nigerian males/ females[#] (200)	3.2 ± 0.3 [–]	–
el Shanti et al.	2000	Jordan		Jordanian (158)	3.62 ± 0.29 [–]	Within 24 h
Chou et al.[b]	2002	Taiwan	Term	Chinese males(156)[#]	3.5 ± 0.8 [–]	Right ear[#]
				Chinese females (128)[#]	3.5 ± 0.6 [–]	Newborn
Fok et al.[a]	2003	Hong Kong	Term	Chinese males/ females[*] (2095)	3.19 ± 0.30 [–]	Within 48 h
Kalcioglu et al.[a]	2005	Turkey	40, Term	Turkish males[#] (20)	3.84 ± 0.64 [Upper limit 3.96]	Right ear Within 24 h
				Turkish females[#] (20)	3.84 ± 0.72 [Upper limit 3.71]	
Agnihotri and Singh[a]	2007	India	'newborn babies'	North Indian males (30)	3.76 ± 0.224* [–]	After 48 h
				North Indian females (30)	3.52 ± 0.261* [–]	
Lian et al.[b]	2008	Singapore	39, Term	Chinese/Malay/Indian/ Others[#] (83)	3.64 ± 0.27[#] [2.95–4.36]	Both ears[#] Within 36 h
			Term	Chinese (50)	3.59 ± 0.30[#] [2.4–4.0]	

[a] EL = length from superaurcle to subaurale or from most superior point on the helix to the inferior point of the external ear
[b] EL = greatest vertical axis
* Significantly different between groups within study
[#] No significant difference between groups within study (either race/gender/different-sided ears)

continued thereafter until advanced age. It is therefore highly debatable whether differences, seen or unseen, at older ages, would transpose into differences at the newborn age.

156.5 The Impact of Race and Geography

Yet one other factor casts further confusion on an already problematic field. Racial, geographical and ethnic variations have long been seen to make a difference in anthropometry, lending a huge diversity to life. For instance, comparisons in anthropometry show that Asians had more subcutaneous fat than did whites and had fat distributions different from whites (Wang et al. 1994). Race was also shown to have a significant and differential effect on the bones in the axial and appendicular skeletons

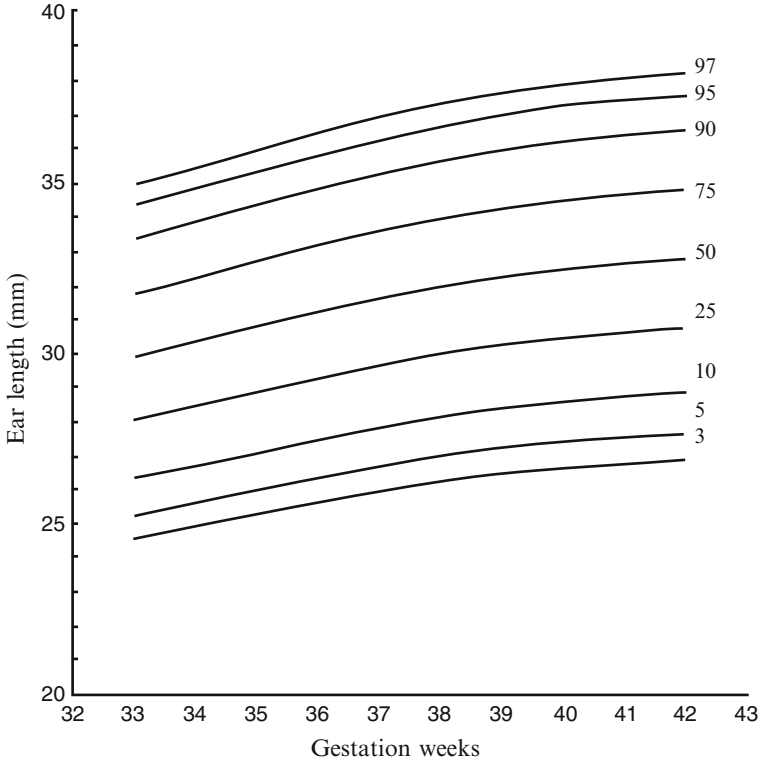

Fig. 156.2 Ear length versus gestation for Hong Kong Males. There is a corresponding increase of ear length with increasing gestation (Reproduced from Fok et al. (2004). With kind permission from Wiley-Blackwell, Oxford, UK)

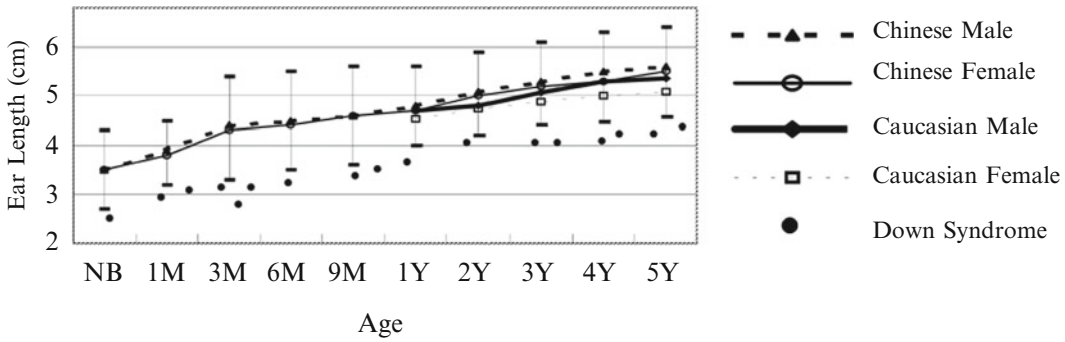

Fig. 156.3 Ear length of normal Chinese neonates, infants and preschool children (Reproduced from Chou et al. (2002). With kind permission from Tsai FJ)

(Glisanz et al. 1998). Similarly, such differences are also likely to be present with regard to anthropometric measurements of the face.

Despite previous work by physical anthropologists documenting differences in facial measurements among races and ethnic groups, this has only been systematically investigated in recent years (Dawei et al. 1997; Farkas et al. 2000; Le et al. 2002). Farkas et al. (2005), who had done much anthropometric work, observed that, with the influx of numerous peoples into North America, the significance of the broader spectrum of races and ethnic groups became important for craniofacial

surgeons and other medical professionals whose work involved the analysis and correction of head and face abnormalities. His study was drawn from 14 measurements in 1,470 subjects of 25 national groups hailing from Europe, the Middle East, Asia, Africa and North America belonging to four races. Interestingly, the regions with single measurements (head, mouth and ear) showed almost no differences though ethnic / racial differences in those regions with multiple measurements (orbits, facial width, etc.) were observed between vertical and horizontal measurements. These nevertheless remained adult studies.

156.6 Anthropometry in Different Populations

There are to date only limited reports of ear anthropometry studies done in different ethnic populations amongst the newborn. Methodologies also differ with the adoption of somewhat varied definitions. To permit reasonable comparison, the methodologies employed should be similar between studies. Despite such restrictions, it is still useful to place studies of different population side by side to give an idea of ethnic and racial variations.

156.7 Methodologies

Early researchers tended to rely on Western studies. Feingold and Bossert (1974), presented one of the earliest papers to aid syndrome delineation. For the purpose of ear anthropometry, the authors, with their cohort of 356 cases, described the use of an instrument made from a pre-calibrated transparent film. Both sides of the instrument were divided into millimetres to allow measurement of both the right and left ears by the same instrument. This method was employed in the Israeli study by Sivan et al. (1983). This method was also adopted by Lian et al. (2008), in a more recent study carried out in Singapore (an Asian country). This therefore permits comparison of values between these ethnically different cohorts. Both Sivan et al. (1983) and Lian et al. (2008) validated their findings by having two independent observers. Hall et al. (1989) recommended the use of a tape measure or a transparent calibrated ruler. Tateishi and Kaajii (1992), employed the use of a sliding calliper in his Japanese cohort. Agnihotri and Singh (2007) as well as Fok et al. (2004) similarly used a vernier calliper in their study of Indian and Hong Kong Chinese babies, respectively. Chou et al. (2001) in his Taiwanese study described the use of a calliper ruler. Golalipour et al. (2003) used a Martins sliding calliper in his cohort of two ethnic groups, the Turkman and the Native Fars groups in the Iran-Gorgan area.

156.8 Ear Length

Not many authors have reported on EL amongst different ethnic groups within the same geographical location (Table 156.2). Lian et al. (2008), in a recent study, revealed no significant differences amongst four different racial groups of different ancestry within the same Asian country. However, it would appear amongst studies with similar methodologies that across the board, although the means of EL measurement amongst different ethnic populations do not vary widely, there remained likely subtle differences, with the Caucasian ear slightly longer than the Asian ear. The upper limits of normality for the Caucasian ear are also higher than the Asian ear. The Israeli and Turkish ears are reportedly amongst the largest newborn ears. Sivan et al. (1983) and Merlob et al. (1984) (Israeli)

reported a mean of 3.90 ± 0.30, whereas Kalcioglu et al. (2006) (Turkish) reported a mean of 3.84 ± 0.64 cm for males and 3.84 ± 0.72 cm for females, with upper limits of norms between 3.96 and 3.71 cm, respectively. By contrast, the African ear (Adeyemo et al. 1998) is closer to the Hong Kong Chinese ear (Fok et al. 2004), being amongst the smallest of the newborn ears. The Jordanian (el-Shanti et al. 2000), Japanese (Tateishi and Kaajii 1992), Indian (Agnihotri and Singh 2007), Taiwanese (Chou et al. 2001) and Singaporean (Lian et al. 2008) ears measure in between, somewhat closer to the Caucasian ear. Interestingly, this pattern is also borne out in the study by Lian et al. (2008), where the general mean EL across different ethnic groups was slightly larger than the Chinese mean, though not statistically significant.

Furthermore, even in exploring similar ethnicities of similar ancestral descent, such as amongst Hong Kong Chinese, Taiwanese and Singaporean Chinese, there also appeared to be differences in EL, with the latter cohort being closer to their Caucasian counterpart, similar to the Japanese ear. One wonders whether the heterogeneous nature of the cosmopolitan Singaporean population, with rising incidences of interracial marriages, has lent weight to anthropometrical changes, leading to narrowing of differences in anthropometrical measurements. By contrast, the Hong Kong Chinese remain a fairly homogeneous group. Notably, however, Taiwan, despite being also a fairly homogeneously Chinese group, albeit with the historical hybrid nature of its society, and possibly earlier Japanese and Western influence, appeared more similar to Singapore.

156.9 Ear Width

Even fewer authors have reported on EW amongst newborns. Some demonstrated graphs but the number of reported numerical values in their reports were too few to permit comparison. Interestingly, despite a relatively shorter ear compared to their Caucasian counterparts, the Japanese baby has the widest neonatal ear, with an EW that is considerably bigger at 2.7 ± 0.21 cm (Tateishi and Kaajii 1992). The Turkish neonate has a smaller EW at 2.01 ± 0.39 cm (Kalcioglu et al. 2006). Again, the Singaporean newborn was more in tandem with their Turkish counterpart (Lian et al. 2008; Kalcioglu et al. 2006). None of these three studies (Table 156.3) showed any significant difference between the genders.

156.10 Ear Position

There is little doubt that a standard ear does not exist. Not only are there differences in EL and EW when looking at different ethnicities, the ear position and setting lend further confusion to ear anthropometry. Hall et al. (1989) described the degree of protrusion of the ear as being measured by the angle that is subtended from the posterior aspect of the pinna to the mastoid plane of the skull. This measurement is seldom measured in the neonate due to the fact that the ear continues to change over the years in childhood before finally reaching a settled position and size in adult ears. Ear position is denoted by the location of the superior attachment of the pinna. Therein lies another potential area of confusion in ear assessment for normality. Hall also described the various ways that this can be studied. Some authors would use an imaginary line between the outer canthi of the eye and the most prominent part of the occiput and confer normality on the ear with the superior attachment of the pinna being on or above this line. Another method would be the use of yet another imaginary line through the inner and outer canthi of the eye, again with normality being conferred on the superior

Table 156.3 Comparison of ear width (EW) of term infants amongst different ethnic populations

Author	Year	Country	Ethnicity (n)	Gestation (weeks)	Mean EW ± SD [Range] (cm)	Ear and Time measured
Tateishi and Kajii[b]	1992	Japan	Entire cohort (100)	37–41,	2.7 ± 0.21 [2.2–3.1]	Left ear[#] 8–64 h (majority within 40 h)
			Japanese males (50) [#]	Term	2.7 ± 0.20 [2.3–3.1]	
			Japanese females (50) [#]		2.6 ± 0.20 [2.2–3.0]	
Kalcioglu et al.[b]	2005	Turkey	Turkish males[#] (20)	40, Term	2.01 ± 0.39 [-]	Right ear
			Turkish females[#] (20)	40, Term	2.00 ± 0.43 [-]	Within 24 h
Lian et al.[b]	2008	Singapore	Chinese/Malay/Indian/ Others[#] (83)	39, Term	2.06 ± 0.14[#] [1.74–2.40]	Both ears[#] Within 36 h

attachment of the pinna being on or above that line. The argument with both methods lies in the fact that the Asian eye is often with a natural upward slant. This would result in unfavourable comparisons with the Caucasian measurements.

A more readily adopted method would be the use of a line drawn through the inner canthi of both eyes (intermedial canthial line – IMCL) and extending it outwards, with normality conferred on the superior attachment of the pinna being on or above this line. This method was adopted by a number of authors, such as Feingold and Bossert (1974), looking at the definition of low-set ears. However, anthropologists more often favour the Leiber method (Hall et al. 1989; Fok et al. 2004), which is more complicated and involved more landmarking, a technique which would be difficult for the practicing clinician.

There is extremely limited literature on studies that look at ear position. The definition of 'low-set ears' has conventionally been taken as the ear which has less than 33% of the vertical ear height above the IMCL. The study by Sivan et al. (1983) was reportedly comparable with Feingold and Bossert (1974), marking approximately 30% above the eyeline. However, Lian et al. (2008) reported that the ears of the babies in their Asian multiracial cohort were 'higher set', at 49 ± 8% of the ear being set above the IMCL, than those of previously studied Caucasian babies. Notably, Golalipour et al. (2003) looked at a different measurement in his study of head shapes and faces amongst two ethnic groups of different ancestry presently living in the same geographical location. Using the term 'auricular height', defined as 'the vertical distance between vertex to external acoustic meatus', the study reported differences in ear placement between those who migrated from central Asia and those who were native to that area, with the former group demonstrating a significantly higher placed ear in relation to the vertex than the latter. This is the only study to date looking at different ethnic groups in the same geographical location. There is clearly room for more studies in this area of anthropometry.

156.11 Applications to Other Areas of Health and Disease

156.11.1 Investigations and Interventions for the Baby with the Abnormal Ear

With objective measurement norms now available for different populations, it would be important to apply these in clinical practice. An abnormal ear has a lot more implications than just the aesthetic value or for the craniofacial surgeon to adjust. It points to a need for full extensive examination of the baby and an attempt to delineate all the potential problems associated with it.

The work-up for the presence of an abnormal ear needs to take into account developmentally associated patterns. For instance, there is often a need to obtain a renal ultrasound to exclude renal abnormalities in the presence of an abnormal ear. There might be a need to explore the auditory tracks and pathways to ensure adequate hearing ability. There would be a need to involve a multidisciplinary team for better management of the child. Genetic counselling and the involvement of the geneticist become important in a suspected genetic disorder, should the abnormal ear form part of a larger syndrome. Management is often long term and, as such, an abnormal ear should only be labelled abnormal in the context of the appropriate population norms; hence, ethnic and racial variations may become significant, especially in multiracial populations.

156.11.2 Further Implications of Ethnic Variations

Just as in ear anthropometry, the impact of ethnic variations should also be considered in measurements of other aspects of the newborn. In particular and pertinent to daily practice would be the weight, length and head circumference of the newborn (Cortés et al. 1992; Schumacher et al. 1990; Golalipour and Heydari 2004/2005). Studies on other facial measurements have also looked at the impact of ethnicity (Madjarova et al. 1999; Fok et al. 2003). Even penile length has been shown to be different between and within populations (Lian et al. 2000; Fok et al. 2005). Ethnicity and race will always remain factors to be considered in anthropometry, even in the most minute part of the body. To be exact in one's science is to take every factor into consideration. Only then can we be sure that we have provided the best of services and care.

Summary Points

- The newborn ear is important for aesthetics, hearing and equilibrium maintenance, as well as serving as an indicator marker for dysmorphology.
- Descriptive examination must therefore be supplemented by objective anthropometric measurements, to aid a complete diagnosis profile.
- Ethnic and race variations are well known to have an impact on various anthropometric measurements.
- Ear length by convention is most often defined as the maximum length measured from the superior to the inferior aspect of the external ear.
- The longest newborn ear is reported amongst the Israeli and Turkish babies, with smallest amongst the Hong Kong Chinese babies.
- There are also differences amongst Chinese of different geographical origins, where Taiwanese and Singaporean Chinese demonstrate longer ears than Hong Kong Chinese babies.
- Ear width is defined as the transverse distance from the palpable anterior base of the tragus through the external auditory canal to the margin of the helical rim at the widest point.
- The longest ear is not necessarily the widest ear. The Japanese newborn ear is the widest amongst limited reports.
- In limited studies, the ear is generally at least one-third above the eyeline or the inter-cathal medial line across both eyes. A low-set ear implies abnormality and is related to many genetic conditions.
- The work-up for any anthropometric abnormality must take ethnic variations into consideration. In the newborn, gestation and in the infant/child, age should also be taken into account in any anthropometric assessment.

Key Points

- Both qualitative and quantitative assessments are important in the delineation of a normal newborn ear, essential to newborn screening and syndromic diagnosis. Ethnic and race variations are well known to have an impact on various anthropometric measurements.
- Ear length by convention is most often defined as the maximum length measured from the superior to the inferior aspect of the external ear. The Middle-Eastern babies tend to have the longest newborn ears. Even within the same ethnic group, EL appears to be impacted by country of origin.
- Ear width is defined as the transverse distance from the palpable anterior base of the tragus through the external auditory canal to the margin of the helical rim at the widest point. The longest ear is not necessarily the widest ear. The Japanese newborn ear is the widest amongst limited reports.
- In limited studies, the ear is generally at least one-third above the eyeline or the inter-cathal medial line across both eyes. A low-set ear implies abnormality and is related to many genetic conditions.

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Chapter 157
Ethnicity and Facial Anthropometry

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Abstract The term of ethnicity is also international and multilingual. An ethnic group or ethnicity is a population of human beings whose members identify with each other, either on the basis of a presumed common genealogy or ancestry.

The human face is a highly rich stimulus that provides diverse information for adaptive social interaction with people.

Cephalometry is one of the important parts of anthropometry, in which the dimensions of the head and face are measured. Cephalometric results are used in forensic medicine, plastic surgery, oral surgery, paediatrics, dentistry, and diagnostic knowledge between the patient and normal populations.

Some descriptive and cross-sectional studies which was set up to determine and compare the face shapes in Fars and Turkman ethnic groups of normal newborns and 17–20 years old males and females in Gorgan (North of Iran). The length and width of faces were determined by using classic cephalometery technique with usage a Martin spreading caliber, and the shape of faces in the ethnic group of Fars and Turkman in both sexes was compared.

Studies indicate that the Hypereuriprosopic type with 34.60% was dominant type in Turkman's male newborns and also dominant type of faces in Fars' male newborns was hypereuriprosopic with 71.9%. Also the mesoprosopic type with 36.01% was dominant in the Turkmans female newborns and the dominant type of face in native Fars female newborns was hypereuryprosopic with 71.22%.

The dominant type of face shape in the native Fars females was Euryprosopic (37.7%) and it was Euryprosopic (51.7%) in Turkman females.

The dominant type of face shape in the native Fars males was mesoprosopic (44%) and it was mesoprosopic (38.4%) in Turkman males.

157.1 Introduction

Studying intra- and interpopulation variations in different morphological characters have long been an interest of anthropologists (Ghosh 2007). The evaluation and measurement of human body dimensions are achieved by physical anthropometry (Chamella 1997). The dimensions of the human body are affected by ecological, biological, geographical, racial, gender, and age

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_157,

factors (Imami-Mibodi 1996; Okupe et al. 1984; Hamill 1979). On the basis of the above factors, anthropometrical studies have been conducted on the age, gender, and racial groups in certain geographical zones (Afak et al. 1998; De Onis et al. 1998). The term 'ethnicity' is already huge and is constantly being added to. This term is also international and multilingual, large parts of it being regrettably inaccessible to readers who depend on English (or any other single language) for their familiarity with this topic.

The differences between regions and disciplines begin with the very definitions of the terms ethnicity, extending to all the ramifications of these terms for the social, psychological, economic, political, and cultural interactions within and between groups of human beings.

Some concepts of ethnicity and race are as follows:

An ethnic group or ethnicity is a population of human beings whose members identify with each other, on the basis of either a presumed common genealogy or ancestry.
Ethnicity connotes shared cultural, linguistic, or religious traits.
Ethnicity is defined in terms of shared genealogy.
The term 'race' refers to the concept of dividing people into populations or groups on the basis of various sets of characteristics and beliefs about common ancestry.
Race connotes shared biological (genetic or phenotypic) traits.
Race is defined in terms of shared genealogy.

Not only the meaning of 'race' has changed over many centuries, but also it is now generally accepted as something created by society. The American Anthropological Association's statement on race is that, "Physical variations in the human species have no meaning except the social ones that humans put on them." While we may not be different biologically, the color of our skin is the most visible difference among us, and it affects the way we interact with each other.

Racial encounters carry a long history of abuse from colonization, which saw the establishment of a major group and a minor group. This condition still thrives today but ethnicity, gender, and economic status further inform the experience of the minority. Ethnicity is best defined as the practices and traditions of a racial group, such as language, religion, behaviors, and culture.

Current understanding of racism can be traced back to the period of industrialization of Europe and the colonization of non-European peoples in the eighteenth century, when there were rapid scientific and technological developments. The ways and cultures of indigenous peoples and people of color were seen as inferior to the white explorers and colonizers, and were therefore exploitable (Enlow 1990; Farkas 1994).

Today, many countries are culturally diverse due to generations of immigration resettlement (refugees who have been selected to establish themselves in a country), diaspora (a dispersion of people from their original homeland), and forced displacement; however, race relations within a country remain tense and unstable. Racial and ethnic minority identities are shaped by the dominant culture, which controls the institutions of power (the legal and education system, media, etc.) that produce and maintain representations and stereotypes. In spite of this, ethnic and racial minorities are defining and creating their own identities.

Multicultural societies help promote cultural acceptance and pluralism (the state of having more than one culture in one geographic area), but they should be careful not to focus on the simple aspects of culture, such as food, dance, music, and clothing, as they do not represent a culture in its complexity and do not disturb the organization and power of the dominant culture.

The human face is a highly rich stimulus that provides diverse information for adaptive social interaction with people. Humans are able to process a face in a variety of ways to categorize it by its identity, along with a number of other demographic characteristics, including ethnicity (or race), gender, and age.

Over the past few decades, much effort has been devoted in the biological, psychological, and cognitive sciences areas, to discover how the human brain perceives, represents, and remembers faces. Computational models have also been developed to gain some insight into this problem. Anthropometrical statistics show the racial and ethnic morphometric differences in the craniofacial complex (Enlow 1990; Farkas 1994).

157.2 Applications to Other Areas of Health and Disease

Enlow in 1990 and Farkas in 1994, based on carefully defined facial landmarks, took 25 measurements on head and face to examine three racial groups (i.e., North American Caucasian, African-American, and Chinese). Farkas identified several differences in these three groups. For example, the Chinese group had the widest faces; the main characteristics of the orbits of the Chinese group were the largest intercanthal width. Further, the soft nose is less protruding and wider in the Chinese group and it had the (relatively) highest upper lip in relation to, for example, mouth width. Enlow also conducted research on the structural basis for ethnic variations in facial form (Enlow 1990; Farkas 1994).

The demographic features, such as race and gender, are involved in human face-identity recognition. Malpass and Kravitz in 1969 and also Brigham and Barkowitz in 1978 reported that humans are better at recognizing faces of their own ethnicity/race than faces of other races (Malpass and Kravitz 1969; Brigham and Barkowitz 1978). Golby et al. showed that same-race faces elicit more activity in brain regions linked to face recognition (Golby et al. 2001). They used functional magnetic resonance imaging (fMRI) to examine if the same-race advantage for face identification involves the fusiform face area (FFA), which is known to be important for face recognition (Puce et al. 1995). O'Toole et al. in 1994 investigate the differences in the way people perceive own- versus other-race faces. They found that the perceived typicality of own-race faces was based both on global shape information and on small distinctive feature markers, whereas the typicality of other-race faces related more to the presence/absence of local distinctive features (O'Toole et al. 1994). O'Toole et al. have shown that people categorize faces of their own-race by sex more efficiently than they categorize faces of another race by sex. The identification of race and gender can help the face-recognition system to focus more on the identity-related features and limit the number of entries to be searched in a large database, improving the search speed and efficiency of the retrieval systems. Ethnicity and gender are also useful for demographic statistics in many social applications. Unlike identity, ethnic categories are loosely defined classes. O'Toole reduces the ethnicity classification into a two-category classification problem, Asian and non-Asian, each of which has relatively distinct anthropometrical features (O'Toole et al. 1996).

Image-based face recognition has been drawing a great deal of attention over the past decade. A number of face-recognition algorithms have been investigated and several commercial face recognition products. In real applications, cross-race, cross-gender, and large-scale face-recognition tasks need to be solved (Zhao et al. 2000).

Cephalometry is one of the important parts of anthropometry, in which the dimensions of the head and face are measured. Cephalometric results are used in forensic medicine, plastic surgery, oral surgery, pediatrics, dentistry, and diagnostic knowledge between the patient and normal populations. Although anthropometric studies of newborns and other age groups and their relationship in health and disease have been achieved, there is currently a background for research in different geographical and racial groups.

157.3 Practical Methods and Techniques

The face measurements determined with a Martin spreading caliber (Fig. 157.1b) included:

- Face length = nasion – gnathion height (Fig. 157.1a-4).
- Face width = bizygomatic breath (Fig. 157.1a-2).

To compute the prosopic index, the following formula is used:

$$\text{Prosopic index} = \frac{\text{Face length}}{\text{Face width}} \times 100$$

The above index was determined on the basis of international anatomical descriptions. Based on this index, the types of face shapes were classified as the following (Banister et al. 1995).

Face Shape	Prosopic Index (PI) Range (%)
Hypereuriprosopic (very broad face)	75 < PI < 79.9 and PI < 75
Euriprosopic (broad face)	80 < PI < 84.9
Mesoprosopic (round face)	85 < PI < 89.9
Leptoprosopic (long face)	90 < PI < 94.9
Hyperleptoprosopic (very long face) (Fig. 157.2)	PI > 95

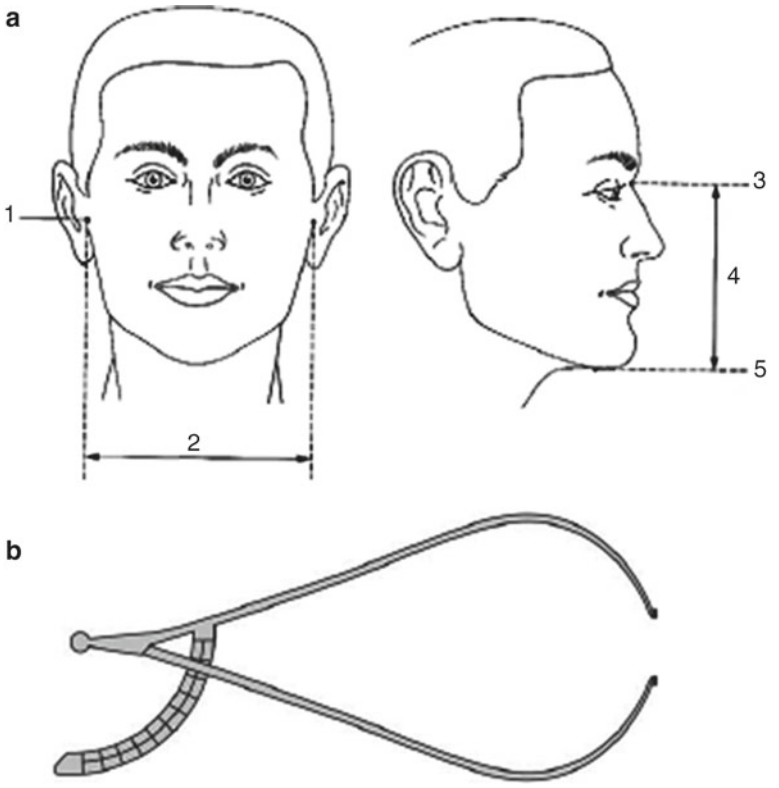

Fig. 157.1 Measurement of Face dimensions. Face length and Face width (**a**) and Martin spreading caliber (**b**). *1* zygoma; *2* face width; *3* nasion; *4* face length; *5* gnathion (Reprinted from Jahanshahi et al. (2008), with permission)

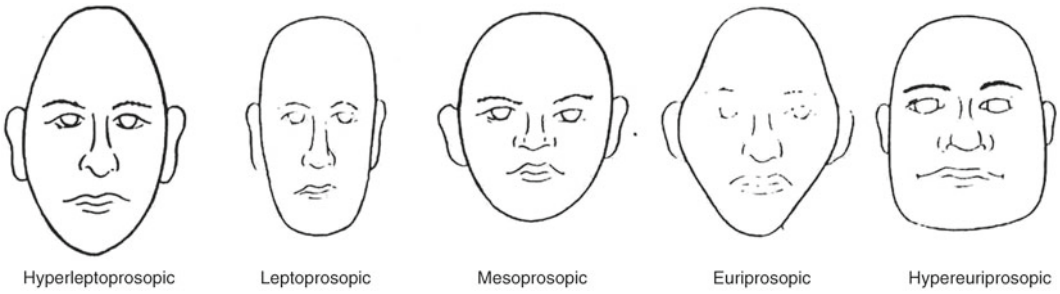

Fig. 157.2 Types of Face shapes. Hypereuriprosopic (*Very broad face*), Euriprosopic (*Broad face*), Mesoprosopic (*Round face*), Leptoprosopic (*Long face*), and Hyperleptoprosopic (*Very long face*) (Reprinted from Jahanshahi et al. (2008). With permission)

Table 157.1 Male newborns (Reprinted from Golalipour, Jahanshahi et al. (2003). With permission)

	Males				
	Fars		Turkman		
	Number	Percent	Number	Percent	*P*-value
Hypereuryprosopic	146	71.9	75	34.6	0.0000
Euryprosopic	31	15.3	53	2.4	0.0263
Mesoprosopic	12	5.9	62	28.6	0.0000
Leptoprosopic	9	4.4	25	11.5	0.0130
Hyperleptoprosopic	5	2.5	2	0.9	0.1981
Total	203	100	217	100	

Distribution of face shapes in Turkman and Fars male newborns

Table 157.2 Female newborns (Reprinted from Golalipour, Jahanshahi et al. (2005). With permission)

	Females				
	Fars		Turkman		
	Number	Percent	Number	Percent	*P*-value
Hypereuryprosopic	151	71.22	59	27.96	0.0000
Euryprosopic	24	11.32	54	25.59	0.0263
Mesoprosopic	15	7.07	76	36.01	0.0000
Leptoprosopic	13	6.13	18	8.53	0.0130
Hyperleptoprosopic	9	4.24	4	1.89	0.1981
Total	212	100	211	100	

Distribution of face shapes in Turkman and Fars female newborns

Morphological features of different races and ethnic groups are not randomly distributed but appear in geographic clusters.

In the north of Iran (southeast of Caspian Sea), there are some different ethnic groups that have been residing for about two centuries. Some of them are: Native Fars, Turkman, and Sistani (Jahanshahi et al. 2008).

Turkman group: The Turkman populations have been living in this area for more than two centuries, having emigrated from central Asia. The Turkman people marry only among themselves because of religious and ethnic concepts. They are therefore almost a 'pure' ethnicity.

Native Fars group: The populations of native Fars were selected from three generations who have lived in this region.

Sistani group: This population emigrated from the east of Iran to the north about 80–100 years ago.

The morphological classification of the face shape in newborns in north of Iran (southeast of Caspian Sea) is depicted in Tables 157.1 and 157.2:

Table 157.3 17–20-year-old females

	Females				
	Fars		Turkman		
	Number	Percent	Number	Percent	*P*-value
Hypereuryprosopic	43	20.8	71	3.5	0.001
Euryprosopic	78	37.7	105	51.7	0.004
Mesoprosopic	46	22.2	14	6.9	0.000
Leptoprosopic	28	13.5	6	3	0.000
Hyperleptoprosopic	12	5.8	7	3.4	NS
Total	207	100	203	100	

The shapes of face in 17–20-year-old females in Fars and Turkman groups

Table 157.4 17–20-year-old males

	Males				
	Fars		Turkman		
	Number	Percent	Number	Percent	*P*-Value
Hypereuryprosopic	8	4	17	8.6	0.059
Euryprosopic	32	16	53	26.8	0.09
Mesoprosopic	88	44	76	38.4	NS
Leptoprosopic	64	32	34	17.2	0.001
Hyperleptoprosopic	8	4	18	9.1	0.04
Total	200	100	198	100	

The shapes of face in 17–20-year-old males in Fars and Turkman group
NS not significant

According to Tables 157.1 and 157.2, the hypereuriprosopic type with 34.60% and the hyperleptoprosopic type with 0.90% were the dominant and the rare types in Turkman male newborns; the dominant and rare types of faces in Fars male newborns were hypereuriprosopic with 71.9% and hyperleptoprosopic with 2.5%, respectively (Golalipour et al. 2003).

In Table 157.2, the mesoprosopic type with 36.01% and the hyperleptoprosopic type with 1.89% were the dominant and the rare types in the Turkman female newborns, and the dominant and rare types of face in native Fars female newborns were hypereuryprosopic with 71.22% and hyperleptoprosopic with 4.24%, respectively.

It was concluded that there is significant difference between the dominant types of faces in the Turkman and native Fars ethnical groups.

The morphological classification of the face shape in adult females and males in north of Iran (southeast of Caspian Sea) is depicted in Tables 157.3 and 157.4:

The means and SD of prosopic index in Turkman males and females were 87.25 ± 5.18 and 81.48 ± 5.28, respectively.

The means and SD of prosopic index in Fars males and females were 88.22 ± 5.21 and 84.48 ± 5.85, respectively.

The dominant type of face shape in native Fars females was euriprosopic with 37.7%, and in Turkman females, it was euriprosopic with 51.7% (Jahanshahi et al. 2008).

The dominant type of face shape in native Fars males was mesoprosopic with 44% and, in Turkman males, it was mesoprosopic with 38.4%.

There were no significant differences between the dominant types in the two sex and racial groups.

Further, the rare type of face shape in native Fars females was hyperleptoprosopic with 5.8% and, in Turkman females, it was leptoprosopic with 3%.

The rare type of face shape in native Fars males was hyperleptoprosopic and hypereuryprosopic with 4% and, in Turkman males, it was hypereuryprosopic with 8.6% (Jahanshahi et al. 2008).

Another study in east of Iran, by Heidari et al. showed that the prosopic index was significantly different in Sistani and Baluchi women and the dominant type of face shapes was euryprosopic with a statistically significant difference between them. The rare types were hypereuryprosopic and hyperleptoprosopic in the Sistani and hyperleptoprosopic in the Baluchi groups (Heidari et al. 2006).

157.4 Conclusion

The study of the face shapes in different parts of Iran indicates that the geographical factor, similar to ethnical factor, can affect the form of the face. Normally, various facial types are encountered in every population so that a certain number of people have thin, broad, or small faces. In children, the PI is lower than in the adults, and through growing up, they gain a longer and narrower face.

Summary Points

- An ethnic group or ethnicity is a population of human beings whose members identify with each other, on the basis of either a presumed common genealogy or ancestry.
- Not only has the meaning of 'race' changed over many centuries, but it is now generally accepted as something created by society as well.
- Cephalometry is one of the important parts of anthropometry, in which the dimensions of the head and face are measured.
- Cephalometric results are used in forensic medicine, plastic surgery, oral surgery, pediatrics, dentistry, and diagnostic knowledge between the patient and normal populations.
- The dominant type of face shape in native Fars females was euriprosopic with 37.7% and, in Turkman females, it was euriprosopic with 51.7%.
- The dominant type of face shape in native Fars males was mesoprosopic with 44% and, in Turkman males, it was mesoprosopic with 38.4%.
- In conclusion, the face shapes in different parts of Iran indicate that the geographical factor, similar to ethnical factor, can affect the form of the face.

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Chapter 158
Anthropometry in the Circumpolar Inuit

Tracey Galloway, T. Kue Young, and Peter Bjerregaard

Abstract The Inuit are an indigenous population whose homeland today comprises Chukotka in Russia, Alaska, northern Canada and Greenland, with an estimated global population of 165,000. The rapid social and economic changes especially over the past half century have been accompanied by a health transition, for which anthropometry is well suited to provide convenient and inexpensive indicators such as stature and obesity. The historical and early ethnographic literature reported the Inuit as characteristically short but with a high sitting height ratio. The Inuit morphology has been attributed to adaptation to the cold Arctic climate, however, secular trends in increasing height and reducing sitting height ratio, especially among children, have been documented. Obesity among the Inuit based on BMI, skinfold thicknesses, and waist circumferences had been uncommon up until the late 1970s and early 1980s. Recent surveys among children in some regions have found an alarming prevalence of obesity at 57% for boys and 45% for girls. Studies on the metabolic correlates of obesity among adult Inuit tend to show a lower degree of blood pressure, plasma glucose, insulin, and atherogenic lipids compared to Europeans at the same levels of BMI, however, imaging studies that localize abdominal fat distribution are lacking. Determining the health consequences of "obesity" classified according to international criteria requires longitudinal monitoring of defined cohorts. While field studies of anthropometry in the Arctic are faced with formidable logistical obstacles, they offer important information for monitoring the health and nutrition status of the population, and the planning and evaluation of health programs and services.

Abbreviations

BMI	Body mass index
CDC	Center for disease control and prevention [United States]
HDL	High density lipoprotein
IBP	International biological program
IOTF	International obesity task force
NCHS	National center for health statistics [United States]
WHO	World Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_158,

158.1 Introduction

The Inuit are indigenous residents of the circumpolar regions of North America, Greenland, and the Chukota Peninsula in Siberia (Table 158.1). The term 'Inuit' is the plural of 'Inuk', which means a person. The term is used to refer collectively to a number of linguistically closely related groups with a variety of regional names, such as Yuit, Yupik, Alutiiq, Inupiat, Inuvialuit, and Kalaallit. It has generally replaced the older term 'Eskimo', which is perceived to be derogatory in some regions, especially in Canada. While the total population of Inuit is low, it has risen rapidly in recent decades. It is estimated that, globally, there are over 165,000 Inuit in the early years of the twenty-first century, including approximately 51,000 in Canada, 57,000 in Greenland and Denmark, 55,000 in the USA, and 1,800 in Russia (Young and Bjerregaard 2008:126).

The age structure of the Inuit population is disproportionately weighted toward children and youth. In social terms, this means a majority of Inuit communities are characterized by relatively young populations whose need of health and social services is not matched by the infrastructure available to them. There are both geographic and political barriers to health and social development in the north, and economic development is unevenly distributed among geographically disparate communities.

In the past 40 years, acculturation to a Western lifestyle has proceeded in the Arctic at a rapidly increasing pace. Inuit communities have experienced a shift from nomadic hunting and gathering to a largely sedentary lifestyle and a transition to a wage-based cash economy. In some jurisdictions, government policy required the forcible removal of children from communities to attend residential schools, where Inuit language and other cultural activities were severely curtailed. Increasing availability of market goods and foods, combined with the impact of settlement and climate change on the availability of country foods, has led to enormous changes in dietary patterns.

There are some substantial differences in the overall health status of the Inuit and their national counterparts. Infant mortality is two to three times those of the non-Inuit population in the same country, and life expectancy at birth of the Canadian and Greenland Inuit is 10–14 years lower than among the non-Inuit. Other significant health problems include infectious diseases, such as tuberculosis and sexually transmitted diseases, and injuries, especially suicide among youths (Niclasen and Bjerregaard 2007). Social statistics too reflect the challenges facing Inuit communities. Poverty is widespread, and education and employment levels are low compared to national levels in Canada, Denmark, and the USA (Young and Bjerregaard 2008).

This chapter examines the use of anthropometric techniques to assess the health and nutrition of the circumpolar Inuit, and discusses some of the methodological challenges of such research.

Table 158.1 Key facts about the circumpolar Inuit

1. The Inuit are indigenous people whose traditional lands occupy the Arctic regions of Canada, Greenland, Alaska and Eastern Russia.
2. In these countries, the Arctic environment is relatively harsh compared with the south. Mean annual temperature is below freezing and the growing season is extremely short with limited rainfall.
3. Humans have occupied Arctic regions for 15 000 years. Today's Inuit are descendents of the Thule cultural group, which occupied Arctic regions 1000 years ago.
4. Historically, Inuit are nomadic hunters, following the migratory patterns of terrestrial and marine mammals, birds and fish. Depending on region and seasonal availability, traditional Inuit diet includes caribou, muskox, seal, walrus, whale, char, cod, halibut and herring.
5. Today, the majority of Inuit live in settled communities. Most Inuit towns have fewer than 1 000 residents. Larger administrative centres such as Iqaluit, Canada and Nuuk, Greenland have populations of 8 000 and 14 000 respectively.

This table lists key historical facts about the circumpolar Inuit history, subsistence pattern, and demography

158.2 Historical Studies of Stature and Body Proportion

There is an abundant ethnographic literature produced by polar explorers whose travels brought them into contact with circumpolar people, for example, the 1631 voyages to Hudson Bay by James and Fox, the 1776 voyage of Captain James Cook to the Pacific Northwest, and Lavrentiy A. Zagoskin's travels in Yukon and Alaska during 1842–1844. All contain similar descriptions of short, physically robust adults, lean and muscular from rigorous outdoor work in the cold Arctic climate (Michael 1967; Oswalt 1999).

Short stature, as a characteristic of Inuit morphology, was reported in early anthropometric studies by anthropologists Franz Boas (1888) and Ales Hrdlicka (1930, 1941). In a 1958 survey of Alaskan National Guardsmen, Mann et al. (1962) recorded adult height on average 2.5 cm shorter than that of the overall Canadian population. Reporting on studies undertaken in1968–1972 for the Human Adaptability Section of the International Biological Program (IBP), Auger et al. (1980) found that Inuit populations in USA, Canada, and Greenland had standing heights consistently below the 50th percentile of the US National Centers for Health Statistics (NCHS) reference. For both men and women, the statures of Alaskan Eskimo people followed the 25th percentile, those of Canadian Inuit ranged nearer the 5th centile, and those of Greenlandic Inuit were intermediate between the 5th and 25th percentiles of height-for-age.

Efforts were made to discover how early in ontogenic development the limitation on stature emerged. In their 1958 survey of Alaskan schoolchildren, Mann et al. (1962) observed that children's height tracked a Canadian population reference closely until the age of 6 years; children 7–19 years had heights significantly below the reference. Other studies found decreased stature evident even earlier in growth. In an examination of data collected by researchers and physicians in Canada and Alaska between 1928 and 1972, Jamison (1990) demonstrated that despite mean recumbent length at birth consistent with the 50th percentile of the NCHS growth reference, by 3 months of age the mean length of Inuit children fell to the 10th percentile of the NCHS and remained there through the first 36 months of life. Heller et al. (1967) and Maynard and Hammes (1970) reported declining length/height and rising weight-for-height percentiles among Alaskan infants within the 1st months of life that persisted into childhood.

A second noted feature of Inuit morphology was described by Danish anthropologist Kaj Birket-Smith, who accompanied the Fifth Thule Expedition of 1921–3. Commenting on the Caribou Eskimo, he wrote: "As a rule the Eskimos are powerfully built and plump without being fat. The trunk is comparatively long and the arms and legs short in relation to the total height" (Birket-Smith 1936, cited in Young 2007). This pattern of short arms and legs relative to total height was incorporated into anthropometric research through use of the sitting height ratio (sitting height/standing height). In a review of Arctic anthropometric data collected during 1880–1928, Stewart (1939) found sitting height values comparable with European and US references, whereas the sitting height ratio was comparatively high in Arctic populations due to their shorter legs. Subsequent studies of circumpolar populations bore this pattern out (Heller et al. 1967; Maynard and Hammes 1970; Auger et al. 1980). Johnston et al. (1982) found significantly shorter leg lengths and higher sitting height ratio among 84 Alaskan children ages 6–17 years when compared with US reference data.

High sitting height ratio complicates interpretation of weight-for-height, as the mass of the body trunk or core is relatively greater than that of the extremities. High weight-for-height has been observed in Inuit populations throughout the twentieth century. Jamison (1990) examined data from North American and Greenland studies as early as 1928, finding high weight-for-age across childhood. Heller et al. (1967), Auger et al. (1980), and Petersen and Brant (1984, cited in Jamison 1990) report high weight-for-height values in Alaskan children from 6 months to 20 years of age. Low stature and high relative sitting height complicate calculation of weight-for-height and other calculated indices of body composition, such as body mass index, in both historical and contemporary populations. As a result, anthropometric assessment of adiposity in circumpolar populations requires a combination of techniques and analytic approaches.

158.3 Inuit Morphology and Cold Adaptation

The pattern of stature and limb proportions in the North American and Greenlandic Inuit is widely interpreted as evidence of physiologic adaptation to cold climate. Inuit populations have been described as fitting the ecological 'rules' of Bergmann and Allen that relate size and shape of the body to climactic variation, as a result of natural selection (Johnston et al. 1982:400).

'Bergmann's rule' is often applied to explain variation in body size among human populations (Steegman 2007). Evolutionary anthropologists, such as Ruff et al. (2005), posit that the adaptive advantage of greater mass per unit of volume arises through the conservation of heat dissipation via limited body surface area per unit of mass in shorter, cold-adapted populations. Further, Ruff argues that this selective advantage is responsible for latitudinal variation in stature among both hominid and contemporary human populations. Steegman reviewed studies of cold adaptation since 1975 and failed to find consistent physiologic evidence in support of Bergmann's rule. For example, in a series of cold immersion studies, McArdle et al. (1984) and Toner et al. (1986) reported equivalent rates of core temperature loss in women and men of varying statures and surface area-to-mass ratios. Gustafsson and Lindenfors (2009) found no demonstrable relationship between latitude and stature across 124 human populations.

Population differences in limb-length proportions are viewed by evolutionary anthropologists as consistent with the thermoregulatory principle described by Allen's rule, which states that species living in warm regions tend to have longer extremities than those living in cold regions. Steegman challenged the heat-conservation advantage of foreshortened extremities. Because of peripheral vasoconstriction, little heat is lost from the distal extremities, regardless of body proportion differences within the human species (Steegman 2007:226). The driver of variability in extremity length and sitting height ratio in circumpolar populations may not be cold, as previously assumed, but a combination of environmental conditions, such as nutrition and infectious disease burden, an idea advanced as early as in 1939 by Stewart (1939:122). Steegman (2007) suggests that circumpolar populations may exhibit thermal adaptation related to both the insulative and metabolic properties of skeletal muscle. Although fat has higher insulative value than muscle, a thickly muscled individual will have much more muscle than subcutaneous fat, resulting in a higher absolute insulative value. Studies of Inuit body composition support ethnographic descriptions of circumpolar people as robustly muscular. Shephard et al. (1973) found that the Canadian Inuit had one-third more lean body mass per centimeter of height than did men from southern Canada. Johnston et al. (1982) observed significantly greater upper-arm circumference in Alaskan Eskimo children compared with a US reference, with mean values falling in the 74th percentile for boys and in the 94th percentile for girls. In this population, greater lean mass was interpreted as an increase in heat-producing tissue and a physiologic adaptation to cold. Other morphologic and physiologic features, such as centripetal fat distribution (Schaefer 1977), brown adipose tissue (Lean and James 1986), and basal metabolic rate (Leonard et al. 2002), offer avenues for investigation of human cold adaptation.

158.4 Adiposity in Historical Studies of Inuit

Historical ethnographic sources describe Arctic populations as relatively lean compared with their European and North American contemporaries. John Murdoch, in his report of the 1881–83 Point Barrow Expedition, described Eskimo people as "of medium height, robust and muscular, inclining rather to spareness than corpulence, though the fullness of the face and the thick fur clothing often gives

the impression of the latter" (Anderson and Eels 1935:26–7). A similar observation was made by Canadian anthropologist Diamond Jenness in his report of the 1913–18 Canadian Arctic Expedition. Jenness described Copper Eskimo people as "of about middle stature, and sturdy and robust in build. The fur clothing in which they are habitually enveloped gives them an exaggerated appearance of corpulence, whereas in reality they incline towards slenderness" (Jenness 1923, cited in Young 2007). These authors highlight a fundamental misconception about Inuit morphology that persists to the present day that historically their high adiposity was perhaps part of an adaptive mechanism for living in cold climate. Commenting on the results of a 1975 Nutrition Canada survey, Schaefer noted the "popular misconceptions of Eskimos eating lots of blubber and being jolly rotund fellows whose presumably ample subcutaneous fat padding helps them to withstand the Arctic cold" (Schaefer 1977:1623).

In fact, analysis of historical sources suggests that obesity was virtually nonexistent in circumpolar populations prior to the twentieth century (Michael 1967; Oswalt 1999). Anthropometric studies repeatedly demonstrated a pattern of low height, with overall body weight comparable to non-Inuit (Boas 1888; Hrdlicka 1930, 1941). The pattern of low prevalence of obesity appears to have continued into the mid-twentieth century. In a 1958 Survey for the US Interdepartmental Committee on Nutrition for National Defense, Mann et al. (1962) observed that obesity was rare among Eskimo men employed by the Alaskan National Guard and that weight in excess of 100% of US actuarial tables was an artifact of excessive bone and muscle mass rather than fat deposits (Mann et al. 1962:43–4). In addition, the low caloric intake reported in numerous nutrition studies suggests Inuit were morphologically lean (Schaefer 1977:1626).

As recently as 1973, researchers recorded very low prevalence of obesity among Greenland Inuit children (Schnohr et al. 2008). In a study of 1,000 adult Inuit conducted during 1964–1970, Schaefer (1977) reported triceps, subscapular, and suprailiac skinfold thicknesses significantly lower than those of the overall Canadian population. Measures of 84 Alaskan Eskimo children 6–16 years of age showed no difference in triceps skinfold thicknesses when compared with a US reference population (Johnson et al. 1982), despite high weight-for-height values. Retrospective analysis of anthropometric data from Greenland (collected between 1962 and 1964) reveals median Inuit BMI in the high percentiles of the WHO reference, despite overwhelming evidence that this was an extremely lean population by any standard (Andersen et al. 2004).

158.5 Secular Trend in Stature

Over the course of the twentieth century, researchers have recorded a secular trend of increasing stature among the Inuit. Schaefer (1970, cited in Jamison 1990) compared measures of children ages 2–14 years taken in 1938 (n = 176) and 1968 (n = 186) in the Eastern Canadian Arctic and found a significant increase in height during this period among both boys and girls. Jamison (1990) compared measures of 71 boys ages 2–13 years taken in 1968 with those of 70 boys taken in 1977 by Petersen and Brant (1984, in Jamison 1990) in Wainwright, Alaska and found that, in 1977, the boys were significantly taller up to age 11 than their 1968 counterparts. Rode and Shephard (1984) compared measures of 9–19-year-old children living in living in Igloolik, Canada, in 1970 (n = 110) and 1980 (n = 205). While in 1970, the authors reported increasing height values relative to earlier studies, they found no evidence of secular trend during the period 1970–80, concluding that secular trend had reached its zenith around 1970 in this population. For all age groups, the 1980 children's mean standing heights remained significantly below that of US, Canadian, and UK references. Subsequent measures taken in 1989 (n = 547) showed a resumption of the trend toward increasing height in this population, with significant differences evident between the 1980 and 1989 samples (Shephard and Rode 1995).

Zammit et al. (1993) compared results of a 1991 study of Labrador Inuit children and adults with historical stature data on Labrador Inuit collected between 1880 and 1928. Evidence suggested that secular trend in stature had occurred over this period, though in the modern study children's mean height still fell between the 10th and 50th percentiles of the NCHS reference. In a study of children from Maniitsoq, Greenland, of ages 5–19 years, Becker-Christensen (2003) compared standing height values from 1996–7 with measurements taken in 1964–5. In the roughly three decades between studies, there was an increase of at least 10 cm in standing height among 14-year-old children. A recent study of 3–5-year-olds from Nunavut, Canada, reported no difference in mean stature between Inuit children and the US Centers for Disease Control (CDC) growth reference (Galloway et al. 2010). It should be noted that some of the above studies incorporated small sample sizes and a wide variety of techniques and personnel. Interpretation of their findings is hampered by lack of methodological consistency. However, taken as a whole, they provide generally consistent evidence of stature increase in Inuit children over decades across a wide geographical area.

Interestingly, while children's standing height increased during the late twentieth century, this increase appears to be the result of a modification in the shape of a child's growth curve, with earlier maturation resulting in an earlier adolescent growth spurt. Rode and Shephard (1984) observed this phenomenon as early as 1984, reporting changes in the timing of growth spurts for height and body mass. Becker-Christensen (2003) reports that the mean height of Greenlandic boys measured in 1996–7 tracks that of their Danish counterparts up to the age of 14 years, when values fall below the reference, achieving a final attained standing height 7 cm below that of Danish boys. Similarly, the mean height of girls follows the Danish curve up to age 11 years, dropping after that point to a final attained height 5 cm below that of Danish children. This pattern of secular trend of earlier physical maturity is supported by data on menarcheal age among the Canadian (Schaefer et al. 1980) and the Greenland Inuit (Becker-Christensen 2003).

It is also interesting to note that, among the Inuit, secular trend in height has been accompanied by a decrease in sitting height ratio (Schaefer 1977), suggesting that children's increased height is the result of increasing leg length. This pattern reflects that observed in other European contexts and suggests that patterns of morphology previously typical of Inuit growth may be changing in response to the environmental stimuli accompanying Westernization.

One of the few studies that looked at childhood determinants of adult stature was conducted in Greenland. Among adults in Greenland assessed during 1999–2007 (n = 2302), height was associated with mother's place of birth, birth cohort, childhood residence, alcohol problems in childhood home, and education among both men and women (Bjerregaard et al. 2009).

158.6 Increasing Prevalence of Obesity

Inuit communities are experiencing the increase in obesity prevalence, which is characteristic of regions experiencing rapid socioeconomic development (Figures 158.1–158.7). Young (1996) has observed that, in past studies, the low prevalence of obesity among Inuit has set them apart from other North American Aboriginal populations. However, recent studies document a trend toward increasing prevalence of obesity among Inuit adults (Table 158.2). Young reports increasing BMI and skinfold thicknesses among Inuit from the Kivalliq region of the Canadian Arctic. According to the 2004 Nunavik Inuit Health Survey, 30% of Inuit adults were overweight (BMI 25–29.9) and 28% were obese (BMI ≥30) (Nolin et al. 2007). Among obese adults, more than one-third had BMI categorized as class II (BMI 35–39.9) or III (BMI ≥40), according to the WHO BMI classification system for adults.

Table 158.2 Selected studies of overweight and obesity in adult Inuit by gender, published 1990 onward

Author(s)	Year(s)	Region	n	Ages	% Overweight		% Obese	
					Men	Women	Men	Women
Ekoé et al. (1990)	1982–84	Canada	778	15+	34	16	14	23
Murphy et al. (1995)	1987	Canada	509	40+	27	51	–	–
Risica et al. (2000)	1994	Alaska	454	25+	36	28	33	16
Andersen et al. (2004)	1998	Greenland	535	50–69	34	16	14	23
Bjerregaard et al. (2002)	1998–2001	Greenland	1310	18+	35	33	16	22
Jørgensen et al. (2003)	1999–2001	Greenland	917	30–6-			18	25
Young et al. (2007)	1990–2001	Alaska, Canada, and Greenland	2545	18+	37	33	16	26
Hiratsuka et al. (2007)	2000–2005	Alaska	1334	40–64	–	32	–	47
Nolin et al. (2007)	2004	Canada	925	18–74	29	30	26	31
Bjerregaard et al. (2009)	1999–2007	Greenland	2302	25+	–	–	19	25

This table lists recent significant contributions to the literature on overweight and obesity prevalence among the circumpolar Inuit

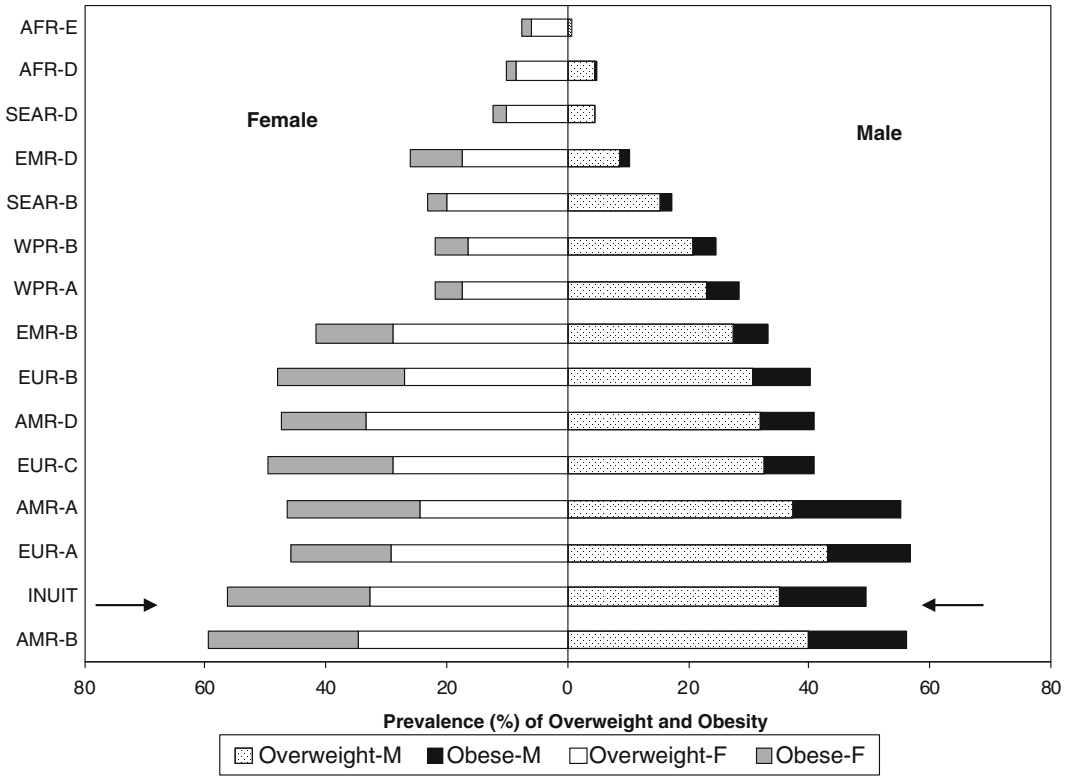

Fig. 158.1 Age-standardized prevalence of overweight and obesity among the Inuit compared to WHO Regions (*AFR* Africa; *SEAR* South East Asia; *EMR* Eastern Mediterranean; *WPR* Western Pacific; *AMR* Americas; *EUR* Europe). Inuit overweight and obesity prevalence is among the highest in the world for both males and females (Reprinted from Young et al. (2007). With permission)

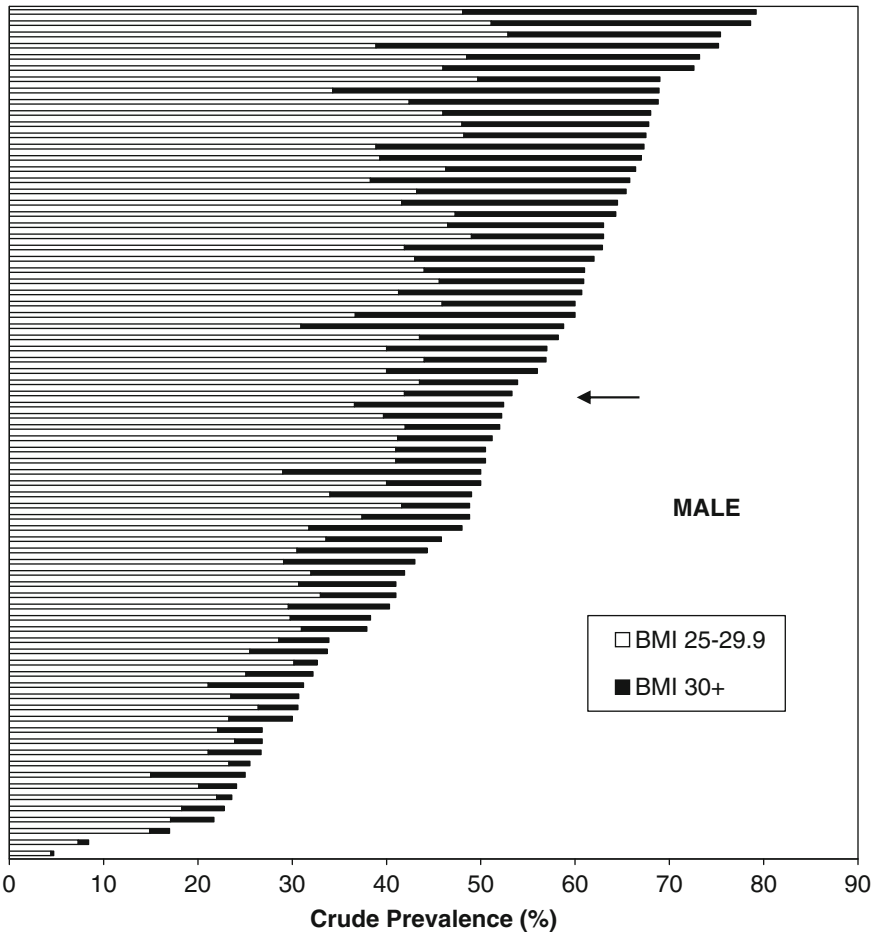

Fig. 158.2 Crude prevalence of obesity and overweight among Inuit men (*arrow*) in global perspective. This figure presents country data for males from the International Obesity Task Force database [www.iotf.org/media]; each *bar* represents a country; *arrow* indicates position of the Inuit (Based on Young 2007)

In a study of Inuit communities in the Bering Straits region of Alaska, Risica et al. (2000) reported that 36% of men and 28% of women were overweight, and 16% of men and 33% of women were obese. More recently, Mohatt et al. (2007) studied members of ten Inuit communities in the Yukon-Kuskokwim delta of Alaska: 32.5% of people ages 18+ years were overweight and 32% were obese ($n = 753$). Similarly, high prevalence of obesity was found among women ages 40–64 years ($n = 1334$) (Hiratsuka et al. 2007). Thirty-two percent of women were overweight and 47% of women were obese; 11% of women had BMI in the class III range. Jørgensen et al. (2003) report significantly higher indices of abdominal obesity (mean BMI, mean waist-to-hip ratio, and mean waist circumference) in Greenland Inuit men and women of ages 30–60 years ($n = 1118$) compared with a Danish reference (Figs 158.2 and 158.3).

An important observation is a pronounced difference in obesity prevalence between adult men and women. Many studies report disproportionately high prevalence of obesity (measured by BMI) and centripetal fat patterning (measured by waist circumference and waist–hip ratio) among Inuit women. Analysis of pooled anthropometric data (BMI and waist circumference) collected between 1990 and 2001 from Canada, Greenland, and Alaska ($n = 2545$) yielded obesity prevalence of 26%

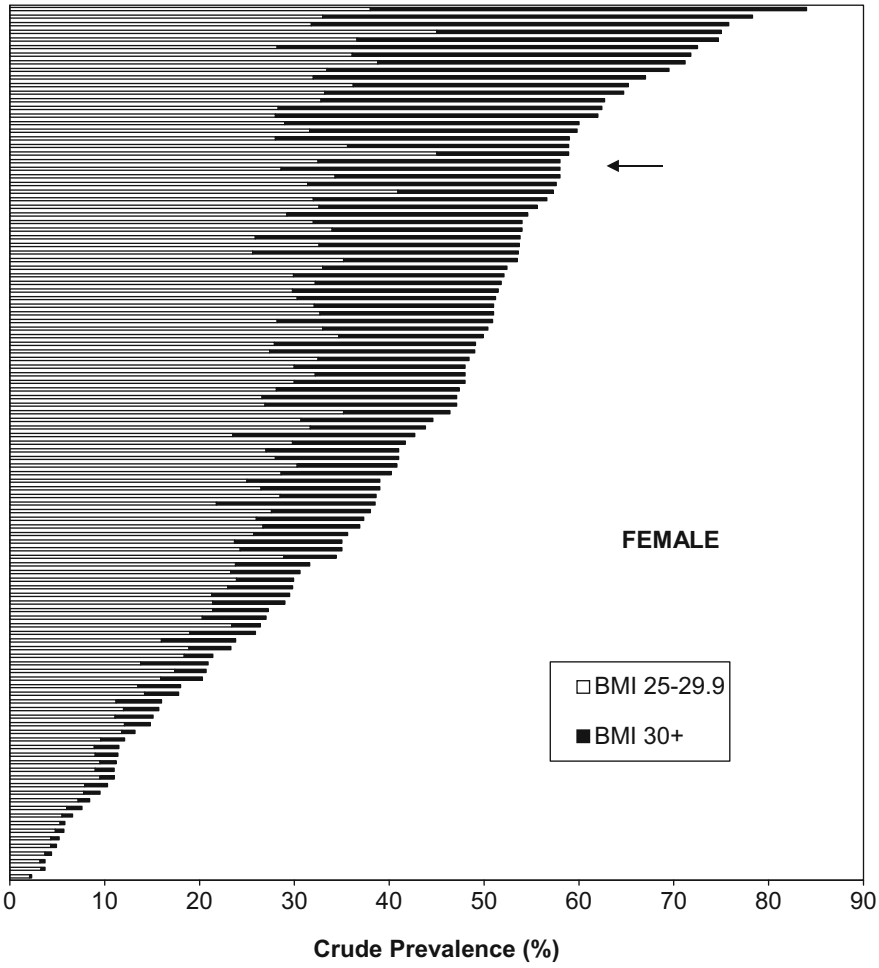

Fig. 158.3 Crude prevalence of obesity and overweight among Inuit women (*arrow*) in global perspective. This figure presents country data for females from the International Obesity Task Force database [www.iotf.org/media]; each *bar* represents a country; *arrow* indicates position of the Inuit (Based on Young 2007)

among Inuit women compared with16% among Inuit men (Young et al 2007). While there were no gender differences in overall overweight and obesity classification in the Nunavik Inuit Health Survey, the proportion of individuals with severe obesity (WHO classes II and III) was significantly greater in women (Nolin et al. 2007). The pattern of higher obesity prevalence in women appears to be somewhat less pronounced in the Greenland data. For example, there were no significant gender differences in the prevalence of central adiposity (defined by waist–hip ratio) among the Greenland Inuit measured during 1999–2002 (Jørgensen et al. 2006). Bjerregaard et al. (2002) report a gender difference in the opposite direction: adult Greenland Inuit men had significantly higher waist circumference than women. What is consistent in both Greenlandic and North American populations is the persistent increase in obesity prevalence among both men and women in recent decades.

It is increasingly recognized that many adult health problems have their origin in childhood, and socioeconomic factors operating during childhood have been shown to be associated with adult obesity among Greenlanders. For men, obesity during adulthood was also associated with their mother's place of birth, whereas for women, adult obesity was associated with alcohol problems at home during their childhood (Bjerregaard et al. 2009).

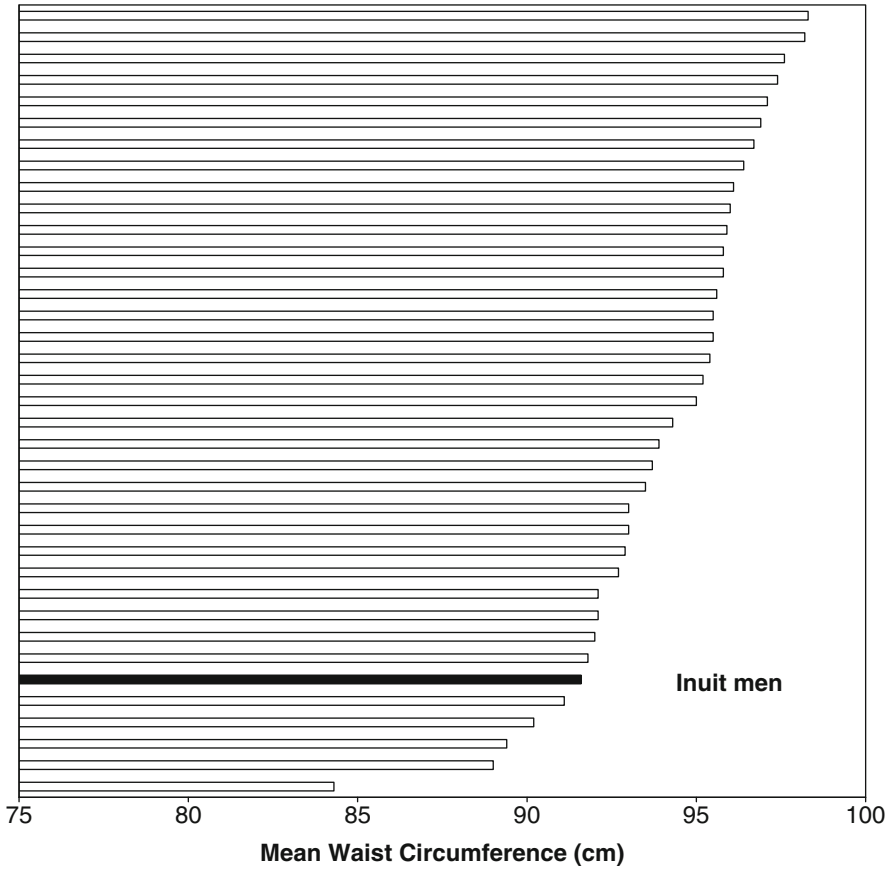

Fig. 158.4 Ranking of age-standardized mean waist circumference of Inuit men ages 35–64 years among MONICA survey populations. This figure presents waist circumference data on males from the WHO MONICA surveys conducted in the 1990s to monitor trends in cardiovascular diseases and relate trends to changes in risk factors and treatment in the population (Available from www.ktl.fi/publications/monica/surveydb/bmi/table635_summary.htm; Based on Young 2007)

The rise in adiposity among circumpolar populations is also evident among children (Table 158.3). Schnohr et al. (2008) report that the prevalence of overweight (using International Obesity Task Force [IOTF] cutoffs) among Greenland Inuit children of ages 2–15 years rose from 13% to 23% in boys and from 13% to 24% in girls between 1973 and 1992. Data on the 5–7-year age group show that the prevalence of overweight has risen from 7% in 1980 to 17% in 2004 (Schnohr et al. 2005). Obesity prevalence for the same age group has risen from 1% to 5% over the same period. Obesity prevalence among Greenlandic children is now among the highest in the world (Schnohr et al. 2008).

Greenlandic data also indicate that the age of onset of obesity is decreasing. Among cohorts of children measured between 1973 and 1992, the age at which 30% of children were overweight decreased from 9.7 to 7.3 years in boys and from 14.7 to 4.6 years in girls (Schnohr et al. 2008). There is evidence that this profile of decreasing age of overweight in onset is part of a constellation of biological processes (including earlier skeletal maturity, earlier adolescent growth spurt, and decreasing age at menarche) accompanying rapid acculturation to a Western lifestyle (Zammit et al. 1994; Becker-Christensen 2003).

Inuit child growth has followed a similar pattern in North America, with rates of overweight increasing dramatically in recent decades. The most recent data on child growth come from the Nunavut Inuit Health Survey, which measured 388 children of ages 3–5 years (Galloway et al. 2010).

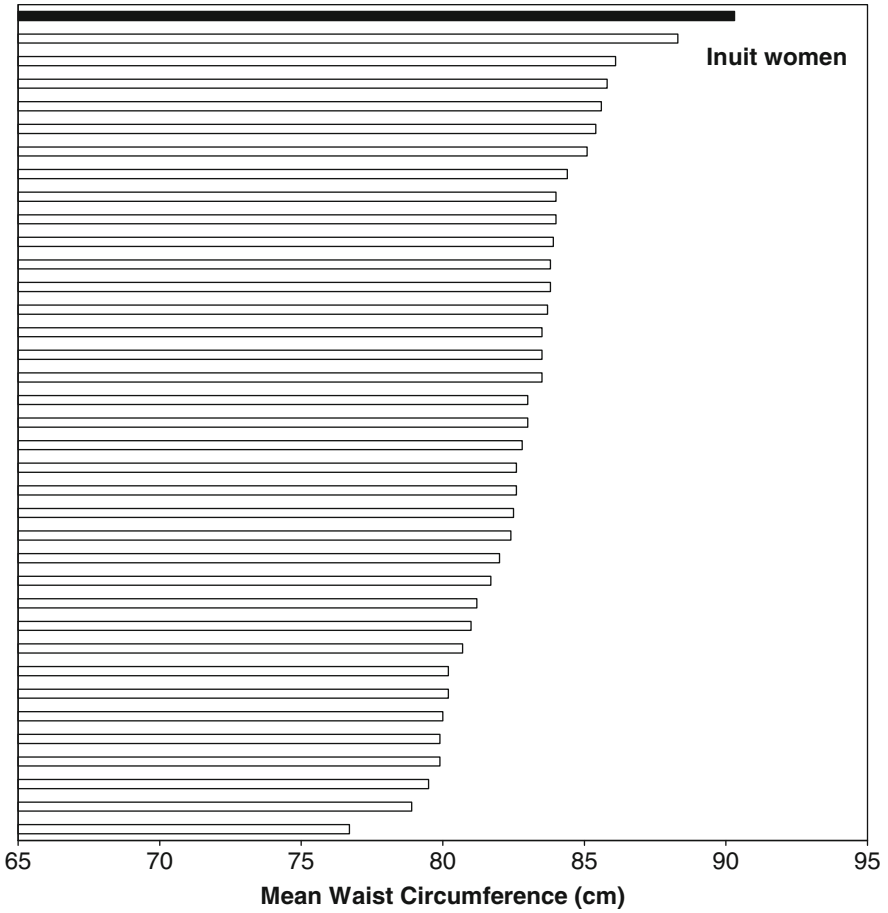

Fig. 158.5 Ranking of age-standardized mean waist circumference of Inuit women of ages 35–64 years among MONICA survey populations. This figure presents waist circumference data on females from the WHO MONICA surveys conducted in the 1990s to monitor trends in cardiovascular diseases and relate trends to changes in risk factors and treatment in the population (Available from www.ktl.fi/publications/monica/surveydb/bmi/table635_summary.htm; Based on Young 2007)

The prevalence of overweight was 27% in this preschool age group (using CDC cutoffs). The prevalence of obesity was 51%, with a gender difference indicating significantly greater obesity prevalence among boys (57%) compared with girls (45%). The large proportion of children in the obese category raises significant concern over future health and metabolic disease risk in children.

158.7 Metabolic Changes Accompanying Obesity

In North American and European populations, the rise in obesity has been accompanied by a concomitant rise in metabolic indicators, such as hypertension, glucose intolerance, and dyslipidemia. While this pattern generally holds true also for the Inuit, there is evidence that the relationship between abdominal obesity and its attendant metabolic changes is different (in the Inuit). Jørgensen et al. (2003) found that at each level of obesity, the Greenlandic Inuit had lower blood pressure, lower

Table 158.3 Selected studies of growth, overweight, and obesity in child Inuit published 1990 onward

Author(s)	Year(s)	Region	n	Ages	% Overweight		% Obese		Reference
Schnohr et al. (2005)	1970-2004	Greenland	3593	5–7					IOTF
	1990-94		363	5–7	13.1		4.2		
	1995-99		776	5–7	17.5		3.6		
	2000-2004		756	5–7	16.5		5.2		
Schnohr et al. (2008)	1973-92	Greenland	3094	2–15	Boys	Girls	Boys	Girls	IOTF
	1973-92		678	2–15	13.3	13.0			
			715	2–15	16.4	18.9			
			576	2–15	18.5	24.6			
			1125	2–15	22.6	24.1			
Galloway et al. (2010)	2007-8	Canada	376	3–5	20.9	32.7	57.1	45.2	WHO

This table lists recent significant contributions to the literature on Inuit child overweight and obesity prevalence

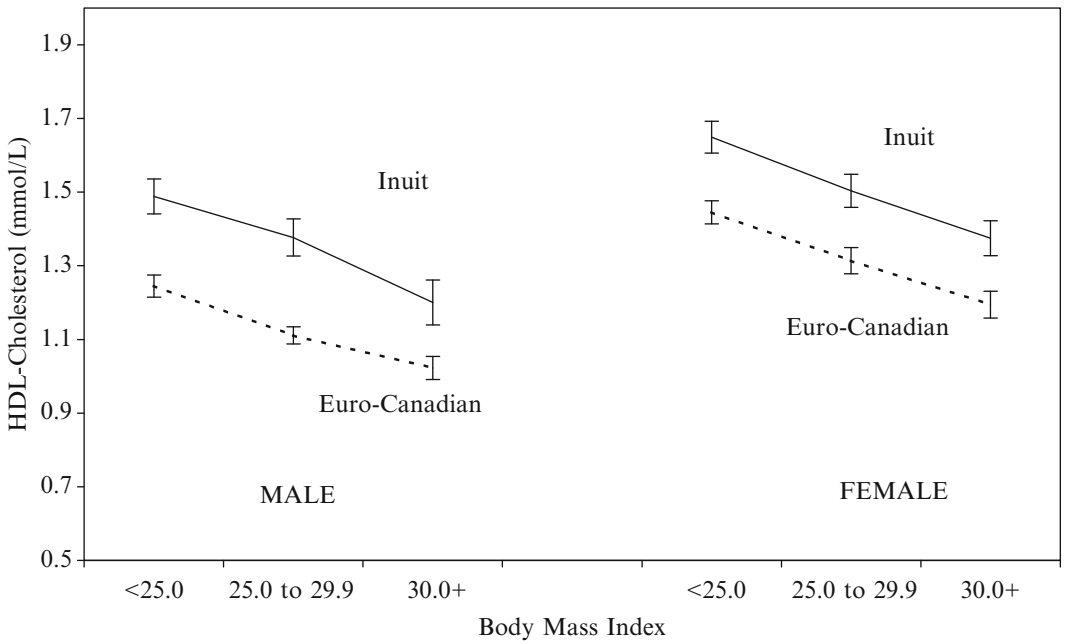

Fig. 158.6 Comparison of mean HDL-cholesterol values by categories of body mass index, sex, and ethnic category. This figure shows higher HDL-cholesterol levels at selected BMI ranges in Inuit compared to Euro-Canadian populations (Based on Young et al. 2007)

levels of 2-h glucose, insulin, and triglyceride, and higher levels of HDL cholesterol than the Danish subjects. This pattern is observed in other Inuit populations in Alaska and Canada (Young et al. 2007) (Fig. 158.6).

There is a dearth of body composition studies among the Inuit. Without imaging studies (e.g., dual X-ray absorptiometry, computed tomography, ultrasonography, and magnetic resonance imaging), it is not known whether the central obesity represented by high waist circumference is predominantly

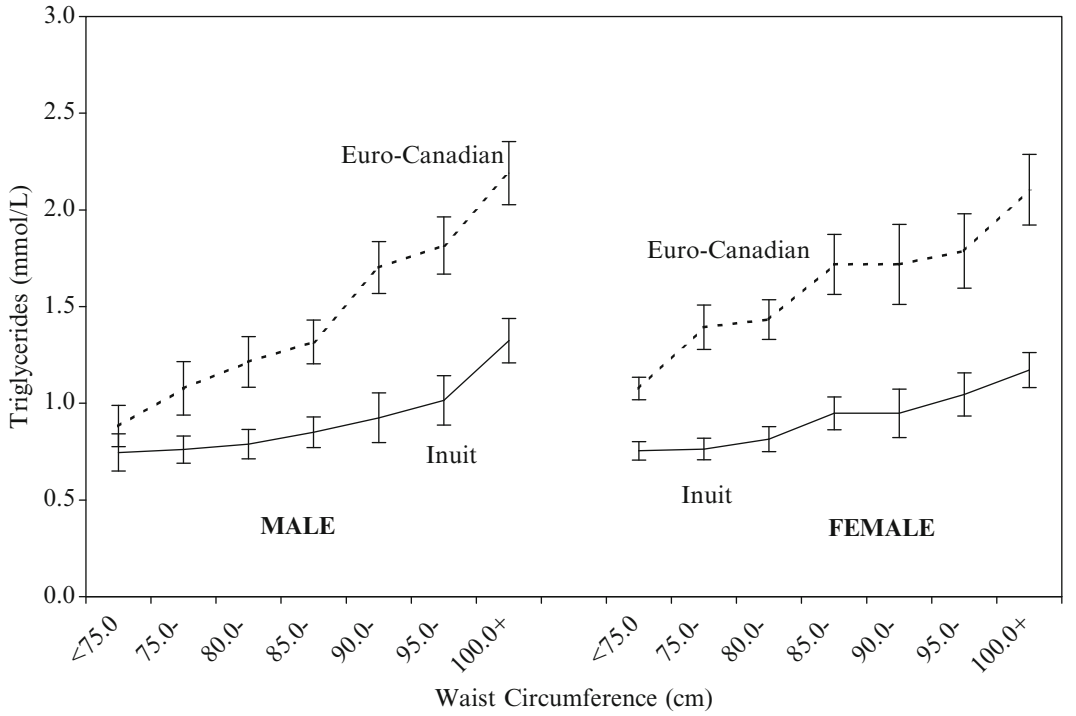

Fig. 158.7 Comparison of mean triglyceride values by categories of waist circumference, sex, and ethnic category. This figure shows higher triglyceride levels at selected categories of waist circumference in the Inuit compared to Euro-Canadian populations (Based on Young et al. 2007)

intra-abdominal or subcutaneous. Subcutaneous adipose tissue is poorly vascularized and therefore relatively metabolically inert, lacking the ability to store extra energy derived from dietary triglycerides. The accumulation of intra-abdominal or visceral fat is a marker of considerable metabolic risk (Fig. 158.7).

Attempts have been made to more accurately describe fat- and lean-mass distribution in the Inuit. Deuterium oxide dilution (Shephard et al. 1973) and underwater weighing (Rode and Shephard 1994) studies have been performed on samples of Canadian Inuit men. These studies report fat-mass estimates much higher than would be predicted from skinfold thicknesses in the same subjects. However, their interpretation is hampered by small sample sizes and a reliance on formulas developed in European populations. As a result, we know relatively little about fat distribution at various levels of BMI or waist circumference in the Inuit. Interpretation of the metabolic disease risk associated with various levels of adiposity is also difficult, prompting researchers to call for Inuit-specific cutoffs for central obesity measures associated with diabetes and cardiovascular disease outcomes (Jørgensen et al 2003; Young et al. 2007; Chateau-Degat et al. 2008). There is ample evidence that Inuit mortality from cardiovascular disease is at least as high as in non-Inuit populations and that Inuit mortality from cerebrovascular disease is significantly higher (Bjerregaard et al. 2003) (Table 158.4).

Table 158.4 Challenges to application of anthropometric reference standards to the Inuit

1. Studies done in the nineteenth and twentieth centuries established that the Inuit were significantly shorter in stature than US and Greenland populations
2. Much of the difference in stature was attributable to higher sitting height ratio in the Inuit. This means that leg length was much shorter in Inuit populations
3. Shorter leg length in the Inuit results in relatively greater body mass per unit of height. Therefore, anthropometric indices based on mass, such as BMI, may give falsely high estimates of adiposity in Inuit
4. While secular trend in height may have diminished differences in sitting height ratio between Inuit and non-Inuit populations, there is little data available on sitting height or fat and lean mass ratios among the contemporary Inuit
5. US, WHO, and IOTF reference standards for BMI in adults and children must be interpreted with caution in the Inuit

This table summarizes the challenges to interpreting anthropometric reference data in circumpolar Inuit, given differences in growth and body proportion, secular trend in height, and a lack of data on body composition

158.8 Methodological and Practical Issues

There are significant barriers to conducting anthropometric research in the circumpolar north, not the least of which is the severe climate. Apart from a few towns which serve as administrative capitals (e.g., Nuuk, Greenland, population 15,000 and Iqaluit, Canada, population 7,000), Inuit communities are widely dispersed throughout the far north. Travel costs are high and travel is dependent on seasonal access via air and sea. Small populations necessitate travel across a broad geographic area in order to compile data on adequate sample sizes. Jurisdictional issues are also relevant, as researchers must negotiate the various national, state, provincial, and territorial bodies that provide services in the north.

Although not unique to the Inuit, the use of 'racial' or 'ethnic' identity is not entirely neutral, as these are socially constructed categories. The methodological approach used to define an ethnic category needs to be in direct proportion to its explanatory power as a variable. Research reports should state clearly the reason for including ethnic categories within the research and how ethnic group classifications were made. For example, in their comparison of metabolic risk among resident Greenlanders and migrants to Denmark, Jørgensen et al. (2006) define 'Inuit' as persons with at least one Inuit parent. In this case, language and migration to Denmark are used as markers of the degree of Westernization, since previous studies have observed increasing metabolic disease risk among acculturated Inuit. The definition of Inuit employed here acknowledges the multifactorial nature of the processes underlying metabolic disease, which is influenced by economic and sociocultural, as well as biologic and genetic factors.

As in many populations where past studies have demonstrated patterns of growth unlike those in Europe and North America, the application of international reference values to Inuit contexts is a matter much discussed in the literature. Twentieth-century studies documenting robust muscularity and high sitting height ratios among the Inuit have led to calls for Inuit-specific growth reference and Inuit-specific norms for BMI, especially from among clinicians.

Secular trend in height has eliminated the need for Inuit-specific stature reference in children. However, recent findings of high obesity prevalence among Inuit children, and observed differences between the metabolic correlates of adiposity among Inuit adults, have led to speculation on whether international standards are appropriate in this context.

The Canadian Paediatric Society (CPS) recommends that the CDC-derived growth charts be used for all Canadian children, including First Nations and Inuit (CPS 2004). Greenland researchers have consistently used Danish or IOTF references, noting that it is overall trends in growth parameters that provide information useful for child health policy and programming (Schnohr et al. 2005, 2008).

The current state of knowledge about adult Inuit body composition is insufficient to the task of creating Inuit-specific cutoffs for obesity and metabolic disease risk. The use of WHO cutoffs facilitates

prevalence estimates and evaluation of temporal trends in Inuit populations. Until more is known about the distribution of fat and lean mass in the Inuit, and the degree of metabolic aberration associated with varying levels of adiposity, international references appear to be the most appropriate means of assessing growth and adiposity in Inuit adults and children.

Finally, there is a lack of methodological standardization that hampers comparisons of growth, body size, and body composition in the Inuit. The inclusion of sitting height in both child and adult studies would permit analysis of secular trend in this area (Charbonneau-Roberts et al. 2005). Standardized protocols incorporating hold-out samples and repeat measures would permit reporting of inter- and intra-observer error and technical error of measurement, features which are, unfortunately, rarely documented in anthropometric studies of the Inuit.

158.9 Applications to Other Areas of Health and Disease

Anthropometric techniques offer a relatively inexpensive, non-technical means by which to assess the health and nutrition status of populations, especially those such as the Inuit, who are undergoing a health transition as a result of rapid social and economic change. Methodologically rigorous anthropometric studies offer a way to:

1. Screen populations for health risks: A wide range of disease processes can be identified through intermittent monitoring of anthropometric status. The geographic isolation and relative dearth of health services in circumpolar regions make the monitoring of health status an ongoing priority for Inuit health policy and service providers.
2. Monitor infant and child growth: Early detection of diseases of infancy and early childhood can be achieved through regular monitoring of growth and nutrition status. In particular, infectious diseases and nutritional impairment are readily identified through regular growth assessment. The young age structure of Inuit populations makes child-growth monitoring a key priority for healthcare providers.
3. Directly monitor obesity prevalence: Obesity has been identified as a key health concern in Inuit populations. Monitoring of overweight and obesity prevalence permits identification of at-risk communities and direction of healthcare resources toward vulnerable populations.
4. Indirectly monitor metabolic changes which accompany obesity: Obesity is a valuable tool for identifying individuals at risk for other changes, such as elevations in plasma glucose, insulin, and atherogenic lipids. While the unique metabolic changes accompanying obesity in the Inuit necessitate caution in interpreting anthropometric indicators in this population, current research is exploring the association between obesity levels and cardiovascular disease risk.

158.10 Conclusion

Human biology in the circumpolar north requires a significant expenditure of resources. Given the high cost of Arctic travel and the logistic challenges of gathering extensive data in geographically isolated communities, anthropometry has served as an inexpensive and informative tool to assess the state of Inuit health and nutrition. Historical studies provided the foundation for the observations of secular trend in stature and BMI which have accompanied the relatively swift and recent changes in

Inuit lifestyle. Concurrent trends toward increasing risk of diabetes and cardiovascular disease have been illuminated by studies describing unique relationships between adiposity and metabolic indicators in Inuit adults. Future studies offer opportunities for monitoring health and nutrition interventions aimed at averting and addressing the major shifts in population health occurring in circumpolar populations.

Summary Points

- The 165,000 Inuit living in four circumpolar countries have undergone a substantial health transition, which can be monitored through anthropometry.
- Historical and ethnographic records indicate that Inuit adults had shorter stature and higher sitting height than European populations, but secular changes in the past half century have reduced or eliminated most of such differences.
- Obesity among the Inuit based on international criteria had been uncommon up until the late 1970s and early 1980s.
- Recent surveys among Inuit children in some regions revealed an alarming prevalence of obesity at 57% for boys and 45% for girls.
- Studies on the metabolic correlates of obesity among adult Inuit tend to show a lower degree of blood pressure, plasma glucose, insulin, and atherogenic lipids compared to Europeans at the same levels of BMI.

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Chapter 159
Anthropometric Measures of Birth and Stature: Perspectives on Russian Mothers and Newborns

Boris N. Mironov

Abstract Using data from St. Petersburg hospitals on the length and weight of 64,087 infants born between 1980 and 2005 and the physical stature and weight of 15,819 mothers born between 1929 and 1989, we find that women's living standards, as measured by their height, improved steadily from the end of World War II up to 1990, which is when women born in 1972 reached adulthood. For mother cohorts born after 1972 and reaching adulthood in the early and mid-1990s, heights declined. Evidence on both the length and weight of babies corroborates this pattern as there is a noticeable connection between the height and weight of newborns and that of their mothers, on the one hand, and social and demographic indicators, on the other. In our data, we see their values trace a "U" shaped curve with troughs near the mid-1990s. Thus, the anthropometric evidence concerning newborns as well as mothers points to the impact of strains on living standards that were prevalent during the period of economic restructuring of the 1990s. This is a general result that confirms a recurring pattern: periods of economic transitions are almost always accompanied by biological stress.

In the Soviet and post-Soviet periods, newborns in Moscow and St. Petersburg were definitely inferior to European and white American newborns in weight and, most likely, in stature as well, as there is a close relationship between stature and weight.

159.1 Introduction

This paper estimates trends in the health and the biological standard of living of women and their newborn babies in St. Petersburg between 1980 and 2005. The data consist of the height and weight of mothers and their newborns, a robust indicator of living conditions (Ward 1993, p. 12). Since 1976, the World Health Organization has used average birth weight of babies as a standard indicator of women's quality of life (Ward 1993, p. 5). Obviously, the anthropometric indicators of the newborn also testify to the level of their physical development; less obviously, their length at birth also testifies to their prenatal conditions. Sensitive to the mother's living conditions throughout her pregnancy,

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_159,

Table 159.1 Key features of Russia

1.	In 1992, Russia's population entered a period of negative growth. This was for the first time in the peacetime history of Russia
2.	As in many Western industrialized nations, Russia's fertility rate has fallen over the course of the twentieth century. In 1920, the average Russian woman was expected to give birth to about 7.5 children in her lifetime; in 2007, that number had fallen to 1.4
3.	In many Western countries, the peak childbearing age for women has increased and now falls between 25 and 29; by contrast, the peak age in Russia has become younger, occurring between ages 20–24
4.	This tendency toward fertility at younger ages is reflected in marriage patterns. Between 1960 and 2007, the average age at marriage of women in Russia fell by 2.7 years, from 26.2 to 23.5
5.	The decline in fertility is contributing to a rapid aging of the Russian population. Between 1960 and 2008, the proportion of males aged 60 and over and females aged 55 and over doubled and reached 21%
6.	The increased death rate, especially dramatic among working-age men, is an important indicator of demographic crisis in Russia
7.	Life expectancy in Russia has dropped. In 2007, Russia had the lowest life expectancy for males in a developed country (61.4 years) and the largest disparity in the world between male and female life expectancy (12.6 years)
8.	The increase in deaths from preventable causes points to problems in Russia's healthcare system

This table lists the key facts of current Russian demographic trends

the size of a fetus will also be affected to some degree by the mother's general living standards prior to conception. Despite gender inequality, women's living conditions undoubtedly reflect larger forces affecting the entire society.

The paper draws on the recumbent length and birth weight of 64,087 babies born in St. Petersburg between 1980 and 2005. In addition, we have data on the physical stature and weight of 15,819 mothers born between 1929 and 1989. The data embrace information from clinics on women of all nationalities, whose delivery lasted a normal length of time and ended in the birth of a singleton. The information was taken mainly from birth records and from archived annual accounts of maternity wards in the Maternity Hospital's archives in St. Petersburg. Nearly 74% of the women were from St. Petersburg, 26% were from the surrounding region (*oblast'*), and less than 1% from other Russian regions.

During the period under study, the mothers' average age increased from 25.3 to 26.8 years. Their average educational attainment was 11.8 years. The social profile of the women in the sample underwent major changes, as indicated in Table 159.1. The share of skilled blue-collar workers decreased from 37.3% to 13.3%, and the share of professionals decreased from 20.8% to 9.3%, while the share of housewives increased dramatically from 4.2% to 51.1%. Although we have no information on the profession and education of housewives, they probably belonged to the well-to-do stratum of the population: as it will be shown further, their biological potential was above average and this testifies to the fact that, at least by birth and by marriage, they belong to the well-to-do stratum of the population – to the socioeconomic class of professionals, top executives, and businessmen. From 91.2% to 95.4% of the women were ethnic Russians, and the rest were divided among 57 other ethnic groups. Thus, our sample consists mainly of information on relatively young, recently married women of ethnic Russian descent, who, by their educational level, material position, and social status, belonged to the middle stratum of St. Petersburg's population (the general characteristics of the sample: age structure, education, social profile, family status, and ethnicity are presented in the Tables 159.1–159.6 of Statistical Supplement).

Histograms, means, medians and modes, coefficients of asymmetry, excess kurtosis, and other characteristics of the distribution of newborns and their mothers by stature and weight show that the sampling data approximate a normal distribution.

Table 159.2 Weight of women by age (Sources: The archives of St. Petersburg hospitals, 1980–2005)

	All mothers				Mother aged 25 and under			
Year of birth	Average age	Height, cm	Weight after delivery, kg	Body mass index	Average age	Height, cm	Weight after delivery, kg	Body mass index
1956–60	30.7	162.7	72.3	27.3	23.2	162.7	70.6	26.7
1961–65	30.0	163.5	71.5	26.7	21.9	163.3	70.2	26.3
1966–70	28.3	164.0	71.0	26.4	22.5	163.9	70.3	26.2
1971–75	25.0	164.5	69.6	25.7	22.5	164.4	69.2	25.6
1976–80	22.3	164.1	68.0	25.3	21.6	164.1	68.0	25.3
1981–85	20.0	164.4	67.2	24.9	20.0	164.4	67.2	24.9

Table 159.3 The consumption of main foods in St. Petersburg, 1940–2002 (kg per capita, annually) (Source: Eliseeva and Gribov (2003), vol. 3, pp. 29–30)

Product	1940	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000	2002
Meat and meat produce	43	62	73	70	80	86	88	89	93	57	42	50
Milk and dairy produce	223	367	433	413	429	427	440	438	451	228	216	288
Eggs	98	112	200	242	276	265	282	286	280	222	265	310
Fish and seafood	12	15	19	20	20	20	21	21	20	8	12	14
Sugar	19	28	45	42	41	41	42	41	47	29	33	37
Oil			7.1	8.3	7.1	7.0	8.5	8.7	9.0	8.3	11.2	14.0
Potatoes	79	92	89	94	88	85	87	76	60	61	70	72
Vegetables and melons	41	72	74	82	81	96	102	101	77	52	51	51
Fruits	4	21	35									
Bread	151	134	123	112	100	94	95	92	108	105	105	104

Table 159.4 Women's and their babies' anthropometry height by socio-demographic characteristics, St. Petersburg 1980–2005 (Sources: The archives of St. Petersburg hospitals, 1980–2005)

		Mothers			Newborns	
	N	Height, cm	Weight after delivery, kg	Body Mass index	Height, cm	Weight, g
Marital status						
Single	126	163.7	65.6	24.49	51.1	3,371
Unlawful matrimony	10,173	164.0	67.8	25.22	51.0	3,379
Lawful matrimony	37,572	163.7	68.2	25.45	51.3	3,438
Education						
Incomplete specialized secondary	237	162.2	69.8	26.53	51.1	3,482
Incomplete secondary	2,465	163.2	69.0	25.90	51.3	3,462
Secondary	2,026	163.5	67.5	25.24	51.2	3,425
Specialized secondary	2,341	163.6	68.3	25.49	51.1	3,429
University	2,849	164.5	68.0	25.15	51.2	3,456
Occupational category						
Unskilled blue-collar workers	194	162.0	70.0	26.67	51.1	3,497
Skilled blue-collar workers	3,243	163.3	68.4	25.65	51.2	3,446
White-collar workers	3,296	163.5	68.4	25.57	51.2	3,437
Professionals with university education	2,097	164.3	68.8	25.46	51.3	3,467
Dependents	3,006	164.1	66.4	24.67	51.1	3,400
Ethnicity						
Russian	9,167	163.8	68.2	25.40	51.2	3,438
Non-Russian	676	162.5	67.2	25.43	51.1	3,413

Table 159.5 The height and weight of women and their newborns by profession, St. Petersburg 1980–2005 (Sources: The archives of St. Petersburg hospitals, 1980–2005)

		Mothers					Newborns	
Profession	N	Age	Order of delivery	Height, cm	Weight after delivery, kg	Body mass index	Height, cm	Weight, g
Junior nurse	40	25.4	1.75	161.3	67.8	26.04	50.8	3,453
Cleaner	58	27.8	2.31	162.2	68.4	26.01	51.0	3,468
Nanny	56	24.0	1.89	162.4	67.8	25.72	50.9	3,382
Caretaker	94	27.9	2.02	162.5	70.7	26.78	51.2	3,502
Cashier	96	25.6	1.56	162.6	68.3	25.83	50.9	3,326
Teacher with secondary education	218	28.3	1.98	162.7	68.9	26.03	51.2	3,436
Cook, confectioner	250	24.5	1.55	163.1	69.4	26.08	51.2	3,479
Salesman	415	24.5	1.36	163.0	68.6	25.80	51.2	3,433
Junior scientific worker	54	30.2	1.62	163.2	66.9	25.15	51.0	3,440
Hospital nurse	417	25.0	1.42	163.4	68.6	25.69	51.2	3,420
Computer operator	270	25.4	1.48	163.4	68.0	25.47	51.2	3,446
Driver, engine driver	46	25.4	1.52	163.7	70.7	26.40	52.0	3,666
Accountant	346	26.6	1.48	163.7	69.5	25.93	51.2	3,436
Secretary	137	25.2	1.38	163.7	68.1	25.40	51.3	3,506
Engineer	1193	28.4	1.53	163.7	68.1	25.42	51.2	3,436
Teacher with university education	360	26.3	1.43	163.9	68.5	25.5	51.3	3,483
Housewife	2285	24.5	1.57	164.2	66.7	24.75	51.0	3,380
Tutor	188	21.0	1.25	164.3	66.4	24.61	50.8	3,361
University student	751	20.9	1.05	164.3	68.4	25.34	51.1	3,403
Doctor	169	29.1	1.49	164.3	70.2	26.03	51.4	3,521

Table 159.6 Main characteristics of mothers and newborns in St. Petersburg in 1980–2005 by maternal ethnicity (Sources: The archives of St. Petersburg hospitals, 1980–2005)

		Mothers					Newborns	
Ethnicity	N	Age	Order of delivery	Height, cm	Weight after delivery, kg	Body mass index	Height, cm	Weight, g
Jewish	29	28.0	1.41	160.4	67.7	26.28	49.9	3,136
Armenian	22	25.0	1.68	160.9	68.7	26.54	50.6	3,361
Azerbaijanian	50	25.4	1.71	161.9	66.3	25.26	50.4	3,275
Tatar	79	26.8	1.44	162.1	64.3	24.47	51.2	3,439
Ukrainian	156	25.4	1.50	163.6	70.1	26.19	51.6	3,467
Russian	9167	25.4	1.51	163.7	68.0	25.37	51.2	3,430
Byelorussian	102	25.1	1.41	164.1	67.2	24.96	51.4	3,447
Georgian	24	25.8	1.61	164.2	72.9	27.04	51.3	3,426
Others	207	25.5	1.66	162.1	65.4	24.57	51	3,405

159.2 Trends in the Biological Status of Women

There is a close relationship between the recumbent length and the weight of the newborn (correlation coefficient is 0.879). On the eve of perestroika, in 1982–1985, the average length of singleton, full-term (born 9 months after conception) newborns (both boys and girls) was 51.4 cm and weight 3,476 g (Fig. 159.1).

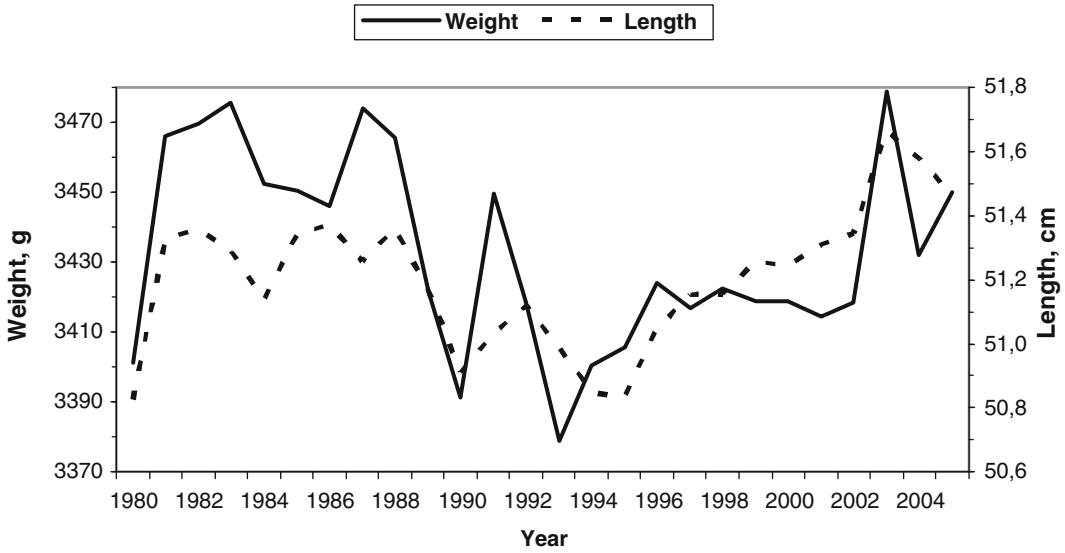

Fig. 159.1 The weight and stature of newborns in St. Petersburg, 1980–2005

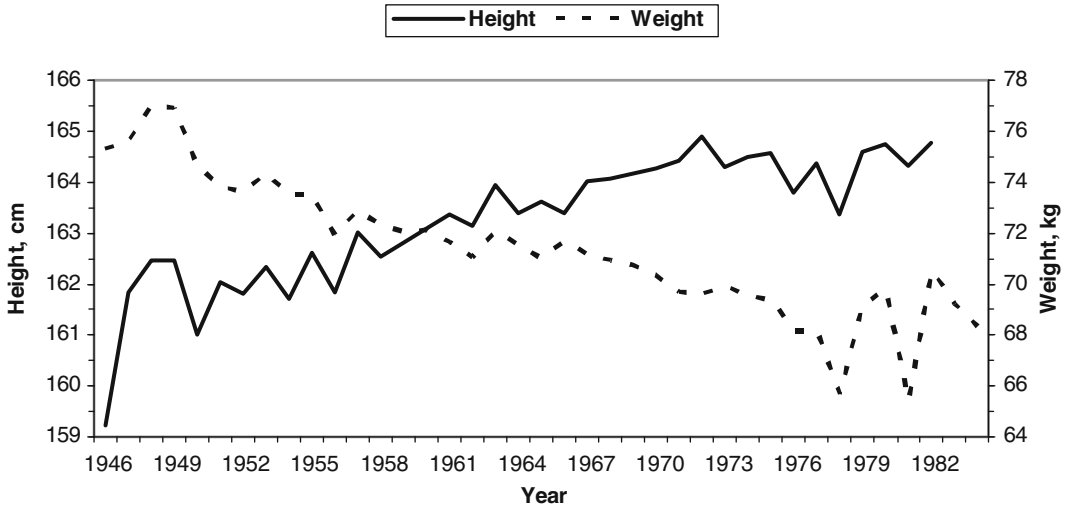

Fig. 159.2 Height and Weight of Women in St. Petersburg, 1946–1985

The following decade, which included both perestroika and the last years of Communism, saw a considerable decrease in both anthropometric attributes: the length of newborns reached a minimum of 50.8 cm in 1995 and weight 3,379 g in 1993. Then, an upward trend began. However, the increase in weight stopped in 1996–2001 and resumed only in 2002. By the end of the period under consideration, both length and weight were back where they started in the early 1980s in the pre-perestroika era: about 51.4 cm and 3,450 g.

For mothers by birth cohort, we find that, from the end of World War II to the early 1970s, their height increased by nearly 6 cm and then the trend changed (Fig. 159.2). The stature of women born in 1976–1978 decreased by about 1 cm and stabilized thereafter at about 164.5. Due to the lack of

information for those born after 1985, it is hard to say whether the trend actually continues or increases in connection with improved living conditions after the turn of the twenty-first century. To summarize, the data are robust in showing the decrease of the St Petersburg women's living standards in the 1990s.

Although there was a considerable reduction in average weight – by nearly 12 kg – this was not necessarily itself a measure of decrease in living standards because the increase in mothers' height of those born before 1976–1980 was more likely linked with the lower average age of this group. The average age at childbirth of women born in 1946–1950 was 35 years and, of those born in the 1980s, 17–20 years. Height naturally also had to decrease, since empirically, with aging, there is a gradual increase in weight. In order to test this conclusion, we selected women aged 25 or less and compared their average weight with that of all women (we can do this for 1956–1985) (Table 159.2).

The comparison shows that the age of these women did not affect their height (of course, since upon reaching 18–20 years of age, height does not increase) but did affect their weight: the younger women of the same year of birth weighed less. However, the lower weight cannot be fully attributed to a lesser age: the weight of women of approximately the same age also decreased from cohort to cohort. Hence, it follows that other factors played a role – above all, diet. Between the post-war period and 1970, the quality of nutrition in St. Petersburg improved markedly and then remained stable between 1970 and 1990 (Table 159.3).

Consumption of food containing high amounts of protein increased: meat – by 2.2 times, milk – by 2, eggs – by 2.9, fish – by 1.7, and vegetables – by 1.9 times. By contrast, consumption of food having less protein decreased: bread – by 28% and potatoes – by 24%. It should be emphasized that overall nutrition improved not only in a quantitative sense but also in terms of quality. At the same time, women expended less energy, since the role of manual labor diminished. Consequently, we conclude that the decrease in women's weight in 1941–1985 had nothing to do with the decrease in their living standards. We assume that the decrease in weight was most likely affected both by fashion – the slim female figure has firmly been established over the last 25 years – and by women's reduction of calories to make delivery easier, because a high-calorie diet increases the size of the fetus, potentially causing a difficult birth. Due to the systematic decrease in women's weight at a rate faster than the increase in height, women's body mass index declined from 28.3 to 24. However, this decline was within the range of normal dietary practice.

Women's living standards depended on many socio-demographic factors. With the available data, we can assess the effect of family status, education, socio-professional status, and ethnicity on their living standards (Table 159.4).

A relationship between socio-professional variables and living standards is more visible when communities are grouped by profession (Table 159.5).

Ethnicity affects anthropometrical indicators of women and their infants. On average, Russian mothers are 1.3 cm taller than their non-Russian counterparts (163.8 against 162.5), their weight is 1 kg more (68.2 against 67.2), and their infants are 0.1 cm taller (51.2 against 51.1) and weigh 25 g more (3,438 against 3,413). The body mass index of mothers is in the range of 24.47–27.04 (Table 159.6).

We explain women's living standards as the result of the interplay of various factors that were changing during the period under study (Table 159.7).

These data suggest three main trends:

1. There was a noticeable connection between the height and weight of newborns and that of their mothers, on the one hand, and social and demographic indicators, on the other;
2. Social and demographic determinants were changing during the period under review; and
3. Anthropometrical indicators were also changing during the same period, sometimes for the worse, sometimes for the better.

Table 159.7 The trend of the main characteristics of mothers and newborns in St. Petersburg, 1980–2005 (Sources: The archives of St. Petersburg hospitals, 1980–2005)

	Mothers								Newborns	
					Weight, kg					
Year	Age	Education	Russian, percent	Order of delivery	Before delivery	After delivery	Height, cm	Body mass index	Weight, g	Height, cm
1980	24.6	11.7		1.39	70.5	67.1	162.0	25.6	3,401	50.8
1981	25.4	11.7		1.45	71.8	68.3	162.4	25.9	3,466	51.3
1982	25.2	11.5		1.45	71.0	67.5	162.6	25.5	3,470	51.4
1983	25.7	11.8	90.3	1.53	72.2	68.7	162.8	25.9	3,476	51.3
1984	25.5	11.6	93.5	1.46	71.8	68.3	162.9	25.8	3,453	51.1
1985	26.0	11.9	91.6	1.50	72.3	68.8	162.9	25.9	3,451	51.3
1986	26.0	11.9	91.8	1.57	72.4	69.0	162.8	26.0	3,446	51.4
1987	26.3	11.8	92.3	1.67	72.7	69.3	162.6	26.2	3,474	51.3
1988	26.1	11.7	91.9	1.62	72.8	69.4	163.5	26.0	3,466	51.4
1989	25.9	11.7	92.0	1.52	71.0	67.6	162.7	25.5	3,422	51.2
1990	25.8	11.7	92.0	1.58	72.2	68.8	163.7	25.7	3,391	50.9
1991	25.3	11.7	92.0	1.49	72.3	68.9	163.8	25.7	3,450	51.0
1992	25.3	11.8	92.0	1.47	70.5	67.1	163.9	25.0	3,419	51.1
1993	25.0	11.6	92.0	1.52	70.6	67.3	164.0	25.0	3,379	51.0
1994	25.9	11.8	92.0	1.51	70.5	67.1	164.1	24.9	3,401	50.8
1995	25.9	11.8	92.0	1.42	70.0	66.6	164.0	24.8	3,406	50.8
1996	26.0	11.6	89.5	1.41	71.2	67.8	164.3	25.1	3,424	51.0
1997	26.1	11.7	91.7	1.51	70.0	66.6	164.1	24.7	3,417	51.2
1998	26.4	12.0	94.8	1.48	70.8	67.4	164.6	24.9	3,423	51.2
1999	26.5	11.8	94.8	1.45	70.7	67.3	164.8	24.8	3,419	51.3
2000	26.7	11.8	86.7	1.49	71.8	68.4	164.9	25.2	3,419	51.2
2001	26.8				72.1	68.7	164.8	25.3	3,415	51.3
2002	26.7				72.0	68.6	164.7	25.3	3,418	51.3
2003	26.9				72.0	68.5	164.6	25.3	3,479	51.7
2004	27.0				72.1	68.7	164.8	25.3	3,432	51.6
2005	27.0				72.2	68.8	164.9	25.3	3,450	51.5
1980–2005	26.0	11.7	91.8	1.5	71.5	68.1	163.7	25.4	3,433	51.2

This then leads to an important question: Was the shift in the anthropometric parameters of St. Petersburg women and their newborns caused by a change in the quality of life of the mothers or by changes in other characteristics (education, occupation, social status, age, and ethnicity)?

159.3 Women's Height: Multiple Regression Analysis

Table 159.8 presents the results of multiple regression analysis of the determinants of mean height for individual data. The explanatory variables are birth cohort, occupational category, marital status, and ethnicity. The regression constant refers to a single, white-collar, Azeri woman, born in 1981–85. Since all variables are dummies, the estimated coefficients should be interpreted group differences from the reference category. The number of cases corresponding to each condition is given in the right-hand column.

Table 159.8 Factors affecting the mean height of women (cm): regression coefficients

Variable	Coefficient	Standard error	*t*-Statistic	*p*	*N*
Year of birth					
1929–1940	–3.39	1.57	–2.16	0.03	11
1941–1945	–1.51	0.71	–2.13	0.03	58
1946–1950	–1.26	0.33	–3.87	0.00	428
1951–1955	–0.50	0.26	–1.92	0.05	1,162
1956–1960	0.12	0.24	0.52	0.60	2,253
1961–1965	0.89	0.23	3.86	0.00	2,704
1966–1970	1.30	0.24	5.51	0.00	2,250
1971–1975	1.74	0.24	7.21	0.00	1,902
1976–1980	1.08	0.28	3.81	0.00	850
1981–1985	Reference group				62
Occupation					
Blue collar	–0.83	0.11	–7.72	0.00	3,330
Professionals	0.56	0.12	4.57	0.00	2,297
Students	0.22	0.13	1.66	0.10	2,079
Housewives	0.27	0.22	1.21	0.23	471
White collar	Reference group				3,503
Marital status					
Living with partner	–0.14	0.19	–0.71	0.48	10,299
Married	0.26	0.21	1.21	0.23	1,267
Single	Reference group				114
Ethnicity					
Russian	1.19	0.28	4.25	0.00	11,037
Armenian	–1.71	1.17	–1.47	0.14	20
Ukrainian	1.19	0.50	2.39	0.02	151
Jewish	–1.78	0.98	–1.81	0.07	29
Byelorussian	1.33	0.58	2.30	0.02	99
Tatar	–0.07	0.64	–0.11	0.91	77
Georgian	1.24	1.10	1.13	0.26	23
Others	–0.33	0.46	–0.74	0.46	196
Azerbaijanian	Reference group				48
Constant	161.80	0.39	419.63	0.00	11,680

The category ‘professionals’ indicates individuals with a university education. Sources: archives of St. Petersburg hospitals, 1980–2005.

The mean height of women born between 1929–1940 and 1971–1975 was increasing; that of women born from 1976 to 1985, by contrast, was decreasing. Mean heights varied by 5.13 cm between the mothers born in the period 1929–1940 and those born in the period 1971–1975. The women born in the period 1971–1975 were 1.74 cm taller than those born in the period 1981–1985. Mean height varied by 3.11 cm between the shortest Jewish women and the tallest Byelorussian women. Professionals were taller than blue-collar workers by 1.39 cm. Women whose marital status was ‘unlawful’ (that is, women in couples that were not officially registered as spouses) were 0.4 cm shorter than those who were legally married. A comparison of paired and multiple coefficients of determination shows that year of birth, ethnicity, and social and marital status account for roughly 3% of the variation in mothers’ height. Also, a comparison permits ranking of factors included in the analysis: year of birth, social status, and ethnicity were more important, and marital status was less. It played the very modest role (Table 159.9).

Table 159.9 Estimation of the determinants of women's mean height: paired and multiple coefficients of determination

Pair coefficients of determination between the stature of women and	Coefficient of determination	*F*-statistic	*p*
1. Year of women's birth	0.020	27.967	0.000
2. Social status of women	0.010	31.353	0.000
3. Ethnicity of women	0.002	3.661	0.000
4. Marital status of women	0.001	9.092	0.000
Multiple coefficients of determination between the stature of women and			
1 + 2	0.027	26.186	0.000
1 + 2 + 3	0.029	17.880	0.000
1 + 2 + 4	0.027	22.983	0.000
1 + 2 + 3 + 4	0.030	16.545	0.000

Table 159.10 Estimation of the determinants of women's mean weight: paired and multiple coefficients of determination

Paired coefficients of determination between the weight of women and	Coefficient of determination	*F*-statistic	*p*
1. Age of women	0.041	85.451	0.000
2. Year of women's birth	0.029	40.124	0.000
3. Social status of women	0.008	26.175	0.000
4. Ethnicity of women	0.003	4.972	0.000
5. Marital status of women	0.0003	2.840	0.058
Multiple coefficients of determination between the stature of women and			
1 + 2	0.044	37.319	0.000
1 + 2 + 3	0.046	30.878	0.000
1 + 2 + 3 + 4	0.049	23.202	0.000
1 + 2 + 3 + 4 + 5	0.050	8.647	0.000

159.4 Women's Weight: Multiple Regression Analysis

Multiple correlation analysis leads to the conclusion that mother's weight variation was accounted for by age, year of birth, social status, ethnicity, and marital status (in order of significance) approximately by 5% (Table 159.10).

Table 159.11 presents the results of multiple regression analysis of the determinants of mean weight for the individual data. The regression constant refers to a 41 and more year old, white-collar, Azeri woman, born in 1981–1985.

The mean women's weight varied by 3.19 kg between the mothers born in 1946–1950 and those born in 1976–1980. The women born in 1976–1980 weighed 1.39 kg less than those born in 1981–1985. The mean weight varied by 9.24 kg between the stoutest Georgian and the slimmest Tatar women. The professionals weighed roughly 1 kg less than the blue-collar workers. The slimmest 14- to 16-year-old mothers weighed 5.78 kg less than the stoutest 31- to 35-year-old mothers.

159.5 Birth Length: Multiple Regression Analysis

Paired and multiple coefficients of determination allow the ranking of factors, as follows: we find that the weight and height of mothers, the gender of newborn, the order of delivery, and the year of birth had the greatest effect, while other factors played modest roles. The combined influence of the

Table 159.11 Factors affecting the mean weight of women (kg): regression coefficients

Variable	Coefficient	Standard error	*t*-Statistic	*p*	*N*
Year of birth					
1929–1940	0.67	2.89	0.23	0.82	11
1941–1945	0.10	1.23	0.08	0.94	58
1946–1950	1.80	0.59	3.07	0.00	428
1951–1955	0.36	0.47	0.77	0.44	1,162
1956–1960	0.18	0.44	0.41	0.68	2,253
1961–1965	0.10	0.43	0.23	0.81	2,704
1966–1970	–0.09	0.44	–0.20	0.84	2,250
1971–1975	–0.61	0.46	–1.33	0.18	1,902
1976–1980	–1.39	0.53	–2.61	0.01	850
1981–1985	Reference group				62
Age					
14–16	–3.20	1.08	–2.97	0.00	68
17–20	–2.40	0.37	–6.55	0.00	1,957
21–25	–1.25	0.33	–3.83	0.00	4,605
26–30	0.99	0.33	3.01	0.00	3,106
31–35	2.58	0.36	7.06	0.00	1,440
36–40	2.05	0.50	4.13	0.00	444
>41	Reference group				60
Occupation					
Blue collar	0.72	0.18	4.03	0.00	3,329
Professionals	–0.28	0.21	–1.34	0.18	2,297
Students	–0.25	0.22	–1.13	0.26	2,078
Housewives	–0.68	0.38	–1.79	0.07	471
White collar	Reference group				3,501
Ethnicity					
Russian	0.15	0.46	0.33	0.74	11,033
Armenian	1.35	1.94	0.70	0.49	20
Others	–2.88	0.76	–3.82	0.00	196
Ukrainian	2.21	0.83	2.67	0.01	151
Jewish	–1.23	1.63	–0.75	0.45	29
Byelorussian	0.08	0.96	0.09	0.93	99
Tatar	–4.05	1.07	–3.80	0.00	77
Georgian	5.19	1.82	2.85	0.00	23
Azerbaijanian	Reference group				48
Constant	67.91	0.59	115.42	0.00	11,676

five factors explains infants' height variation by approximately 8.4%, as the multiple determination coefficient shows. The influence of all ten factors accounts for 8.6% of the variation in infants' height (Table 159.12).

Table 159.13 presents the results of multiple regression analysis of the determinants of birth length. The regression constant refers to a boy born in 2000–2005 by the slimmest and shortest mother.

The mean birth height increased between 1980 and 1989 and between 2000 and 2005, while it decreased between 1990 and 1999. The mean height varied by 0.3 cm between the infants born in 1985–1989 and those born in 1990–1999. It varied by 1 cm between the shortest and the tallest women, and it varied by 1.4 cm between the slimmest and stoutest mothers. Boys were 0.3 cm longer than girls.

With regard to social factors, mean height at birth varied by 0.25 cm between infants born by students versus those born by professionals, by 0.27 cm between those born by women with legal

Table 159.12 Estimation of the determinants of birth length: paired and multiple coefficients of determination

Pair coefficients of determination between the stature of newborns and	Coefficient of determination	*F*-statistic	*p*
1. Weight of mothers	0.047	97.56	0.00
2. Height of mothers	0.023	40.41	0.00
3. Gender of newborn	0.022	264.07	0.00
4. Year of newborns' birth	0.005	17.29	0.00
5. Order of delivery	0.010	16.79	0.00
6. Year of mothers' birth	0.005	7.71	0.00
7. Age of mothers	0.003	7.62	0.00
8. Social status of mothers	0.002	7.98	0.00
9. Marital status of mothers	0.002	15.33	0.00
10. Ethnicity of mothers	0.002	3.91	0.00
Multiple coefficients of determination between the stature of women and			
1 + 2	0.053	51.67	0.00
1 + 2 + 3	0.074	68.77	0.00
1 + 2 + 3 + 4	0.082	50.56	0.00
1 + 2 + 3 + 4 + 5	0.084	203.00	0.00
1 + 2 + 3 + 4 + 5 + 6	0.082	170.16	0.00
1 + 2 + 3 + 4 + 5 + 6 + 7	0.082	146.87	0.00
1 + 2 +3 + 4 + 5 + 6 + 7 + 8	0.084	69.79	0.00
1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9	0.084	30.82	0.00
1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 + 10	0.086	8.50	0.00

Table 159.13 Factors affecting mean birth length (cm): regression coefficients

Variable	Coefficient	Standard error	*t*-Statistic	*p*	*N*
Year of birth					
1980–1984	0.1	0.04	3.474	0.001	3,061
1985–1989	0.2	0.04	5.930	0.000	2,932
1990–1994	–0.1	0.04	–3.034	0.002	2,809
1995–1999	–0.1	0.04	–3.435	0.001	2,743
2000–2005	Reference group				275
Mother's height					
149–153 cm	–0.5	0.27	–4.874	0.000	42
154–158 cm	–0.3	0.09	–4.261	0.000	468
159–163 cm	–0.2	0.06	–2.616	0.009	2,059
164–168 cm	0.1	0.06	0.889	0.374	2,829
169–173 cm	0.2	0.06	2.253	0.024	4,289
174–178 cm	0.5	0.07	5.686	0.000	1,601
132–148 cm	Reference group				467
Mother's weight					
48–57 kg	–0.7	0.06	–10.116	0.000	1,533
58–67 kg	–0.2	0.05	–3.914	0.000	4,859
68–77 kg	0.2	0.06	4.411	0.000	3,639
78–87 kg	0.4	0.07	6.099	0.000	1,268
88–97 kg	0.5	0.10	5.029	0.000	357
98–108 kg	0.7	0.18	4.037	0.000	87
31–47 kg	Reference group				77
Gender					
Girl	–0.3	0.02	–16.889	0.000	5,862
Boy	Reference group				5,958
Constant	51.2	0.07	760.618	0.000	

Table 159.14 Social factors affecting mean birth height (cm): regression coefficients

Variable	Coefficient	Standard error	*t*-Statistic	*p*	*N*
Occupation					
Blue collar	0.09	0.04	2.48	0.01	3,330
Professionals	0.10	0.04	2.40	0.02	2,297
Students	–0.15	0.04	–3.41	0.00	2,079
Housewives	–0.04	0.08	–0.58	0.56	471
White collar	Reference group				3,503
Marital status					
Living with partner	0.05	0.07	0.80	0.42	10,299
Married	–0.22	0.07	–2.99	0.00	1,267
Single	Reference group				114
Ethnicity					
Russian	0.21	0.10	2.19	0.03	11,037
Armenian	–0.37	0.41	–0.91	0.36	20
Others	0.12	0.16	0.75	0.45	196
Ukrainian	0.61	0.17	3.55	0.00	151
Jewish	–1.07	0.34	–3.13	0.00	29
Byelorussian	0.40	0.20	1.96	0.05	99
Tatar	0.16	0.22	0.74	0.46	77
Georgian	0.49	0.38	1.29	0.20	23
Azerbaijanian	Reference group				48
Constant	50.92	0.12	439.67	0.00	11,680

versus unofficial marital status, and birth height varied by 1.68 cm between those born by Jewish versus by Ukrainian women (Table 159.14).

159.6 Birth Weight: Multiple Regression Analysis

Our analysis of determinants of mean birth weight offers results analogous to the ones reached above. Paired and multiple coefficients of determination allow a hierarchal ranking of factors: weight and height of mothers, gender of newborn, order of delivery, and year of birth; others played a modest role. The combined influence of the five key factors explains roughly 10% of the variation in birth weight. The influence of all ten factors accounts for 10% of the variation in mean birth height (Table 159.15).

The results of multiple regression analysis of the determinants of mean birth weight are summarized in Table 159.16. The regression constant refers to a boy born to a mother of minimal weight and weight between the years 2000 and 2005.

Mean weight at birth decreased in 1980–1999 and increased in 2000–2005. Mean weight varied by 64.05 g between the infants born in 1980–1984 and those born in 1995–1999. It varied by 349.88 g between the slimmest and the stoutest mothers and by 123.96 g between the shortest and the tallest women. Boys were heavier than girls by 63.17 g.

With regard to social factors, mean weight of infants varied by 66.5 g between students and professionals, by 30.09 g between women with legal versus unregistered marriages, and by 352.65 g between Jewish versus Ukrainian women (Table 159.17).

Hence, overall statistical analysis shows a tendency toward increase in the stature and weight of newborns and their mothers in the Soviet period and a tendency toward decrease in their stature and weight in the post-Soviet period, along with the recovery of both in the period between 2000 and 2005. Our analysis also suggests that these trends were determined by changing conditions in overall quality of life and not by a change in the social and demographic profiles of the mothers themselves.

Table 159.15 Estimation of the determinants of mean birth weight: paired and multiple coefficients of determination

Paired coefficients of determination between the stature of newborns and	Coefficient of determination	*F*-statistic	*p*
1. Weight of mothers	0.058	122.917	0.000
2. Height of mothers	0.024	42.569	0.000
3. Gender of newborn	0.021	253.953	0.000
4. Year of newborns' birth	0.003	9.399	0.000
5. Order of delivery	0.018	31.067	0.000
6. Year of mothers' birth	0.006	9.360	0.000
7. Age of mothers	0.006	13.403	0.000
8. Social status of mothers	0.004	11.424	0.000
9. Marital status of mothers	0.003	19.984	0.000
10. Ethnicity of mothers	0.001	3.041	0.002
Multiple coefficients of determination between the stature of women and			
1 + 2	0.062	390.192	0.000
1 + 2 + 3	0.082	354.217	0.000
1 + 2 + 3 + 4	0.086	101.536	0.000
1 + 2 + 3 + 4 + 5	0.097	102.378	0.000
1 + 2 + 3 + 4 + 5 +6	0.098	17.932	0.000
1 + 2 + 3 + 4 + 5 + 6 + 7	0.098	17.734	0.000
1 + 2 + 3 + 4 + 5 + 6 + 7 + 8	0.101	5.629	0.000
1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9	0.101	7.137	0.000
1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 + 10	0.099	9.847	0.000

Table 159.16 Factors affecting mean birth weight (g): regression coefficients

Variable	Coefficient	Standard error	*t*-Statistic	*p*	*N*
Year of birth					
1980–1984	36.41	8.28	4.40	0.00	3,330
1985–1989	23.05	8.33	2.77	0.01	2,297
1990–1994	–16.43	8.38	–1.96	0.05	2,079
1995–1999	–27.64	8.47	–3.27	0.00	471
2000–2005	Reference group				3,503
Mother's weight					
48–57 kg	–173.04	13.76	–12.58	0.00	10,299
58–67 kg	–58.01	11.37	–5.10	0.00	1,267
68–77 kg	48.09	11.74	4.10	0.00	114
78–87 kg	98.75	14.16	6.97	0.00	11,037
88–97 kg	131.24	21.12	6.21	0.00	20
98–108 kg	176.84	38.94	4.54	0.00	196
31–47 kg	Reference group				151
Mother's height					
149–153 cm	–16.99	56.51	–0.30	0.76	29
154–158 cm	–85.78	20.09	–4.27	0.00	99
159–163 cm	–53.57	13.66	–3.92	0.00	77
164–168 cm	–30.64	12.97	–2.36	0.02	23
169–173 cm	9.55	12.37	0.77	0.44	48
174–178 cm	38.18	14.33	2.66	0.01	11,680
132–148 cm	Reference group				3,330
Gender					
Girl	–63.17	3.79	–16.65	0.00	2,297
Boy	Reference group				2,079
Constant	3,450.87	14.35	240.47	0.00	471

Table 159.17 Social factors affecting mean birth weight of infants (grams): regression coefficients

Variable	Coefficient	Standard error	*t*-Statistic	*p*	*N*
Occupation					
Blue collar	26.39	7.75	3.41	0.00	3,330
Professionals	30.54	8.68	3.52	0.00	2,297
Students	–35.96	9.11	–3.95	0.00	2,079
Housewives	–28.40	16.17	–1.76	0.08	471
White collar	Reference group				3,503
Marital status					
Living with partner	39.09	14.29	2.74	0.01	10,299
Married	–26.25	15.80	–1.66	0.10	1,267
Single	Reference group				1,14
Ethnicity					
Russian	47.59	20.80	2.29	0.02	11,037
Armenian	–24.54	87.06	–0.28	0.78	20
Others	32.26	33.88	0.95	0.34	196
Ukrainian	90.97	37.00	2.46	0.01	151
Jewish	–261.68	73.25	–3.57	0.00	29
Byelorussian	68.92	43.20	1.60	0.11	99
Tatar	48.06	47.75	1.01	0.31	77
Georgian	77.76	81.55	0.95	0.34	23
Azerbaijanian	Reference group				48
Constant	3,344.40	24.76	135.05	0.00	11,680

159.7 St. Petersburg Newborns in a Historical and Comparative Perspective

It is of interest to look at St. Petersburg newborns in a historical and comparative perspective. The available information for 1933–2005 shows that, in Moscow and St. Petersburg, the stature and weight of children varied synchronously and also that newborns in St. Petersburg have always been inferior in size and weight to Muscovite newborns (Table 159.18).

There is nothing surprising in the synchrony of the newborns' stature and weight variations: the residents of both cities experienced approximately similar living conditions. From the available information for Moscow during the 1875–1930 period, we can see some of the changes affecting living standards of newborns and their mothers in St. Petersburg. Between 1875 and 1914, there was a tendency toward increase in the stature and weight of newborns, with maximum indicators of both achieved on the eve of World War I. In the 1920s, the stature and weight of newborns began to decrease and this continued until the mid-1940s. Then, in the post-World War II period, anthropometrical indicators began to improve again. The pre-World War II level was achieved by the early 1950s and the pre-Soviet level – in the 1960s. Then, the tendency changed again, and indicators continued to decrease up to the beginning of the twenty-first century. During the period between 2001 and 2005, weight and height at birth reached parity with measurements for the 1950s.

Let us compare the St. Petersburg birth weight with all-Russian birth weight (Sukhanova 2006, p. 124) (Fig. 159.3).

Between 1998 and 2004, live-born children in Moscow were only 31 g or 0.9% heavier than their counterparts in St. Petersburg and 33 g or 1% heavier than newborn babies in Russia as a whole. Hence, it may be suggested that the female standards of living in St. Petersburg and Russia were

Table 159.18 Length and weight of newborns in St. Petersburg and Moscow in 1875–2005 (Sources: Popov 1959; Nikitiuk 1972; Tretyak et al. 2005)

	St. Petersburg						Moscow	
	Boys		Girls		Both		Boys and girls	
Year of birth	Height, cm	Weight, g	Height, cm	Weight, g	Height, cm	Weight, g	Height, cm	Weight, g
1875–1884							52.1	3,476
1885–1894							52.2	3,472
1895–1904							52.4	3,518
1905–1914							52.7	3,553
1915–1919							52.6	3,507
1920–1924							53.0	3,496
1925–1929							52.7	3,476
1930–1934							51.1	3,399
1933	50.8	3,354	50.3	3,240	50.5	3,297	51.0	3,396
1938–1940	50.9	3,436	50.2	3,316	50.5	3,376	50.6	3,358
1941	50.8	3,311	50.2	3,176	50.5	3,244	50.8	3,433
1942	49.0	2,829	48.4	2,708	48.7	2,769	50.6	3,375
1943	50.8	3,290	49.7	3,225	50.2	3,258	49.9	3,338
1944		3,374		3,251		3,313	50.6	3,350
1945	51.1	3,438	50.3	3,292	50.7	3,365	51.1	3,295
1933–1940	50.8	3,416	50.2	3,297	50.5	3,356	51.0	3,396
1941–1945	50.4	3,248	49.7	3,130	50.0	3,189	50.6	3,358
1945–1949							51.0	3,327
1950–1954							51.3	3,414
1955–1959							51.6	3,464
1960–1964							52.1	3,438
1966–1967	52.7	3,563	52.3	3,431	52.5	3,497	52.7	3,510
1980–1984	51.5	3,518	51.0	3,399	51.2	3,456		
1985–1989	51.7	3,525	51.0	3,381	51.3	3,450	51.3	
1990–1994	51.3	3,472	50.7	3,351	50.9	3,406		
1995–1999	51.3	3,459	50.7	3,333	51.1	3,417		3,434
2000–2004	51.4	3,485	50.8	3,367	51.5	3,435	51.9	3,447
1980–2005	51.5	3,493	50.9	3,368	51.2	3,433		

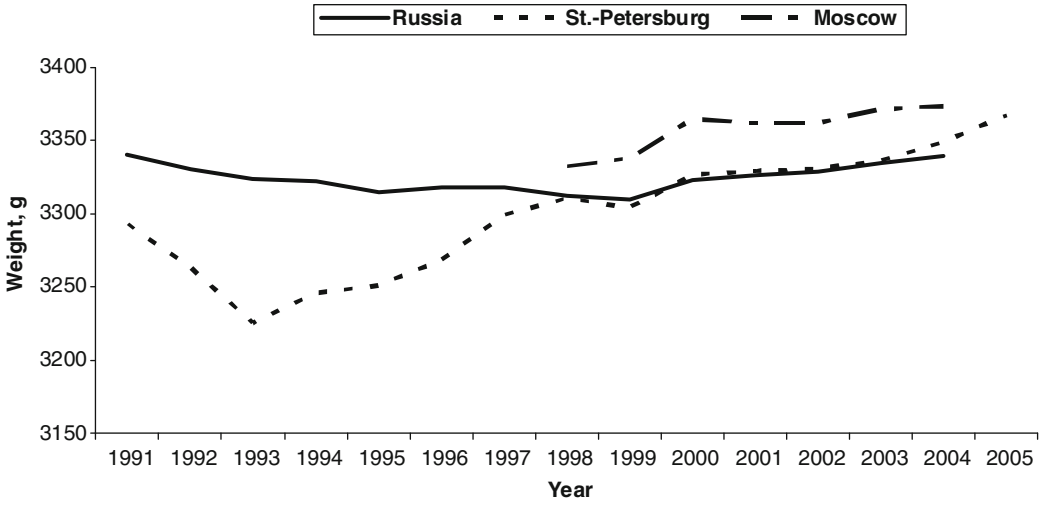

Fig. 159.3 Mean weight of children born in Russia, St. Petersburg, and Moscow, 1991–2005. Stillbirths are not included (Source: Archive of the Central Research Institute on Information, the Ministry of Health of the Russian Federation, Moscow; Sukhanova 2006, p. 124)

nearly equal, and they were inferior to the living standards of Moscow women. The dynamics of the mean weight in Russia, St. Petersburg, and Moscow were synchronous.

International comparisons are difficult due to the incomparability of the data. Our data for Russia allow us to measure children born alive, single, and at term, while available foreign data usually only provide information on live births (Table 159.19).

Between 1980 and 2005, the average weight of all St. Petersburg live-born infants was 5–7% less than those born at term, and according to the information for 2001–2005, their stature was 2.2% smaller (Table 159.20).

If we decrease the weight of Russian newborns by 5–7% and stature by 2%, then we can see that newborns in Moscow and St. Petersburg in the 1970–1980s are inferior to West-European and white American newborns both in stature and weight. From the last third of the nineteenth to the first third of the twentieth century, corrections should be even greater, as the share of children with low birth weight at that time was greater than in 1980–2005. According to the calculations made by Peter Ward, the share of children with low-birth-weight deficit in 1870–1930 in Austria, Great Britain, USA (whites), and Canada was within the interval from 5.7% to 15.2% and, in the 1970–1980s, from 3.6% to 7.7%, that is, almost a twofold decrease (Ward 1993, p.134). Between 1870 and 1899, Moscow children born at term were only 3% heavier than American whites and 7% heavier than British, Canadian, and Irish children. Corrections in Russian data eliminate the advantage of the Moscow infants and the more so of the St. Petersburg children who have always been less in stature and weight than the Moscow infants. It is possible that, in 1900–1913, the difference in weight between Moscow and West-European infants somewhat smoothed out, but, nevertheless, equality did not follow. In the Soviet and post-Soviet periods, Moscow and St. Petersburg newborns were definitely inferior to European and white American newborns in weight and, most likely, in stature, as there is a close relationship between stature and weight. Between 1870 and 1980, the stature and weight of newborns in the West increased. In Russia, this favorable tendency was observed until 1913, but, during the Soviet period, it was replaced by a tendency toward decrease.

Table 159.19 International comparison of the height and weight of newborns of both sexes, 1870–1970s (Source: Ward (1993), pp. 146–162)

	1874–1899		1900–1913		1914–1920		1921–1930		1970s
	Height, cm	Weight, g	Height, cm	Weight, g	Height, cm	Weight, g	Height, cm	Weight, g	Weight, g
Moscow	52.1	3,471	52.8	3,563	52.3	3,514	52.7	3,479	3,482
St. Petersburg							50.5	3,297	3,453
Vienna	50.0	3,121	50.2	3,132	49.6	3,083	49.8	3,180	3,320
Dublin		3,240	49.5	3,356	49.3	3,334	49.5	3,353	3,473
Edinburgh	49.8	3,232	51.0	3,150	50.6	3,174			3,062
Boston		3,363		3,333					3,480
Boston		3,126							3,230
Montreal		3,230		3,119					3,303

Dates pertain to live births and full-term deliveries in Russia; live and stillbirths in Scotland; and live birth in Austria, Canada, Ireland, and USA

Table 159.20 Characteristics of newborn and their mothers in St. Petersburg, 1980–2005 (Sources: The Archives of St. Petersburg Hospitals, 1980–2004)

Years	Weight of full-term babies, g	Weight of all newborns, g	Premature births, %	Retarded births, %	Women with anemia, %	Abnormal births, %
1980–1984	3,532	3,324	5.2	1.3	0.8	6.2
1985–1989	3,548	3,321	7.3	1.9	1.7	5.3
1990–1994	3,462	3,287	9.0	4.0	4.5	6.2
1995–1999	3,460	3,268	10.5	7.0	13.1	14.5
2000–2004	3,451	3,246	10.1	6.0	12.2	8.7

159.8 Discussion and Conclusion

Based on the data on the physical stature and weight of women and the length of birth weight of newborns, we conclude that the living standards of women in St. Petersburg steadily improved after World War II. The height of women increased until the birth cohorts of ca.1972 (Fig. 159.2), who reached adulthood near 1990. Women born thereafter reached their final height at a time when the Soviet era was drawing to a close. The height of these women who reached their final height in the 1990s declined by as much as 1.3 cm, implying that their living standards decreased in the post-Soviet era. Essentially, the height of women traces an inverse 'U'-shaped curve.

This pattern is corroborated by the fact that, during the transition from the command economy to a market economy from 1990 to 1996, per capita gross domestic product decreased by nearly 39% (Gaidar 2005, p. 381). In addition, life expectancy of women peaked in 1967 at 74 years, a level maintained until 1987, when it then began to decline. By 1993, when it reached its lowest level, it had declined to 71 years. Thereafter, it began to slowly rise again to 72 years in 2002–2005 (Eliseeva and Gribov 2003, vol. 2, p. 81). Furthermore, in 1995–1999, there was also a marked increase in the number of premature births (by a factor of 1.9 compared to 1980–1984) and of retarded births (by a factor of 5.4). There was also a rise in the number of pregnant women with anemia (by a factor of 16.4) and women having abnormal births (by a factor of 2.3) (Table 159.20). Yet, the weight and BMI of the women was also in decline during most of the period under consideration, which was a positive development as the women had been rather overweight at the outset.

The decrease in the women's living standards in the 1990s resulted from the worsening of diet (Table 159.3) as well as a decline in real income and wages. According to the official data in St. Petersburg from 1991 to 1999, the buying power of the average income decreased by a factor of 2.4 (Eliseeva and Gribov 2003, vol. 3, p. 26). Although official data on incomes do not take secondary or shadow earnings into full account (and these sometimes represented as much as 40% of total family income), the anthropometric data, an indicator of total actual consumption and, consequently of all income, suggest that full income must have been decreasing as well. There is further supporting evidence of a widespread subjective feeling of dissatisfaction that also impacted overall living standards (Zdravomyslov and Iadov 2003, pp. 464–479; Patrushev 2001; pp. 120–129).

In addition to the height of mothers, we have provided evidence here that both length and weight of babies trace a 'U'-shaped curve with troughs near the mid-1990s with amplitudes in the annual data of ca. 0.6 cm and 70 g (Fig. 159.1). Thus, the anthropometric results for newborns as well as for their mothers point to the stress on standards of living that was experienced during the restructuring of the Soviet economy. This is a general result that we can recognize as a recurring pattern: economic transitions are almost always accompanied by biological strains. This was the case during the Neolithic agricultural revolution, during the Industrial Revolution, and also, it seems, in the post-Communist 'velvet Revolution' in St. Petersburg as well (Komlos 1998).

159.9 Applications to Other Areas of Anthropometry

This inquiry is set in four distinct but interrelated contexts: history of human growth, living standards and nutrition, inequality and poverty, and women's economic status. Weight and length at birth are strongly conditioned by the health and nutritional status of mother and, therefore, they are linked to circumstances specific to women. Because weight and length at birth are sensitive to environment factors acting during the 9 months of gestation as well as to the long-range effects of changes in living conditions, they reflect both short- and long-term trends. The analysis of newborn weight and length complements studies on growth patterns and achieved height in the past.

Summary Points

The analysis above allows us to draw the following conclusions:

- A tendency toward increase in the length and weight of newborns was observed in the Soviet period and a tendency toward decrease in both was observed in the post-Soviet period: the average length of single-born boys and girls decreased from 51.4 to 50.8 cm and weight from 3,476 to 3,379 g between the early 1980s and the early 1990s.
- By 2000–2005, both length and weight had nearly returned to where they started in the early 1980s in the pre-perestroika era.
- Variation in mean height and weight of infants can be attributed to their mother's weight and height, the child's gender, the order of delivery, and the year of their mothers' birth. The key factors account for about 8% of the variation in newborns' height and roughly 10% of the variation in weight.
- For mothers by birth cohort, from the end of World War II to the early 1970s, height increased by nearly 6 cm, while decreasing by about 1 cm for birth cohorts from 1973 to 1978.
- A reduction in average women's weight in 1945–1985 by nearly 12 kg was most likely affected both by changes in fashion (the slim female figure has firmly been established over the last 25 years) and by an overall reduction in calories by women, which made delivery easier.
- Variation in women's mean height and weight was determined by year of birth, social and marital status, ethnicity, and age. The key factors account for up to 3% of the variation in women's height and up to 5% of the variation in women's weight.
- Anthropometric indicators of newborns and their mothers point to women's living standards steadily improving from the end of World War II through to the early 1980s. Thereafter, they declined until the late 1990s.
- Other indicators point to a serious slump in the women's living standards in the 1990s: per capita gross domestic product decreased by 39%; and life expectancy of women declined from 74 in 1960s to 71 years in the early 1990s. Meanwhile, the number of women having abnormal births drastically increased.
- These negative trends in women's living standards were determined by changing conditions of life rather than by any significant change in the women's social and demographic profiles. The most important factor affecting these negative trends in female standards of living was the worsening diet and decline in real incomes and wages.
- There is a noticeable connection between the height and weight of newborns and that of their mothers, on the one hand, and social and demographic indicators, on the other.

- In the Soviet and post-Soviet period, the Moscow and the St. Petersburg newborns were definitely inferior to European and white American newborns in weight and, most likely, in stature, as there is a close relationship between stature and weight.
- Russian anthropometric results confirm the view that economic transitions are almost always accompanied by stresses and challenges to health and other biological indicators of well-being.

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Chapter 160
Body Composition in a Multiethnic Community in New Zealand

Elaine Rush

Abstract This chapter summarizes evidence of ethnic differences in body composition from a multiethnic community in Auckland, New Zealand. The people measured were apparently healthy, aged 18–82 years and selected for a range of body mass index (BMI) within each age group. Because the measurement of body composition was by a single dual xray absorptiometry (DXA) machine, strong evidence has been provided for ethnic differences in the relationship between BMI and percentage body fat. Furthermore there are marked differences in both men and women by ethnicity of regional fat distribution, leg length and appendicular skeletal muscle mass.

The ethnic comparison is limited by the absence of concurrent measurements of chronic disease risk associated with BMI and fat distribution, however national health surveys clearly demonstrate that South Asian, Pacific and Maori have a higher prevalence of risk than European. The relationship is confounded by the concurrent evidence that lower socioeconomic status is associated with increased obesity and risk. Within an ethnicity, and by sex, risk increases with body weight for height, BMI. BMI may help inform international comparisons and public health *action points* within a population. BMI should not be used as an arbitrary cutoff point to label a person; ethnic origin should also be considered and further tests administered.

Further evidence is provided from longitudinal studies that within an ethnicity, weight for height tracks from birth, throughout childhood and into adulthood, providing support for the developmental origins of health and disease and the importance of early intervention.

Abbreviations

ASSM	Appendicular skeletal muscle mass
BMC	Bone mineral content
BMI	Body mass index
DXA	Dual energy xray absorptiometry
FM	Fat mass

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_160,

FFM Fat free mass
PBF Percent body fat
WHO World Health Organisation

160.1 Introduction

160.1.1 Body Mass Index

Using evidence for association of body mass index (BMI) with risk factors for morbidity and mortality, the World Health Organization (WHO) has set standard desirable BMI values for populations (WHO Consultation on Obesity 1999). Evidence for association of increased mortality with increasing BMI continues to accumulate. Recently, strong evidence that mortality is lowest at a BMI of 22.5 to 25 kg/m^2 has been provided from 57 prospective studies of 900,000 Western European and North American adults(Whitlock et al. 2009). Furthermore, this collaborative analysis shows that for the same BMI, yearly deaths of males are almost twice the yearly deaths of female; yearly deaths from ischemic heart disease are three times higher than stroke and yearly deaths of current smokers are twice as high as nonsmokers. The evidence also very clearly shows that BMI is a strong predictor of overall mortality above and below 22.5 to 25 kg/m^2 and that the progressive excess mortality above this range is related to vascular disease. No clear cutoff values for increased risk were seen making precise definitions of overweight and obesity dubious.

160.2 Obesity

While the WHO definition of obesity (a BMI above 30 kg/m^2) is used for monitoring populations over time and comparing country statistics, it is often used as a risk factor for identifying individuals at risk. Obesity is more accurately defined as having an excess of body fat – however, the exact amount of fat has not been determined and is confounded by variations in risk being dependent on where in the body the fat is located. In particular, it is the accumulation of intra-abdominal fat and the closely associated waist measurement that has been found to improve the sensitivity for prediction of risk.

160.3 Geographical Origins

Globally, there is large variation in body size and shape (Ruff 2002) and the pattern of disease risk and mortality also varies widely. Due to a global increase in longevity, the prevalence of chronic diseases that are associated with aging and increased weight for height are increasing. In general, for an increase in BMI the proportion of body fat also increases. Interpretation of the variation in body size among populations becomes more difficult with migration and intermarriage. New Zealand, relatively geographically isolated in the South Pacific, is an example of a country where body composition in relation to ethnicity and the effects of migration can be studied.

160.4 Ethnicity in New Zealand

New Zealand, once predominantly Māori (the indigenous people) and European now, has an increasingly multiethnic population; in the 2006 census, 67.6% of the population identified themselves as European in origin, 14.6% Maori, 6.9% Pacific Island, and 9.2% as Asian (Statistics New Zealand 2006). Most Asian were of Chinese (3.8%) and Indian (2.7%) origin. Some people identified with more than one ethnicity so figures do not always sum to 100%. In 2006 more than one in five New Zealand people were born overseas, the median age was 36 years compared with 26 years in 1971 and life expectancy at birth had increased to 78 years for males and 82 years for females. However, as in many countries, there are large disparities among ethnic groups in health and life expectancy which are associated with both ethnicity and socioeconomic status (Ministry of Health and Statistics New Zealand 2009). Europeans live longer compared with Māori and Pacific and have higher socioeconomic standing (Table 160.1).

Ethnicity is defined, by Statistics New Zealand (Statistics New Zealand 2005), as "the ethnic group that people identify with or feel they belong to" and as such "is a measure of cultural affiliation, as opposed to race, ancestry, nationality or citizenship." Māori and Pacific peoples have the highest incidence and age-adjusted prevalence obesity, cardiovascular disease, and type 2 diabetes (Ministry of Health 2002, 2004). Maori and Pacific children appear to follow the same trend of increased size and associated risk (Ministry of Health 2008). In the census and in health statistics, ethnicity is by self-identification. Consequently, the analysis of associations among body size, ethnicity, socioeconomic status, and health risks has many errors and assumptions. An understanding of the differences in body composition among ethnic groups may contribute to a better understanding of the associations with disease risk. In particular, it is important to consider the lean component of body composition, a large proportion of which is found in skeletal muscle tissue. Skeletal muscle tissue plays a large role in the regulation of metabolism, particularly with increased physical activity.

The choice of method of measurement of body composition is limited by availability of equipment, access, cost, invasiveness, and the suitability of the measurements to address the research question. Over a number of years on a single dual energy X-ray absorptiometry (DXA) machine (model DPX + with software version 3.6y; Lunar Radiation Corp., Madison, WI, USA), we have undertaken a number of studies to answer questions about ethnic differences in the relationships between body fatness and body size, fat distribution, muscularity, bone mineral mass, and leg length. The following sections describe the practical methods used and, in particular, compare Pacific and Asian-Indian men and women, ethnic groups arguably at opposite extremes in terms of muscularity and fatness and very different in geographic origin.

Table 160.1 Independent life expectancy at birth of the Maori population compared with Non-Maori

	Non Maori		Maori	
	Males	Females	Males	Females
Life expectancy	79.0	83.0	70.4	75.1
Independent life expectancy	68.8	70.4	62.0	64.2
Healthy life expectancy	71.5	74.6	64.2	67.6

This table describes the disparity between Maori and Non Maori in the number of years expected to be lived free of functional limitation needing assistance (independent life expectancy) and the equivalent number of years of full health that a person can expect to live (healthy life expectancy) Material adapted from Ministry of Health and Statistics New Zealand (2009)

160.5 Practical Methods and Techniques

160.5.1 Sample Selection

When comparisons of body composition between ethnic groups are made, it is important that the subjects measured within each group cover the range of ages and body compositions of interest. This means that subjects are not randomly drawn from the population or are similar in proportions, but that they are selected to represent a range of age, BMI, and fatness.

160.5.2 Measurement

One relatively direct way of measuring body composition (fat mass (FM), fat-free soft tissue (lean), and bone mineral content (BMC)) is using a single DXA machine with the subjects lying supine in light clothing. The rising prevalence of increased body size means that for some studies both arms of a person may exceed the scanning area of the DXA. This may be overcome by positioning the subject so that one arm is not completely scanned. Subsequently, the data from the completely scanned arm are used to replace the data from the incomplete arm (Micklesfield et al. 2007).

Fat-free mass (FFM) is calculated as the sum of lean and BMC. Percentage of fat mass FM was calculated as FM/(FM + FFM) * 100. A quality-control check of DXA data is to compare body mass determined from DXA measurements (FFM + FM) with the actual body mass determined by weighing the subject.

160.5.3 Fat Distribution

Increased waist circumference as a measure of abdominal obesity is recognized as a marker of dysfunctional adipose tissue (Despres and Lemieux 2006) and, moreover, the ratio of waist-to-hip girth measurements has been shown to be a stronger predictor of myocardial infarction than BMI in a number of ethnicities, including European and Asian-Indian (Yusuf et al. 2005). The comparison among ethnic groups of the amount of FM, lean, and BMC in these areas of the body may provide further insights into ethnic differences in the underlying body composition that determines risk. DXA scans are limited in that they are two dimensional and assumptions are made within the manufacturers software algorithms about the amount and type of tissue behind the radio-opaque bone (Table 160.2). Therefore to examine the abdominal and hip area, regions of interest selected had minimal bone included within their borders. The hip measurement is closely related to the thigh measurement and the top of the thighs is where the largest mass of muscle in the body is located. More lean and less fat in the upper thigh area would translate into reduced metabolic risk (Snijder et al. 2003). Because of the following three factors – reduced bone mass, abdominal fat purportedly representing increased metabolic risk, and increased thigh area representing increased muscle mass and reduced fat mass – the two regions of interest below (illustrated in Fig. 160.1) were selected to examine ethnic differences in body composition.

Based on the criteria of Ley et al. (1992), abdominal fat was obtained from the analysis of a region of interest positioned with the lower horizontal border on top of the iliac crest and the upper border parallel and approximately passing through the junction of the T12 and L1 vertebrae. The sides of

Table 160.2 Features of DXA scans

While DXA scans are a reference method for measurement of lean, bone mineral, and fat components of body composition, there are limitations and strengths of this technique
At an equipment level, the reliability of a single machine is good but between machines and manufacturers the differences may be large. Machines are not portable and require expert operation. Reference phantoms are expensive, not easily portable and may not match the population of interest in size and composition
Manufacturers do not provide the equations used to derive body composition and validation against four compartment models of body composition
The gray-scale scan has two dimensions, and the composition within (e.g., the head) and behind bone (e.g., the superior gluteal region and the neck) is assumed
Strengths of the technology are that the scans have a very low dose of radiation; the time taken for the scans is relatively short and they are not invasive. Regional body composition analysis is possible and appendicular muscle may be derived. The use of DXA for validation of field techniques such as bioimpedance, for ethnic comparisons, and for longitudinal studies provides useful information

This table describes features of DXA scans, which are used to measure the lean, bone mineral and fat components of body composition
DXA dual energy X-ray absorptiometry

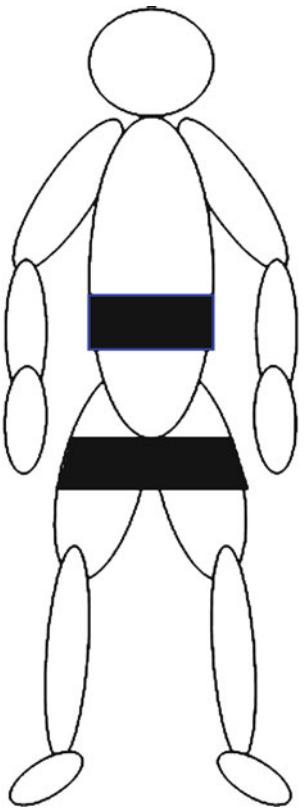

Fig. 160.1 Regions of interest of the whole-body DXA scan. Cartoon to demonstrate the regions of interest (*shaded black*) of the abdominal and thigh regions of the whole-body DXA scan. DXA = dual energy X-ray absorptiometry. Unpublished figure from the author

this region were adjusted to include the borders of the abdominal tissue scanned, and the fat content of this total region was reported as abdominal fat. A region of interest of identical height was placed over the thighs with the upper horizontal border positioned immediately below the ischial tuberosities and the lateral margins were adjusted to follow the shape of the thighs. The fat content of this region was reported as thigh fat.

160.5.4 Appendicular Skeletal Muscle Mass

Appendicular skeletal muscle mass (ASMM) was derived from the DXA scans as total limb mass minus the sum of limb fat and wet bone mass, estimated as BMC divided by 0.55. In this model, mass of the skin and associated dermal tissues is assumed to be negligible relative to the skeletal muscle component (Heymsfield et al. 1990).

160.5.5 Leg Length

Relative to height, a longer leg length is associated with greater muscle mass (Gallagher et al. 1997). Total subject skeletal, femoral, and tibial lengths were measured on the right side using the pixelated DXA image. Total skeletal length (DXA height) was measured as the distance from the apex of the cranium to the plantar surface of the calcaneus bone. Femur bone length was measured from top of the femoral head (greater trochanter) to middle patellar surface, and tibia bone length was measured from the superior intercondylar eminence to the inferior surface medial malleolus. Dimensions were measured in pixels and converted to centimeters based on a DXA scan of a standard ruler. Leg length was determined as the sum of the lengths of the femur and tibia bones. The ratio of leg length to DXA height was used as an index of relative leg length.

160.6 Ethnic Variations in Body Composition

160.6.1 Relationship Between BMI and Body Fat

We have been able to show that, generally speaking, for the same body size, height, and weight, a European adult has more fat and less muscle than a Maori or Pacific person (Table 160.3; Rush et al. 1997, 2009). On the other hand, an Asian-Indian person has more fat and less muscle than a European for the same size.

Examination of Fig. 160.2 emphasizes some fundamental patterns of difference. First of all, it can be clearly seen that for the same BMI, in general, a woman of any ethnicity has more body fat than a man; about 10% more of the total body mass of a women is fat compared to a man. The plateau of body fatness in women in these groups was about 50% of body mass while in men very few were seen to have body fat more than 40%. Similarly very few women had less than 15% body fat but for men a number were below 15%. Therefore, the differences in body fat by sex are a fundamental, biological difference.

The second feature of Fig. 160.2 that should be noted is that the BMI scale is logarithmic. Even with this transformation to linearize the relationship with PBF, some curvilinearity can be observed with a plateau of total PBF as BMI increases. This is because as fat mass increases, the fat-free mass required to maintain this extra mass also increases (Kyle et al. 2006).

Furthermore, in a study across two countries and five ethnic groups (summarized in Table 160.2; Rush et al. 2007), it was shown that for a BMI of 30 kg/m^2, Pacific Island women had the lowest PBF (~38% BF) and Asian-Indian women the greatest PBF (~48% BF). South African black women, European, and Māori had similar values of total PBF for a BMI of 30 kg/m^2 (40% BF). The explanation for these ethnic differences in the relationship may lie in linear body proportions and quantity and location of adipose tissue, skeletal muscle, and bone mineral content.

Table 160.3 Comparison of BMI and corresponding percent total body fat in different ethnicities

SA European[a]		SA Black[a]	NZ European		Māori	Pacific Island	Asian-Indian	Chinese[b]
BMI, kg/m^2	Body fat, %	Approximate BMI equivalent, kg/m^2	BMI, kg/m^2	Body fat, %	Approximate BMI equivalent, kg/m^2			
Women								
20	24.3	18.4	20	25.6	18.6	19.7	14.8	18.5
25	32.4	23.8	25	34.9	25.6	27.0	20.3	23.2
30	38.9	29.4	30	42.5	33.1	35.0	26.3	27.8
35	44.5	35.2	35	49.0	41.3	43.6	32.8	32.4
40	49.3	41.1	40	54.6	49.9	52.8	39.6	37.1
45	53.6	47.1	45	59.5	59.0	62.4	46.9	41.7
Men								
			20	10.7	20.7	20.9	14.9	18.0
			25	20.6	25.9	27.4	19.5	22.5
			30	28.7	31.1	34.1	24.3	27.0
			35	35.5	36.3	41.1	29.3	31.5
			40	41.5	41.4	48.3	34.4	36.0
			45	46.7	46.7	55.7	39.8	40.5

Comparison of BMI and corresponding percent body fat with estimated BMI equivalents derived for predicting body fat percent from BMI

SA South African; *NZ* New Zealand; *PBF* percent body fat

[a]Percent body fat and BMI equivalents calculated at the average age for each ethnic group (SA data adapted from Rush et al. 2007)

[b]Chinese data adapted from Wen (2008) and remaining numbers adapted from Rush et al. (2009)

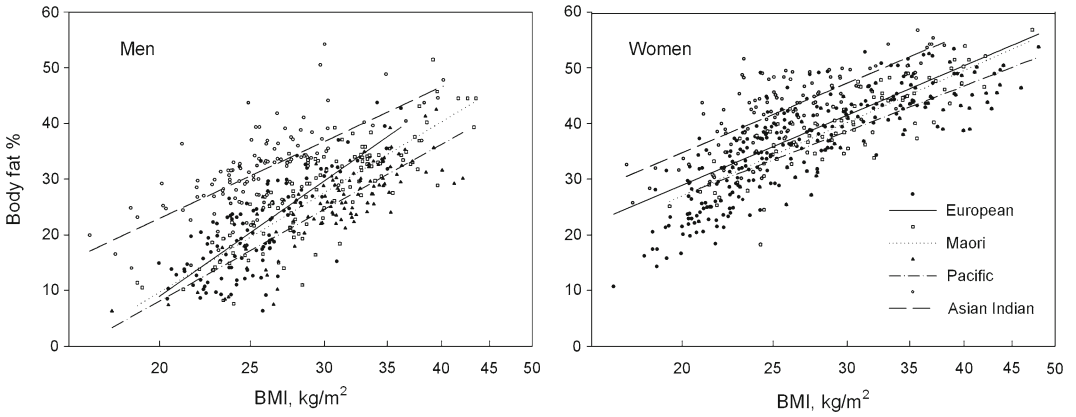

Fig. 160.2 Relation between percent body fat and BMI in different ethnicities. Relation between PBF and BMI of European (*closed circles*), Maori (*open circles*), Pacific Island (*closed triangles*), and Asian-Indian (*open triangles*) men (*upper panel*) and women (*lower panel*). The linear regressions are: PBF = 117.7log$_{10}$(BMI) – 144.2 (SEE = 5.2%, r^2 = 0.61, n = 124) for European men (*solid line*); PBF = 101.3log$_{10}$(BMI) – 122.0 (SEE = 4.6%, r^2 = 0.74, n = 109) for Maori men (*dashed line*); PBF = 93.6log$_{10}$(BMI) – 113.6 (SEE = 4.1%, r^2 = 0.68, n = 104) for Pacific Island men (*dotted line*); PBF = 78.6log$_{10}$(BMI) –79.4 (SEE = 5.0%, r^2 = 0.52, n = 117) for Asian-Indian men (*dash-dot line*); PBF = 103.5log$_{10}$(BMI) – 09.7 (SEE = 4.8%, r^2 = 0.72, n = 186) for European women (*solid line*); PBF = 74.8log$_{10}$(BMI) – 70.3 (SEE = 3.9%, r^2 = 0.72, n = 90) for Maori women (*dashed line*); PBF = 65.2log$_{10}$(BMI) – 57.8 (SEE = 4.1%, r^2 = 0.65, n = 97) for Pacific Island women (*dotted line*); and PBF = 71.0log$_{10}$(BMI) – 57.7 (SEE = 4.4%, r^2 = 0.60, n = 107) for Asian-Indian women (*dash-dot line*). PBF = percent body fat, BMI = body mass index, SEE = standard error of the estimate Material of the author (Rush et al. 2009)

160.6.2 Fat Distribution

DXA technology was developed and validated against a chemical model of fat (all that is soluble in ether), lean, and BMC. Therefore, the analysis is not able to differentiate between what is adipose tissue and the fat content of other tissues. Skeletal muscle cells contain more droplets of fat in both athletes and sedentary, obese people (Goodpaster et al. 2001). In the abdominal area, there is a relatively small proportion of muscle and fat measurement in this region of interest includes both the fat content of subcutaneous adipose tissue and the intra-abdominal fat. There are marked ethnic variations of the quantity of abdominal fat. In our study (Rush et al. 2009) after adjustment for height, weight, and age, fat mass in the abdominal area was higher for Asian-Indian men and women than all other ethnic groups. Conversely, Pacific men and women had the lowest amount of abdominal fat. The same differences between Asian-Indian and Pacific were observed for adjusted thigh fat mass. Thigh fat mass also includes subcutaneous and inter- and intramuscular fat content. Thigh fat mass was significantly higher in Europeans than the other ethnic groups. The ratio of abdominal to thigh fat mass was lowest in European and highest in Asian-Indian men, whereas in women, this ratio was also the lowest in European but Asian-Indian women had a lower value than Pacific. These ethnic and sex patterns of difference in fat distribution were still seen after adjustment for age and did not completely eliminate the ethnic differences in the relationship of percentage total body fat to BMI.

160.6.3 Appendicular Skeletal Muscle Mass

For both men and women, the highest ASMM was observed in the Pacific group and the lowest ASMM in the Asian-Indian group, both before and after adjustment for age, height, and weight. ASMM did not differ between Maori and European men or women after adjustment. Inclusion of ASMM in the PBF–BMI regression models reduced but did not completely eliminate the ethnic differences.

160.6.4 Leg Length

In the women studied, adjusted for height, age, and weight, Asian-Indian and Pacific women had the longest legs and Māori women the shortest. European, Maori, and Asian-Indian men had legs of a similar length and Pacific men had the longest legs. The significant difference in leg lengths was about 1 cm – with average leg length in women about 75 cm and in men 82 cm. Leg length and height, when added to the percentage of BF–BMI regression models, did not significantly affect the ethnic differences observed.

160.6.5 Age

Longitudinal studies to show changes in total body fat and ASSM with aging are difficult. This cross-sectional study of healthy adults showed after adjustment for height and weight that in both men and women, within ethnicity, the percentage of total body fat increased with age. The exception was in Asian-Indian men where no relationship of percentage total body fat with age was able to be shown.

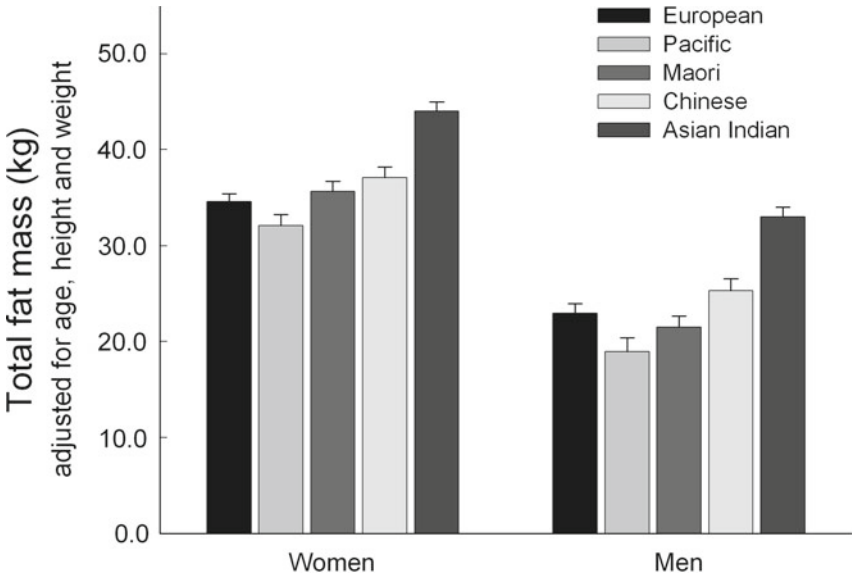

Fig. 160.3 Differences in total fat mass (kg) for European, Pacific, Maori, Chinese, and Asian-Indian men and women adjusted for age, height, and weight (Chinese data adapted from (Wen 2008), all other data adapted from (Rush et al. 2009))

ASMM, after controlling for weight and height, decreased linearly with age in European and Māori men and women but not in Pacific or Asian-Indian men or women. Abdominal fat as a percentage of total fat and the ratio of abdominal to thigh fat increased with age in all ethnic groups, men and women.

160.6.6 Chinese and Asian-Indian Differences

Recently, as a follow-up to the previous study, using measurements on the same DXA machine, we have been able to add 43 (M20, F23) New Zealand Chinese, aged 30–39 years and compare with the existing data for European (M29, F37), Maori (M23, F23), Pacific (M15, F23), and Asian-Indian (M29, F25) for the same age range (Wen 2008).

For a fixed BMI, Chinese had a higher PBF than European and less PBF than Asian-Indian. At a PBF equivalent to a BMI of 30 kg m^{-2} in Europeans, BMI values for Asian-Indian and Chinese women were 5.8 and 2.2 BMI units lower than European, respectively, and for Asian-Indian and Chinese men, BMI values were 8.2 and 3.0 units lower (Table 160.2). In addition, Chinese had a significantly higher central-to-appendicular fat ratio than both Asian-Indian and European ($P < 0.001$). Chinese men and women had relatively more central fat than European and Asian-Indian.

The relationship between total PBF and BMI for Asian-Indian and NZ Chinese differs from Europeans and from each other, which indicates that different BMI thresholds for obesity, defined by PBF, may be required for these Asian ethnic groups**.**

In this multiethnic subsample (Wen 2008) adjusted for age, height, and weight, Asian-Indians had the highest total FM and Pacific the lowest (Fig. 160.3), while Chinese had an intermediate value. Yet, Pacific and Asian-Indian people in New Zealand have higher rates of type 2 diabetes mellitus and other vascular diseases than European (Ministry of Health 2008).

160.7 Applications to Other Areas of Health and Disease

It must be emphasized that measurement of body size is not a functional measure. BMI may help inform *action points* for a population rather than being an arbitrary cutoff point to label a person. There is a limit to all health budgets and when an action point is decided then it infers that there is budget and expertise to be able to provide treatment. What is known is that increasing body mass for height in general is accompanied by an increase in risk for all ethnic groups. There is also increased risk for those who are underweight – as in all physiological systems there is an optimal, homeostatic equilibrium. Functional capacity of the population must be considered as well as physical size and body composition.

The prevalence of obesity and type 2 diabetes follows a socioeconomic gradient. In New Zealand, as in other countries, highest rates of chronic disease are observed among groups with the lowest levels of education and income and in the most deprived areas. Inequitable access to healthy foods is one mechanism by which socioeconomic factors influence the diet and health of a population. With the current recession and global food shortage, incomes drop and prices rise, and energy-dense foods that are nutrient poor become the only way to provide daily calories at an affordable price. By contrast, nutrient-rich foods and high-quality diets not only cost more but are consumed by more affluent groups (Solomons 2009). Affluence and deprivation tend to track through life as do food and activity patterns. Therefore, the pattern of differences shown among ethnic groups is confounded by economic status. Furthermore, there is an intergenerational effect, epigenetics, and culture that influences the body composition of future generations.

From conception, the diet and activity of the mother influence the environment for the child. Seventy-five percent of cell divisions take place before birth, and birthweight is a strong predictor of the future growth trajectory of the child. This has been shown clearly in the Pacific Island family study where birthweight is a strong predictor of body weight at the age of 6 years (Rush et al. 2009).

At 2 years of age, body fatness was determined by bioimpedance analysis in 142 children, 78 girls and 64 boys. The mothers' of these children were diagnosed and treated for gestational diabetes (Rowan et al. 2008). In these children body fatness differed by sex, with girls having more fat than boys. Body fat also differed by ethnicity, and adjusted for age, height, and weight; Asian-Indian children had the most body fat and European the least Fig. 160.4 (unpublished data). Birthweight was positively associated with body weight at 2 years ($r = 0.47$, $P < 0.0001$). Both birthweight and weight at 2 years were positively related to the mothers' weight 2 years post-partum ($r = 0.35$, $P < 0.0001$ and $r = 0.32$, $P < 0.0001$, respectively). Birthweight is a retrospective marker of the intrauterine availability of nutrients, oxygen, and hormones that program tissue development (Fowden et al. 2006). The developmental origin of health and disease (DOHaD) concept is an emerging paradigm for relating evolutionary biology to contemporary health issues such as increased body mass and fat accumulation.

It is clear that adaptations to the environment are initiated in utero and in early life, and this is referred to as programming. At a molecular level, the mechanism is epigenetic, which results in permanent structural and metabolic changes which occur because of the way DNA is expressed. On a macro-level, the public health consequence of programming challenges the one-size-fits-all norm and shows the need for prescreening prior to some interventions. In some cases, individualized, rather than collectively applied, preventive, or remedial measures will be the safest option.

Particularly in a multiethnic community, it must not be assumed that the path to obesity is the same or a simple case of exercising too little and eating too much. For example, in Asian-Indian mothers, low-vitamin-B12 and -protein intake during pregnancy have been shown to be associated with increased adiposity and cardiovascular disease risk factors in the 6-year-old offspring (Yajnik et al. 2008). Vegetarianism has been practiced for many generations in the majority of Indian communities. While the Asian-Indian New Zealand population is only 2.5% of the total population,

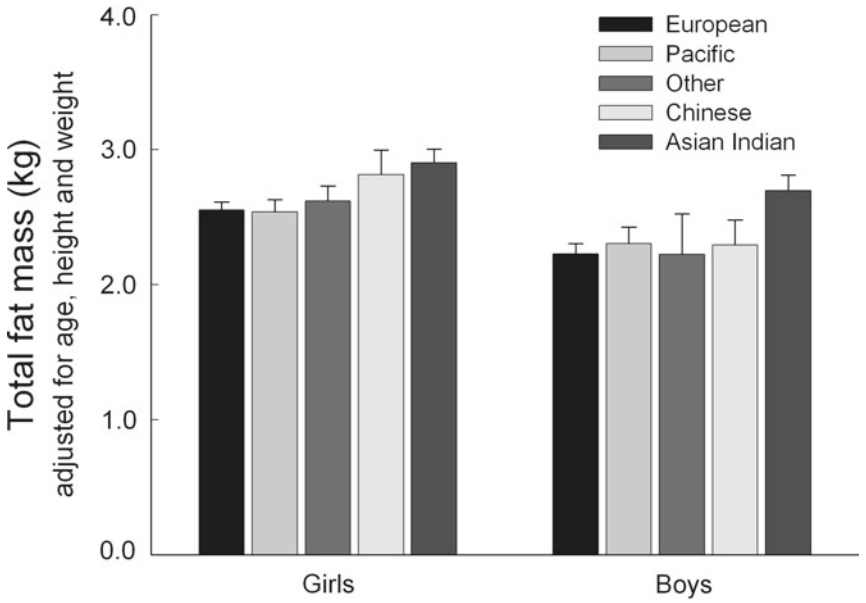

Fig. 160.4 Differences in total fat mass (kg) in 2-year-old children by sex and ethnicity. Differences in total fat mass (kg) adjusted for height, weight, and age in European, Pacific, Other, Chinese, and Asian-Indian girls and boys aged 2 years. All children's mothers were diagnosed with gestational diabetes mellitus during pregnancy (Rowan 2009 unpublished data)

hospitalization and mortality rates due to cardiovascular disease and the prevalence of self-reported diabetes are two and three times higher than that of the total population (Ministry of Health 2006).

Another example of intergenerational effect is gestational diabetes mellitus (GDM). GDM has a higher prevalence in non-European NZ ethnic groups. Children of mothers with GDM are born larger and are more likely to be obese and have type 2 diabetes in later life. The problem therefore may compound with successive generations. More studies and modeling are required to be able to target treatment to the most at-risk populations, with the greatest chance of reducing the risk and breaking the cycle. In the meantime, ethnic-specific measures of body composition may help identify those at higher risk and inform public health initiatives and health care across the lifespan.

Summary Points

- The relationship between BMI and body fatness is not linear, and varies by ethnicity.
- An understanding of the relationship between BMI and body-fat percentage in different ethnicities will enable a better prediction of disease risk.
- In general, women have about 10% more of their body weight as fat compared with men.
- BMI is more useful as a tool to help inform action points for populations, rather than as an arbitrary cutoff point for individuals.
- Increased weight for height is a risk factor for chronic disease in later life.
- The developmental origins of health and disease paradigm emphasize the importance of the intrauterine environment for future health.
- Birthweight is a strong predictor of future weight and therefore risk for vascular disease, as well as other diseases associated with increased weight for height.

Acknowledgments Participants, Sarah Bristow, Associate Professor Lindsay Plank and Dr Janet Rowan.

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Chapter 161
Anthropometric Measurements in Australian Aborigines

Srinivas Kondalsamy-Chennakesavan, Leonard S. Piers, Sidya Raghavan, and Kerin O'Dea

Abstract Aborigines have inhabited Australia for many thousands of years. They led a 'hunter-gatherer' lifestyle prior to European contact. They are known to have lower sitting-height to stature ratio with long legs, relatively short trunks and narrow across the torso and hips (a 'linear' body build). European expeditions in the early twentieth century confirm that overweight and obesity was rarely observed. In the second half of the twentieth century, the traditional lifestyle of Aborigines had transitioned to a westernised lifestyle. Associated with such a transition to western lifestyle is the epidemic of non-communicable chronic health conditions such as diabetes, cardio-vascular diseases and renal failure.

Average weight and Body Mass Index (BMI) of Aborigines have increased over time. However, this increase is not uniform across Aboriginal Australia. There are major differences in the body habitus profile between different clan groups/communities. In spite of these variations, the pattern of preferential central obesity in both men and women is uniform in almost all the communities. This could have provided a survival advantage under conditions of traditional lifestyle (with its 'feast-and-famine' pattern of food intake) experienced by Aborigines prior to European contact.

Our studies have shown that BMI significantly underestimated overweight and obesity when compared to other indices of body fat. Aborigines have preferential central fat deposition and exhibit consistently higher waist-hip ratios when compared to other Australians. Also, prevalences of overweight and obesity depend on the anthropometric definitions used. The relationship of surrogate estimates of body composition such as S4 for subcutaneous fat and height^2/resistance for FFM (fat free mass) to body weight and BMI are significantly different between Aboriginal people and European Australians.

Even at lower levels of body habitus profiles, Aborigines have increased risk for chronic conditions. Also, anthropometric characteristics differ substantially among different Aboriginal communities and stereotyping and generalisations should be avoided.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_161,

Abbreviations

ABS	Australian Bureau of Statistics
AHtR	Abdominal- height ratio
ASMM	Appendicular skeletal muscle mass
AusDiab	Australian diabetes, obesity and lifestyle study
BIA	Bioelectrical impedance analysis
BMD	Bone mineral density
BMI	Body mass index
CAT	Computer assisted tomography
CVD	Cardiovascular disease
DxA	Dual energy x-ray absorptiometry
FFM	Fat free mass
FM	Fat mass
IMT	Carotid intima-media thickness
MetS	Metabolic syndrome
MRI	Magnetic resonance imaging
NT	Northern territory
NZ	New Zealand
SA	South Africa
SFT	Skinfold thickness
VAT	Visceral adipose tissue
WA	Western Australia
WHO	World Health Organisation
WHR	Waist-hip ratio

161.1 Introduction

This chapter provides an overview of anthropometry amongst Australian Aborigines. Even though there are a number of measurements used in anthropometry, we have focussed on easily obtainable and commonly used measurements in clinical practice. This chapter is organised into three distinct parts. The first part deals with a review of published findings on anthropometric measurements (height, weight, and derived measurements such as BMI) by time period, age and gender. The second part examines the relationship of adiposity and body-fat distribution to BMI in Australians of Aboriginal and European ancestry. The final part addresses applications to other areas of health and disease.

161.2 Part 1: A Brief Background

Aborigines have inhabited Australia for many thousands of years. They have adapted to the harsh environmental conditions that vary from warm and humid tropical climate in the north to colder climate in the south. They had led a hunter-gatherer, nomadic life in the past. However, their lifestyle has undergone dramatic changes since European settlement, and contemporary Aborigines, with few exceptions, lead a westernised way of life. A number of studies have shown that the anthropometric

measurements of Aborigines are different when compared to other ethnic groups. The relationships of these measurements to health and diseases are also different amongst Aborigines when compared to non-Aborigines. The current health status of Aborigines is one of the poorest in the developed world with major disparities in life expectancy when compared to the Australian population.

For part one, a literature review was conducted to retrieve information on anthropometric measurements. The traditional lifestyle of Australian Aborigines changed most dramatically in the latter half of the twentieth century. This necessitated reviewed studies to be classified as those done prior to the year 1970 where the impact of westernisation was much less pronounced and those done later. This arbitrary cutoff also serves to assess the changes in body habitus profiles of contemporary Aborigines in comparison with the profiles documented earlier. Studies conducted prior to the 1970s collected a number of anthropometric features ranging from skeletal measurements to the commonly used measures of height and weight. These studies had different aims, with some trying to elucidate the origin of Aborigines or trace their ancestry, whereas others focussed on evaluation of health status. We have also obtained and analysed original data on 383 Aborigines (203 men and 179 women) collected by Abbie between 1957 and 1963 and used in his seminal publications (Abbie 1957, 1968; Macho and Freedman 1987).

As this part of the chapter focuses on commonly used measurements that are clinically useful, we have extracted details on height and weight and calculated BMI. The methods and the environment in which these measurements were taken differed significantly between the studies. It is beyond the scope of this chapter to illuminate the similarities and differences in the methodology and readers are advised to consult the original publications for detailed information.

Similar measurements from studies conducted after 1970 have also been reviewed to provide an overview of anthropometric measurements of contemporary Australian Aboriginal adults. The survey conducted by the Australian Bureau of Statistics (ABS) in 1994 is the only national survey of Aborigines where height and weight were measured and collected. Apart from this survey, a number of researchers have conducted independent studies on a smaller scale in different geographical regions. The objectives of these smaller studies varied greatly – some were community-wide health assessments and others were targeted studies evaluating risk factors for diabetes, cardiovascular disease and/or other health-care conditions. Most studies have focussed on Aborigines living in remote areas, despite over 70% of the Indigenous population living in urban centres.

Detailed information on anthropometric measurements from nine major studies was used for this review. Six of these studies were conducted prior to 1970 and will be presented first followed by studies done later. Amongst these six, four studies included Aborigines in the Northern Territory (NT) (Campbell et al. 1936; Howells 1937; Macho and Freedman 1987); the fifth study included Aborigines in the NT and Western Australia (WA) (Prokopec 1977) and the sixth study was conducted in Queensland (Douglas 2005). Norgan (1994) reviewed five of these studies and compiled information related to body mass indices and provided detailed interpretation of low BMI in Australian Aborigines. Norgan's work shows that the mean BMI amongst men varied from 18.8 kg/m^2 in Beswick to 23.8 kg/m^2 in the southeast. Similarly, average BMI amongst women varied from 17.6 kg/m^2 in Arnhem Land to 23.2 kg/m^2 in Yalata. Overall, men and women had an average BMI of 20.3 and 19.2 kg/m^2, respectively. The only other study prior to 1970 but not included in Norgan's review was conducted in 1965 amongst Cape York Aborigines. This study reported that the average BMI amongst men and women was 18.7 and 19.9 kg/m^2, respectively (Douglas 2005). Even though these studies were conducted amongst different clan groups and communities from a wide geographical area, the uniform pattern of slender build with low average BMI remains uniform.

Figure 161.1 shows the results of our reanalyses of Abbie's data collected between 1951 and 1963 by age group and gender. As expected, men were taller than women. While heights fluctuated across the age groups, numbers were small. Men were generally lean with a mean BMI fluctuating around

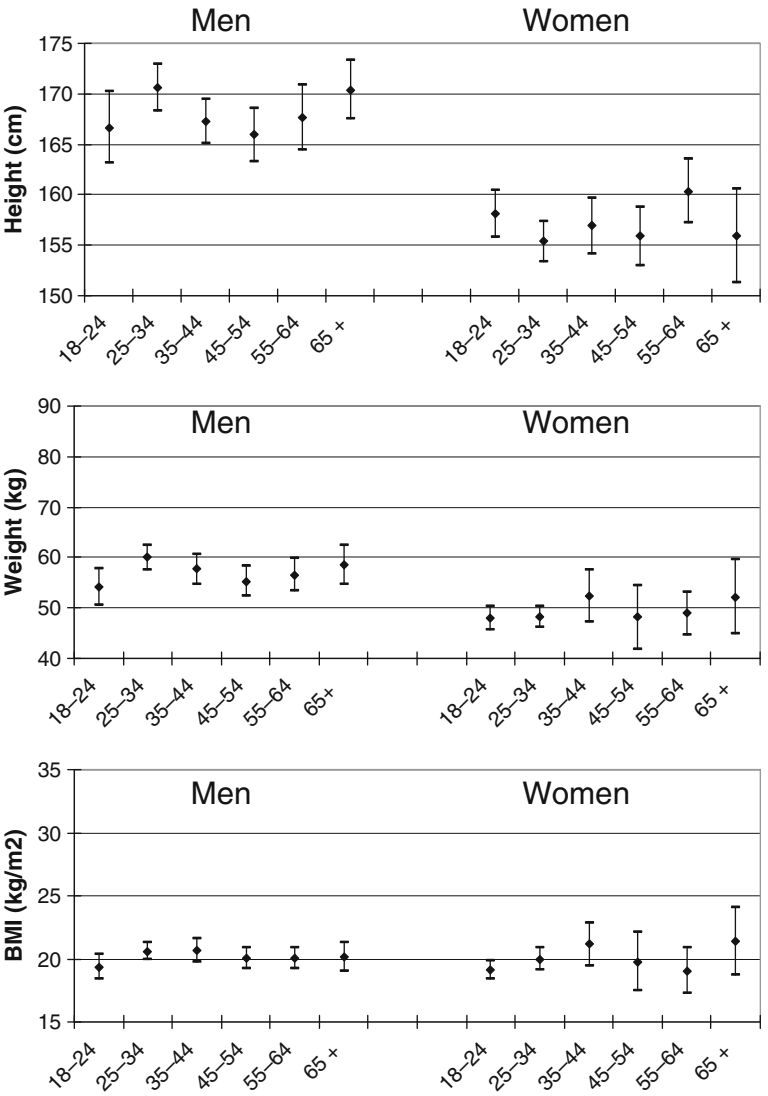

Fig. 161.1 Mean height, weight and BMI with 95% CI by sex and age groups. (Source: Data collected by Abbie between 1957–1961 and obtained from http://www-personal.une.edu.au/~pbrown3/resource.html)

20 kg/m^2. BMI in women also fluctuated around 20 kg/m^2, and varied more widely in the older age groups. None of the variations with age were statistically significant.

As noted above, we have presented anthropometric measurements from three of the studies conducted after 1970. One of these three was a national survey of Aboriginal and Torres Strait Islanders conducted by the Australian Bureau of Statistics in 1994 (Cunningham and Mackerras 1998), whereas the other two were our studies in remote NT and central Australia between 1995 and 2003 (Kondalsamy-Chennakesavan et al. 2008a; Piers et al. 2003).

Figure 161.2 shows height, weight and BMI by age groups and gender based on the national survey of Aboriginal and Torres Strait Islanders (Cunningham and Mackerras 1998). Height in Aboriginal males tended to fall slightly with age until age 65+. Females were shorter with a trend towards shorter stature from the age of 45 years. Amongst males, weight and BMI rose up to the age of 44 years after which there were declines. In women, weight and BMI increased steadily up to the age of 64 years after which they fell.

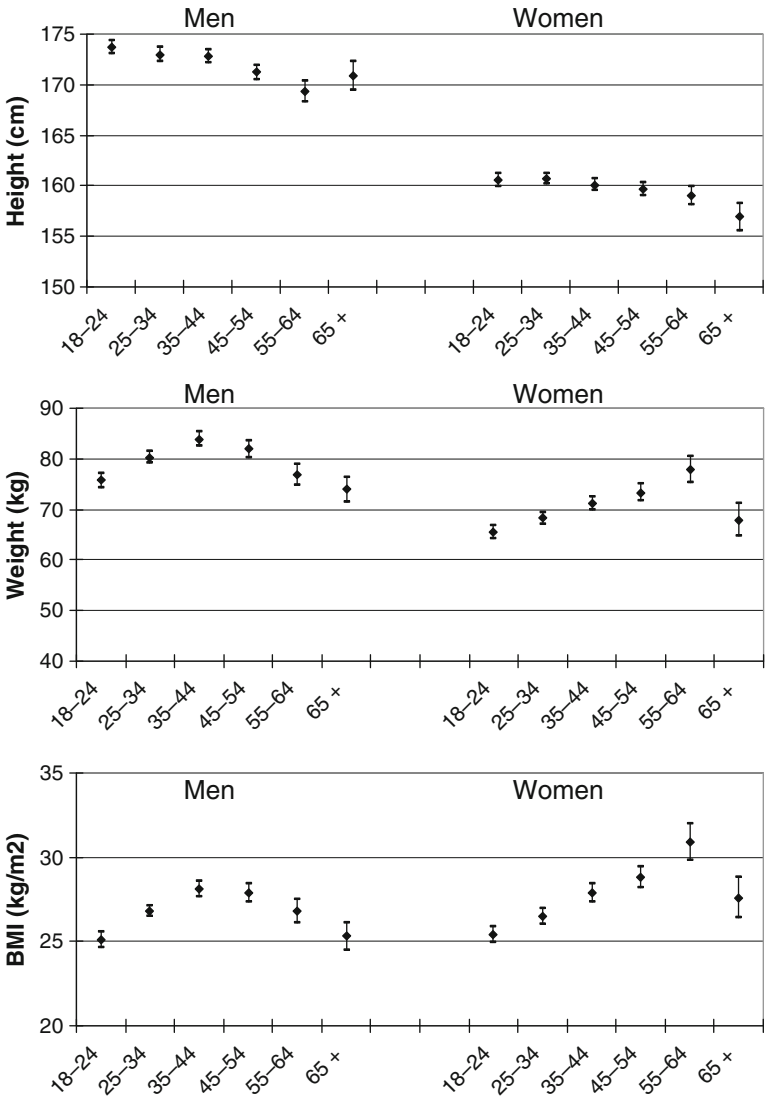

Fig. 161.2 Mean height, weight and BMI with 95% CI by sex and age groups (Source: NATSIS 1994)

We have previously published information on anthropometric measurements of Aborigines living in three remote communities (Wadeye, Nauiyu and Borroloola) and compared them with a nationally representative survey (AusDiab) in Australia (Kondalsamy-Chennakesavan et al. 2008a). In brief, these communities were in the Top End of the Northern Territory. Body habitus profiles were collected using standardised methods as part of a chronic disease screening and management program. Figure 161.3 shows the extent to which these Aboriginal communities differ in their anthropometric measurements. The average differences in waist circumference between communities were as high as 12 cm amongst men and 6 cm amongst women. Similarly, average differences in weight were as high as 19 kg in men and 16 kg in women. The most striking differences between the Aboriginal populations and AusDiab were the marked differences in body-fat distribution. In contrast to AusDiab participants, in the Aboriginal populations both men and women exhibited a central fat deposition with little difference between the sexes.

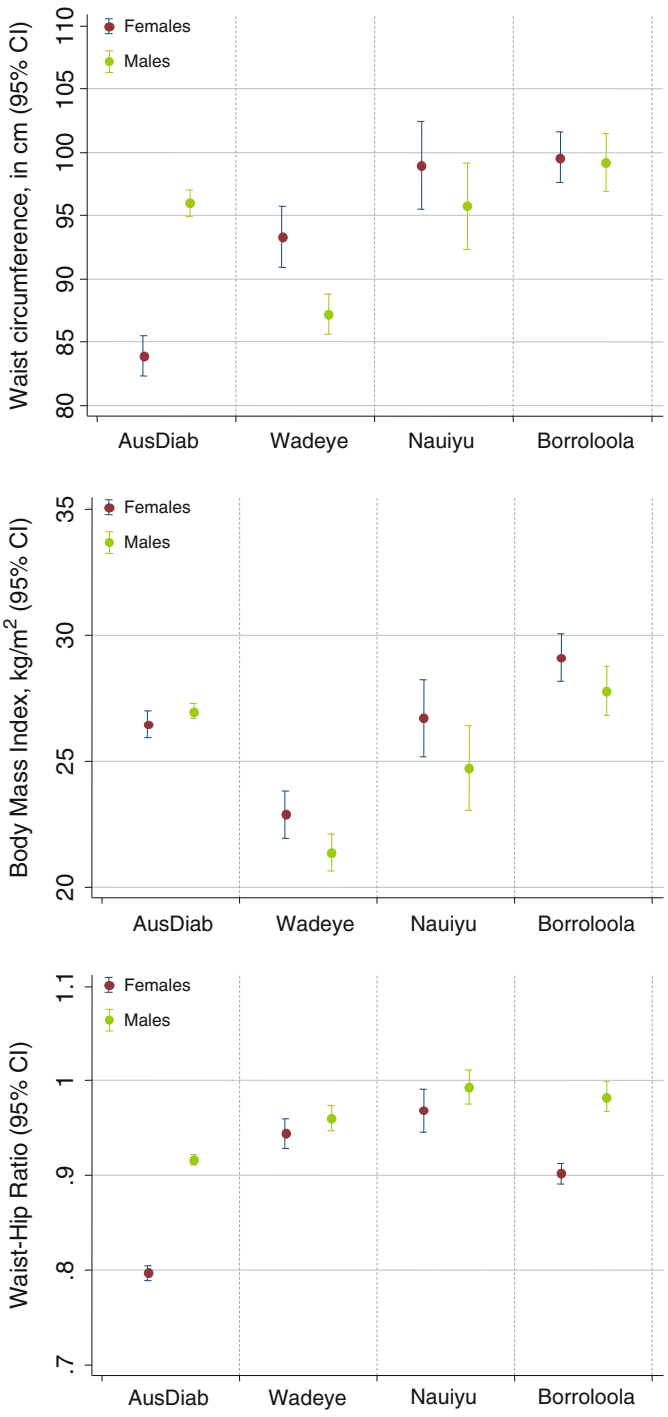

Fig. 161.3 Selected anthropometric measurements by sex and community (Source: Kondalsamy-Chennakesavan et al. (2008a) (printed with permission))

Table 161.1 shows rates of overweight and obesity by community and gender. Amongst females, when compared to their AusDiab counterparts, Aboriginal women from all the three communities had significantly ($P < 0.001$) higher rates of overweight and/or obesity by any definition, with the exception of females in Wadeye who had a lower prevalence by BMI. When compared to their AusDiab

Table 161.1 Prevalences of obesity and overweight by community and gender (Source: Kondalsamy-Chennakesavan et al. 2008a)

	Females					Males				
	Australians	Wadeye	Nauiyu	Borroloola	P[a]	Australians	Wadeye	Nauiyu	Borroloola	P[a]
Obese by BMI	22.7%	10.8%	31.5%	42.1%	<0.001	19.7%	2.6%	12.7%	33.6%	<0.001
Overweight and or obese by BMI	52.2%	28.5%	61.6%	70.2%	<0.001	67.8%	14.1%	40.0%	66.4%	<0.001
Obese by WC	33.4%	65.9%	72.7%	76.5%	<0.001	26.2%	8.6%	20.4%	45.1%	<0.001
Overweight and or obese by WC	56.0%	87.0%	87.0%	92.9%	<0.001	54.7%	19.6%	44.9%	66.2%	<0.001
Obese by WHR	20.5%	90.4%	89.3%	76.8%	<0.001	9.2%	25.0%	39.5%	43.1%	<0.001
Overweight and or obese by WHR	45.3%	93.6%	97.3%	96.3%	<0.001	58.0%	70.6%	86.0%	87.1%	<0.001

BMI Body Mass Index; *WC* Waist Circumference; *WHR* Waist-Hip Ratio

[a]Significance test for differences in the distribution

counterparts, Aboriginal males in Wadeye and Nauiyu were significantly ($P < 0.001$) less overweight and/or obese by BMI and waist circumference. In contrast, using the waist–hip ratio criterion, Aboriginal males from all the three communities were significantly ($P < 0.001$) more overweight and/or obese. In aggregate, the proportions of Aboriginal and AusDiab females with BMI ≥25 were similar. In contrast, proportionally less Aboriginal males had BMI ≥25 than their AusDiab counterparts (37% vs. 68%, $P < 0.001$). Waist circumference classified many more Aboriginal than AusDiab women as overweight or obese (89.7% vs. 56%, $P < 0.001$), but fewer Aboriginal than AusDiab men (41.2% vs. 54.7%, $P < 0.001$). By waist–hip ratio, almost all Aboriginal people of both sexes were overweight or obese, at levels vastly higher than the AusDiab data, 95.6% vs. 45.3% for females ($P < 0.001$), and 78.7% vs. 58% for men ($P < 0.001$) (Kondalsamy-Chennakesavan et al. 2008a).

There are a number of factors influencing the nutritional status of contemporary Aborigines. Some of these factors are probably genetic; however, there are important socio-environmental and lifestyle-related influences. Age also seems to be a strong determinant of body habitus profiles. Lower body weight in those aged 65+ amongst both men and women may suggest a 'cohort phenomenon' related to different social-environmental influences early in their lives. It is also possible that this phenomenon represents a 'healthy survivor' effect as more than half the Aboriginal population died by the age of 55 years (Kondalsamy-Chennakesavan et al. 2008a).

To summarise, when compared to the studies conducted prior to 1970, recent studies have shown that the average weight has increased significantly in recent years. There is also a significant difference in average waist–hip ratios between Aborigines and non-Indigenous Australians. However, these changes and differences are not uniform across Aboriginal Australia and there are wide variations between Aboriginal communities.

161.3 Part 2: The Relationship of Adiposity and Body-Fat Distribution to Body Mass Index (BMI) in Australians of Aboriginal and European Ancestry

161.3.1 A Brief Background and Methods

Body mass index (BMI) and the waist-to-hip circumference ratio (WHR) are now used conventionally as indices of obesity and fat distribution in epidemiological studies. Although some general limitations of these indices are recognised, there are others that affect their use in relative risks for disease which are not well recognised. For example, differences in sex, ethnicity and especially age can result in substantial misclassification of obesity and fat distribution (Baumgartner et al. 1995). Cutoff points for obesity as defined by the WHO are based on BMI values. However, these cutoff points are based on studies on the relationship between BMI and morbidity and mortality in Western populations (Lew and Garfinkel 1979; WHO 1990).

We have previously shown that BMI has poor sensitivity and positive predictive value in identifying overweight/obese individuals when classified by per cent body fat, measured using deuterium dilution, in Australians of European ancestry (Piers et al. 2000). In recent years, several studies have shown a different relationship between BMI and per cent body fat amongst ethnic groups. For example, Gurrici et al reported that Indonesians had, for the same per cent body fat, a BMI about 3 units lower than Dutch Europeans (Gurrici et al. 1998). A meta-analysis of available data likewise showed that there were differences in the relationship of BMI to per cent body fat between various ethnic groups (Deurenberg et al. 1998).

Australian Aboriginal people have an extremely high and increasing prevalence of obesity, with its associated health problems (Cunningham and Mackerras 1998). Amongst adults aged 18 years or more, about 25% of Aboriginal men and 28% of Aboriginal women may be classified as obese based on measures of BMI (McLennan and Madden 1999). Furthermore, in addition to the absolute amount of body fat, anatomical distribution is important as it is a known risk factor for ill health. While BMI, WHR and waist circumference have been shown to be powerful independent predictors of type 2 diabetes (Carey et al. 1997; Ledoux et al. 1997), there is evidence that WHR is a better screening measure for type 2 diabetes risk than BMI (Haffner et al. 1992).

As body-fat distribution may also vary between ethnic groups (Baumgartner et al. 1995; Gasperino 1996; Lovejoy et al. 2001), we were interested in determining if body weight, BMI and body-fat distribution were related in the same manner to body composition in young (18–35 years of age), healthy (non-diabetic) Australians of Aboriginal and European ancestry. The methods used and detailed results have been published earlier (Piers et al. 2003). In brief, we analysed data from 397 participants: 250 Aboriginal people (120 women and 130 men) and 147 European Australians (100 women and 47 men). Participant characteristics are presented in Table 161.2.

161.3.2 Results

161.3.2.1 Differences in Anthropometric Measurements Between Aborigines and Europeans

Aboriginal people were significantly shorter and weighed less than their European Australian counterparts. While mean BMI was similar in women ($P = 0.285$), Aboriginal women had significantly greater mean waist circumference and mean waist-to-hip ratios ($P < 0.0005$) compared to European Australian women. In contrast, mean BMI was significantly lower in Aboriginal men compared to European Australian men ($P = 0.011$), and waist-to-hip ratio was significantly ($P = 0.007$) higher in Aboriginal men compared to European Australian men.

Skinfold thickness (SFT) measurements are said to provide an estimate of the size of the subcutaneous fat depot, which in turn provides an estimate of total body fat (Durnin and Rahaman 1967). Such estimates are based on two assumptions: (a) the thickness of the subcutaneous fat reflects a constant proportion of the total fat and (b) the skinfold sites selected for measurements, either singly or in combination, represent the average thickness of the entire subcutaneous tissue (Lukaski 1987). In addition, it is still unclear if ethnic-specific equations are required to estimate FFM (fat-free mass) and FM (fat mass) using bioelectrical impedance analysis (BIA) (Ellis et al. 1999) as there is evidence of population specificity in the validity of BIA (Chertow et al. 1997). As such, we chose to compare directly measured variables (SFT and height^2/resistance) rather than derived estimates of FM and FFM using regression equations generated from data that did not include Aboriginal people. We also restricted the analysis to healthy young people aged between 18 and 35 years, analysed data from women and men separately, and excluded pregnant women altogether.

161.3.2.2 Differences in Skinfold Thickness Between Aborigines and Europeans

The mean sum of the four skinfold thicknesses (S4) was higher in Aboriginal women compared to European Australian women ($P < 0.0005$). While their mean trunk SFT was significantly higher ($P < 0.0005$), the limb SFT of Aboriginal women tended to be lower than that of European Australian

Table 161.2 Participant characteristics

	Women				Men			
	European Australians (n = 100)		Aboriginal Australians (n = 120)		European Australians (n = 47)		Aboriginal Australians (n = 130)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	24.5	3.5	25.3	4.7	25.8	4.2	24.8	5.3
Height (cm)	165.8	6.9	160.2[a]	5.5	178.8	7.2	172.1[a]	6.3
Weight (kg)	60.2	6.9	57.3[a]	10.8	76.3	10.5	66.8[a]	11.1
Body Mass Index (kg/m^2)	21.9	2.2	22.3	4.1	23.8	2.6	22.5[a]	3.2
Waist (cm)	68.5	5.0	77.7[a]	11.3	80.7	8.2	79.7	9.2
Hip (cm)	94.0	10.7	92.7	8.5	97	5.9	93.2[a]	6.6
Waist to Hip ratio (WHR)	0.72	0.04	0.84[a]	0.07	0.83	0.05	0.85[a]	0.06
Height^2/resistance (cm^2/Ω)	45.1	5.4	36.3[a]	5.4	67.6	7.5	52.7[a]	8.4
	Geometric mean	95%CI	Geometric mean	95%CI	Geometric mean	95%CI	Geometric mean	95%CI
Sum of 4 skinfold thicknesses (mm)	54.5	51.3, 57.9	68.7[a]	63.5, 74.3	42.0	37.4, 47.1	42.2	39.7, 46.0
Limb SFT (mm)	25.8	24.3, 27.5	23.6	21.9, 25.3	13.7	12.2, 15.5	13.5	12.6, 14.5
Trunk SFT (mm)	28.3	26.4, 30.2	44.6[a]	41.0, 48.7	27.9	24.6, 31.5	28.9	26.6, 31.4

[a]Significantly different ($P < 0.05$) from European Australians of same sex

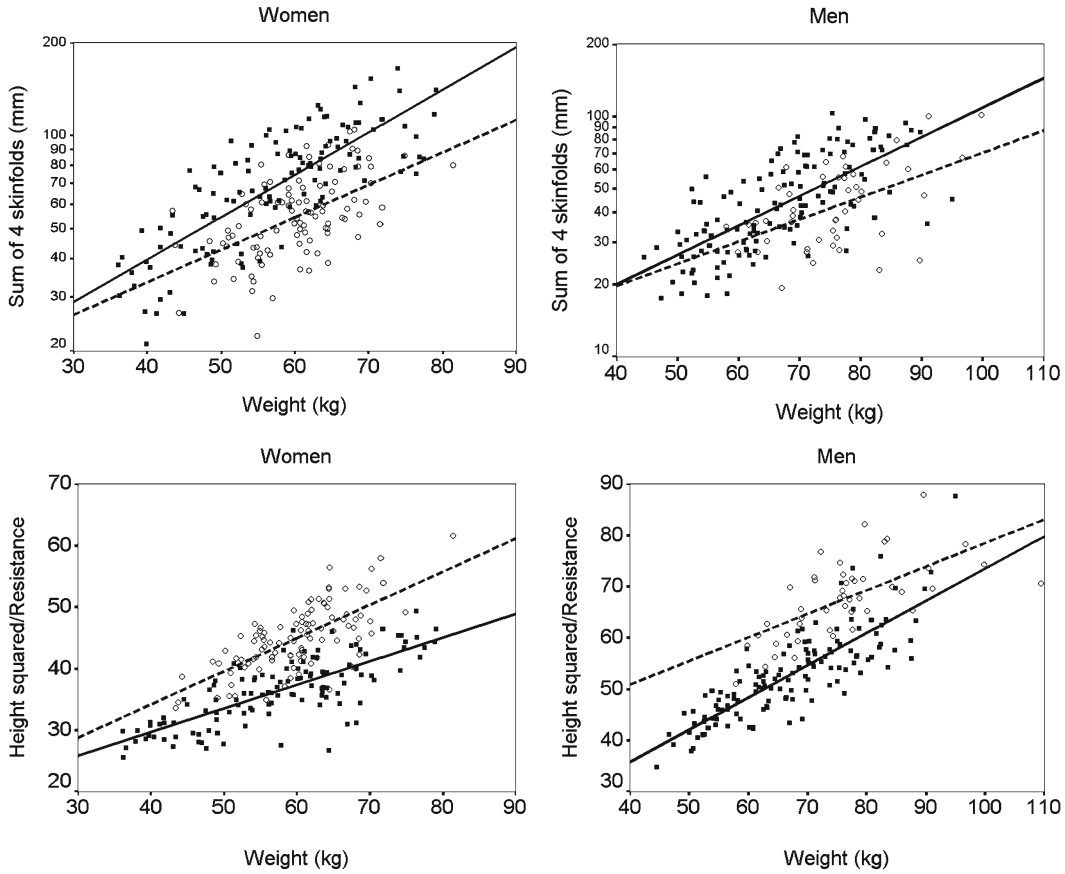

Fig. 161.4 Relationship of body weight to surrogate measures of fat mass (Sum of 4 skinfold thicknesses) and fat-free mass (height^2/resistance) in Australians of Aboriginal (*filled squares*, *solid line*) and European (*open circles*, *broken line*) ancestry

women ($P = 0.06$). There was no significant difference in S4 between Aboriginal and European Australian men ($P = 0.485$), nor were there significant differences in limb and trunk SFT. Both Aboriginal men and women had significantly higher ($P < 0.0005$) mean resistance values, but significantly lower ($P < 0.0005$) height^2/resistance ratios compared to their European Australian counterparts.

161.3.2.3 Relationship of Body Weight and BMI to Surrogate Measures of Fat Mass and Fat-Free Mass

Figures 161.4 and 161.5 show the relationships of body weight and BMI to $\log_{10}$ S4, and height^2/resistance, by sex and ethnicity. On modelling body weight in women as a function of ethnicity, $\log_{10}$ S4, height^2/resistance, height and their interactions, there was no significant interaction between ethnicity and any of the other independent variables ($P > 0.05$). However, the coefficient for ethnicity was significant ($P = 0.01$), with Aboriginal women being 2.0 kg heavier, for the

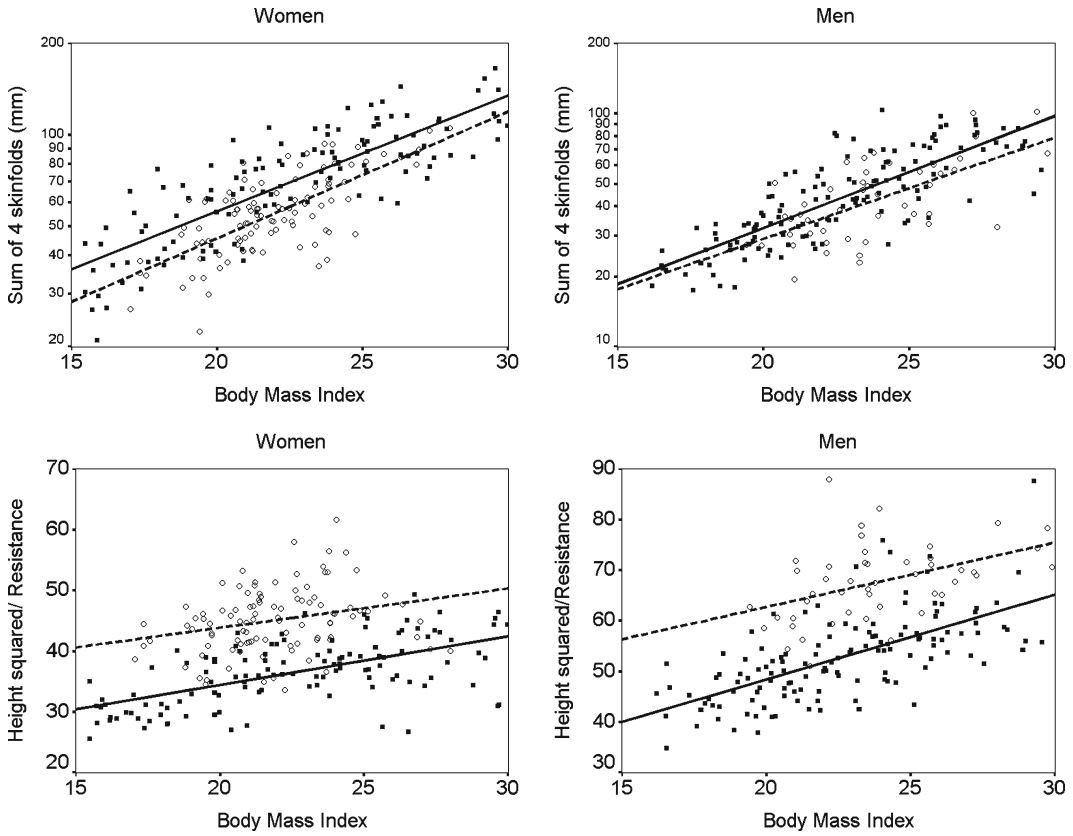

Fig. 161.5 Relationship of body mass index (kg/m^2) to surrogate measures of fat mass (sum of 4 skinfold thicknesses) and fat-free mass (height^2/resistance) in Australians of Aboriginal (*filled squares*, *solid line*) and European (*open circles*, *broken line*) ancestry

same height, $\log_{10}$ S4 and height^2/resistance values, than their European Australian counterparts. On modelling body weight in men as a function of ethnicity, $\log_{10}$ S4, height^2/resistance, height and their interaction terms, there was no significant interaction between ethnicity and any of the other independent variables ($P > 0.05$). However, the coefficient for ethnicity was significant ($P < 0.00005$), with Aboriginal men being 3.8 kg heavier, for the same height, $\log_{10}$ S4 and height^2/resistance values, than their European Australian counterparts (Fig. 161.4).

On modelling BMI in women as a function of ethnicity, $\log_{10}$ S4, height^2/resistance and their interactions, there was a significant interaction between $\log_{10}$ S4 and ethnicity ($P < 0.01$). Because of this interaction, the coefficient of the ethnicity variable could not be interpreted, except to say that the relationship of $\log_{10}$ S4 and height^2/resistance to BMI was different between the two ethnic groups (Fig. 161.5). On modelling BMI in men as a function of ethnicity, $\log_{10}$ S4, height^2/resistance and their interactions, the interaction terms were not significant ($P > 0.05$). However, the coefficient for ethnicity was significant ($P < 0.05$). Hence, for any given combination of S4 and height^2/resistance, Aboriginal men had a BMI that was ~1.2 kg/m^2 higher than European Australian men (Fig. 161.5). As the analysis was restricted to those who were 18–35 years of age, 'age' was not included in any of the analyses.

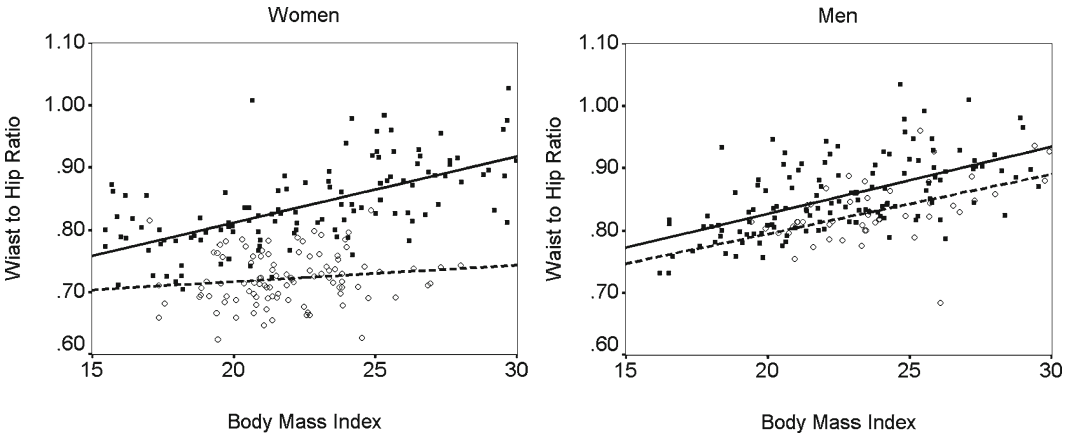

Fig. 161.6 Relationship of waist-to-hip circumference ratio with body mass index (kg/m^2) in Australians of Aboriginal (*filled squares*, *solid line*) and European (*open circles*, *broken line*) ancestry

161.3.2.4 Relationship of Waist-to-Hip Circumference to Body Mass Index

Figure 161.6 shows the relationship of WHR to BMI in Aboriginal and European Australian men and women. On modelling WHR as a function of BMI and ethnicity in women, Aboriginal women had significantly greater WHR ($P < 0.0005$), but as there was significant interaction between ethnicity and BMI ($P = 0.01$), this difference could not be quantified. Aboriginal men had a WHR that was 0.036 units higher for any given BMI compared to European Australian men ($P < 0.0005$).

161.3.3 Discussion

If one accepts that S4 is a surrogate marker of subcutaneous FM and height^2/resistance representative of FFM, then for the same S4, height^2/resistance and height, both Aboriginal men and women had a higher body weight, by 3.8 and 2.0 kg, respectively, compared to their European Australian counterparts. We assume that part of this difference in body weight was due to non-subcutaneous fat, as this component of FM was not accounted for in the regression model. Given the significantly higher WHR, in both Aboriginal men and women when compared to the corresponding European Australian group, we speculate that this unaccounted body weight was probably intra-abdominal visceral fat. Direct methods of body composition, such as computer assisted tomography (CAT) and/or magnetic resonance imagining (MRI), would be required to confirm this.

Our results indicate that this group of Aboriginal women was shorter and proportionately less heavy than European Australian women, and consequently had a similar mean BMI. However, while Aboriginal men were also shorter, they weighed considerably less than European Australian men and therefore had a significantly lower mean BMI. Nevertheless, for any given combination of S4 (subcutaneous fat) and height^2/resistance value (fat-free mass), Aboriginal men had a BMI that was approximately 1.2 kg/m^2 greater than European Australian men. This would indicate that for any given BMI, the ratio of FM to FFM was greater in Aboriginal men. The significant interaction of ethnicity and body composition variables in women indicated that the relationship of these surrogate measures of body composition to BMI was significantly different in the two ethnic groups. However, the magnitude of the difference could not be assessed.

The data support the results of the WHO consultation on obesity which, while recommending BMI be used to classify obesity, recognise that Aboriginal Australians "…*tend to have a deceptively low BMI; a healthy BMI for this range appears to be between 17 and 22*, …" (WHO 1998). Subsequently, the WHO also released provisional recommendations that overweight and obese BMI cutoff points for Asian populations in the Asia-Pacific region be reduced to 23 and 25 kg/m^2, respectively (WHO 2000).

Differences in SFT and WHR between Aborigines and Europeans are more pronounced in women than in men. Indeed, the differences in body build/composition between women and men are much less apparent amongst Aborigines than amongst Europeans. This is consistent with the chronic disease risk profiles: Aboriginal women have little, if any, gender protection against CVD and diabetes (O'Dea et al. 1993). Aboriginal men in this study (Piers et al. 2003) had significantly narrower hips, an observation that has been made before (Abbie 1957), but had a similar mean waist circumference compared to European Australian men. A difference in hip circumference between Aboriginal and European Australian women was not evident; but Aboriginal women had a significantly greater waist circumference. Consequently, both Aboriginal men and women had significantly greater mean waist-to-hip circumference ratios, as compared to their European Australian counterparts, suggesting that they have a greater mass of abdominal fat even at this young age. This difference was evident at any level of BMI (up to 30 kg/m^2). The health risks associated with centrally deposited fat are well documented (Pi-Sunyer 1993). Our observations on waist circumference and WHR are in keeping with observations made in an earlier study involving Aboriginal Australians (Rowley et al. 1997). They are also consistent with the significantly higher prevalence and incidence of risk factors in Aboriginal Australians for the insulin resistance syndrome, as compared to the general Australian population (Daniel et al. 1999). Wang and Hoy, after investigating waist circumference, waist-to-hip ratio, BMI, and weight and hip circumference as risk factors for type 2 diabetes in Aboriginal Australians, also concluded that waist circumference is the best body-size measurement in predicting diabetes in Aboriginal people (Wang and Hoy 2004). This is consistent with most studies in homogeneous populations. However, when making comparisons across different ethnic groups, the best differentiator is WHR as it better accounts for differences in body build (Maple-Brown et al. 2007a, b).

161.3.3.1 Comparison with Other Studies in Australian Aborigines

In 16 Australian Aboriginal women and 16 healthy age- and weight-matched Caucasian women using dual-energy X-ray absorptiometry, Raja et al reported that body composition showed no significant ethnic differences in height, total body bone mineral density, total and appendicular skeletal muscle mass, and per cent body fat (Raja et al. 2003). The lack of difference may have been related to significant non-Aboriginal (European) admixture in this very small group of urban Indigenous women. Most other reports have reached different conclusions. For example, Kagawa et al compared ethnic differences in anthropometry, including size, proportions and fat distribution, and body composition in a cohort of 70 Caucasian Australian (44 boys, 26 girls) and 74 urban Australian Indigenous (36 boys, 38 girls) children (aged 9–15 years) (Kagawa et al. 2009). Anthropometric measures (stature, body mass, eight skinfolds, thirteen girths, six bone lengths and five bone breadths) and body composition assessment using dual-energy X-ray absorptiometry were conducted. Body composition variables, including total body-fat percentage and percentage abdominal fat, were determined and, together with anthropometric indices, including BMI (kg/m^2), abdominal:height ratio (AHtR) and sum of skinfolds, ethnic differences were compared for each sex. After adjustment for age, Indigenous girls showed significantly ($P < 0.05$) greater trunk circumferences and proportion of overweight and obesity than their Caucasian counterparts (Kagawa et al. 2009).

Furthermore, Sellers et al recently described the prevalence and clinical characteristics of the metabolic syndrome (MetS) in a cohort of Australian Aboriginal children (Sellers et al. 2008). They measured BMI, waist circumference, skin fold thickness, body-fat percentage, insulin resistance and the prevalence of metabolic syndrome in 486 children aged 9–14 years from the Darwin Health Region in the Northern Territory. Using an age- and sex-specific definition, 14% of the children in the cohort had metabolic syndrome, 6.4% were overweight, 4.9% were obese and 26.2% had an elevated waist circumference. Waist circumference was significantly associated with insulin resistance as measured by the 'Homeostasis Model Assessment of Insulin Resistance' ($P < 0.001$). They concluded that measurement of waist circumference may help identify Aboriginal children at high risk for metabolic syndrome (Sellers et al. 2008).

161.3.3.2 Comparison with Similar Studies on Aboriginal People in Other Countries

Leslie et al carried out a study to determine if ethnic differences in body composition affect differences in bone mineral density (BMD) between Canadian white and Aboriginal women (Leslie et al. 2008). An age-stratified population-based sample of 206 Aboriginal women and 177 white women underwent multisite bone density measurements and total body soft tissue composition analysis. The authors reported that the ratio of lean mass to fat mass was lower in Aboriginal than white women ($p < 0.001$). When BMD was adjusted for body composition variables, no significant difference was observed between Aboriginal and white women. Apparent ethnic differences in weight- and BMI-adjusted BMD between Canadian white and Aboriginal women were explained by a lower ratio of lean mass to fat mass in Aboriginal women, combined with a smaller increment in BMD from fat mass versus lean mass in both populations (Leslie et al. 2008). In another Canadian study, Silha et al compared the relationship between body composition, insulin resistance and inflammatory adipokines in Aboriginal Canadian women, who are at high risk of vascular disease, with white Canadian women. A subgroup of the First Nations Bone Health Study population, consisting of 131 Canadian Aboriginal women and 132 matched white women, was utilised. Body composition was determined by whole-body dual X-ray absorptiometry, and blood analytes were measured after an overnight fast. First Nation (Aboriginal) women were more insulin resistant than white women, and this was explained by trunk fat, but not total fat. Despite the increased insulin resistance, inflammatory adipokines are not significantly increased in First Nation (Aboriginal) women compared with white women (Silha et al. 2007).

Lear and co-workers investigated if body-fat distribution differs across ethnic groups in Canada (Lear et al. 2007a). They compared the relation between abdominal adipose tissue and total body fat amongst persons living in Canada of Aboriginal, Chinese and South Asian origin with persons of European origin. They reported that BMI significantly underestimated visceral adipose tissue (VAT) in all non-European groups. Throughout a range of total body fat mass, VAT was not significantly different between the Aboriginals and the Europeans. With total body fat >9.1 kg, Chinese participants had increasingly greater amounts of VAT than did the Europeans. The authors concluded that compared with Europeans, the Chinese and South Asian cohorts had a relatively greater amount of abdominal adipose tissue, and this difference was more pronounced with VAT. No significant differences were observed between the Canadian Aboriginals and the Europeans. In a related study, Lear et al hypothesised that VAT was an independent risk factor for atherosclerosis (Lear et al. 2007b). They studied healthy men and women ($n = 794$), matched for ethnicity (Canadian Aboriginal, Chinese, European and South Asian), and BMI range (<25, 25 to 29.9, or ≥30 kg/m^2) and assessed VAT (by computed tomography scan), carotid atherosclerosis (by ultrasound), total body fat, cardiovascular risk factors, lifestyle and demographics. They observed that VAT was associated

with carotid intima-media thickness (IMT), plaque area and total area (IMT area and plaque area combined) after adjusting for demographics, family history, smoking and per cent body fat in men and women. In men, VAT was associated with IMT and total area after adjusting for insulin, glucose, homocysteine, blood pressure and lipids. This association remained significant with IMT after further adjustment for either waist circumference or the waist-to-hip ratio. In women, VAT was no longer associated with IMT or total area after adjusting for risk factors. The authors concluded that VAT is the primary region of adiposity associated with atherosclerosis and likely represents an additional risk factor for carotid atherosclerosis in men. Most, but not all, of this risk can be reflected clinically by either the waist circumference or waist–hip ratio measures (Lear et al. 2007b).

161.3.3.3 Studies from Multi-Ethnic Populations

Rush et al investigated body-size and body-fat relationships and fat distribution in young healthy men drawn from New Zealand European, Pacific Island, and Asian Indian populations (Rush et al. 2004). A total of 114 healthy men (64 European, 31 Pacific Islanders, 19 Asian Indian) aged 17–30 years underwent measurements of height, weight and body composition by total body dual-energy X-ray absorptiometry (DXA). For the same BMI, per cent body fat (%BF) for Pacific Islander men was 4% lower and, for Asian Indian men, was 7–8% higher, compared to Europeans. Compared to European men for the same %BF, BMI was 2–3 units higher for Pacific Islanders and 3–6 units lower for Asian Indians. The ratio of abdominal fat to thigh fat, adjusted for height, weight and %BF, was significantly higher for Asian Indian men than European ($P = 0.022$) and Pacific Island ($P = 0.002$) men. Appendicular skeletal muscle mass (ASMM), adjusted for height and weight, was highest in Pacific Island and lowest in Asian Indian men. The authors concluded that the relationship between %BF and BMI is different for European, Pacific Island and Asian Indian men which may, at least in part, be due to differences in muscularity. Asian Indians have more abdominal fat deposition than their European and Pacific Island counterparts. Use of universal BMI cutoff points is not appropriate for comparison of obesity prevalence between these ethnic groups (Rush et al. 2004).

Rush et al also investigated body composition differences, especially the relationship between BMI and per cent body fat (%BF), amongst five ethnic groups of women (Rush et al. 2007). Seven hundred and twenty-one apparently healthy women aged 18–60 years (BMI: 17.4–54.0 kg/m^2) were from South Africa (SA, 201 black, 94 European) and New Zealand (NZ, 173 European, 76 Maori, 84 Pacific, 93 Asian Indian). Anthropometry, including waist circumference, and total, central and peripheral body fat, bone mineral content and ASMM derived from dual X-ray absorptiometry were obtained. The authors reported that at a BMI of 30 kg/m^2, SA European women had a %BF of 39%, which corresponded to a BMI of 29 for SA black women. For a BMI of 30 kg/m^2 in NZ Europeans, equivalent to 43% body fat, the corresponding BMIs for NZ Maori, Pacific and Asian Indian women were 34, 36 and 26 kg/m^2, respectively. Central fat mass was lower in black SA than in European SA women ($P < 0.001$). In NZ, Pacific women had the lowest central fat mass and highest ASMM, whereas Asian Indian women had the highest central fat mass, but lowest ASMM and bone mineral content. The authors concluded that the relationship between %BF and BMI varies with ethnicity and may be due, in part, to differences in central fatness and muscularity. Use of universal BMI or waist cut-points may not be appropriate for comparison of obesity prevalence amongst differing ethnic groups, as they do not provide a consistent reflection of adiposity and fat distribution across ethnic groups (Rush et al. 2007).

Duncan et al. have proposed several factors to help explain the dependency of the BMI/per cent body fat relation on ethnicity (Duncan et al. 2004). The first factor they propose is body build/frame

size (as measured by wrist and knee girths), which tends to vary amongst different ethnic groups. A number of studies have noted that ethnic populations with relatively high levels of BF at a given BMI also have a more slender build (Deurenberg et al. 1999; Gurrici et al. 1999). Furthermore, Deurenberg et al found that correcting for body build eliminated most of the ethnic-specific differences associated with per cent body fat prediction equations for bioelectrical impedance analysis (BIA) in Chinese, Malay and Indian Singaporeans (Deurenberg et al. 2002). A second factor that may contribute to ethnic-specific relationships between BMI and %BF is variation in sitting height relative to total height. Australian Aborigines with long legs (low sitting height) generally have a lower BMI and, as such, per cent body fat may be underestimated from BMI – particularly for those in the 'normal weight' range (Norgan 1994). Finally, there may be differences in physical activity level amongst ethnic groups. More active individuals are likely to have a higher proportion of muscle mass and, therefore, the potential for overestimation of per cent body fat from BMI (Deurenberg et al. 1999).

Indigenous Australians, however, are a diverse group of people and these results are not necessarily generalisable to all Aboriginal Australians. The Aboriginal people we studied were from central Australia and north Queensland. Rutishauser and McKay have observed similar characteristics in the Kimberley region of Western Australia (Rutishauser and McKay 1986). They found that for a given sum of skinfold thickness, Aboriginal women from north-western Australia had a mean BMI that was 2 units lower than age-matched Caucasians, suggesting a greater proportion of body fat. Comparable data from south-eastern Australia is not available, although greater WHR in Aboriginal people in the 'healthy' BMI range was reported in at least one study (Guest and O'Dea 1993). Body-fat distribution may be modulated by a number of factors, including neuroendocrine responses (Bjorntorp 1999) and it should not be assumed that the present observations arise only from genetic characteristics.

Our study indicates that Aboriginal Australian people have a very different body-fat distribution, consistent with a greater amount of abdominal fat compared to their European Australian counterparts – and that this is particularly evident in women. Because of the much smaller differential in body-fat distribution between Aboriginal men and women than between men and women in populations of European origin, gender specific cutoffs derived from European populations are unlikely to be appropriate for Indigenous populations. In addition, the relationship of surrogate estimates of body composition, S4 for subcutaneous fat and height^2/resistance for FFM, with body weight and BMI is significantly different between Aboriginal people and non-Indigenous Australians. Therefore, the currently recommended classification of weight status, based on BMI, may be inappropriate for use in the Australian Aboriginal population.

161.4 Part 3: Applications to Other Areas of Health and Disease

Anthropometric measurements are useful to monitor changes in body habitus profiles and develop strategies to minimise risks associated with such adverse changes. These measurements are also used to assess the nutritional status of hospitalised patients and to provide appropriate intervention to improve their status. Anthropometric measurements can also be used as independent predictors of certain chronic conditions and to develop validated models of risk assessment.

We have reviewed the associations of body-size measurements with chronic health conditions and found that the relationships are different amongst Aborigines when compared to other population groups. We have "shown that waist to height ratio was a better predictor for proteinuria amongst Aborigines whereas waist–hip ratio was the best predictor amongst Australians. For cardiovascular

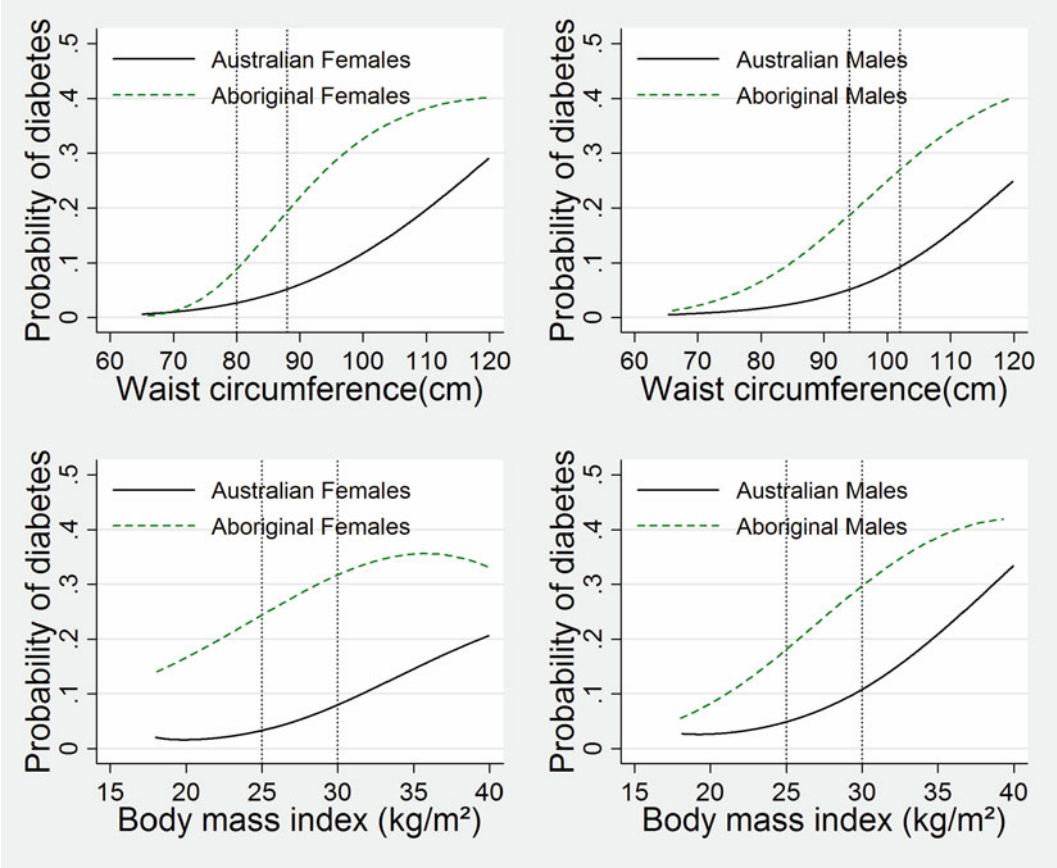

Fig. 161.7 Waist circumference and BMI, and predicted probabilities of diabetes (Source: Kondalsamy-Chennakesavan et al. (2008b))

events, waist circumference had better predictive abilities amongst Aborigines whereas waist–hip ratio had better predictive abilities amongst Australians. For diabetes, waist circumference was the best predictor amongst Aborigines whereas amongst Australians, waist–height ratio was the best predictor. Coronary heart disease risk functions predicted using Framingham calculations underestimate the risk amongst Aboriginal people and cannot be readily used in remote Aboriginal settings" (Kondalsamy-Chennakesavan et al. 2008a).

Risk for certain chronic conditions can be quantified using body-size measurements. We have quantified the risk of diabetes by body habitus profiles (Kondalsamy-Chennakesavan et al. 2008b) amongst Aborigines and compared them to the nationally representative Australian dataset (AusDiab). Even at lower levels of body-size measurements, Aborigines tend to exhibit elevated risk for diabetes (Fig. 161.7). Similarly, elevated risk at lower levels of body habitus profiles amongst Aborigines is also evident for hypertension and proteinuria. Such differences in risk profiles and differential association of body habitus measurements with disease conditions indicate that public health interventions need to be targeted at prevention of excessive weight gain in order to tackle the epidemic of chronic conditions amongst Aborigines and to close the health gap between Aborigines and other Australians.

Summary Points

- The average weight (and BMI) of contemporary Aborigines has increased significantly when compared to the average weight (and BMI) documented in studies conducted prior to 1970.
- Aborigines have preferential central fat deposition and exhibit consistently higher waist–hip ratios when compared to the general Australian population.
- Prevalences of overweight and obesity depend on the anthropometric definitions used.
- There is a wide variation in body habitus profiles between Aboriginal communities.
- The relationship of surrogate estimates of body composition, S4 for subcutaneous fat and height^2/resistance for FFM, with body weight and BMI is significantly different between Australian Aborigines and Australians of European origin.
- Increases in body habitus profiles elevate the risk of chronic conditions such as diabetes.

Key Features of Australian Aborigines

- Aborigines are the original inhabitants of Australia. In the past, they led a hunter-gatherer lifestyle.
- Associated with westernisation, their body habitus profiles show significant changes.
- Caution must be exercised when overweight and obesity are defined amongst Aborigines using cutoffs derived from other populations.

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Chapter 162
Secular Changes in Anthropometric Indices of Children and Adolescents: Studies from Korea

Joong-Myung Choi and Ji-Yeong Kim

Abstract This chapter assesses the secular growth changes in anthropometric measures with reference to Korean children and adolescents during the last four decades. The review describes the data from 68,790 boys and 62,557 girls that were recruited across the nation in 2005. Anthropometric measures included weight, height, and etc. This review compared the results of previous nationwide growth studies with the present study. It is indicated in this chapter that the growth and developmental status of Korean children and adolescents has been changed substantially compared with those in 1965, 1975, 1984 and 1997. The data presented in this chapter show a distinct secular increase in growth in body height and weight of Korean children and adolescents spanning this period. A nationwide survey every 5 years would be beneficial to establish a reference standard for the growth of children and adolescents according to the socioeconomic, environmental and nutritional changes.

162.1 Introduction

The term 'secular trend' is used to describe a slow, continuous change in growth and development over successive generations in the same regions (Ulijaszek et al.1998). Secular changes are best documented by body height and weight and weight-for-height (Hauspie et al.1997). Height is the physical attribute that is currently being analyzed most frequently (Vignerová et al. 2006). Although the mechanisms underlying a secular trend in growth measures are not fully understood, previous studies suggest that environmental and nutritional improvements are important causes of the secular increase (Malina 1979, 1990; Taranger 1983; Susanne 1985; Van Wieringen 1986; Tanner 1992). Genetic components also play a role in growth regulation, even though few studies have demonstrated that genetic factors have a major effect on the extent of growth. Secular changes in growth and maturation have been observed in many countries during the past two centuries (Van Wieringen 1986; Eveleth and Tanner 1990; Malina 1990; Hauspie et al. 1996), and studies of many countries have revealed a gradual increase in the mean height of adults, as well as children and adolescents (Vignerová et al. 2006). During the course of the past two centuries in many industrialized countries, striking increases in the mean stature and an earlier sexual maturation, usually called positive

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_162,

secular growth change, have been observed (Hauspie et al. 1996). Nevertheless, recent studies show that secular trends in growth and maturation are more pronounced in less advantaged groups of a population, such as those living in rural areas or from lower socioeconomic backgrounds, compared with more advantaged groups (Hauspie et al. 1996, 1997). Studies carried out in developing countries, especially in the past two decades, reveal a sharp and significant secular trend in growth (Zellner et al. 2004). The results of two anthropometric studies undertaken in Turkey in 1993 and 2003 revealed that Turkish children between the ages of 7 and 15 consistently demonstrated positive secular growth trends. In all of the age groups, both Turkish boys and girls in a 2003 survey were taller and heavier than their peers from the 1993 survey (Simsek et al. 2005). Further longitudinal studies are still needed to interpret the relationship between the socioeconomic status and anthropometric growth in developing countries. Unlike developing countries, the rate of secular growth change has gradually diminished in developed nations, including in Western European countries, Japan, and North America (Simsek et al. 2005), which means that societal improvements cannot fully explain secular trends in some populations in spite of continued improvements in quality of life and health (Ducros 1980; Henneberg and van den Berg 1990; Hauspie et al. 1997; Henneberg 1997; Pretty et al. 1998; Tracer et al. 1998). According to Zellner and Jaeger in a study published in 2004, a leveling off in the height trends of German schoolchildren is consistent with a wide range of studies from other European countries, which also indicate a slowing down or recent halt of the secular changes in the height of schoolchildren at the end of the twentieth century (Zellner et al. 2004). Diminishing secular increases in developed countries may indicate that the adult stature has almost reached a plateau (Hauspie et al. 1997).

The southern part of the Korean peninsula has experienced one of the most rapid economic growth developments since the Korean War in the 1950s. It has been suggested that Korean children and adolescents have showed positive secular changes in anthropometric profiles that are associated with significant improvements in the standards of healthcare, hygiene, nutrition, socioeconomic status, social welfare, and education during the past four decades. However, few studies are available to support this suggestion. In 1965, 1975, 1984, and 1997, nationwide cross-sectional growth studies were performed, showing that Korean children and adolescents had become taller and heavier than children in previous generations. In this study, we expected to observe distinct positive secular changes in the anthropometric profiles of Korean children and adolescents resulting from the rapid socioeconomic development.

In this review, we present growth data for height and weight from the fifth nationwide growth study in 2005 and compare the results of all five nationwide growth studies to assess secular growth changes in Korean children and adolescents during the past four decades. We also compare the results from Korean surveys with Japanese data to analyze the different growth patterns of children in developing and developed countries.

162.2 Methodological Considerations

The first nationwide cross-sectional anthropometric survey in Korea was carried out during the summer months of 1965 and included 16,213 boys and 16,612 girls (Moon and Yun 1978). The second nationwide study was conducted in June 1975 and consisted of 40,149 boys and 37,865 girls (Moon and Yun 1978).

The third study, conducted from April to October 1984, included 61,780 boys and 59,393 girls (Shim and Ko 1986). There have been limitations in analyzing and interpreting the historical data because the studies that were conducted in 1965, 1975, and 1984 recorded only the means and sample sizes.

We gathered these data from previous publications. The fourth survey was conducted from January 1997 to August 1998 and included 57,449 boys and 51,965 girls. In the fifth study, 68,790 boys and 62,557 girls aged between 0 and 20 years were recruited across the nation. Data collection for the fifth survey took place from April 2005 to March 2006. Quality control of the data from the fourth and fifth surveys was done with the cooperation of all the organizations involved in these studies, such as the Korea Center for Disease Control and Prevention, the Korean Society of Pediatrics, and the Medical School of Kyunghee University. Staffs from the Korea Center for Disease Control and Prevention were sent to the schools where surveys were conducted to check whether trained researchers were measuring the children in an appropriate way. The Korean Society of Pediatrics supervised the part of the surveys that was conducted at the hospitals for infants. Academic personnel, including medical professors, junior doctors in the residency of preventive medicine, and other researchers, such as statisticians at the Medical School of Kyunghee University, performed quality control for the data. They received all the data from hospitals and schools, eliminated outliers from the data set, and analyzed the data statistically.

Exclusion criteria were provided for each study. Details about the exclusion criteria applied to the first three studies have been published previously (Moon and Yun 1978; Shim and Ko 1986). Infants with a birth weight <2,500 g were excluded from the fourth and fifth studies. Children whose disorders were diagnosed as a growth hormone deficiency, growth-related disorder, or other chronic debilitating conditions were also excluded from the sample of the last two surveys. Children who were twins or had non-Korean parents were not included in these surveys.

The sample was stratified according to age, sex, and province. Infants aged 0–2 were measured at well-baby clinics in 26 university hospitals. From the age of 2–20, subjects were measured at day-care centers, kindergartens, elementary schools, middle schools, high schools, and universities.

The ages of all of the children were assessed from the hospital and school registers, based on birth certificates. In the first year of life, babies were divided by 1-month intervals. From the age of 1–2, infants were categorized at intervals of 3 months. Preschool children aged 2–7 were divided by 6-month intervals. For the ages of 7–20, the intervals were of 1 year.

The trained researchers measured the stature and weight of the subjects while they were in light clothing and no shoes. The height of infants up to 2 years of age was measured to 0.1-cm sensitivity in the supine position. The international standard measuring instrument, SECA 210 (Germany), was used. From the age of 2, standing height was measured to the nearest 0.1 cm using the standard measuring instrument (SECA 225, Germany). Infants aged 0–2 were weighed on calibrated baby scales. The weights of older children and adolescents were measured using calibrated mechanical step-scales. Weight was recorded to the nearest 0.1 kg.

Descriptive statistics were utilized to interpret the age- and gender-specific means of the height and weight. SAS (Statistical Analysis System, SAS Inc., USA) version 9.1 was used to perform statistical analysis. Curves were created using Microsoft Office Excel 2003.

162.3 Anthropometric Changes in Children and Adolescents from 1965 to 2005 in Korea

The mean heights of boys and girls revealed by surveys performed in 1965, 1975, 1984, 1997, and 2005 are represented in Tables 162.1 and 162.2. These tables also include a summary of the differences between the mean heights of the 1965 survey and the remaining surveys. A comparison among these five national surveys shows a positive secular trend in the mean heights for Korean boys (Table 162.1) and girls (Table 162.2) aged 0–20 years. The most remarkable changes are apparent

Table 162.1 Mean height of boys (cm) and changes relative to 1965 (The source of data regarding the years of 1965, 1975, and 1984 are from Moon and Yun (1978) and Shim and Ko (1986). With permission)

Age (year)	Year of the survey								
	1965	1975		1984		1997		2005	
	Mean	Mean	Difference	Mean	Difference	Mean ± SD[a]	Difference	Mean ± SD[a]	Difference
0	50.4	51.1	0.7	51.4	1.0	50.8 ± 2.6	0.4	51.5 ± 3.0	1.1
1	74.8	75.8	1.0	77.8	3.0	77.8 ± 3.1	3.0	78.9 ± 3.5	4.1
2	82.7	85.5	2.8	87.9	5.2	87.7 ± 4.3	5.0	90.4 ± 4.2	7.7
3	89.0	91.9	2.9	94.6	5.6	95.7 ± 4.4	6.7	98.2 ± 4.3	9.2
4	95.5	97.9	2.4	101.8	6.3	103.5 ± 4.6	8.0	104.7 ± 4.4	9.2
5	100.6	105.0	4.4	108.4	7.8	109.6 ± 4.7	9.0	111.0 ± 4.7	10.4
6	106.7	110.6	3.9	113.9	7.2	115.8 ± 4.8	9.1	117.0 ± 4.7	10.3
7	112.5	117.7	5.2	120.4	7.9	122.4 ± 5.7	9.9	124.9 ± 5.4	12.4
8	118.1	122.6	4.5	125.6	7.5	127.5 ± 6.1	9.4	130.6 ± 5.4	12.5
9	123.7	127.3	3.6	130.5	6.8	132.9 ± 6.0	9.2	136.1 ± 5.8	12.4
10	128.3	131.9	3.6	135.2	6.9	137.8 ± 6.4	9.5	141.3 ± 6.2	13.0
11	132.6	136.0	3.4	140.3	7.7	143.5 ± 7.1	10.9	147.5 ± 6.9	14.9
12	136.7	140.0	3.3	144.9	8.2	149.3 ± 7.8	12.6	154.3 ± 7.9	17.6
13	143.4	147.5	4.1	152.6	9.2	155.3 ± 8.4	11.9	162.0 ± 7.7	18.6
14	149.4	153.6	4.2	159.2	9.8	162.7 ± 7.1	13.3	167.2 ± 6.8	17.8
15	156.2	158.2	2.0	164.0	7.8	167.8 ± 6.5	11.6	170.6 ± 6.1	14.4
16	162.5	164.1	1.6	167.2	4.7	171.1 ± 5.8	8.6	172.2 ± 5.6	9.7
17	165.9	166.4	0.5	168.3	2.4	172.2 ± 5.9	6.3	173.1 ± 5.7	7.2
18	167.8	167.3	–0.5	168.9	1.1	172.5 ± 6.0	4.7	174.2 ± 5.6	6.4
19	168.7	168.1	–0.6	169.9	1.2	173.2 ± 5.7	4.5	174.5 ± 5.7	5.8
20	168.9	168.7	–0.2	170.2	1.3	173.4 ± 5.7	4.5	174.2 ± 5.6	5.3

The mean heights of boys revealed by surveys performed in 1965, 1975, 1984, 1997, and 2005 are represented in the table. Results are expressed as mean ± SD for the years of 1997 and 2005

Standard deviations for the first three studies are not available

[a]*SD* standard deviation

during the growth spurt period of puberty. As for boys, the greatest difference in mean height was evident at the age of 13 (143.4 cm, 1965; 162.0 cm, 2005). Thirteen-year-old boys have grown an average of 18.6 cm taller during the past four decades. The most significant height change in boys from 1965 to 1984 occurred at the age of 14 (143.4 cm, 1965; 159.2 cm, 1984). Between 1965 and 1975, the greatest height change in boys was only 5.2 cm, which was found at the age of seven (Table 162.1). Between 1965 and 2005, the mean height of 12-year-old girls increased by 15.5 cm, which is the most remarkable difference in mean height in girls (138.7 cm, 1965; 154.2 cm, 2005). Girls aged 12 years had grown taller by 12.2 cm between 1965 and 1997 (138.7 cm, 1965; 150.9 cm, 1997). Between 1965 and 1975, the greatest height change in girls was 4.9 cm, which was found at the age of 7 (Table 162.2). The mean heights of boys and girls have also changed at the age of 17 (boys, 165.9 cm in 1965 and 173.1 cm in 2005; girls, 155.5 and 160.2 cm, respectively). An increase in the mean height is found in other age groups too.

Tables 162.3 and 162.4 describe the positive secular trend in the mean weights for Korean boys (Table 162.3) and girls (Table 162.4) aged 0–20 years. Between 1965 and 2005, for boys, we found that the greatest relative increase in weight occurred at 14 years of age (39.7 kg, 1965; 60.9 kg, 2005). Boys of any age group did not gain more than 3 kg between 1965 and 1975. The most remarkable increase in weight for boys was 7.7 kg at the age of 14, from 1965 to 1984 (39.7 kg, 1965; 47.4 kg, 1984) (Table 162.3). The most significant change in mean weight in girls (an increase of 14.7 kg) during the past 40 years (36.2 kg, 1965; 50.9 kg, 2005) occurred at the age of 13. The greatest weight

Table 162.2 Mean height of girls (cm) and changes relative to 1965 (The source of data regarding the years of 1965, 1975, and 1984 are from Moon and Yun (1978) and Shim and Ko (1986). With permission)

Age (year)	Year of the survey								
	1965	1975		1984		1997		2005	
	Mean	Mean	Difference	Mean	Difference	Mean ±SD[a]	Difference	Mean ± SD[a]	Difference
0	50.0	50.8	0.8	50.5	0.5	50.1 ± 2.5	0.1	50.9 ± 2.8	0.9
1	72.8	74.8	2.0	76.2	3.4	76.9 ± 3.5	4.1	77.6 ± 3.7	4.8
2	81.5	84.6	3.1	86.9	5.4	87.0 ± 4.1	5.5	89.0 ± 4.2	7.5
3	87.7	90.2	2.5	92.9	5.2	94.2 ± 4.4	6.5	97.0 ± 4.3	9.3
4	94.0	97.1	3.1	100.9	6.9	102.1 ± 4.5	8.1	103.4 ± 4.3	9.4
5	100.2	103.7	3.5	108.1	7.9	108.6 ± 4.7	8.4	109.9 ± 4.5	9.7
6	106.5	109.2	2.7	113.4	6.9	114.7 ± 4.7	8.2	116.0 ± 4.9	9.5
7	112.0	116.9	4.9	119.4	7.4	121.1 ± 6.1	9.1	123.7 ± 5.4	11.7
8	117.3	121.6	4.3	124.9	7.6	126.0 ± 6.1	8.7	129.6 ± 5.7	12.3
9	122.0	126.5	4.5	130.1	8.1	132.2 ± 6.4	10.2	135.5 ± 6.1	13.5
10	128.6	131.8	3.2	135.5	6.9	137.7 ± 7.0	9.1	142.3 ± 6.7	13.7
11	133.5	137.5	4.0	141.8	8.3	144.2 ± 7.6	10.7	148.6 ± 6.7	15.1
12	138.7	142.0	3.3	147.8	9.1	150.9 ± 7.2	12.2	154.2 ± 6.1	15.5
13	144.8	148.1	3.3	152.1	7.3	155.0 ± 6.1	10.2	157.5 ± 5.4	12.7
14	149.0	152.0	3.0	154.9	5.9	157.8 ± 5.5	8.8	159.0 ± 5.3	10.0
15	152.9	154.0	1.1	155.8	2.9	159.0 ± 5.2	6.1	159.7 ± 5.4	6.8
16	154.7	155.6	0.9	156.7	2.0	160.0 ± 5.2	5.3	160.4 ± 5.2	5.7
17	155.5	156.3	0.8	156.6	1.1	160.4 ± 5.2	4.9	160.2 ± 5.0	4.7
18	155.7	156.6	0.9	157.3	1.6	160.5 ± 5.2	4.8	161.3 ± 5.1	5.6
19	155.7	157.0	1.3	157.2	1.5	160.1 ± 5.0	4.4	161.6 ± 5.3	5.9
20	155.9	157.1	1.2	157.6	1.7	160.4 ± 5.0	4.5	161.3 ± 5.1	5.4

The mean heights of girls revealed by surveys performed in 1965, 1975, 1984, 1997, and 2005 are represented in the Tables. Results are expressed as mean ± SD for the years of 1997 and 2005

Standard deviations for the first three studies are not available

[a]*SD* standard deviation

change in girls from 1965 to 1984 occurred at the age of 14 (39.8 kg, 1965; 46.8 kg, 1985) (Table 162.4). During the past four decades, the mean weight of 20-year-old boys increased by 12.8 kg, whereas that of girls increased by 4.1 kg. During the past 40 years, the weight of girls has changed less than that of boys.

During the past 40 years, the mean height of the Korean population shows more variation than that of the Japanese population (Figs. 162.1 and 162.2) (Japanese Ministry of Education, Culture, Sports, Science and Technology 2007). Japanese children have undergone more stable and slower secular changes in growth development than Korean children have during the past 40 years. A comparison of the heights of Korean children younger than 13 years in 2005 with those of children in 1965 shows that present-day Korean children reach similar heights 3 years earlier. However, current Japanese children attain similar heights at only 1 year earlier compared with Japanese children in 1965 (Figs. 162.1 and 162.2).

162.4 The Implications of Anthropometric Changes

The data presented in this review show a distinct secular increase in body height and weight of Korean children and adolescents during the past four decades. The growth and developmental status of Korean children and adolescents has changed substantially compared with those in 1965, 1975,

Table 162.3 Mean weight of boys (kg) and changes relative to 1965 (The source of data regarding the years of 1965, 1975, and 1984 are from Moon and Yun (1978) and Shim and Ko (1986). With permission)

Age (year)	Year of the survey								
	1965	1975		1984		1997		2005	
	Mean	Mean	Difference	Mean	Difference	Mean ± SD[a]	Difference	Mean ± SD[a]	Difference
0	3.2	3.3	0.1	3.4	0.2	3.4 ± 0.5	0.2	3.5 ± 0.6	0.3
1	8.9	9.6	0.7	10.3	1.4	10.4 ± 1.2	1.5	10.7 ± 1.3	1.8
2	10.8	11.8	1.0	12.6	1.8	12.9 ± 1.8	2.1	13.5 ± 1.7	2.7
3	12.7	13.3	0.6	14.4	1.7	15.1 ± 1.9	2.4	15.6 ± 1.9	2.9
4	14.6	14.9	0.3	16.0	1.4	17.0 ± 2.1	2.4	17.5 ± 2.2	2.9
5	16.0	16.7	0.7	18.0	2.0	19.0 ± 2.4	3.0	19.9 ± 3.1	3.9
6	16.7	18.5	1.8	19.7	3.0	21.4 ± 3.1	4.7	22.4 ± 3.7	5.7
7	19.1	20.6	1.5	22.3	3.2	24.7 ± 4.3	5.6	26.8 ± 5.4	7.7
8	20.4	22.7	2.3	24.2	3.8	27.6 ± 5.4	7.2	30.4 ± 6.2	10.0
9	23.0	24.9	1.9	26.7	3.7	31.0 ± 6.4	8.0	34.5 ± 7.5	11.5
10	25.4	27.4	2.0	29.5	4.1	34.5 ± 7.5	9.1	38.8 ± 8.8	13.4
11	28.8	29.7	0.9	32.4	3.6	38.6 ± 8.6	9.8	43.9 ± 10.2	15.1
12	31.7	32.2	0.5	35.5	3.8	42.8 ± 9.4	11.1	49.5 ± 11.3	17.8
13	34.7	37.4	2.7	41.5	6.8	47.2 ± 9.9	12.5	55.8 ± 12.3	21.1
14	39.7	42.1	2.4	47.4	7.7	53.9 ± 10.3	14.2	60.9 ± 12.8	21.2
15	44.9	46.1	1.2	52.2	7.3	58.5 ± 10.4	13.6	64.9 ± 12.7	20.0
16	50.7	52.5	1.8	56.2	5.5	61.2 ± 9.5	10.5	66.9 ± 11.8	16.2
17	54.5	55.8	1.3	58.2	3.7	63.2 ± 9.8	8.7	68.7 ± 12.2	14.2
18	57.0	57.1	0.1	59.8	2.8	63.8 ± 9.1	6.8	69.6 ± 10.9	12.6
19	58.1	58.0	–0.1	60.2	2.1	66.0 ± 8.8	7.9	70.6 ± 10.9	12.5
20	58.2	59.3	1.1	61.9	3.7	66.6 ± 8.5	8.4	71.0 ± 10.5	12.8

This table describes the positive secular trend in the mean weights for Korean boys aged 0–20 years. Results are expressed as mean ± SD for the years of 1997 and 2005

Standard deviations for the first three studies are not available

[a]*SD* standard deviation

1984, and 1997. This review provides valuable findings about secular trends in growth because all the data analyzed in this research were from five cross-sectional anthropometric surveys involving subjects recruited across the whole nation.

Anthropometrical studies of conscripts and schoolboys show that an increase in the height of 17-year-old boys commenced in the nineteenth century (Lintsi and Kaarna 2006). It has commonly been understood that secular changes in growth result from the combined effect of changes in overall body size at all ages and changes in the period of time needed for the completion of growth (Hauspie et al. 1997). Usually, a positive secular growth change is accompanied by an advance in sexual maturation (Fredriks et al. 2000).

If the largest gain in height or weight over the period examined occurs around pubertal age, this reflects earlier puberty and thus a shortening of the growth period (Loesch et al. 2000). In this review, there has been a trend toward increased height among Korean boys and girls aged 0–20 years since the 1965 data were collected. Height is determined in part by genetics and in part by childhood living conditions, including nutrition, housing conditions, the occurrence of diseases, and strenuous work at young ages (Nyström-Peck and Lundberg 1995). Persistent international differences in the mean height across birth cohorts demonstrate continuing differences in childhood living conditions between countries (Cavelaars et al. 2000; Komlos and Kriwy 2002; Krawczyski et al. 2003; Gyenis and Joubert 2004; Sander 2004). In Korea, between 1965 and 2005, significant improvements were observed in the socioeconomic conditions and health of the population. Evaluation of socioeconomic and health indicators in the southern part of the Korean peninsula during the past four decades

Table 162.4 Mean weight of girls (kg) and changes relative to 1965 (The source of data regarding the years of 1965, 1975, and 1984 are from Moon and Yun (1978) and Shim and Ko (1986). With permission)

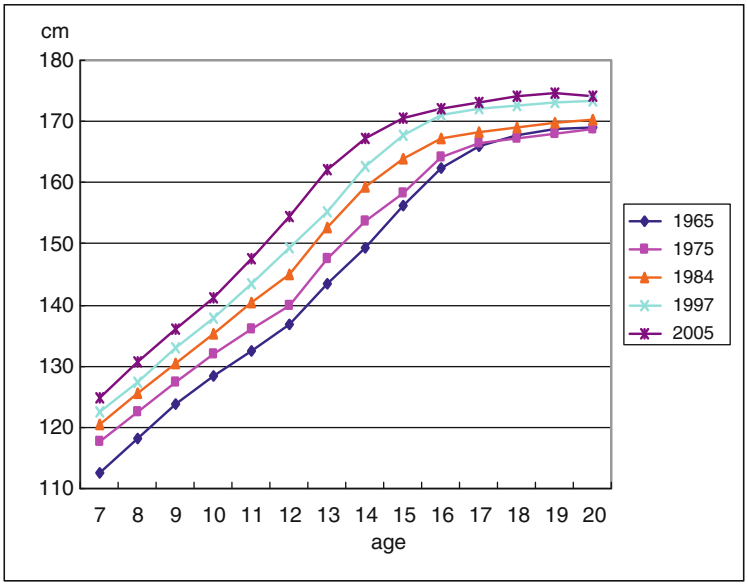
Age (year)	Year of the survey								
	1965**	1975**		1984**		1997		2005	
	Mean	Mean	Difference	Mean	Difference	Mean ± SD[a]	Difference	Mean ± SD[a]	Difference
0	3.2	3.3	0.1	3.2	0.0	3.3 ± 0.5	0.1	3.4 ± 0.5	0.2
1	8.3	9.1	0.8	9.5	1.2	10.0 ± 1.2	1.7	10.1 ± 1.4	1.8
2	10.3	11.5	1.2	12.0	1.7	12.5 ± 1.5	2.2	12.8 ± 1.6	2.5
3	12.3	12.8	0.5	13.6	1.3	14.2 ± 1.8	1.9	15.1 ± 1.9	2.8
4	13.9	14.3	0.4	15.7	1.8	16.4 ± 2.1	2.5	16.9 ± 2.2	3.0
5	15.5	16.1	0.6	17.3	1.8	18.4 ± 2.2	2.9	19.2 ± 2.8	3.7
6	17.5	17.9	0.4	19.1	1.6	20.7 ± 2.8	3.2	21.5 ± 3.4	4.0
7	19.1	20.0	0.9	21.2	2.1	23.6 ± 3.8	4.5	25.4 ± 4.8	6.3
8	20.9	22.0	1.1	23.5	2.6	26.2 ± 4.9	5.3	29.0 ± 5.9	8.1
9	23.4	24.2	0.8	26.1	2.7	30.0 ± 6.1	6.6	32.7 ± 6.5	9.3
10	25.2	27.0	1.8	29.2	4.0	33.6 ± 7.0	8.4	37.5 ± 7.7	12.3
11	29.1	30.5	1.4	33.6	4.5	37.8 ± 8.3	8.7	42.5 ± 9.1	13.4
12	32.9	33.6	0.7	38.2	5.3	43.1 ± 8.6	10.2	47.3 ± 9.3	14.4
13	36.2	38.7	2.5	43.1	6.9	47.0 ± 8.3	10.8	50.9 ± 8.9	14.7
14	39.8	43.5	3.7	46.8	7.0	50.7 ± 8.0	10.9	53.2 ± 8.8	13.4
15	44.5	46.7	2.2	49.6	5.1	52.5 ± 7.8	8.0	55.2 ± 9.3	10.7
16	47.6	49.1	1.5	51.2	3.6	54.4 ± 7.7	6.8	55.7 ± 8.7	8.1
17	49.6	50.6	1.0	51.8	2.2	54.6 ± 7.2	5.0	56.0 ± 9.0	6.4
18	50.3	50.8	0.5	51.9	1.6	54.7 ± 6.7	4.4	55.4 ± 7.9	5.1
19	51.1	51.2	0.1	51.5	0.4	54.9 ± 6.2	3.8	55.7 ± 7.8	4.6
20	51.5	52.0	0.5	51.8	0.3	55.7 ± 5.4	4.2	55.6 ± 8.7	4.1

This table describes the positive secular trend in the mean weights for Korean girls aged 0–20 years. Results are expressed as mean ± SD for the years of 1997 and 2005

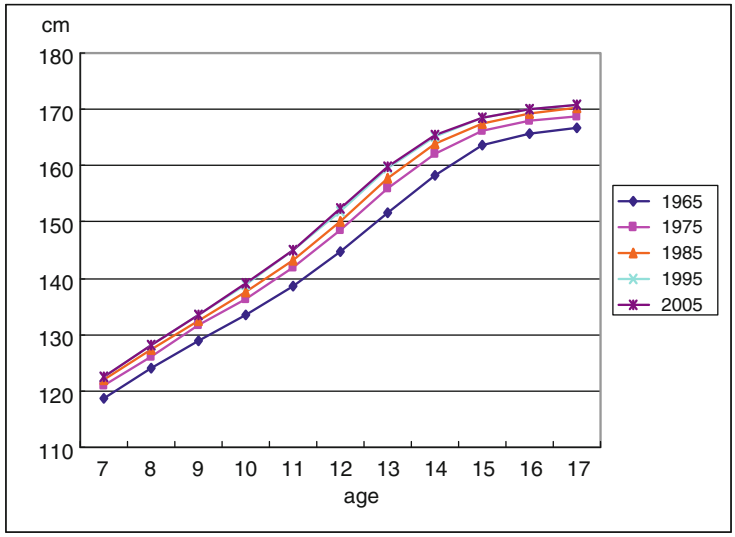
Standard deviations for the first three studies are not available

[a]*SD* standard deviation

is represented in Table 162.5 (Korea National Statistical Office Internet 2007). The period between 1965 and 1984 is characterized by a positive trend in the difference in the mean height of Korean children and adolescents of all ages, more significantly for boys aged 0–11 years and girls aged 0–14 years. After 1984, the increase in mean height of boys older than 11 years and girls older than 14 years exceeded the changes in height taking place between 1965 and 1984 (Fig. 162.3). This change means that there has been an increase in the average height of the Korean population from one generation to another. This increase in the mean height in infants and younger children (0–11-year-old boys and 0–14-year-old girls) occurred more drastically during the period between 1965 and 1984, which experienced a very rapid development in the Korean economy and living conditions after the Korean War. It is generally assumed that an improvement in the quantity and quality of food is the most important cause of secular growth change (Fredriks et al. 2000). After 1984, in Korea, the general wealth of the population has increased considerably and significantly more children had easy access to food. Easier access to infant healthcare and the institution of a vaccination program also affected secular growth change in a positive way during this period. In many studies, the differences in somatic development between children from various social backgrounds were evaluated (Drachler et al. 2002; Langnäse et al. 2002; Armstrong et al. 2003). Socioeconomic status and the quality of healthcare and nutrition are regarded as factors, which, in combination with genotype, have the strongest impact on the growth and development of an individual (Vignerová et al. 2006). Such improvements in the socioeconomic and socio-hygienic conditions and the public-health status of



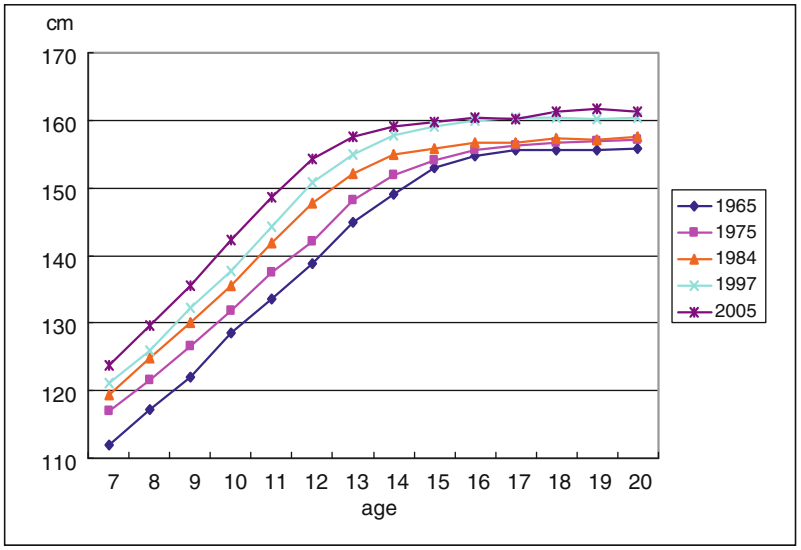
(Korean boys)



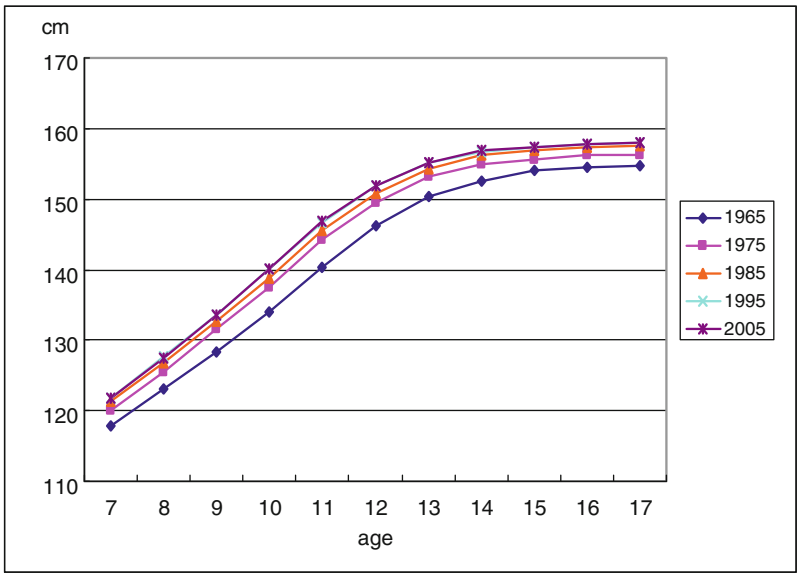
(Japanese boys)

Fig. 162.1 The comparison of mean height between Korean and Japanese boys during past four decades. The figure shows the mean heights for Korean boys aged 7–20 years during past 40 years in the comparison with those of Japanese boys (The source of data regarding Japanese boys is the Japanese Ministry of Education, Culture, Sports, Science and Technology (2007). With permission)

the Korean population occurred more remarkably between 1965 and 1984 than during the period between 1984 and 2005. This may explain why the positive secular trend in height has diminished in Korean infants and younger children after 1984. A secular trend in the mean weight of Korean children and adolescents during the past four decades is different in pattern from that of the height. The increase during the past two decades (1984–2005) in the mean weight of boys older than 7 years and girls older than 5 years exceeded the changes in weight that occurred between 1965 and 1984 (Fig. 162.4). A pattern of secular trend in the Korean children's weight shows a sharp increase between 1984 and 2005. Unlike the pattern for stature, the secular trend of increased weight occurred mostly during the past two decades (Figs. 162.3 and 162.4).



(Korean girls)



(Japanese girls)

Fig. 162.2 The comparison of mean height between Korean and Japanese girls during past four decades. The figure shows the mean heights for Korean girls aged 7–20 years during the past 40 years in comparison with those of Japanese girls (The source of data regarding Japanese girls is the Japanese Ministry of Education, Culture, Sports, Science and Technology (2007). With permission)

162.5 Further Considerations

A significant secular increase in height and weight measurements were found in Korean infants, children, and adolescents aged 0–20 years during the past four decades. In all of the age groups, both boys and girls in the 2005 survey were taller and heavier than their peers from the 1965 study.

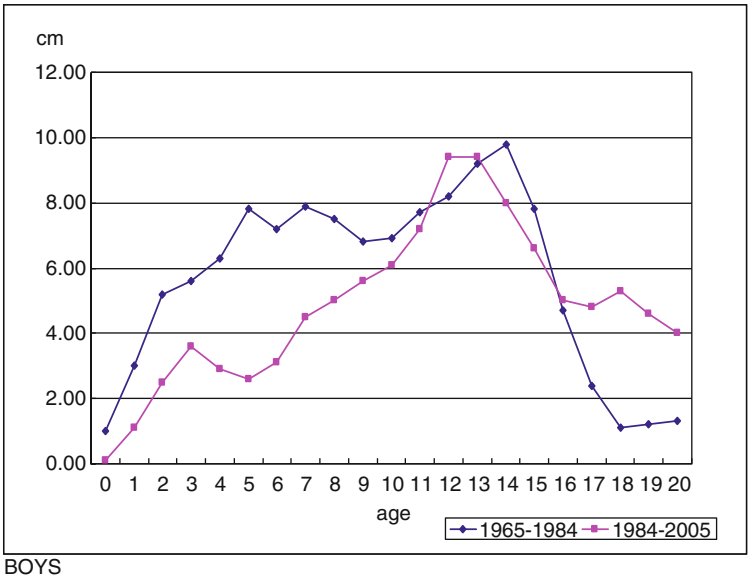
Table 162.5 Selected Indicators of socioeconomic status and health, South Korea (The source of data is the Korea National Statistical Office (2007). With permission)

Indicator	1970	1975	1984	1997	2005
Life expectancy at birth (years)	61.9	63.8	67.8	74.4	78.6
Infant mortality rate per 1,000 live births	57.5	38.0	23.0[a]	13.2[b]	3.8
GDP (100,000,000 Korean Won)	27,639	103,861	751,263	4,911,348	8,652,409

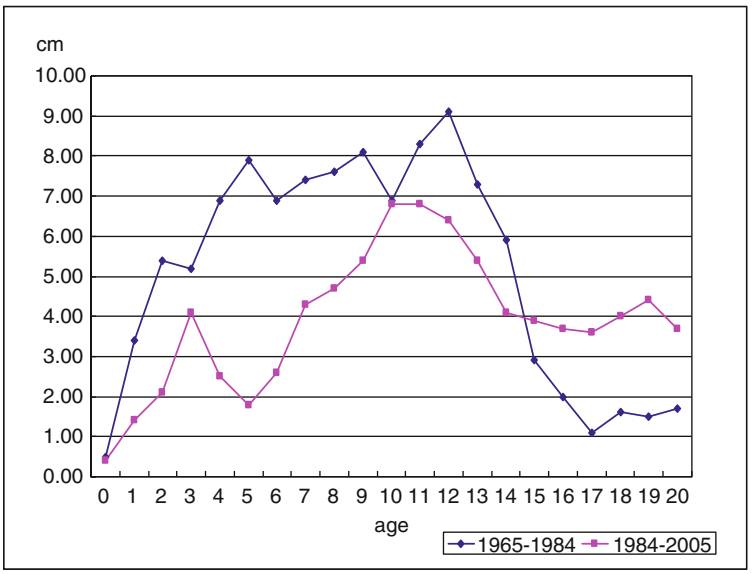
Evaluation of socioeconomic and health indicators in the southern part of the Korean peninsula during past four decades is represented in this table

[a]Infant mortality rate for 1984 was not available. Instead, the number for 1985 was represented

[b]Infant mortality rate for 1997 was not available. Instead, the number for 1995 was represented

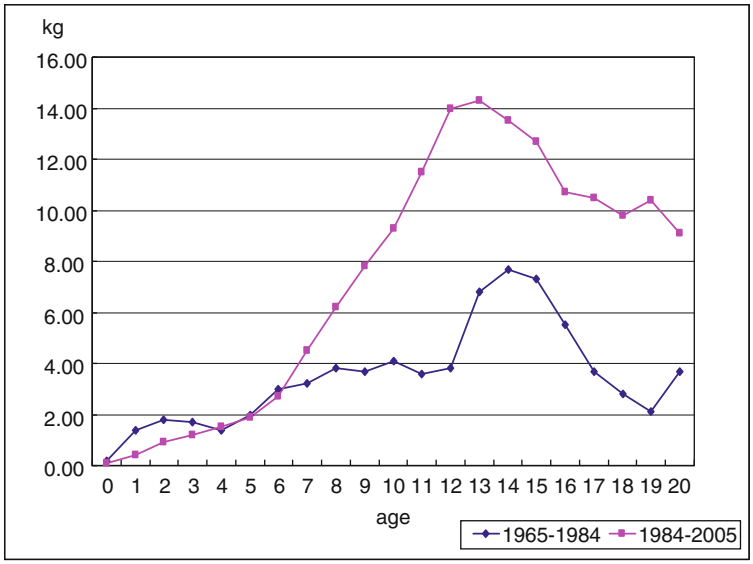


BOYS

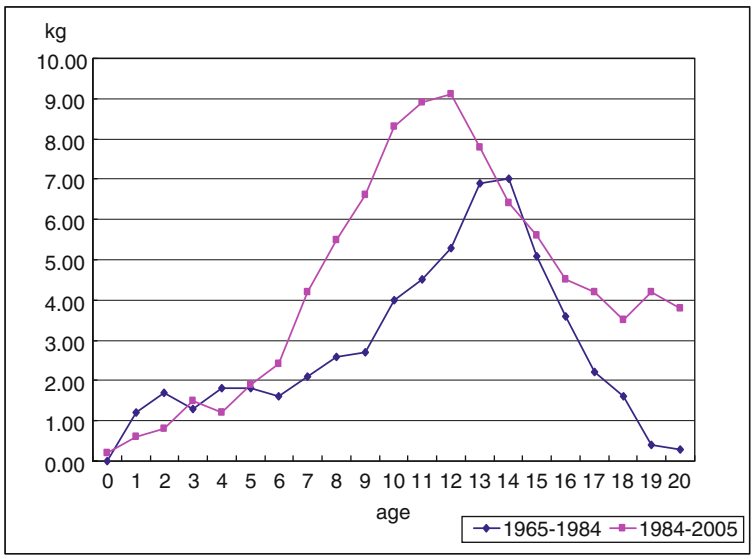


GIRLS

Fig. 162.3 Secular differences in mean height between the first two decades, the past two decades, and total 40 years. The figure shows secular differences in mean height of Korean boys and girls between the first two decades, the past two decades, and total 40 years (The source of data regarding the years of 1965 and 1984 are from Moon and Yun (1978) and Shim and Ko (1986). With permission)



BOYS



GIRLS

Fig. 162.4 Secular differences in mean weight between the first two decades, the past two decades, and total 40 years. The figure shows secular differences in mean weight of Korean boys and girls between the first two decades, the past two decades, and total 40 years (The source of data regarding the years of 1965 and 1984 are from Moon and Yun (1978) and Shim and Ko (1986). With permission)

This secular trend may have important implications for other developing countries with many changes in socioeconomical conditions. The comparison between Korean and Japanese data in this research also supports the effect of rapid socioeconomic changes in less developed nations on the secular growth trend of children. The positive secular changes of children observed in developing countries (in this research, Korea) are more distinct than those in developed world (in this research, Japan), and this supports the necessity of regular nationwide growth survey for children, especially in less developed areas. The positive secular change in both the height and weight of Korean children underscores the need for an update in growth standards. Regular research studies of anthropometrical characteristics are an essential and relatively inexpensive component of the follow-up analysis, allowing for the examination of the health of a population of children and adolescents

(Vignerová et al. 2006). Thus, a nationwide survey every 5 years would be beneficial to such analysis by establishing a reference standard for the growth of children and adolescents according to the socioeconomic, environmental, and nutritional changes.

Summary Points

- Korean children and adolescents have showed positive secular changes in anthropometric profiles that are associated with significant improvements in the standards of healthcare, hygiene, nutrition, socioeconomic status, social welfare, and education during the past four decades.
- A secular trend in the mean weight of Korean children and adolescents during the past four decades is different from that of the height in pattern.
- A pattern of secular trend in the Korean children's weight shows a sharp increase between 1984 and 2005. Unlike the pattern for stature, the secular trend of increased weight occurred mostly during the past two decades.
- During the past 40 years, the mean height of the Korean population shows more variation than that of the Japanese population.
- The positive secular changes of children observed in developing countries are more distinct than those in developed world, and this supports the necessity of regular nationwide growth survey for children, especially in less developed areas.

Key Features of Secular Changes

Table 162.6 Key features of secular changes

1. Secular change means a long-term and steady variation
2. The anthropometric indices are the measurements of the human individuals, such as weight, height, and circumferences
3. Changes in nutrition, socioeconomic status, and the quality of healthcare lead to secular changes in anthropometric measurements of the population

This table lists the key features of secular changes including the meaning of the secular change and the anthropometric indices. This also briefly explains the association between the social backgrounds and the secular changes in anthropometric measurements

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Chapter 163
Determinants of Central Adiposity: An Iranian Perspective

Leila Azadbakht, Ahmad Esmaillzadeh, and Pamela J. Surkan

Abstract Although obesity is a major health problem, most recent studies suggest that the pattern of body fat distribution is more important than overall body mass. Abdominal obesity has been associated with a substantially elevated risk of chronic diseases and mortality. While most risk factors are shared worldwide, both non-dietary and dietary determinants of abdominal adiposity can vary across populations. Iranian studies reveal that physical activity, unemployment, menopause, marriage, smoking and depression are the most important non-dietary factors. Regarding the dietary determinants of central adiposity, three classes of exposure include dietary patterns, food groups/foods, and nutrient intake. According to studies in Iran, a healthy dietary pattern mainly based on whole grains, fruits, vegetables, and unhydrogenated vegetable oil, is inversely associated with central adiposity. Also, based on Iranian studies, dairy consumption as well as fruit and vegetable intake are inversely correlated with central adiposity as well as with metabolic syndrome, for which one of the major components is large waist circumference. Hydrogenated vegetable oil is directly correlated with central adiposity and with metabolic syndrome both in Iranians and some other populations. Factors that appear to be protective for central fat accumulation among Iranians include high fiber, vitamin C and calcium consumption. Insulin resistance is one of the major problems related to central adiposity; therefore, individuals with central adiposity are at risk for other diseases, such as type 2 diabetes and cardiovascular disease. Being physically active and consuming a diet with a low glycemic index that is rich in whole grains, fruits, vegetables, and unhydrogenated vegetable oil are recommended to prevent central adiposity for Iranian population.

Abbreviations

ATP III	Adult Treatment Panel III
BMI	Body mass index
CI	Confidence interval
HVO	Hydrogenated vegetable oil
OR	Odds ratio

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_163,

TFA Trans fatty acid
TG Triglyceride concentration
WC Waist circumference
WHO World Health Organization
WHR Waist to hip ratio

163.1 Introduction

Obesity has become an important health problem, which is correlated with increased risk of many chronic diseases (Wei et al. 1997). However, current evidence suggests that attention should be placed on the pattern of body fat distribution rather than on simply overall body weight or obesity (Wei et al. 1997). One reason is that central adiposity is a better indicator of other chronic diseases, such as metabolic syndrome, type 2 diabetes, and cardiovascular diseases as well as increased mortality (Janssen et al. 2004). To assess central adiposity, most researchers have used the World Health Organization (WHO) cutoffs or the Adult Treatment Panel III (ATP III). These utilize waist circumference and waist-to-hip ratio as two major criteria in determining central fat accumulation (Reeder et al. 1997).

The prevalence of central adiposity is rising at an alarming rate worldwide (Reeder et al. 1997). According to a population-based study of adolescents and adults over 15 years old living in the 28 provinces of Iran, abdominal obesity was present in 43.4% of women, 9.7% of men, 28.5% of urban residents, and 23.0% of rural residents (Kelishadi et al. 2008). In Tehran, the capital of Iran with the most industrialized lifestyle, 67% of women and 33% of men older than 20 are centrally obese (Azadbakht et al. 2005a). A study of secular trends in central fat accumulation in Iran showed a 6% and 9% increase of central adiposity between 1998 and 2002 in men and women, respectively (Azizi et al. 2005). Compared to the US population, the mean of both waist circumference (WC) and waist-to-hip ratio (WHR) among Iranian women is higher than among American women (Sarrafzadegan et al. 2009). The prevalence of central obesity is about 38.6% (46.3% in females and 29.8% in males) in USA (Ford et al. 2002), 65% in Oman (Al–Riyami and Afifi 2003), 63% in a sample of Japanese Brazilians (Barbieri et al. 2009), and 55% in Indian women (Beegom et al. 1995).

Although obesity has genetic determinants, social and environmental factors also contribute to the problem. Among the factors important in different populations, socioeconomic status, gender, marital status, physical activity, educational level, and dietary habits can be mentioned (Al–Riyami and Afifi 2003; Beegom et al. 1995; Azadbakht and Esmaillzadeh 2008).

Regarding diet, research has focused on dietary patterns, food groups/specific foods, and nutrients. Given that central adiposity is a risk factor for severe chronic diseases, understanding its determinants is critical. Therefore, in this chapter, we discuss the non-dietary and dietary determinants of central adiposity mainly based on studies of the Iranian population.

163.2 Non-dietary Determinants of Central Adiposity

Aging and genetics are two important non-dietary determinants of central adiposity but are not amenable to behavioral intervention, underscoring the importance of lifestyle factors related to this problem. However, these lifestyle-related risk factors can be very similar to those for obesity, resulting in high correlations and actually colinearity between central adiposity and obesity. Physical inactivity

Table 163.1 Important non-dietary determinants of central adiposity among Tehranian adults

Lifestyle factors	Odds ratio	95%CI
Physical activity		
Light[b]	2.11[a]	1.40–2.53
Moderate[c]	1.13	0.91–1.42
Heavy[d]	1.00	–
Parity		
0	1.00	–
One to two	1.02	0.83–1.42
Three or more	1.31	1.18–1.62
Marital status		
Single	1.00	–
Married	1.31	1.10–1.82

[a] $P < 0.05$

[b] Those who had a sedentary lifestyle: considered as a light physical activity level

[c] Those with maximum daily 30 min exercise: considered as moderate lifestyle

[d] Those with active lifestyle and doing more than 30 min exercise: considered as heavy physical activity level

is one of the most important risk factors for central adiposity, both in Iran and in other parts of the world (Hajian-Tilaki and Heidari 2007; Al–Riyami and Afifi 2003). The role of increased daily physical activity in minimizing age-related increases in abdominal obesity has also recently been highlighted (Holcom et al. 2004). Both depression and unemployment in Iranian women were associated with higher odds ratios of being centrally obese (Azadbakht and Esmaillzadeh 2008). One interpretation is that unemployed women's poor control over household economic resources may be a cause of depression and may also be linked to women's lack of activities, including physical activities apart from housework. Furthermore, easy availability of food at home might encourage obesity in the unemployed female population, which largely consists of housewives (Azadbakht and Esmaillzadeh 2008). Therefore, these factors may contribute to the central fat accumulation. Consistent with the literature from other countries (Al–Riyami and Afifi 2003; Moreira and Padrao 2006; Beegom et al. 1995), results of the Iranian Adults Study showed that socioeconomic status is also correlated with central adiposity (Azadbakht and Esmaillzadeh 2008). As observed elsewhere (Shimokata et al. 1989), smokers in Iran have higher probability of being centrally obese (Azadbakht and Esmaillzadeh 2008). A longitudinal study in USA has also shown that smokers gained more weight on the waist and less on the hips than predicted from gain in body mass, producing a gain in WHR (Shimokata et al. 1989). Menopause is also a risk factor related to central fat accumulation, which is thought to be associated with the role of sexual hormones, such as higher levels of testosterone during this period (Azadbakht and Esmaillzadeh 2008). Married Iranian women are more centrally obese compared to single ones (Azadbakht and Esmaillzadeh 2008), a finding that may possibly be explained by weight gain after each pregnancy and/or lactation. Multiparous Iranian women also had higher waist-to-hip ratios (WHR), which lends credence to the potential role of pregnancy and lactation in increasing the risk of central adiposity.

A recent study in the north of Iran also showed that similar factors were associated with central obesity: more sedentary behavior, low education, high parity, a family history of obesity, marriage at earlier age, and aging (Hajian-Tilaki and Heidari 2007). Given the multiethnic nature of Iran, comparing the results of studies from different parts of the country can be useful to form a national overview. In Table 163.1, odds ratios are displayed for the most important lifestyle factors related to central adiposity.

163.3 Dietary Determinants of Central Adiposity

Regarding the dietary determinants of central adiposity, we will consider three classes of exposures: (1) dietary patterns, (2) food groups and foods, and (3) nutrient intake.

163.3.1 Dietary Patterns and Central Adiposity

Studying central adiposity with an approach based on dietary patterns that reflects individual dietary behaviors can provide information about the nutritional etiology of obesity. Due to colinearity between food and nutrient intakes, a multivariate approach that specifies dietary patterns has the potential to resolve concerns about confounding factors and interactions between foods and nutrients (Esmaillzadeh et al. 2008). The links between dietary patterns and different forms of obesity are especially relevant in the case of Iran because of the high prevalence of a particular type of obesity, the so-called Middle-Eastern pattern, which makes Iranians particularly susceptible to increased risk of obesity-related comorbidities. The predominant characteristic of this pattern of obesity is central fat accumulation and enlarged waist circumference (WC), particularly among women (Esmaillzadeh and Azadbakht 2008a).

Limited data are available linking dietary patterns to obesity among Iranians. Through factor analysis, three major dietary patterns, Western, healthy, and Iranian, have been identified among Iranian female teachers (Esmaillzadeh and Azadbakht 2008). Individuals with scores in the top quintile of the healthy pattern were less likely to have general obesity (defined as BMI ≥30) and to have central adiposity, whereas those in the upper quintile of the Western pattern had greater odds for both general and central obesity (Table 163.2).

Although the Iranian dietary pattern and overall obesity were not associated, individuals in the top quintile of the Western dietary pattern had greater odds of being centrally obese (Esmaillzadeh and Azadbakht 2008a). These findings agree with other studies from both developing and developed settings. Overall, it seems that the nutrition transition in developing countries helps to promote Western dietary patterns, which, in turn, might account for the high prevalence of obesity in these countries. To date, no further reliable studies are available regarding dietary patterns and obesity among Iranians. Prospective studies will need to be conducted in Iran to confirm the current available findings.

163.3.2 Food Group, Food Intake, and Central Adiposity

Among Iranians, dietary intake of foods and food groups has also been related to the prevalence of overweight and obesity. In a cross-sectional study of Iranian adults, it has been reported that dairy intake was inversely associated with body mass index (BMI) and prevalence of obesity. Specifically, there was a lower likelihood of obesity for those in the top quartile of dairy intake (OR = 0.73, 95%CI = 0.40–0.83 for men and OR = 0.69, 95%CI = 0.34–0.80 for women) compared to those in the lowest quartile (Mirmiran et al. 2005). Fruit and vegetable intakes are also inversely related to obesity and central adiposity. Compared to individuals in the lowest quintile, those in the highest quintile of fruit intake are less likely to be obese (43% vs. 23%, $P < 0.05$) and to have a smaller waist circumference (98 ± 10 cm vs. 86 ± 11 cm, $P < 0.01$). This influence on waist circumference was also the case for those in the highest quintile of vegetable intake versus those with the lowest intake

Table 163.2 Adjusted odds ratios (95% CI) for general and central obesity in Iranian women across quintiles of dietary pattern scores[a,b]

	Healthy pattern score			*P* for	Western pattern score			*P* for	Iranian pattern score			*P* for
	1 (*n* = 97)	3 (*n* = 97)	5 (*n* = 97)	trend[c]	1 (*n* = 97)	3 (*n* = 97)	5 (*n* = 97)	trend	1 (*n* = 97)	3 (*n* = 97)	5 (*n* = 97)	trend
General obesity[d]	1.00	0.76 (0.38, 1.29)	0.41 (0.20, 0.75)	<0.05	1.00	1.85 (0.94, 3.41)	2.48 (1.20, 4.61)	<0.01	1.00	0.81 (0.54, 1.59)	0.88 (0.49, 1.45)	0.74
Central obesity[e]	1.00	0.66 (0.37, 1.11)	0.48 (0.27, 0.67)	<0.05	1.00	2.42 (1.34, 4.59)	5.33 (2.85, 10.6)	<0.01	1.00	2.08 (1.09, 3.65)	1.61 (0.94, 2.61)	0.41

[a] Values are OR (95% CI)

[b] Adjusted for age, smoking, current estrogen use, and socioeconomic status, physical activity, energy intake

[c] From Mantel–Haenszel extension chi-square test

[d] General obesity: BMI >=30 kg/m^2

[e] Central obesity: WC >88 cm

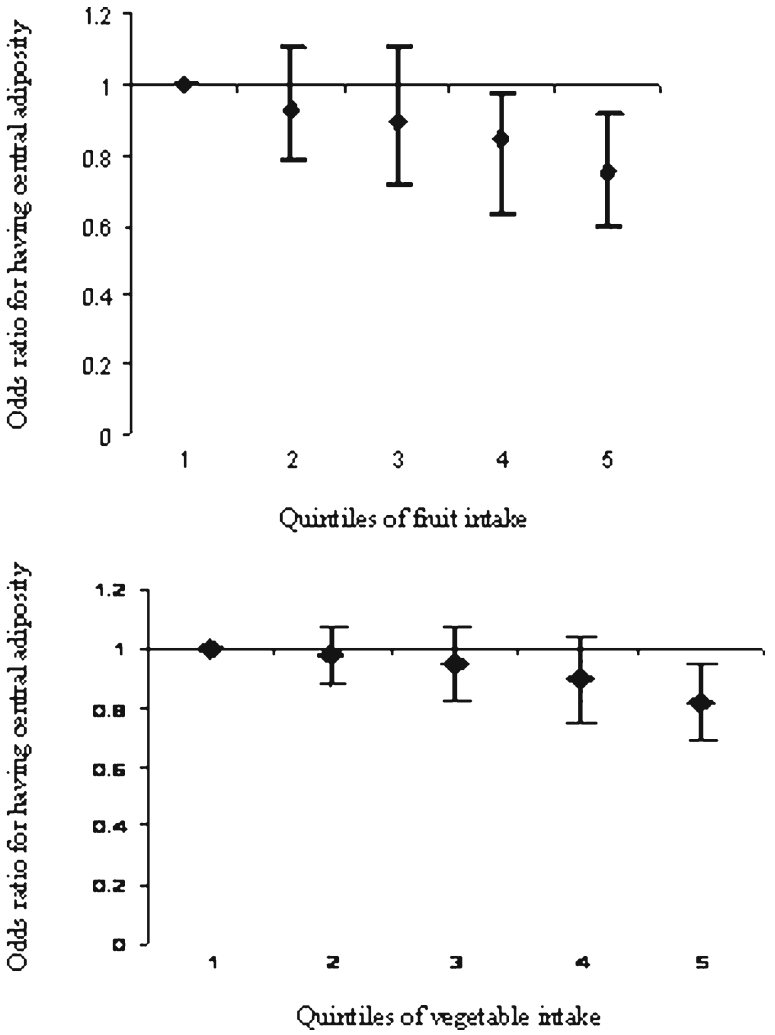

Fig. 163.1 Risk of central adiposity across quintiles of fruit and vegetable intake in Iranian women. Central adiposity was defined as having waist circumference >88 cm

(88 ± 12 cm vs. 97 ± 12 cm, $P < 0.01$) (Esmaillzadeh et al. 2006). The risk of central adiposity in Iranian women across different quintiles of fruit and vegetable intake is shown in Fig. 163.1.

Whole and refined grains have also been related to the risk of central obesity among Iranians. A hypertriglyceridemic waist phenotype has been defined as concurrently having serum triglyceride concentration (TG) ≥ 150 mg/dl and waist circumference (WC) ≥80 cm for men and TG≥150 mg/dl and WC ≥79 cm for women. In a cross-sectional study of 827 Iranian adults aged 18–74 years, a significant decreasing trend was observed for the risk of having a hypertriglyceridemic waist phenotype across quartile categories of whole-grain intake (odds ratios among quartiles: 1.00, 0.95, 0.90, and 0.78, respectively, P for trend = 0.02). Higher consumption of refined grains was associated with higher odds of having a hypertriglyceridemic waist phenotype (1.00, 1.38, 1.65, and 2.1, P for trend = 0.01). However, no significant association was observed with obesity generally (BMI >=30 kg/m^2) (Esmaillzadeh et al. 2005).

Table 163.3 Risk of central obesity according to levels of calcium and vitamin C intake in Iranian adults.

Nutrient intake (mg)	Odds ratio	95% CI
Vitamin C intake		
0–56	2.31*	1.25–4.25
57–80	1.82*	1.08–3.06
81–116	1.36	0.78–2.36
>116	1.00	–
Calcium intake		
0–398	1.30*	1.07–3.78
399–579	1.13	0.78–2.36
580–773	1.12	0.731.86
>773	1.00	–

These results are derived from a cross-sectional study on 926 women in Iran. The vitamin C intake or calcium intake was categorized according to the quartiles of these nutrients intake in the population
*$P < 0.05$

Few data are available showing the relation between food type and central adiposity. A cross-sectional study among Iranian women concluded that red-meat intake was not significantly associated with central adiposity (Azadbakht and Esmaillzadeh 2009). However, it was inversely correlated with metabolic syndrome (Azadbakht and Esmaillzadeh 2009). In a study of Japanese-Brazilians, those in the highest tertile of red-meat intake had the lowest risk of being centrally obese (OR = 0.50; 95%CI: 0.30; 0.82) (Barbieri et al. 2009). In light of the limited research on this topic, further prospective studies are needed to better define the relationship between red-meat intake and central adiposity.

Another study with Iranian women revealed that those with hydrogenated vegetable oil consumption (HVO) in the highest quintile had the largest WHR compared to those with consumption levels in the lowest quintile (Esmaillzadeh and Azadbakht 2008). HVO consumption is widespread in Iran, exposing the population to large quantities of trans fatty acids (TFAs). The TFA content of HVOs used in Iranian households is 23–36%. Trans-fat intake is associated with abdominal adiposity and insulin resistance (Kavanagh et al. 2007). In fact, 4.2% of all calories consumed by Iranians are derived from TFAs, which is about twice the amount consumed in many developed countries (Mozaffarian et al. 2007).

163.3.3 Nutrient Intake and Central Adiposity

Regarding the correlation between nutrient intake and central adiposity, results from research in Iranian adults showed that consumption of vitamin C, calcium, and fat was either positively or negatively related to central fat accumulation (Azadbakht and Esmaillzadeh 2008). Vitamin C as well as calcium can reduce fat absorption and may reduce the abdominal adiposity. Calcium can inhibit fat and fatty-acid absorption. Furthermore, it can affect the levels of agouti, a signaling peptide expressed in human adipocytes that stimulates calcium flux into the cells. The resulting effects on lypolysis and lypogenesis can trigger the deposition of fat in adipocytes. Agouti itself increases fatty acid synthetase activity and inhibits lipolysis (Azadbakht and Esmaillzadeh 2008). High quantities of refined carbohydrate intake and simple sugars are also directly correlated with abdominal adiposity (Esmaillzadeh et al. 2005). In Table 163.3, the odds ratios for having central adiposity among Iranian adults by different group of nutrient intake are displayed.

163.4 Application to Other Areas of Health and Disease

Central adiposity is directly associated with insulin resistance and, as such, insulin disturbance is the core problem associated with central obesity. Central adiposity is also one of the components of the metabolic syndrome, such that subjects with central obesity are at risk for type 2 diabetes and cardiovascular diseases (Reeder et al. 1997). It is possible that central adiposity might be correlated with increasing inflammation and oxidative stress biomarkers, which are the new risk factors for cardiovascular diseases. If so, by preventing central adiposity, we can protect against cardiovascular diseases, coronary problems, metabolic syndrome, and type 2 diabetes. According to research from Iran, there was an inverse association between fruit and vegetable intake and metabolic syndrome as well as between fruit and vegetable intake and C-reactive protein (Esmaillzadeh et al. 2006).

Figure 163.2 shows the risk of metabolic syndrome by quintile of the fruit and vegetable intake in the Iranian population.

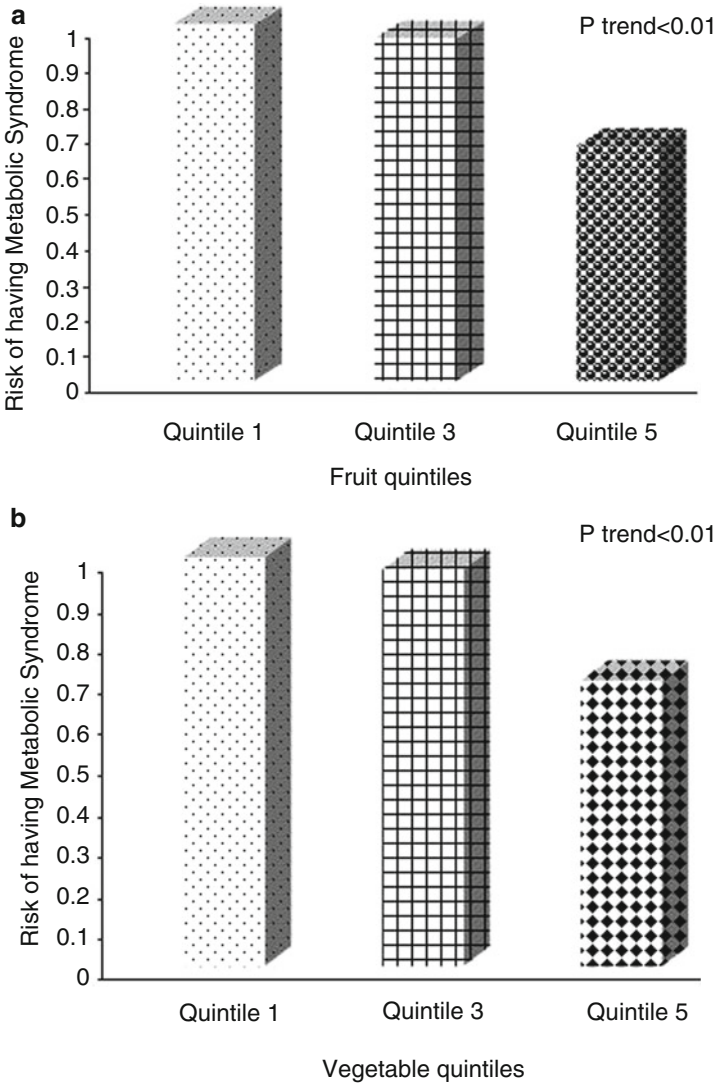

Fig. 163.2 Risk of metabolic syndrome by quintile of fruit and vegetable intake in the Iranian population. Those with the highest quintile of vegetable intake have a 30% lower chance of having the metabolic syndrome compared to those with intake in the lowest quintiles. Persons with fruit intake in the highest quintile had a 34% lower risk of having this syndrome compared to those with intake in the lowest quintile

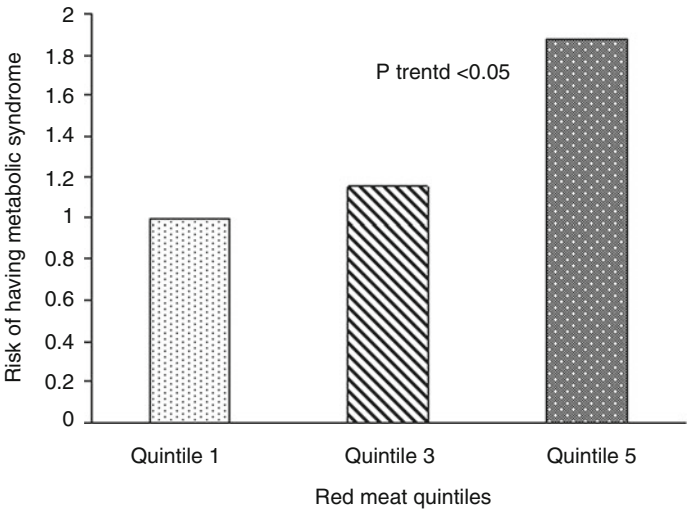

Fig. 163.3 Adjusted odds ratios for metabolic syndrome across quintile categories of red-meat intake. Individuals with the highest quintile of red-meat intake are at highest risk for metabolic syndrome

Whole-grain intake (Esmaillzadeh et al. 2005) and dairy consumption (Azadbakht et al. 2005b) were also inversely associated with the metabolic syndrome. However, there was a direct positive correlation between red-meat intake (Azadbakht and Esmaillzadeh 2009) and hydrogenated vegetable oil (Esmaillzadeh and Azadbakht 2008a, b) with metabolic syndrome. Figure 163.3 presents the odds ratios for metabolic syndrome by quintile of red-meat intake.

163.5 Practical Guidelines

To reduce the prevalence of abdominal adiposity, physical activity and dietary modification might be useful for the Iranian population. Therefore, we recommend a low glycemic index diet containing a large quantity of vegetables, whole grains, fruits, and low-fat dairy products with moderate amounts of non-hydrogenated vegetable oil, olive oil, fish, and poultry, and a low amount of red meat and refined grain as well as doing regular daily exercise. Our recent publications in Iran revealed that Dietary Approaches to Stop hypertension (DASH) eating pattern has a beneficial effects on reducing waist circumference and cardiovascular risks (Azadbakht 2011a, b). Increasing the dietary diversity especially regarding the fruit and vegetable and whole grain could also be related to lower waist circumference among this population (Azadbakht 2011c)

Summary Points

- Having a low physical activity level, unemployment, depression, smoking, being postmenopausal, and married are some important determinants of central adiposity, especially among the Iranian population.
- Eating a diet rich in vegetables, fruits, whole grains, and low-fat dairy products might be associated with lower risk for having central adiposity, based on Iranian studies.
- Calcium and vitamin C intake in sufficient quantities can reduce the risk of abdominal adiposity among Iranians.

- Hydrogenated vegetable oil can increase the risk of having central adiposity among Iranian adults.
- Central adiposity is a risk factor for metabolic syndrome, type 2 diabetes, and cardiovascular diseases.
- There is an inverse association between fruit-, vegetable-, dairy-, and whole-grain intake and metabolic syndrome among the Iranian population. However, red-meat intake and hydrogenated-vegetable-oil consumption are directly associated with this syndrome in Iran. Central adiposity is a major component of metabolic syndrome.

Key Features of Central Adiposity

Table 163.4 highlights key points related to the determinants of central adiposity.

Table 163.4 Key points: determinants of central adiposity

• Physical activity can reduce the risk of being centrally obese among Iranians
• Eating a diet rich in whole grains, vegetables, and fruits and containing low quantities of trans fats, hydrogenated fats, refined grains, and red meat is recommended for the prevention of central adiposity in Iran
• Low calcium intake and low vitamin C intake can be related to abdominal adiposity among Iranians

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Chapter 164
Anthropometry and the Prevalence of Child Obesity in China and Japan

Liubai Li, Hui Li, and Hiroshi Ushijima

Abstract Despite the huge socioeconomic differences between China and Japan, the rapid increase of child obesity in both countries is alarming. The prevalence of overweight and obesity in children has increased two to four fold in the two countries over the past three decades.

In the 2002 China National Nutrition and Health Survey (2002 CNHS), the prevalence of overweight and obesity in children and adolescents was 3–4 times to that 30 years ago. In children aged 0–6 years, 3.4% of the children were overweight and 2.1% were obese, according to WHO recommended weight-for-height *Z*-score (WHZ) criteria (overweight: 2< WHZ ≤3,obesity: WHZ >3). For Chinese children and adolescents aged 7–17 years, the prevalence of overweight and obesity in 2002 CNHS were 4.5% and 2.1%, respectively, analyzed by using body mass index (BMI) cut-offs for Chinese children and adolescents (made by the Chinese Obesity Work Group, COWG). Using the same criterion, prevalence of overweight and obese students aged 7–22 years in 2005 were 8.72% and 5.01%, respectively, in urban areas, and were 4.61% and 2.63% in rural areas. Urban children have a higher risk of being overweight and obese than rural children.

Prevalence of overweight and obese children in Japanese is estimated by using the Percentage Overweight or Percentage of Standard Weight for Height (POW). The prevalence of overweight and obesity in boys and girls increased from 6.1% to 7.1%, respectively, in the time-period from 1976 to 1980, to 11.1% and 10.2% in 1996 to 2000 estimated by using the 85th percentile BMI cut-off values.

Overall, boys have a higher prevalence of being overweight and obese, and the increasing trend was most evident in 9–11 year old children in both countries.

Weight-for-height *Z*-scores and BMI cut-offs for Chinese children and adolescents are frequently used for child overweight and obesity screening in China. POW is usually used for child overweight and obesity screening in Japan. In this chapter, we present obesity related anthropometrical indices in population and the cut-offs for child overweight and obesity in the two countries.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_164,

Abbreviations

BMI	Body mass index
COWG	The Chinese Obesity Work Group
2002 CNHS	The 2002 China National Nutrition and Health Survey
DEXA	Dual-energy X-ray absorptiometry
GH	Growth hormone
GHRH	Growth hormone releasing hormone
HC	Hip circumference
NCHS	National Center for Health Statistics
PBF	Percent body fat (or fat%)
POW	Percentage Overweight
WC	Waist circumference
WHR	Waist to hip ratio (WHR = WC/HC)
WHO	The World Health Organization
WHZ	Weight-for-height *Z*-score

164.1 Introduction

Obesity has become an epidemic in many parts of the world (including Asia) in the past three decades. Its impact on children's health and their later life is becoming a greater concern. Despite the large socioeconomic differences between China and Japan, the rapid increase of child obesity in Chinese and Japanese children is alarming. Obesity prevention has become an important public, health issue both in China and Japan.

Identifying children in high risk of overweight and obesity is important in obesity control. The World Health Organization (WHO) has established body mass index (BMI) (BMI = weight (kg)/height[m]^2) cutoffs for defining child overweight and obesity in the world (Cole 2000). However, ethnic differences in body composition limit its worldwide use. For actual reporting, the identification of child overweight and obesity in China and Japan is often based on their national criteria.

In this chapter, we report the prevalence of child overweight and obesity in China and Japan, and present the anthropometric indices relating to child overweight and obesity identification in the two countries.

164.2 Prevalence of Child Obesity

164.2.1 Prevalence of Overweight and Obesity in Chinese Children

The rapid socioeconomic development and urbanization in China transitioned nutrition toward the lifestyle in Western society (high-fat food, high-energy intake, sedentary lifestyle, etc.) and resulted in the child, obesity epidemic. In the 2002 China National Nutrition and Health Survey (2002CNHS) data sets, the prevalence of overweight and obesity in children and adolescents was three to four times that 30 years ago. About one-fourth of Chinese children are now overweight or obese (Wang 2005). In children aged 0–6 years, 3.4% of children were overweight and 2.1% were obese, according to

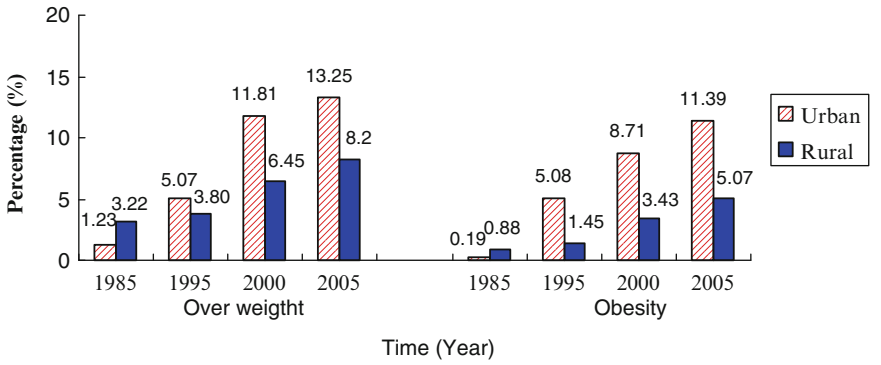

Fig. 164.1 Trends of overweight and obesity prevalence in Chinese boys aged 7–22 years from 1985 to 2005. Prevalence of overweight and obesity increased rapidly both in urban and rural areas (estimated by using the WHZ criterion for Chinese children). Sample size: $n > 200{,}000$ in 1985, $n > 100{,}000$ in 1995, $n > 100{,}000$ in 2000, and $n = 152201$ in 2005 (Research group on the physical fitness and health in Chinese students 2007)

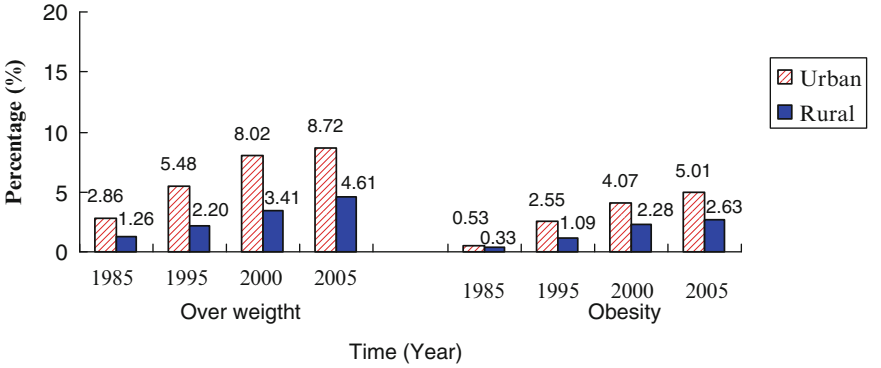

Fig. 164.2 Trends of overweight and obesity prevalence in Chinese girls aged 7–22 years from 1985 to 2005. Prevalence of overweight and obesity increased rapidly both in urban and rural areas (estimated by using the WHZ criterion for Chinese children). Sample size: $n > 200{,}000$ in 1985, $n > 100{,}000$ in 1995, $n > 100{,}000$ in 2000, and $n = 151{,}162$ in 2005 (Research group on the physical fitness and health in Chinese students 2007)

WHO-recommended weight-for-height *Z*-score (WHZ) criteria (overweight: 2 <WHZ ≤3, obesity: WHZ >3) (De Onis et al. 1996). In children and adolescents aged 7–17 years, the prevalence of overweight and obesity in 2002 was 4.5% and 2.1%, respectively – as analyzed by using BMI cutoffs for Chinese children recommended by The Chinese Obesity Work Group (COWG) (The Chinese Obesity Work Group 2004). The secular trends in the prevalence of child overweight and obesity were frequently reported. In a nine-city child growth survey of 112,945 urban children in 2005, about 6.25% of children aged 0–7 years were reported to be overweight and 3.19% were obese, according to the weight-for-height definition in the NCSH/WHO reference (over 10% as overweight and over 20% as obese). The prevalence of obesity has increased 2.78 times in the past 20 years, and the annual incremental rate was 6.9% (The Ministry of Health, China 2008).

In China, there are significant residential and gender differences in the prevalence of overweight and obesity in children. Urban children had a relatively higher prevalence than rural children, and boys had a higher prevalence than girls. Figures 164.1 and 164.2 show the increasing secular trends of childhood overweight and obesity in children and youths aged 7–22 years by using data of The National Survey on Chinese Students' Constitution and Health (in 1985, 1995, 2000, and 2005)

(Research group on the physical fitness and health in Chinese students 2007). Rates were estimated by using the WHZ criterion for Chinese children (Ministry of Education, China 2003).

The prevalence of overweight and obesity in 1985 was only 0.2% and 0.1% in boys and girls, respectively. This has increased to 25.4% for boys aged 7–9 years and 25.5% for boys aged 10–12 years. These numbers have increased to 17.0% in girls aged 7–9 years and 14.3% in girls aged 10–12 years. The prevalence was comparable to the average level seen in some developed countries (Cheng-Ye 2007).

164.2.2 Prevalence of Overweight and Obesity in Japanese Children

Westernized food pattern and lifestyles may account for the increasing rate of child overweight and obesity in Japan. The annual school health body check results showed the current prevalence of child overweight and obesity in Japanese children (Fig. 164.3) and described its secular trends (Fig. 164.4). Child overweight and obesity have increased rapidly in recent decades (School health statistics 2008).

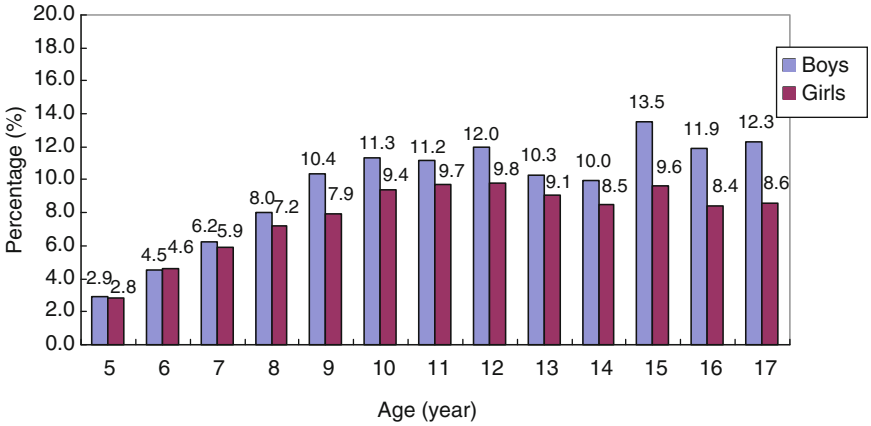

Fig. 164.3 Prevalence of child overweight and obesity in Japanese children in 2008. Prevalence of overweight and obesity was around 10% in most age groups of Japanese children in 2008 (School health statistics 2008)

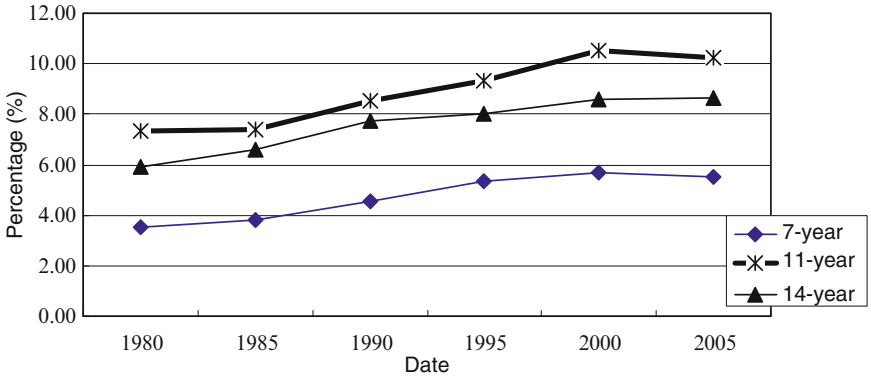

Fig. 164.4 Secular trends in the prevalence of overweight and obesity in Japanese children from 1980 to 2005. The prevalence of overweight and obesity in Japanese children increased rapidly from 1980 to 2005 (School health statistics 2008)

It was estimated that the mean (age-adjusted) BMI increased by 0.32 kg/m^2 per 10 years in boys and by 0.24 kg/m^2 per 10 years in girls, and the increases were remarkable in small towns (Yumi et al. 2004).

Overall, in both countries, prevalence of overweight and obesity was higher in boys than in girls, and the increasing trend was most evident in 9–11-year-old boys and girls.

164.3 Anthropometry of Chinese Children

The most frequently measured anthropometric indices are height, body weight, waist girth, hip girth, and skinfold thickness (usually triceps and subscapular skinfold thickness for body-fat estimation). We will present some anthropometric indices relating to the screening criterion for childhood overweight and obesity as well as its application to Chinese children.

164.3.1 Weight-for-Height Z-Scores and BMI Cutoffs

The prevalence of overweight and obesity in children owing to overnutrition can be measured either by the proportion of children with weight-for-height above +2 *Z*-score (WHZ>2), or with BMI above the 85th and the 95th percentiles of the same gender and age (WHO 2006; The Ministry of Health, China 2008). In China, both criteria are used in child overweight and obesity screening. Tables 164.1–164.3 display the mean (SD) and percentile values of weight-for-length/height and BMI for Chinese children under 7 years of age. The data were obtained in 2005 from well-nourished healthy children with rate of malnutrition (both undernutrition and overweight) less than 4% (The Ministry of Health, China 2008).

For children over 7 years, the previously used WHZ criterion (Ministry of Education, China 2003) is now being gradually replaced by the BMI-based criterion since the construction of the BMI cutoff values for child overweight and obesity screening by the COWG in 2004 (The Chinese Obesity Work Group 2004). The new BMI cutoff criterion was based on national data sets of 24,257 Chinese children and adolescents aged 7–18 years in 2000. The reference data excluded data of the malnourished children and used health outcomes (blood pressure, blood lipids, etc.) as predictive disease variables. The BMI cutoffs were constructed using the LMS method, and made the curve pass through BMI cutoff values for Chinese adults (24 kg/m^2 for overweight and 28 kg/m^2 for obesity) (The Chinese Obesity Work Group 2004). The criterion is now widely used in overweight and obesity screening in Chinese children and adolescents. In 2009, BMI cutoffs for overweight and obesity screening in Chinese children aged 2–18 years were established using the LMS methods and the two national data sets (Hui Li et al. 2009). Table 164.4 displays BMI distributions in Chinese Han ethnic children in Beijing areas in 2000 (combined urban and rural children).

Table 164.1 Weight-for-length (kg) for Chinese children under 7 years old (45–105 cm) (used in 0–3-year-old children) (Data source: Ministry of Health of China et al. 2009. With permission)

	Weight for length (kg)										
	Z-scores				Percentiles (weight, kg)						
Length (cm)	Median	+1SD	+2SD	+3SD	25th	50th	75th	85th	90th	95th	97th
Boys											
45	2.20	2.42	2.65	2.90	2.06	2.20	2.53	2.43	2.49	2.57	2.63
48	2.84	3.12	3.42	3.74	2.66	2.84	3.02	3.13	3.20	3.31	3.38
51	3.47	3.81	4.18	4.58	3.25	3.47	3.70	3.82	3.91	4.05	4.13
54	4.25	4.67	5.12	5.62	3.99	4.25	4.53	4.68	4.79	4.96	5.07
57	5.15	5.66	6.21	6.81	4.84	5.15	5.49	5.67	5.81	6.01	6.14
60	6.06	6.65	7.30	8.01	5.70	6.06	6.45	6.67	6.83	7.06	7.22
63	6.94	7.61	8.34	9.15	6.53	6.94	7.38	7.63	7.80	8.07	8.25
66	7.74	8.47	9.28	10.19	7.30	7.74	8.23	8.50	8.69	8.98	9.18
69	8.46	9.24	10.12	11.10	7.98	8.46	8.98	9.28	9.48	9.80	10.01
72	9.12	9.94	10.88	11.93	8.61	9.12	9.66	9.98	10.20	10.53	10.76
75	9.72	10.59	11.57	12.69	9.19	9.72	10.29	10.62	10.85	11.21	11.45
78	10.31	11.22	12.25	13.42	9.75	10.31	10.91	11.25	11.49	11.87	12.12
81	10.91	11.86	12.94	14.17	10.33	10.91	11.54	11.89	12.15	12.54	12.80
84	11.53	12.52	13.64	14.94	10.94	11.53	12.18	12.56	12.82	13.23	13.50
87	12.17	13.20	14.37	15.73	11.55	12.17	12.85	13.24	13.51	13.94	14.22
90	12.83	13.90	15.12	16.54	12.19	12.83	13.53	13.94	14.22	14.67	14.96
93	13.51	14.62	15.90	17.38	12.85	13.51	14.24	14.66	14.96	15.42	15.73
96	14.23	15.38	16.72	18.29	13.54	14.23	14.99	15.43	15.74	16.22	16.55
99	15.00	16.22	17.63	19.30	14.27	15.00	15.80	16.26	16.59	17.10	17.45
102	15.83	17.12	18.64	20.45	15.06	15.83	16.68	17.18	17.53	18.07	18.45
105	16.71	18.11	19.76	21.74	15.89	16.71	17.63	18.16	18.54	19.14	19.54
Girls											
45	2.33	2.57	2.85	3.17	2.18	2.33	2.49	2.58	2.65	2.75	2.82
48	2.91	3.21	3.55	3.94	2.72	2.91	3.11	3.22	3.30	3.42	3.51
51	3.51	3.87	4.27	4.73	3.29	3.51	3.74	3.88	3.98	4.12	4.22
54	4.27	4.70	5.18	5.73	4.01	4.27	4.55	4.71	4.83	5.00	5.12
57	5.09	5.58	6.14	6.78	4.79	5.09	5.42	5.60	5.73	5.94	6.07
60	5.93	6.49	7.13	7.85	5.59	5.93	6.30	6.51	6.66	6.89	7.05
63	6.75	7.38	8.08	8.88	6.37	6.75	7.16	7.40	7.57	7.82	7.99
66	7.51	8.18	8.95	9.82	7.09	7.51	7.95	8.21	8.39	8.67	8.85
69	8.19	8.92	9.74	10.68	7.75	8.19	8.67	8.95	9.14	9.44	9.64
72	8.82	9.59	10.46	11.46	8.35	8.82	9.33	9.62	9.82	10.14	10.35
75	9.39	10.20	11.13	12.18	8.90	9.39	9.93	10.23	10.45	10.78	11.01
78	9.95	10.80	11.77	12.88	9.44	9.95	10.52	10.84	11.06	11.41	11.65
81	10.54	11.43	12.45	13.62	10.00	10.54	11.13	11.47	11.71	12.07	12.32
84	11.16	12.10	13.16	14.39	10.59	11.16	11.78	12.13	12.38	12.77	13.03
87	11.80	12.79	13.92	15.21	11.21	11.80	12.45	12.83	13.09	13.50	13.77
90	12.50	13.54	14.73	16.11	11.87	12.50	13.18	13.58	13.85	14.29	14.58
93	13.24	14.34	15.60	17.08	12.57	13.24	13.96	14.38	14.68	15.13	15.44
96	14.02	15.19	16.54	18.11	13.31	14.02	14.79	15.23	15.55	16.03	16.36
99	14.82	16.07	17.52	19.22	14.07	14.82	15.64	16.12	16.46	16.98	17.34
102	15.64	16.98	18.55	20.39	14.84	15.64	16.52	17.03	17.40	17.96	18.35
105	16.48	17.93	19.63	21.65	15.62	16.48	17.43	17.98	18.38	18.99	19.41

Table 164.2 Weight-for-height (kg) for Chinese children under 7 years old (65–125 cm) (Data source: Ministry of Health of China et al. 2009. With permission)

	Weight for length (kg)										
	Z-scores				Percentiles (weight, kg)						
Height (cm)	Median	+1SD	+2SD	+3SD	25th	50th	75th	85th	90th	95th	97th
Boys											
65	7.67	8.39	9.19	10.09	7.22	7.67	8.15	8.42	8.61	8.90	9.09
68	8.40	9.17	10.04	11.02	7.92	8.40	8.91	9.20	9.41	9.72	9.93
71	9.05	9.88	10.80	11.85	8.55	9.05	9.60	9.91	10.13	10.46	10.69
74	9.66	10.53	11.50	12.61	9.13	9.66	10.23	10.56	10.79	11.14	11.38
77	10.25	11.15	12.18	13.35	9.70	10.25	10.85	11.19	11.43	11.80	12.05
80	10.85	11.79	12.87	14.09	10.28	10.85	11.47	11.83	12.08	12.47	12.73
83	11.47	12.45	13.57	14.86	10.88	11.47	12.12	12.49	12.75	13.16	13.43
86	12.11	13.13	14.30	15.65	11.49	12.11	12.78	13.17	13.44	13.87	14.15
89	12.77	13.83	15.04	16.46	12.13	12.77	13.46	13.87	14.15	14.59	14.89
92	13.44	14.54	15.82	17.30	12.78	13.44	14.17	14.59	14.88	15.34	15.65
95	14.15	15.30	16.64	18.20	13.46	14.15	14.91	15.35	15.66	16.14	16.47
98	14.92	16.13	17.54	19.19	14.20	14.92	15.72	16.18	16.50	17.01	17.36
101	15.75	17.03	18.54	20.33	14.98	15.75	16.59	17.08	17.43	17.97	18.34
104	16.62	18.00	19.64	21.61	15.80	16.62	17.53	18.06	18.44	19.03	19.43
107	17.54	19.04	20.85	23.04	16.65	17.54	18.53	19.10	19.52	20.17	20.61
110	18.50	20.16	22.18	24.67	17.54	18.50	19.59	20.23	20.69	21.41	21.91
113	19.54	21.39	23.67	26.56	18.48	19.54	20.75	21.47	21.98	22.80	23.37
116	20.66	22.74	25.36	28.76	19.47	20.66	22.01	22.83	23.42	24.36	25.01
119	21.87	24.24	27.29	31.37	20.54	21.87	23.41	24.34	25.02	26.11	26.88
122	23.19	25.91	29.50	34.48	21.69	23.19	24.95	26.03	26.82	28.10	29.01
125	24.64	27.78	32.04	38.18	22.94	24.64	26.66	27.91	28.84	30.36	31.45
Girls											
65	7.43	8.11	8.87	9.73	7.02	7.43	7.88	8.13	8.31	8.59	8.77
68	8.12	8.85	9.67	10.60	7.68	8.12	8.60	8.87	9.07	9.36	9.56
71	8.76	9.52	10.39	11.39	8.29	8.76	9.26	9.55	9.76	10.07	10.28
74	9.33	10.14	11.06	12.11	8.84	9.33	9.87	10.17	10.39	10.72	10.94
77	9.90	10.74	11.71	12.81	9.38	9.90	10.46	10.78	11.00	11.35	11.59
80	10.48	11.37	12.38	13.54	9.94	10.48	11.07	11.40	11.64	12.01	12.25
83	11.10	12.03	13.09	14.31	10.53	11.10	11.71	12.06	12.31	12.70	12.96
86	11.74	12.72	13.84	15.13	11.14	11.74	12.38	12.76	13.02	13.42	13.70
89	12.42	13.46	14.64	16.01	11.80	12.42	13.11	13.50	13.78	14.20	14.49
92	13.16	14.26	15.51	16.98	12.50	13.16	13.88	14.30	14.59	15.05	15.35
95	13.94	15.10	16.44	18.01	13.24	13.94	14.70	15.14	15.46	15.94	16.27
98	14.74	15.98	17.42	19.11	14.00	14.74	15.56	16.03	16.36	16.88	17.24
101	15.56	16.89	18.44	20.27	14.76	15.56	16.43	16.94	17.30	17.86	18.24
104	16.39	17.83	19.51	21.52	15.54	16.39	17.34	17.89	18.28	18.88	19.30
107	17.27	18.82	20.66	22.88	16.35	17.27	18.29	18.88	19.31	19.97	20.42
110	18.18	19.87	21.90	24.37	17.19	18.18	19.29	19.94	20.41	21.14	21.64
113	19.15	21.01	23.25	26.03	18.08	19.15	20.37	21.08	21.60	22.41	22.96
116	20.20	22.25	24.76	27.91	19.02	20.20	21.54	22.33	22.90	23.80	24.43
119	21.32	23.58	26.40	30.02	20.03	21.32	22.79	23.67	24.31	25.33	26.03
122	22.52	25.03	28.21	32.39	21.10	22.52	24.15	25.13	25.85	26.99	27.79
125	23.79	26.59	30.20	35.07	22.24	23.79	25.60	26.70	27.51	28.80	29.71

Table 164.3 Median (SD) and percentiles of BMI (kg/m^2) for Chinese children under 7 years old (Data source: Ministry of Health of China et al. 2009. With permission)

Age (year/month)	BMI (kg/m^2)								
			Percentiles						
	Median	SD	25th	50th	75th	85th	90th	95th	97th
Boys									
0 month	13.07	1.14	12.35	13.07	13.83	14.25	14.55	15.00	15.30
3 month	17.48	1.56	16.48	17.48	18.52	19.10	19.50	20.10	20.50
6 month	17.96	1.66	16.94	17.96	19.06	19.69	20.12	20.79	21.23
9 month	17.62	1.59	16.66	17.62	18.67	19.27	19.69	20.34	20.77
12 month	17.19	1.49	16.29	17.19	18.18	18.74	19.14	19.75	20.17
15 month	16.78	1.42	15.91	16.78	17.72	18.26	18.64	19.23	19.63
18 month	16.47	1.39	15.64	16.47	17.39	17.91	18.28	18.86	19.25
21 month	16.26	1.36	15.45	16.26	17.16	17.67	18.04	18.60	18.98
2.0 year	16.07	1.32	15.27	16.07	16.94	17.44	17.80	18.35	18.72
2.5 year	15.73	1.27	14.96	15.73	16.57	17.05	17.39	17.93	18.29
3.0 year	15.66	1.26	14.91	15.66	16.49	16.97	17.31	17.85	18.22
3.5 year	15.45	1.26	14.71	15.45	16.28	16.76	17.11	17.65	18.02
4.0 year	15.32	1.28	14.57	15.32	16.16	16.65	17.00	17.55	17.93
4.5 year	15.23	1.32	14.47	15.23	16.10	16.60	16.97	17.54	17.93
5.0 year	15.22	1.38	14.43	15.22	16.12	16.66	17.04	17.64	18.06
5.5 year	15.27	1.46	14.43	15.27	16.23	16.79	17.20	17.85	18.30
6.0 year	15.35	1.56	14.46	15.35	16.36	16.97	17.41	18.12	18.61
6.5 year	15.45	1.68	14.51	15.45	16.54	17.20	17.67	18.44	18.97
Girls									
0 month	13.00	1.22	12.26	13.00	13.81	14.27	14.59	15.09	15.43
3 month	16.69	1.51	15.77	16.69	17.69	18.26	18.66	19.27	19.69
6 month	17.41	1.55	16.47	17.41	18.43	19.02	19.43	20.06	20.49
9 month	17.19	1.49	16.29	17.19	18.17	18.73	19.13	19.74	20.15
12 month	16.74	1.41	15.89	16.74	17.67	18.21	18.58	19.16	19.55
15 month	16.32	1.35	15.49	16.32	17.21	17.73	18.09	18.65	19.03
18 month	16.03	1.33	15.23	16.03	16.91	17.41	17.77	18.31	18.69
21 month	15.84	1.31	15.05	15.84	16.71	17.20	17.56	18.10	18.47
2.0 year	15.67	1.30	14.89	15.67	16.53	17.02	17.37	17.91	18.27
2.5year	15.40	1.28	14.64	15.40	16.24	16.73	17.07	17.60	17.96
3.0year	15.42	1.28	14.65	15.42	16.26	16.76	17.11	17.65	18.03
3.5 year	15.27	1.29	14.50	15.27	16.12	16.61	16.97	17.52	17.90
4.0 year	15.15	1.32	14.38	15.15	16.02	16.53	16.89	17.46	17.84
4.5 year	15.06	1.36	14.27	15.06	15.95	16.48	16.85	17.44	17.84
5.0 year	14.99	1.41	14.18	14.99	15.91	16.45	16.84	17.45	17.88
5.5 year	14.96	1.46	14.12	14.96	15.91	16.48	16.88	17.52	17.96
6.0 year	14.96	1.51	14.09	14.96	15.95	16.53	16.96	17.63	18.09
6.5 year	14.97	1.58	14.07	14.97	16.00	16.61	17.05	17.76	18.25

164.4 Anthropometry of Japanese Children

164.4.1 Percentage Overweight (POW) (% OW)

For defining obesity in childhood, the Ministry of Health, Labor and Welfare of Japan has adopted percentage overweight (POW) as the parameter in overweight and obesity screening. Box 164.1 shows the calculation of POW and the cutoff values of the criterion.

Table 164.4 Mean (SD) and percentiles of BMI (kg/m^2) for Chinese children aged 6–17 years

	BMI (kg/m^2)							
				Percentiles (%)				
Age(years)	*n*	Mean	SD	25th	50th	75th	85th	95th
Boys								
6	216	15.7	2.3	14.3	15.1	16.3	17.2	19.9
7	227	16.0	2.3	14.4	15.4	17.0	18.4	20.9
8	210	16.4	2.2	14.8	15.7	17.6	18.6	20.7
9	214	16.9	2.6	15.2	16.3	17.9	19.3	22.8
10	200	16.9	2.4	15.3	16.6	17.9	18.9	21.6
11	210	18.0	2.9	15.8	17.3	19.6	20.8	23.7
12	204	18.8	3.4	16.3	18.1	20.7	22.2	26.7
13	204	19.3	3.3	17.3	18.5	20.9	22.2	25.8
14	207	20.2	3.5	17.8	19.4	21.8	23.7	27.3
15	210	20.2	3.2	18.0	19.4	21.8	23.4	26.5
16	188	21.0	3.3	18.7	20.4	22.5	23.7	27.9
17	156	21.3	3.1	19.1	20.8	23.3	24.6	27.2
Girls								
6	206	15.1	1.5	14.2	14.8	15.8	16.4	18.2
7	248	15.3	2.2	13.9	15.0	16.3	17.1	19.4
8	198	15.8	2.1	14.3	15.4	16.5	17.9	20.2
9	214	16.1	2.4	14.5	15.7	17.3	18.1	20.4
10	202	16.9	2.7	15.0	16.4	18.4	20.1	21.9
11	200	17.3	2.4	15.3	17.0	18.8	19.7	21.5
12	211	18.4	3.0	16.3	18.0	19.9	21.1	24.8
13	207	19.1	3.2	16.8	18.3	20.3	22.6	25.2
14	208	19.5	2.8	17.6	19.0	20.7	21.9	24.1
15	199	20.0	2.8	18.0	19.5	21.8	22.9	25.2
16	203	20.6	2.7	18.7	20.2	22.1	23.4	26.4
17	156	20.6	2.6	18.7	20.4	22.1	23.1	26.0

Data of the physical fitness and health surveillance of Beijing school students, measured in 2000

Box 164.1 Calculation of POW and the Cutoffs of Child Overweight and Obesity

1. Calculation of POW(% OW):
   % OW = 100 × (measured weight-standard weight-for-height)/standard weight-for-height
   Standard weight-for-height = a × measured height (cm) – b
   Here, 'a' and 'b' are coefficients. Both 'a' and 'b', as well as *Standard weight-for-height values* are available in the website of the Japanese government (School health statistics 2008)
2. The criteria for overweight and obesity screening (Japan society for the study of obesity 2004)
   Overweight and obesity are defined as *POW ≥15%* for children before school age (6 years), and *POW ≥20%* thereafter
   Normal weight: – 20% < %OW < +20%
   Mild obesity: +20% ≦ %OW < +30%
   Moderate obesity: +30% ≦ %OW < +50%
   Severe obesity:+50% ≦ %OW

In 2003, The Japanese Society for the Study of Obesity issued a new clinical diagnostic criterion for 'obesity disease'. According to the new criteria, obesity in childhood (<18 years old) was defined as: POW >20% and percent body fat (PBF) >25% for boys, POW >20% and PBF >30% for girls younger than 11 years, and PBF >35% for girls aged 11 years or older (Kohtaro et al. 2003).

164.4.2 BMI Reference Values for Japanese Children

In some studies, reference values of BMI for Japanese children were constructed by using data in the national school health check (Tables 164.5 and 164.6) (Mikako et al. 2007b).

164.4.3 Body Composition in Japanese Children and Adolescents

Obesity definitions according to fat% cutoff values in Japanese children are as follows (Japan Society for the Study of Obesity 2004), regardless of the measurement technique:

All boys: fat% >25%;
Girls <11 years: fat%>30%; girls ≦ 11 years: fat% >35%

164.4.4 Central Obesity

In Japan, either waist circumference (WC) ≥80 cm or visceral adipose tissue area ≥60 cm^2 in children is defined as obese (Kohtaro et al. 2003, 2005). Table 164.7 displays the adjusted WC means for children at different ages. The WC reference was prepared from national health check data. WC_1 was measured at the level of maximum waist narrowing and WC_2 was measured at the level of the top of the iliac crest (Mikako et al. 2007a).

Table 164.5 Mean (SD) and percentile references of BMI for Japanese boys aged 2–18 years (BMI in kg/m^2) (Reprinted from Mikako et al. (2007b), with kind permission of Wiley-Blackwell and the authors)

Age	Mean and Z-scores					Percentiles (BMI in kg/m^2)					
(years)	Mean	SD	+1SD	+2SD	+2.5SD	25th	50th	75th	90th	95th	97th
2	16.5	1.3	17.8	19.3	20.1	15.7	16.5	17.3	18.2	18.7	19.1
3	16.0	1.3	17.3	18.7	19.5	15.3	16.0	16.8	17.6	18.2	18.5
4	15.6	1.2	16.8	18.3	19.1	14.9	15.6	16.4	17.2	17.7	18.1
5	15.4	1.2	16.6	18.2	19.2	14.6	15.4	16.2	17.0	17.6	18.0
6	15.3	1.3	16.6	18.5	19.6	14.6	15.3	16.2	17.1	17.7	18.2
7	15.4	1.5	16.9	19.0	20.4	14.6	15.4	16.3	17.4	18.1	18.7
8	15.6	1.7	17.3	19.8	21.7	14.7	15.6	16.7	17.9	18.8	19.4
9	16.0	1.9	17.9	21.0	23.5	15.1	16.0	17.2	18.6	19.7	20.5
10	16.5	2.1	18.6	22.2	25.2	15.5	16.5	17.8	19.4	20.6	21.6
11	17.0	2.3	19.3	23.2	26.7	15.9	17.0	18.4	20.2	21.5	22.6
12	17.5	2.4	19.9	24.1	27.8	16.3	17.5	19.0	20.9	22.3	23.5
13	18.1	2.5	20.6	24.8	28.3	16.9	18.1	19.7	21.5	23.0	24.1
14	18.7	2.5	21.2	25.3	28.5	17.5	18.7	20.3	22.1	23.6	24.7
15	19.3	2.5	21.8	25.7	28.7	18.1	19.3	20.9	22.7	24.1	25.1
16	19.9	2.5	22.4	26.2	28.9	18.6	19.9	21.5	23.3	24.6	25.6
17	20.4	2.5	22.9	26.6	29.2	19.1	20.4	22.0	23.8	25.1	26.0
18	20.8	2.5	23.3	26.9	29.5	19.5	20.8	22.4	24.2	25.5	26.4

Table 164.6 Mean (SD) and percentile references of BMI for Japanese girls aged 2–18 years (BMI in kg/m^2) (Reprinted from Mikako et al. (2007b), with kind permission of Wiley-Blackwell and the authors)

Age	Mean and *Z*-scores					Percentiles (BMI in kg/m^2)					
(years)	Mean	SD	+1SD	+2SD	+2.5SD	25th	50th	75th	90th	95th	97th
2	16.2	1.3	17.5	18.9	19.7	15.4	16.2	17.1	17.9	18.4	18.7
3	15.9	1.3	17.2	18.7	19.5	15.1	15.9	16.7	17.6	18.1	18.5
4	15.6	1.3	16.9	18.4	19.4	14.8	15.6	16.4	17.3	17.8	18.2
5	15.3	1.3	16.6	18.3	19.3	14.5	15.3	16.2	17.1	17.7	18.1
6	15.1	1.5	16.6	18.4	19.6	14.3	15.1	16.0	17.0	17.7	18.2
7	15.1	1.6	16.7	18.7	20.1	14.3	15.1	16.1	17.2	17.9	18.5
8	15.3	1.7	17.0	19.4	21.0	14.4	15.3	16.4	17.6	18.5	19.1
9	15.7	1.9	17.6	20.3	22.2	14.7	15.7	16.9	18.3	19.2	19.9
10	16.3	2.1	18.4	21.4	23.5	15.2	16.3	17.6	19.1	20.2	21.0
11	16.9	2.2	19.1	22.4	24.6	15.7	16.9	18.3	19.9	21.1	21.9
12	17.6	2.4	20.0	23.4	25.6	16.3	17.6	19.1	20.8	22.0	22.9
13	18.4	2.5	20.9	24.3	26.6	17.1	18.4	20.0	21.8	23.0	23.9
14	19.2	2.5	21.7	25.1	27.2	17.9	19.2	20.9	22.6	23.8	24.6
15	19.9	2.5	22.4	25.6	27.5	18.5	19.9	21.5	23.2	24.3	25.1
16	20.3	2.4	22.7	25.7	27.5	19.0	20.3	21.8	23.4	24.5	25.3
17	20.5	2.3	22.8	25.6	27.2	19.2	20.5	22.0	23.5	24.5	25.2
18	20.6	2.2	22.8	25.4	26.9	19.4	20.6	22.0	23.4	24.4	25.0

Table 164.7 Adjusted mean value of waist circumference in Japanese children aged 6–18 years

Adjusted mean of waist circumference (cm)				
WC_1			WC_2	
Age (year)	Boys	Girls	Boys	Girls
6.0	50.57	50.38	52.59	54.27
6.5	51.45	50.72	53.90	54.95
7.0	52.34	51.15	55.20	55.75
7.5	53.25	51.76	56.44	56.80
8.0	54.18	52.45	57.67	58.01
8.5	55.13	53.12	58.91	59.30
9.0	56.10	53.81	60.25	60.46
9.5	57.09	54.53	61.66	61.57
10.0	58.05	55.42	63.05	62.77
10.5	58.97	56.56	64.31	64.09
11.0	59.86	57.73	65.46	65.54
11.5	60.73	58.71	66.56	67.12
12.0	61.62	59.48	67.68	68.60
12.5	62.54	60.18	68.94	69.94
13.0	63.52	60.92	70.42	71.30
13.5	64.53	61.66	71.95	72.63
14.0	65.55	62.30	73.40	73.69
14.5	66.54	62.85	74.64	74.43
15.0	67.48	63.31	75.71	74.97
15.5	68.32	63.68	76.60	75.41
16.0	69.06	63.98	77.31	75.80
16.5	69.74	64.25	77.87	76.17
17.0	70.39	64.50	78.40	76.62
17.5	71.01	64.74	78.94	77.18
18.0	71.62	64.99	79.47	77.83

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WC_1: measured at the level of maximum narrowing waist narrowing
WC_2: measured at the level of the top of the iliac crest

164.5 Applications to Other Areas of Health and Disease

Child overweight and obesity relate to many health problems and diseases. Overweight can be a consequence of an original disease and is also related to a number of non-communicable chronic diseases (e.g., hypertension, diabetes, metabolic syndromes, and cancer). Obesity adversely affects virtually every organ system. The following clinical correlates may be related to overweight and obesity.

164.5.1 Clinical Correlates

- Acquired hypothalamic lesions: infectious (sarcoid, tuberculosis, arachnoiditis, and encephalitis), vascular malformation, neoplass, and trauma.
- Cushing's syndrome: hypercortisolism.
- Growth hormone (GH) deficiency: impaired production of GH (pituitary) or GHRH (hypothalamus).
- Hypothyroidism: hypothalamic, pituitary, or thyroidal.
- Behaviors: child eating disorder (binge eating).
- Cardiometabolic abnormalities.

164.6 Practical Methods and Techniques in BMI Calculation and WC Measurement

164.6.1 BMI Calculation

BMI correlates well with body fat and is relatively unaffected by height. BMI is calculated as either the body weight (kg) divided by the stature (height [m]) squared (wt/ht^2) or body weight (lb) × 703 divided by the height (stature) squared (wt [lb] × 703/[Ht(in)^2]).

164.6.2 Measuring Waist Circumference

To measure the waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug but does not compress the skin and is parallel to the floor. The measurement is made at the end of a normal expiration.

164.7 Key Points of Different Screening Criteria

164.7.1 Weight-for-Height Z-Score (WHZ) and BMI Z-Score in Chinese Children

There were no significant differences in the prevalence estimation when using the two criteria (WHZ and BMI *Z*-score derived from data of Chinese children) in identifying overweight Chinese

children. For example, the prevalence of overweight boys and girls was 3.62% and 2.91% by using WHZ and was 3.72% and 2.76% by using BMI *Z*-score, respectively, in the nine-city child (0–7 years) nutrition survey, 2006.

Similarly, there was no significant difference between WHZ of China and WHO in the overweight prevalence estimation. Prevalence of child (under five) overweight in the above data sets was 2.98% and 3.07%, respectively, when using WHZ of China and WHO, as screening criteria.

For BMI *Z*-scores, significant difference was found using BMI *Z*-scores of China and the WHO in overweight prevalence estimation. In the above data sets, the prevalence of overweight was 3.26% and 2.94%, respectively, when using BMI *Z*-scores of China and WHO (Capital institute of pediatrics 2009).

164.7.2 POW and BMI Percentiles in Japanese Children

In screening child overweight and obesity, the two systems (POW and BMI percentiles) differed in the prevalence estimation. The traditional standard weight system, POW, underestimated the prevalence of child obesity when compared to the 95th BMI percentile systems (Mikako 2009).

164.8 The Chinese Obesity Work Group (COWG)

The Chinese Obesity Work Group (COWG) has greatly promoted works in obesity prevention and control in China. Table 164.8 shows the key facts of COWG.

Table 164.8 Key facts of the Chinese Obesity Work Group (COWG)

1. The Chinese Obesity Work Group (COWG) was established after a symposium titled 'Obesity in China' by the International Life Science Institute Focal Point in China (ILSI Focal Point in China) was presented in July 2000. The threat of an obesity epidemic in China and the urgent need for identifying BMI cutoff values for obesity screening and preventive strategies spurred its formation
2. The commission of COWG provides technical support for policy making in obesity and obesity-related disease prevention and control in China
3. COWG is composed of 13 medical institutions (and 46 other cooperating institutions), universities, and disease prevention and control institutions in China. Experts working in various fields (e.g., clinical medicine, public health, and bioinformatics and so on) are commissioned members to the group
4. Using available national health survey data sets, COWG has set BMI cutoffs for overweight and obesity screening both for Chinese adults and children. Cross-sectional data covering 240,000 people and longitudinal data of 620,000 people were analyzed for identifying the health risks of obesity
5. After 9 months, ILSI Focal Point in China held a symposium titled 'Obesity and disease risks in China' in June 2001. In this symposium, the BMI cutoffs for Chinese adults were issued. BMI cutoffs are defined as follows: healthy weight: $18.5 \leq \text{BMI} < 24.0$, overweight: $24 \leq \text{BMI} < 28.0$, and obesity: $\text{BMI} \geq 28$
6. COWG issued BMI cutoffs for overweight and obesity screening in Chinese children and adolescents in 2004. The cutoffs were determined based on the analysis of national data sets on physical fitness and health surveillance of Chinese school students
7. COWG is now continuing work on strategies of obesity and obesity-related disease prevention and control

This table lists the key facts of The Chinese Obesity Work Group including the establishment, the commission, and the contributions of COWG in China.

Summary Points

- Prevalence of child overweight and obesity in China and Japan increased rapidly in the past three decades.
- The most commonly used anthropometric indicators in child overweight screening are WHZ and BMI percentiles, which are determined, respectively, either by 2 < WHZ ≤3 for overweight and WHZ >3 for obesity or by BMI >85th percentile values in the same age and sex populations.
- Prevalence of child overweight and obesity may be significantly different when using different screening criteria.
- Waist and hip circumferences and WHR are important indices for obesity-related diseases.
- Thresholds of anthropometric indices (weight-for-height and BMI) may be used for guidance by decision makers to select nutrition-related interventions. However, they must be used with caution in the clinic settings for individual patients, taking into consideration contextual and trend analyses.
- Children with BMI percentiles >85th should be educated on the risks of being overweight.

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Chapter 165
Optimal Waist Circumference Cutoffs for Abdominal Obesity in Chinese

Weiping Jia and Jiemin Pan

Abstract Obesity has become a global epidemic and is a major risk factor for the development of metabolic abnormalities and cardiovascular disease. With the rapid economic development in China, the prevalence of overweight and obesity has been rising, estimated 22.4% of the adult population is overweight and 3.01% is obese in 1990s. It is categorized as abdominal obesity if fat is accumulated in the abdomen. Theoretically, abdominal obesity should be determined by visceral adipose tissue (VAT) precisely measured by magnetic resonance imaging (MRI) or computerized tomography (CT) scanning. While, waist circumference is widely used clinically to estimate the abdominal fat for its convenience and strong correlation with VAT. The waist circumference increased with aging in Chinese population and was quite similar in men and women especially in the subgroup with age over 60 years. Based on a cross-sectional survey, the accumulation of visceral fat at the level of visceral fat area (VFA) over 80 cm^2 in Chinese linked with high prevalence of the metabolic syndrome (MetS). The corresponding waist circumference cut-offs were 87.5 cm in men and 84.3 cm in women. Therefore, it was demonstrated that the optimal cut-offs of waist circumference were 90 cm in men and 85 cm in women. Another prospective study demonstrated that the MetS based on the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (JCDCG) definition was a significant predictor for the development of CVD in total subjects. This study furthermore confirmed that the waist circumference cut-offs with 90 cm in men and 85 cm in women were more suitable than the IDF recommended in Chinese population.

Abbreviations

BMI	Body mass index
CRP	C-reactive protein
CT	Computerized tomography
CVD	Cardiovascular disease
FFAs	Free fatty acids
FPG	Fasting plasma glucose

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_165,

IDF	International Diabetes Federation
JCDCG	The Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults
MetS	Metabolic syndrome
MONICA	Multinational monitoring of trends and determinants in cardiovascular disease
MRI	Magnetic resonance imaging
NCEPIII	National Cholesterol Education Program Adult Treatment Panel III
RBP4	Retinol binding protein 4
ROC	Receiver operating characteristic
VAT	Visceral adipose tissue
VFA	Visceral fat area
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio

165.1 Introduction

The prevalence of obesity is rising rapidly worldwide. Although obesity may be considered as a disease in its own right, it is also one of the key risk factors for a wide range of illness and diseases. It has been listed as one of the ten major contributors to the global disease burden. Additionally, obesity can lead to social problems and psychological disorders. Obese individuals generally have an increased volume of adipocytes and abnormal high body fat percentage (body fat%) and fat deposits in certain parts of the body. It is categorized as 'central' or 'abdominal' obesity if fat is accumulated in the abdomen, which has metabolic influences. It has been demonstrated that obesity, especially abdominal obesity, plays an important role in the development of the metabolic syndrome (MetS) and cardiovascular diseases. With the rapid economic development in China since its reform and opening-up policy, the prevalence of overweight and obesity has been rising; an estimated 22.4% of the adult population was overweight and 3.01% obese in the 1990s. In 2000, the Working Group on Obesity in China conducted a meta-analysis of available data that included body mass index, waist circumference, hypertension, and serum lipid and glucose from more than 240,000 subjects located in 21 provinces, municipalities, and autonomous regions in China. On the basis of the meta-analysis, a BMI of 24 was recommended by the group as the cutoff point for overweight and a BMI of 28 for obesity; waist circumferences of 85 cm for men and 80 cm for women were recommended as the cutoff points for central obesity (Chinese Center for Disease Control and Prevention 2004, Table 165.1). Recently, the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (JCDCG) proposed a new definition of MetS, in which abdominal obesity is defined as the waist circumference >90 for men and >85 cm for women (JCDCG 2007, Table 165.2). The optimal cutoff of waist circumference was based on data from several Chinese population studies. This review discussed the prevalence and features of obesity in China and summarized the available data on the linkage between central obesity and the risk of diabetes mellitus (DM), cardiovascular disease (CVD), and MetS.

Table 165.1 BMI combined with WC cutoff points and risk for disease[a] in Chinese adults

		Waist circumference (cm)		
Classification	BMI (kg/m^2)	Men:<85 Women:<80	Men:85–95 Women:80–90	Men: ≥95 Women: ≥90
Underweight[b]	<18.5	Ö[b]	Ö[b]	Ö[b]
Acceptable range	18.5–23.9	Increased	Increased	Moderately severe
Overweight	24.0–27.9	Increased	Moderately severe	Very severe
Obesity	≥28	Moderately severe	Severe	Very severe

This table lists the recommendations for BMI and WC cutoff points for overweight and obesity in Chinese and the assessment of obesity-related disease using these two measurements
BMI body mass index; *WC* waist circumference
[a]Related diseases are hypertension, diabetes mellitus, dyslipidemia, and clustering of risk factors
[b]Underweight may be a sign of other health problems

Table 165.2 Definition of MetS according to 2007 JCDCG criteria

MetS was defined as having at least three of the following metabolic abnormalities	
Abdominal obesity	Waist circumference >90 cm for men and >85 cm for women
Hypertriglyceridemia	Serum triglycerides ≥1.7 mmol/L
Low high-density-lipoprotein cholesterol	High-density-lipoprotein cholesterol <1.04 mmol/L for both men and women
Elevation of blood pressure	Blood pressure ≥130/85 mmHg or known treatment for hypertension
Impaired glucose tolerance or diabetes	FPG ≥6.1 mmol/L and/or 2h-PG ≥7.8 mmol/L and/or diagnosed diabetic mellitus

This table illustrates the components of MetS and the definition of each metabolic disorder according to 2007 JCDCG criteria
MetS metabolic syndrome; *FPG* fasting plasma glucose; *2h-PG* 2h plasma glucose

165.2 The Feature of Abdominal Obesity in Chinese

Body fat is mainly composed of cells that contain triglyceride stores. It can be divided into two main parts: subcutaneous and intra-abdominal (Ronti et al. 2006). Most of the visceral fat is located in the intra-abdominal space including intraperitoneal and retroperitoneal space, which is commonly influenced by gender, age, ethnicity, and physical activity (Klein et al. 2007).There has been a general trend that Chinese people with obesity tend to abdominal obesity rather than generalized obesity. Theoretically, abdominal obesity should be determined by visceral adipose tissue (VAT) precisely measured by magnetic resonance imaging (MRI) or computed tomography (CT) scanning, which is suggested as a standard method by the International Diabetes Federation. A single slice at the L4–L5 intervertebral level is used to measure the amount of fat, expressed in cubic centimeters (Alberti et al. 2006). The Japan Society for the Study of Obesity used visceral fat area (VFA) more than 100 cm^2 to define abdominal obesity (Examination Committee of Criteria for 'Obesity Disease' in Japan 2002). In Korea, VFA over 103.8 cm^2 was associated with an increased risk of obesity (Kim et al. 2006). In a cross-sectional study on the relationship between abdominal obesity and waist circumference in a Chinese population, VFA over 80 cm^2, which was calculated at the cross-sectional MRI scan between L4 and L5 vertebrae, was linked with high prevalence of MetS (Bao et al. 2008).

165.3 Waist Circumference: An Anthropometrical Measurement of Abdominal Obesity

As mentioned earlier, increased visceral adipose tissue, which is also called abdominal fat, is closely related with increased risk for cardiometabolic diseases. Though MRI or CT scanning is a widely accepted measurement of abdominal obesity, the inconvenience and high cost limit the 'platinum standard' measurement in clinical use and epidemiological survey. By contrast, anthropometrical measurements including body mass index (BMI), waist-to-hip ratio (WHR), and waist circumference (WC), used as surrogate markers for abdominal fat mass to discriminate for the presence of abdominal obesity, are simple and noninvasive for assessing visceral fat accumulation. We analyzed the area under receiver operating characteristic (ROC) curve of the anthropometric measurements in 690 Chinese adults (305 men and 385 women) for the determination of visceral obesity. The results showed that waist circumference had an excellent correlation with VAT ($r = 0.73–0.77$) and, in terms of sensitivity and specificity, waist circumference had better accuracy for measuring abdominal obesity and in diagnosing abdominal obesity in Chinese adults, compared with BMI and WHR (Jia et al. 2003).

165.4 Practical Methods and Techniques: The Accurate Method of Measuring Waist Circumference

Different anatomic landmarks are used to measure WC including the midpoint between the lowest rib and the iliac crest, the umbilicus, the narrowest or widest WC, just below the lowest rib, and just above the iliac crest. A recent systematic review evaluated the influence of different WC protocols on the relationship to morbidity and mortality (Ross et al. 2008). The most commonly used landmarks were the minimal waist (33%), the midpoint between the lowest rib and the iliac crest (26%), and the umbilicus (27%). However, WC protocol did not influence outcome of all-cause and CVD mortality, CVD, and DM. Thus, different anatomic landmarks seem not to influence clinical outcomes. In order to measure waist circumference precisely, the subject is required to stand straight with his/her feet spread 30–40 cm apart and arms hanging freely. The measurement is made at the end of a normal expiration. A soft, inflexible, measuring tape is placed perpendicular to the long axis of the body and horizontal to the floor and applied with tension, ensuring that the tape is clinging to but not pressing the skin. The tape measurement is read with 1-mm accuracy. The guidelines for prevention and control of overweight and obesity in Chinese adult used the WHO 1998 protocol (WHO 1998), the midpoint between the lowest rib and the iliac crest, as the WC measurement protocol in China (Chinese Center for Disease Control and Prevention 2004).

165.5 The Characteristics of Waist Circumference in the Chinese

The Chinese have smaller waist circumference levels compared with the Caucasians. We compared the waist circumference of the Chinese population with that of Caucasians from the multinational monitoring of trends and determinants in cardiovascular disease (MONICA) project and found that the waist circumference in the Chinese, particularly in men, was much smaller than that in Caucasians. From 1998 to 2000, a group of 2,776 randomly selected adults aged from 20 to 94 years living in Shanghai was investigated. Among this survey population, the prevalence of overweight (determined

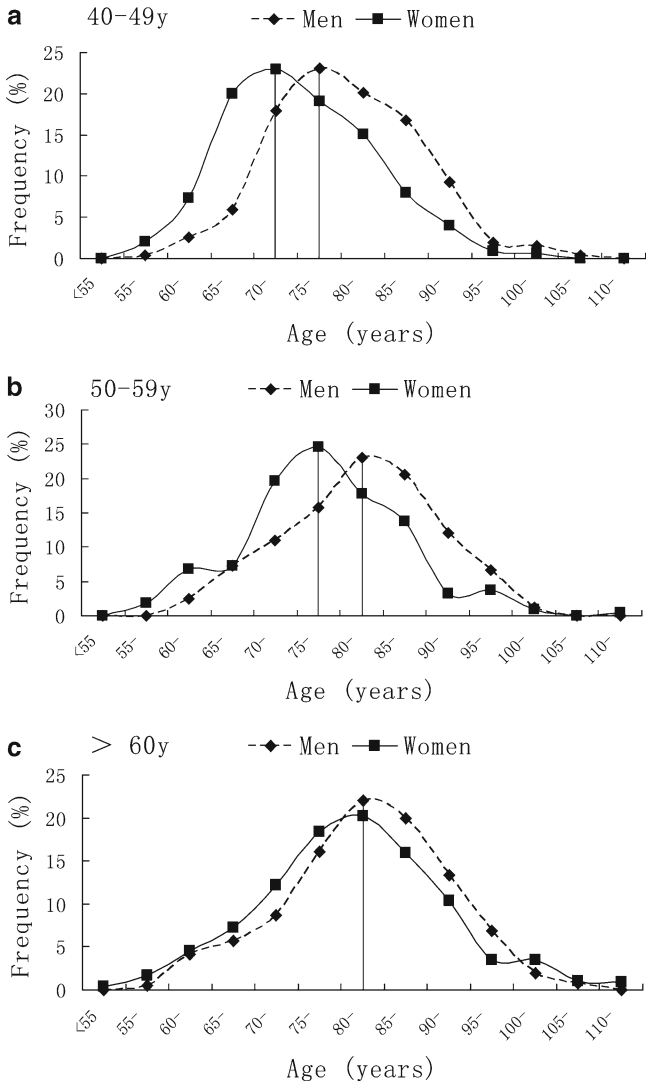

Fig. 165.1 Frequency distribution of waist circumference (WC) in the urban population survey in Shanghai, China (n = 2776, means ± SD). This figure shows frequency distribution of waist circumference in each sex in a Shanghai urban Chinese population survey and the characteristics of each subgroup after age and gender stratification. (**a**) age 40–49 years subgroup, men 80.3 ± 8.5 cm, women 74.6 ± 8.5 cm; (**b**) age 50–59 years subgroup, men 81.8 ± 8.5 cm, women 77.5 ± 9.2 cm; (**c**) age > 60 years subgroup, men 82.6 ± 9.5 cm, women 81.0 ± 10.6 cm. *Solid line*: women; *dotted line*: men (Reprinted from Jia et al. (2002). With permission from John Wiley & Sons)

by WHO definition) was 29.5% and obesity was 4.3%, with a greater number of women being obese than men. The average waist circumference in this study was 80.8 cm in men and 76.2 cm in women. After age stratification, the peak frequency distribution of waist circumference was shifted to the right with aging, and this phenomenon was more obvious in women. The difference of waist circumference between men and women less than 60 years of age was about 5 cm, regardless of different mean WC values within different age groups. Among women older than 60 years, the waist circumference further increased so that the average waist circumference was similar in men and women, at 82.6 and 81.0 cm, respectively (Jia et al. 2002, Fig. 165.1). Thus, the WC cutoff recommended by IDF could overestimate the difference between men and women.

165.6 Application to Other Areas of Health and Disease: The Relationship Between Waist Circumference and the Metabolic Syndrome

The MetS is composed of a cluster of metabolic disorders, such as hyperlipidemia, hypertension, elevated blood glucose level, insulin resistance, and microalbuminuria, associated with increased risk for cardiovascular disease and DM. Abdominal obesity, in particular, is considered as a fundamental element of the MetS. The more visceral fat accumulates, the more metabolic components increase (Reaven 1988; Kaplan 1989). A number of expert associations recommended different definitions for the MetS, in which most components were identical except for the obesity cutoff. Many epidemiological studies were conducted in China on the prevalence of MetS using different definitions. All these studies indicated that the MetS had become very common in China and that the frequency of the syndrome differed with definitions and regions in China (Feng et al. 2006; He et al. 2006; Yang et al. 2007). In the unified worldwide definition of MetS proposed by the International Diabetes Federation (IDF) in 2005, central obesity was regarded as a predominant element, and waist circumference cutoffs differ with gender and ethnicity. Waist circumference cutoff of 90 and 80 cm was proposed for Chinese men and women, respectively. The gender variation was larger than in our previous study. However, the IDF left the optimal cutoffs open for better data to link them to risk (Alberti et al. 2005). We carried out a cross-sectional study, which enrolled 1,140 individuals (525 men, 615 women) aged from 35 to 75 years to analyze VFA and the frequency of MetS. There was a linear increase in the number of metabolic syndrome components in those individuals with VFA less than 80 cm^2, and the prevalence of diabetes, dyslipidemia and of the aggregation of diabetes, dyslipidemia, and hypertension, components of the MetS had reached a plateau with VFA over 80 cm^2. Thus, it was suggested that the accumulation of visceral fat at the level of VFA over 80 cm^2 in the Chinese is linked with high prevalence of the MetS. The corresponding waist circumference cutoffs were 87.5 cm in men and 84.3 cm in women. Therefore, it was demonstrated that the appropriate cutoffs of waist circumference were 90 cm in men and 85 cm in women, which were associated with high risk of the MetS (Bao et al. 2008, Fig. 165.2, Table 165.3). Given the evidence above,

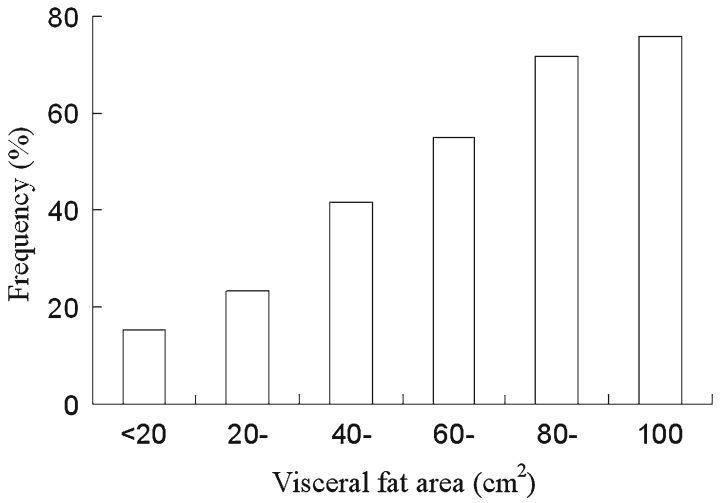

Fig. 165.2 The frequency of two or more components of the metabolic syndrome including hyperglycemia, hypertension, and dyslipidemia, except body fat parameters (waist circumference or BMI, $n = 1140$). This figure reflects the relationship between visceral fat area and the metabolic syndrome. The subjects were divided into six VFA subgroups from VFA <20 cm^2 to VFA ≥100 cm^2. The frequency of two or more components of the MetS without anthrometric indices of overweight/obesity was elevated with increased VFA. In individuals with VFA over 80 cm^2, the frequency was close to those with VFA over 100 cm^2 (Reprinted from Bao et al. (2008). With permission from Elsevier)

Table 165.3 Sensitivity and specificity of waist circumference to identify VFA in association with the MetS (n = 1140) (Reprinted from Bao et al. (2008). With permission from Elsevier)

			Waist circumference					
	n	VFA (cm^2)	Cutoff (cm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	J value
Men								
Total	525	80	87.5	75.9	78.1	90.2	60.8	0.54
Age <50	174	80	87.5	72.0	81.4	90.4	67.5	0.53
Age ≥50	351	80	88.3	71.3	83.8	92.5	53.0	0.55
Women								
Total	615	80	84.3	75.8	75.8	86.0	67.2	0.52
Age <50	208	70	81.5	77.2	72.3	78.6	74.7	0.50
Age ≥50	407	90	86.3	74.4	72.4	84.5	64.9	0.47

This table shows the best cutoffs of WC corresponding to the visceral fat area in association with the MetS. The corresponding cutoffs were selected by the largest Youden index which indicated the best trade-off between sensitivity and specificity by ROC curves

MetS metabolic syndrome, *NPV* negative predictive value, *PPV* positive predictive value, *VFA* visceral fat area

Table 165.4 Key Facts of the Chinese Joint Committee for developing Chinese guidelines on prevention and treatment of dyslipidemia in adults (JCDCG)

1. Dyslipidemia is lipid metabolic disorder. As an atherogenic factor, it is correlated with diabetes and metabolic syndrome
2. Chinese epidemiological studies demonstrated that dyslipidemia was an independent risk factor for cardiovascular disease in the Chinese population and a multifactorial estimation could improve the prevention and treatment of dyslipidemia
3. The guidelines were drafted by Chinese Society of Cardiology, Chinese Diabetes Society, Chinese Society of Endocrinology, and Chinese Society of Laboratory Medicine, based on several large-scale clinical trials
4. The guidelines consist of the subsections including lipid profile testing, classification of dyslipidemia, cardiovascular risk evaluation, trials-based evidence in lipid-lowering therapy, and treatment of dyslipidemia

This table lists the key features of the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (JCDCG) including the basic concept of dyslipidemia, the purpose of the guidelines, the composition of the joint committee, and the subsections of the guidelines

in 2007, JCDCG proposed a set of criteria to define the MetS. In the revised definition, the WC cutoff points of 90 and 85 cm were suggested for Chinese men and women in order to detect abdominal obesity (Table 165.4).

165.7 Application to Other Areas of Health and Disease: The Optimal Waist Circumference Cutoffs in the Prediction of Diabetes and Cardiovascular Disease

Adipose tissue is viewed not only as an energy depot, but also as an active endocrine organ. Abdominal obesity is one of risk factors for CVD. Though the etiology of increased cardiovascular risk in patients with abdominal obesity is not known clearly, there are many potential theories on the issue. Increased levels of free fatty acids (FFAs) due to obesity and VAT worsen insulin resistance. The increase in VAT mass possibly reflects the lack of capacity of the subcutaneous tissue to store the energy excess that accumulates in liver, muscle, and pancreas, worsening insulin resistance (Despres et al. 2006). An inflammatory factor, C-reactive protein (CRP), produced by the liver and

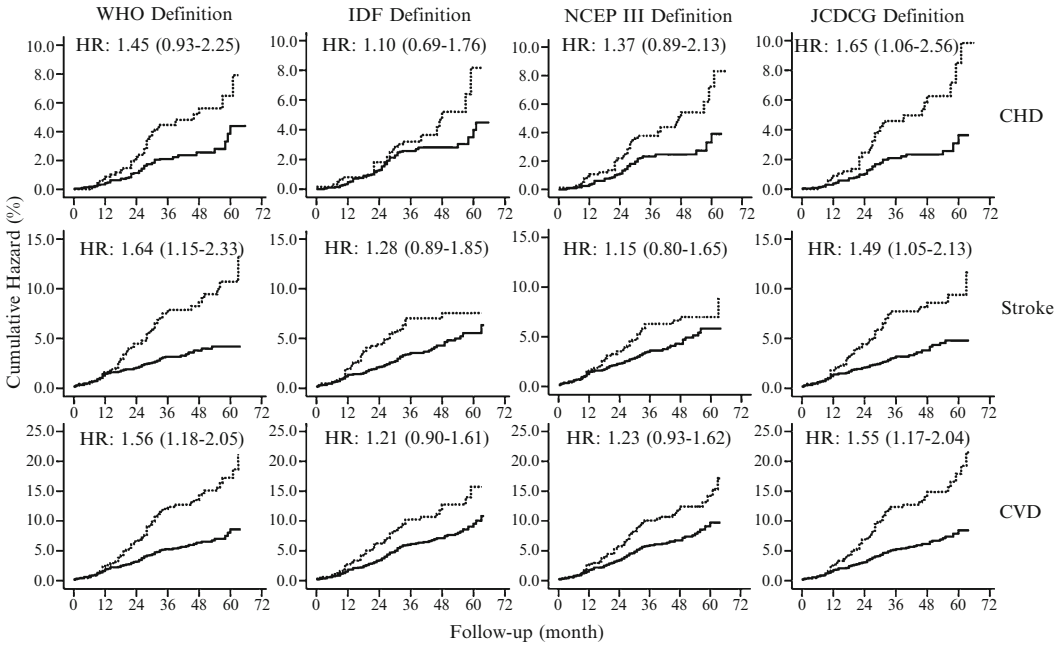

Fig. 165.3 The evaluation of MetS based on different definitions to predict future CVD events with age-adjusted Cox proportional hazard model ($n = 2788$). This figure shows the cumulative hazard of cardiovascular disease (*CVD*), coronary heart disease (*CHD*), and stroke in 2,788 Chinese subjects with and without metabolic syndrome, defined by the WHO, the IDF, the National Cholesterol Education Program Adult Treatment Panel III (NCEPIII), and the Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (*JCDCG*) definitions, using multivariate Cox regression analysis. *Solid line*: without metabolic syndrome; *dotted line*: with metabolic syndrome. *HR* hazard ration; *CHD* coronary heart disease; *CVD* cardiovascular disease (Reprinted from Wang et al. (2010). With permission from Elsevier)

correlating with atherosclerosis, is increased obviously in patients with visceral obesity (Lemieux et al. 2001). A prospective cohort study in a middle-aged and older Chinese population suggests that elevated high-sensitivity CRP (≥2.0 mg/L) is an effective predictor of the risk of composite CVD events during a 5.5-year period (Jiang et al. 2009). Additionally, several adipokines, including adiponectin, leptin, retinol binding protein4 (RBP4), and visfatin, derived from adipose tissue mediate glucose, lipid metabolism, and insulin sensitivity (Scherer 2006; Jia et al. 2007). Further investigations will be needed to illustrate the comprehensive pathophysiology. A community-based cohort study prospectively evaluated the predictive value of the MetS for CVD in a Chinese population using different MetS definitions including those from the World Health Organization (WHO), the IDF, the National Cholesterol Education Program Adult Treatment Panel III (NCEPIII), and JCDCG. Totally 2,788 subjects were included and followed up for 5.5 years. The results showed that the prevalence of MetS, according to JCDCG definition, was similar to those by the WHO, the IDF, and the NCEPIII definitions. While the MetS based on the JCDCG or WHO criterion was a significant predictor for the development of CVD in total subjects, the MetS based on the IDF or the NCEPIII criterion was not (Wang et al. 2010, Fig. 165.3). In addition, a 7.8-year follow-up study was conducted to identify the appropriate VAT cutoff and the corresponding waist circumference cutoffs for defining abdominal obesity in predicting diabetes. At the end of the study, 290 participants were followed up. The optimal waist circumference cutoffs were 88 cm in men and 82 cm in women, quite similar to the cutoffs JCDCG recommended (Ye et al. 2009). These results furthermore confirmed that the waist-circumference thresholds of 90 cm in men and 85 cm in women are more suitable for obesity-related risk assessment than the IDF recommended in the Chinese population.

Summary Points

- With the rapid economic development in China, the prevalence of overweight and obesity has been rising.
- Waist circumference is correlated with risk for DM, CVD, and MetS.
- Waist circumference is a widely used anthropometric measurement to estimate abdominal fat due to its convenience and strong correlation with visceral fat.
- Waist circumference increased with aging in Chinese population and was quite similar in men and women, especially in the subgroup with age over 60 years.
- The optimal cutoff of WC is 90 cm in men and 85 cm in women in the Chinese population.

Acknowledgements This work was funded by the Major Program of Shanghai Municipality for Basic Research (08dj1400601), Chinese National 973 Project (2007CB914702), and Project for Shanghai Key Laboratory of Diabetes Mellitus (08DZ2230200).

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Chapter 166
Usefulness of Skinfold Thickness Measurements for Determining Body Fat Distribution and Disease Risk for Japanese Men and Women

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Abstract Subscapular and triceps skinfold thickness (SSF and TSF) as well as body mass index (BMI) were investigated as indices for body fat distribution between 1976 and 2007 in rural and urban communities in conjunction with the Circulatory Risk in Communities Study (CIRCS). Mean BMI did not change between 1976 and 1987 and increased thereafter for men of every age group in both rural and urban communities. There were no remarkable changes in BMI levels for women of any age groups, except for rural women aged 40–49 and urban women aged 40–59 whose mean BMI declined over time. Mean SSF and TSF did not change from between 1976 and 1987 and increased thereafter for men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean SSF declined over time. BMI, SSF and TSF correlated positively with systolic and diastolic blood pressures and total cholesterol in each survey period for both men and women of rural and urban communities. BMI and SSF correlated positively with serum glucose for rural women and for urban men and women in every survey period, but not for rural men, for whom correlations were weak between 1976 and 1991 and became stronger thereafter. The skinfold thickness measurement is useful to obtain a clearer picture of long-term trends for body fat distribution as well as for its influence on cardiovascular risk factors, which would be difficult to obtained with BMI measurement only.

Abbreviations

BMI	Body mass index
SF	Skinfold thickness
SSF	Subscapular skinfold thickness
TSF	Triceps skinfold thickness
TC	Serum total cholesterol
GL	Serum glucose
FGL	Fasting serum glucose
CIRCS	The Circulatory Risk in Communities Study

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_166,

166.1 Introduction

The Japan National Nutrition and Health Survey (Ministry of Health, Labor and Welfare 2009) has provided data on long-term trends for mean body mass index (BMI). Mean BMI has increased in men aged 30–79 years and in women aged 60–79 years since the 1950s and either has not changed substantially or has actually declined in women aged 30–59 years since the 1970s. However, no national data on trends for skinfold thickness are available. The Circulatory Risk in Communities Study (CIRCS, Table 166.1) has investigated cardiovascular risk factors, incident cardiovascular disease, and their long-term trends in Japanese communities (Imano 2009). In that study, not only BMI but also subscapular and triceps skinfold thickness (SSF and TSF) were measured as indices for body-fat distribution. This chapter deals with (1) long-term trends for BMI, SSF, and TSF between 1976 and 2007 and (2) correlations between these indices and cardiovascular risk factors in Japanese men and women of rural and urban communities.

166.2 Methodological Considerations

The subjects were residents aged 40–79 years from two communities: Ikawa town (Kitamura et al. 2008; Shimamoto et al. 1989), Akita Prefecture (a northeastern rural community) and the Minami-Takayasu district (Kitamura et al. 2008), Yao City, Osaka Prefecture (a southwestern urban community). Annual cardiovascular risk surveys were conducted in those communities since 1963 as part of the CIRCS (Imano et al. 2009).

Table 166.1 Key features of the Circulatory Risk in Communities Study (CIRCS)

1. CIRCS is a new generic name of the prior and ongoing epidemiological study consisting of five Japanese communities' studies
2. The study started in 1963 for the prevention of cardiovascular disease, which was the most common cause of death for Japanese
3. The five communities are as follows
   (a) Ikawa town, Akita Prefecture: a northeastern rural community
   (b) Ishizawa and Kita-utetsu district, Yurihonjo City, Akita Prefecture: a northeastern rural community
   (c) Minami-Takayasu district, Yao City, Osaka Prefecture: a southwestern urban community
   (d) Noichi district, Konan City, Kochi Prefecture: a southwestern rural community; and
   (e) Kyowa district, Chikusei City, Ibaraki Prefecture: a central rural community
4. The study consists of Akita-Osaka Study, Ikawa Study, and Kyowa Study
5. The main research topic of the study is to investigate cardiovascular risk factors, incident cardiovascular disease (stroke, coronary heart disease, and sudden death) and their long-term trends
6. Study implementation institutes are Osaka Medical Center for Health Science and Promotion and the departments of public health in three universities, that is, Osaka University, University of Tsukuba, and Ehime University School of Medicine
7. The measurement of cardiovascular risk factors has been standardized by the same research institute, the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network
8. The ascertainment system for cardiovascular disease has used the same diagnostic criteria throughout all study periods
9. The study found that stroke, especially cerebral hemorrhage, strongly related to hypertension and also related to low serum cholesterol levels
10. The incidence of stroke has declined substantially, while that of coronary heart disease remained low in those communities

This table lists the key features of the Circulatory Risk in Communities Study (CIRCS)

The study period was divided into eight terms of 4 years each: (1) 1976–1979, (2) 1980–1983, (3) 1984–1987, (4) 1988–1991, (5) 1992–1995, (6) 1996–1999, (7) 2000–2003, and (8) 2004–2007. The earliest individual datum was used within each term of the surveys as well as age- and sex-specific numbers of participants in conjunction with measurements of BMI, SSF, and TSF in rural and urban communities throughout the study period (Table 166.2).

Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Keys calipers were used for measuring SSF and TSF to the nearest millimeter. SSF was measured about one centimeter below the tip of the inferior angle of the right scapula, at an angle of about 45° to the vertical. TSF was measured over the midpoint of the muscle belly, midway between the olecranon, and the tip of the acromion of the right upper arm, with the upper arm hanging vertically (Durnin and Rahaman 1967).

Age- and sex-specific trends for BMI, SSF, and TSF were investigated in rural and urban communities during the past three decades, from 1976 to 2007.

Blood was drawn from seated participants into a plain, siliconized glass tube followed by separation of the serum. Fasting was not required. Serum glucose was measured with the cupric-neocuproine method between 1976 and September 1986 and with the hexokinase method, thereafter. Glucose values (mmol/L) obtained using the first method were adjusted with the formula: 0.047 × (glucose concentration in mg/dL) - 0.541, as we reported previously (Iso et al. 2004).

Serum total cholesterol was measured at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network (Nakamura et al. 2003).

Systolic and diastolic blood pressures (SBPs and DBPs, Table 166.3) in the right arm were measured by trained physicians using standard mercury sphygmomanometers, based on the unified epidemiological methods (Kirkendall et al. 1980; Shimamoto et al. 1989). The participants were seated and had rested for 5 min prior to the blood-pressure measurements.

This study described age- and sex-specific mean values and sex-specific age-adjusted means of BMI, SSF, and TSF, and sex-specific Spearman correlations of BMI, SSF, and TSF with cardiovascular risk factors, such as SBP, DBP, serum total cholesterol and glucose. These calculations were performed for every survey period for participants in both rural and urban communities. The correlations between these indices and serum glucose levels were also calculated but only in fasting (time after meal >=8 h) samples. For 32% of the participants, fasting serum glucose data were available. All analyses were conducted with the SAS System for Windows (version 9.1; SAS Inc., Cary, NC). All p-values for statistical tests were two tailed, and values of <0.05 were regarded as statistically significant.

166.3 Trend for BMI, SSF, and TSF

Tables 166.4–166.6 show age- and sex-specific trends for mean values of BMI, SSF, and TSF in rural and urban communities. Mean BMI did not change from 1976–1979 to 1984–1987 and increased thereafter for men of each age group in both rural and urban communities (Table 166.4 and Fig. 166.1). For men aged 40–79, age-adjusted mean BMI was 22.9 kg/m^2 in 1976–1979, 22.9 kg/m^2 in 1984–1987, and 23.9 kg/m^2 in 2004–2007 in the rural community, and the corresponding values for the urban community were 22.4, 22.6, and 23.9.

There were no remarkable changes in BMI levels for women of all age groups except for rural women aged 40–49 and urban women aged 40–59 whose mean BMI declined gradually over time.

Table 166.2 Age- and sex-specific numbers of participants with measurement of body mass index (BMI) and skinfold thickness (SF) in rural and urban communities between 1974–1976 and 2004–2007

	Rural										Urban									
	40–49 year		50–59 year		60–69 year		70–79 year		40–79 year		40–49 year		50–59 year		60–69 year		70–79 year		40–79 year	
	BMI	SF	BMI	SF	BMI	SF	BMI	SF	BMI	SF	BMI	SF	BMI	SF	BMI	SF	BMI	SF	BMI	SF
Men																				
1976–1979	338	293	260	220	193	130	75	37	866	680	171	150	145	131	184	167	78	34	578	482
1980–1983	293	279	323	316	216	210	106	101	938	906	292	280	219	209	208	198	105	92	824	779
1984–1987	322	312	361	346	240	235	126	122	1,049	1,015	287	281	256	253	238	233	133	126	914	893
1988–1991	264	261	321	313	257	252	137	136	979	962	256	255	256	256	270	268	116	116	898	895
1992–1995	243	238	267	264	281	277	135	134	926	913	214	212	264	260	320	317	109	108	907	897
1996–1999	210	209	202	202	326	326	151	150	889	887	158	156	254	253	365	357	129	129	906	895
2000–2003	146	144	222	218	294	292	188	188	850	842	128	127	207	207	400	394	166	166	901	894
2004–2007	93	93	205	206	251	250	200	200	749	749	153	153	200	198	473	472	236	239	1,062	1,062
Women																				
1976–1979	389	360	340	282	241	179	90	48	1,060	869	340	296	338	303	262	234	92	40	1,032	873
1980–1983	380	371	404	394	301	296	142	135	1,227	1,196	611	583	444	416	304	272	139	104	1,498	1,375
1984–1987	420	416	451	446	335	332	158	154	1,364	1,348	702	694	501	500	357	352	171	157	1,731	1,703
1988–1991	348	345	402	398	367	361	145	138	1,262	1,242	720	719	557	557	399	399	168	166	1,844	1,841
1992–1995	303	303	364	363	383	381	180	180	1,230	1,227	659	658	630	628	439	437	169	166	1,897	1,889
1996–1999	299	298	342	342	416	416	222	223	1,279	1,279	505	500	673	673	501	498	196	195	1,875	1,866
2000–2003	229	229	345	344	382	382	254	257	1,210	1,212	382	379	653	648	564	558	221	220	1,820	1,805
2004–2007	165	165	299	300	338	342	270	277	1,072	1,084	406	405	547	543	682	684	264	271	1,899	1,903

Age- and sex-specific numbers of participants were shown with measurements of body mass index (*BMI*), subscapular skinfold thickness (*SSF*), and triceps skinfold thickness (*TSF*) in rural and urban communities. The earliest individual data was used within each term of individuals who participated in the surveys

Table 166.3 Key facts of systolic and diastolic blood pressures

1. Systolic blood pressure is the highest arterial blood pressure by systole of the left ventricle of the heart
2. Diastolic blood pressure is the lowest arterial blood pressure during diastole of the heart
3. Higher blood pressure levels cause higher risk of stroke and coronary heart disease
4. CIRCS showed the shift of stroke burden from severe/moderate hypertension to mild hypertension
5. The early management of hypertension and primary prevention of high blood pressures have become important for the prevention of stroke

This table lists the key facts of systolic and diastolic blood pressures relating to cardiovascular disease

Mean SSF did not change from 1976–1979 to 1984–1987 and increased thereafter for both men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean SSF did not change materially over time (Table 166.5 and Fig. 166.2). For men aged 40–79, age-adjusted mean SSF was 11.4 mm in 1976–1979, 11.2 mm in 1984–1987, and 15.7 mm in 2004–2007 in the rural community and 13.7, 12.9, and 16.2 mm in the urban community. The corresponding mean SSF for women aged 40–79 was 17.5, 18.5, and 22.3 mm in the rural community and 18.6, 18.3, and 19.2 mm in the urban community. The increase in mean SSF was thus more evident for rural than for urban women.

Mean TSF did not change from 1976–1979 to 1984–1987 and increased thereafter for men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean TSF did not change materially over time (Table 166.6 and Fig. 166.3). For men aged 40–79, age-adjusted mean TSF was 6.6 mm in 1976–1979, 7.1 mm in 1984–1987, and 8.8 mm in 2004–2007 in the rural community and 8.5, 7.7, and 10.0 mm in the urban community. The corresponding mean TSF for women aged 40–79 was 15.1, 16.0, and 19.5 mm in the rural community, and 17.5, 16.0, and 18.3 mm in the urban community.

As mentioned earlier, in both a rural and an urban Japanese community, mean BMI in men of all age groups in the 40–79-year age bracket showed an increasing trend between the 1980s and the early 2000s. For women, however, there was no remarkable change in mean BMI, except for an actual decline in mean BMI for middle-aged rural and urban women. These BMI trends were generally comparable with national trends, according to the Japan National Nutrition and Health Survey (Ministry of Health, Labour and welfare 2009).

Mean SSF and TSF levels increased between the 1980s and early 2000s for men and women of all age groups in both the rural and urban community. This increasing trend was more evident for rural than for urban women. In Japan, there have been major changes in lifestyles since the 1960s, as a result of westernization along with socioeconomic development. Total energy intake has declined consistently since the 1970s mainly because of a reduction in carbohydrate intake, whereas fat intake increased from the 1960s to the 1970s but reached a plateaue thereafter. As a result, fat intake as a percent of energy has increased from the 1960s to the 1990s. The increase in mean SSF and TSF for both men and women may thus be attributable to this increase in fat intake as a percent of energy and to a decline in physical activity due to motorization and/or mechanization.

The increase or stabilization in mean SSF and TSF in spite of the declining trend for mean BMI among middle-aged women is an interesting phenomenon. It may reflect a reduction in muscle mass and a relative increase in body fat, probably due to the reduction in physical activity for both rural and urban women aged 60–79 years, that is, mostly postmenopausal women. The increase in mean SSF and TSF and in SSF in particular was more pronounced when compared with that for middle-aged women, but mean BMI remained stable or increased slightly. This phenomenon may be partly due to the depletion of estrogen hormone, which leads to changes in body fat distribution (Folsom et al. 1993).

Table 166.4 Age- and sex-specific trends for body mass index(kg/m^2) in rural and urban communities between 1974–1976 and 2004–2007

	Rural										Urban									
	40–49 year		50–59 year		60–69 year		70–79 year		40–79 year		40–49 year		50–59 year		60–69 year		70–79 year		40–79 year	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean[a]	SE	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean[a]	SE
Men																				
1976–1979	23.3	2.6	23.0	2.4	22.6	2.7	22.0	3.0	22.9	0.1	22.7	3.0	22.7	2.7	22.0	2.7	21.7	2.7	22.4	0.1
1980–1983	23.7	2.9	22.8	2.7	22.4	2.9	21.9	2.9	22.9	0.1	22.8	2.6	22.9	2.9	21.9	2.5	22.2	2.6	22.5	0.1
1984–1987	23.6	2.9	22.9	2.7	22.4	2.7	21.8	3.1	22.9	0.1	22.8	2.6	23.0	2.9	22.4	2.9	21.7	2.8	22.6	0.1
1988–1991	23.7	2.9	23.3	2.8	22.9	3.1	22.3	3.0	23.2	0.1	23.4	2.9	23.1	2.6	22.7	2.9	21.9	2.7	22.9	0.1
1992–1995	23.7	2.8	23.2	2.9	22.7	2.9	22.5	3.1	23.1	0.1	23.8	3.0	23.7	2.6	23.0	2.8	22.1	3.0	23.3	0.1
1996–1999	23.9	2.8	23.9	3.0	23.3	2.9	23.2	3.3	23.6	0.1	23.6	3.0	23.9	2.7	23.1	2.7	22.6	3.0	23.4	0.1
2000–2003	23.9	3.4	24.2	2.9	23.9	3.0	22.8	3.3	23.7	0.1	23.7	3.1	23.9	2.8	23.7	2.8	23.0	2.8	23.6	0.1
2004–2007	24.6	3.9	24.4	2.9	23.8	2.8	23.0	3.1	23.9	0.1	24.4	3.3	24.2	2.9	23.9	2.8	23.5	2.6	23.9	0.1
Women																				
1976–1979	23.7	3.2	24.2	3.5	24.3	3.8	23.9	3.9	24.0	0.1	22.9	3.1	23.5	3.4	23.1	3.7	23.1	3.8	23.1	0.1
1980–1983	23.6	3.3	24.3	3.5	24.1	3.6	23.6	3.6	23.9	0.1	22.9	3.0	23.1	3.1	22.7	3.2	22.7	3.6	22.9	0.1
1984–1987	23.9	3.5	24.3	3.4	24.0	3.6	23.7	3.5	24.0	0.1	22.6	2.9	23.1	3.1	22.8	3.1	22.4	3.3	22.8	0.1
1988–1991	23.5	3.4	24.5	3.5	24.6	3.6	24.4	3.9	24.2	0.1	22.6	3.0	23.1	2.9	23.0	3.2	22.6	3.2	22.9	0.1
1992–1995	23.6	3.2	24.0	3.2	24.2	3.3	23.9	3.9	23.9	0.1	22.6	2.9	23.2	3.0	23.2	3.1	22.9	3.1	23.0	0.1
1996–1999	23.4	3.3	24.3	3.5	24.9	3.5	24.2	3.6	24.2	0.1	22.3	2.8	22.8	2.9	23.4	3.1	22.7	3.3	22.9	0.1
2000–2003	23.2	3.6	24.3	3.7	24.9	3.5	24.4	3.7	24.2	0.1	22.2	2.9	22.7	2.9	23.2	3.1	23.3	3.3	22.8	0.1
2004–2007	23.1	3.9	24.1	3.7	24.2	3.4	24.6	3.8	24.1	0.1	22.3	3.3	22.7	3.2	22.9	3.0	23.3	3.3	22.8	0.1

Mean body mass index (BMI) did not change from 1976–1979 to 1984–1987 and increased thereafter for men of each age group in both rural and urban communities. There were no remarkable changes in BMI levels for women of all age groups, except for rural women aged 40–49 and urban women aged 40–59 whose mean BMI declined gradually over time

SD standard deviation, *SE* standard error

[a]Age-adjusted

Table 166.5 Age- and sex-specific trends for subscapular skinfold thickness (mm) in rural and urban communities between 1974–1976 and 2004–2007

	Rural										Urban									
	40–49 year		50–59 year		60–69 year		70–79 year		40–79 year		40–49 year		50–59 year		60–69 year		70–79 year		40–79 year	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean[a]	SE	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean[a]	SE
Men																				
1976–1979	11.9	5.0	11.0	4.4	11.2	5.3	12.1	5.3	11.4	0.2	13.8	6.3	13.8	5.7	13.6	5.7	12.4	4.8	13.7	0.2
1980–1983	12.3	5.6	11.1	5.3	10.8	5.0	10.5	4.3	11.4	0.2	13.0	5.5	14.0	6.3	12.2	5.6	13.0	5.5	13.0	0.2
1984–1987	12.3	5.3	11.3	5.1	10.4	5.2	10.2	5.0	11.2	0.2	13.3	5.6	13.5	5.7	12.6	5.5	11.5	5.0	12.9	0.2
1988–1991	13.5	5.9	12.5	5.3	12.3	5.6	11.6	4.4	12.6	0.2	14.6	6.1	14.3	5.7	13.9	5.9	12.7	4.9	14.0	0.2
1992–1995	13.5	5.3	12.9	5.1	13.0	6.2	11.9	5.1	12.9	0.2	15.0	6.0	15.9	5.9	15.0	5.9	13.5	5.4	15.0	0.2
1996–1999	15.0	6.0	14.4	6.2	13.5	5.6	13.9	7.4	14.1	0.2	15.5	6.2	15.5	5.9	14.9	5.7	14.4	5.9	15.1	0.2
2000–2003	16.2	6.6	15.6	6.2	15.8	7.0	13.9	6.9	15.4	0.2	15.6	6.4	15.9	5.8	15.8	5.8	14.2	4.8	15.5	0.2
2004–2007	18.0	7.5	16.5	6.4	15.2	5.7	14.3	4.9	15.7	0.2	17.4	6.6	17.0	6.4	15.9	5.7	15.3	4.9	16.2	0.2
Women																				
1976–1979	18.2	7.5	17.9	8.2	16.5	7.3	14.1	6.1	17.5	0.3	18.2	7.1	20.2	8.0	17.5	7.4	15.6	6.1	18.6	0.3
1980–1983	18.8	8.3	19.7	8.1	17.9	8.2	15.7	6.7	18.6	0.2	18.7	7.3	19.3	7.4	16.9	7.1	15.2	6.7	18.2	0.2
1984–1987	19.3	8.0	19.4	7.6	17.8	7.9	14.4	6.4	18.5	0.2	18.7	7.2	19.2	8.1	17.9	7.6	15.6	7.4	18.3	0.2
1988–1991	20.5	8.4	21.7	8.2	20.3	7.9	16.7	7.0	20.5	0.2	19.8	8.0	20.9	8.4	19.4	7.8	17.3	7.9	19.7	0.2
1992–1995	21.3	8.3	22.2	8.6	21.2	8.2	18.0	8.2	21.1	0.2	20.2	8.2	21.5	8.3	20.5	7.8	17.8	7.6	20.4	0.2
1996–1999	21.7	8.8	23.0	8.7	22.0	8.6	18.6	8.0	21.7	0.2	19.0	7.6	19.8	7.6	19.6	7.7	17.4	7.7	19.3	0.2
2000–2003	23.6	10.4	25.1	9.8	25.2	9.1	21.6	9.4	24.2	0.2	18.2	7.3	19.9	7.4	19.4	7.6	18.3	8.0	19.2	0.2
2004–2007	22.2	10.4	24.1	9.3	22.5	8.2	19.9	8.1	22.3	0.3	18.7	8.3	20.1	8.0	19.2	7.5	18.6	7.7	19.2	0.2

Mean subscapular skinfold thickness (SSF) did not change from 1976–1979 to 1984–1987 and increased thereafter for both men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean SSF did not change materially over time

SD standard deviation; *SE* standard error

[a]Age-adjusted

Table 166.6 Age- and sex-specific trends for triceps skinfold thickness (mm) in rural and urban communities between 1974–1976 and 2004–2007

	Rural										Urban									
	40–49 year		50–59 year		60–69 year		70–79 year		40–79 year		40–49 year		50–59 year		60–69 year		70–79 year		40–79 year	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean[a]	SE	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean[a]	SE
Men																				
1976–1979	6.7	3.2	6.7	3.8	6.3	2.8	6.9	3.2	6.6	0.1	8.5	5.1	8.4	4.4	8.3	3.8	9.0	4.9	8.5	0.2
1980–1983	7.7	4.5	7.1	4.2	7.0	4.2	8.1	4.6	7.4	0.1	7.9	4.6	8.0	4.1	7.9	4.5	8.3	4.9	8.0	0.2
1984–1987	7.7	3.9	7.0	3.4	6.5	3.2	6.7	3.3	7.1	0.1	8.0	3.3	7.7	3.2	7.5	3.2	7.0	3.1	7.7	0.1
1988–1991	7.6	3.2	7.0	2.5	6.7	2.8	6.7	2.8	7.1	0.1	8.3	3.4	8.2	2.7	8.2	3.4	7.7	2.6	8.2	0.1
1992–1995	8.0	3.2	7.3	2.9	7.5	3.4	7.3	3.0	7.5	0.1	8.6	3.1	8.7	3.0	8.5	4.2	8.0	3.0	8.5	0.1
1996–1999	8.7	3.5	8.0	3.3	7.6	3.0	8.0	3.8	8.0	0.1	8.8	3.1	8.3	3.1	8.5	2.9	8.5	3.0	8.5	0.1
2000–2003	9.4	3.7	8.6	3.7	8.8	3.5	8.3	3.5	8.7	0.1	10.1	5.0	9.0	3.7	9.2	3.5	8.9	3.0	9.2	0.1
2004–2007	10.3	4.9	9.2	4.1	8.4	3.5	8.1	3.1	8.8	0.2	11.0	5.0	10.4	4.6	9.7	4.6	9.4	3.4	10.0	0.1
Women																				
1976–1979	16.0	5.7	15.7	6.3	13.7	5.6	11.9	4.7	15.1	0.2	17.7	5.9	18.3	6.1	16.4	6.0	16.1	6.5	17.5	0.2
1980–1983	17.1	6.8	18.3	6.8	15.8	6.7	14.3	6.0	17.0	0.2	16.9	6.5	17.7	6.2	15.7	6.4	14.7	6.4	16.7	0.2
1984–1987	16.9	6.3	16.7	6.2	14.9	6.2	12.8	5.3	16.0	0.2	16.6	5.4	16.7	5.9	15.2	5.3	13.7	5.4	16.0	0.1
1988–1991	17.6	6.0	17.3	5.9	16.0	6.0	14.6	5.4	16.8	0.2	16.8	5.5	17.5	5.9	15.9	5.5	14.6	5.6	16.6	0.1
1992–1995	18.5	5.5	17.7	5.9	17.1	5.7	14.9	5.7	17.4	0.2	17.4	5.8	18.2	5.2	17.5	5.6	15.3	5.2	17.4	0.1
1996–1999	18.9	5.8	18.6	6.1	18.3	6.0	15.2	5.8	18.1	0.2	17.1	5.8	17.6	5.5	18.1	5.8	16.1	5.6	17.4	0.1
2000–2003	20.1	7.0	20.6	6.6	20.0	6.3	17.7	6.2	19.7	0.2	17.8	5.9	18.5	5.5	18.4	5.9	17.6	5.8	18.2	0.1
2004–2007	20.1	6.9	20.9	6.5	19.0	6.2	17.7	6.1	19.5	0.2	18.3	6.4	18.9	6.3	18.3	5.8	17.6	6.4	18.3	0.1

Mean triceps skinfold thickness (TSF) did not change from 1976–1979 to 1984–1987 and increased thereafter for men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean TSF did not change materially over time

SD standard deviation; *SE* standard error

[a]Age-adjusted

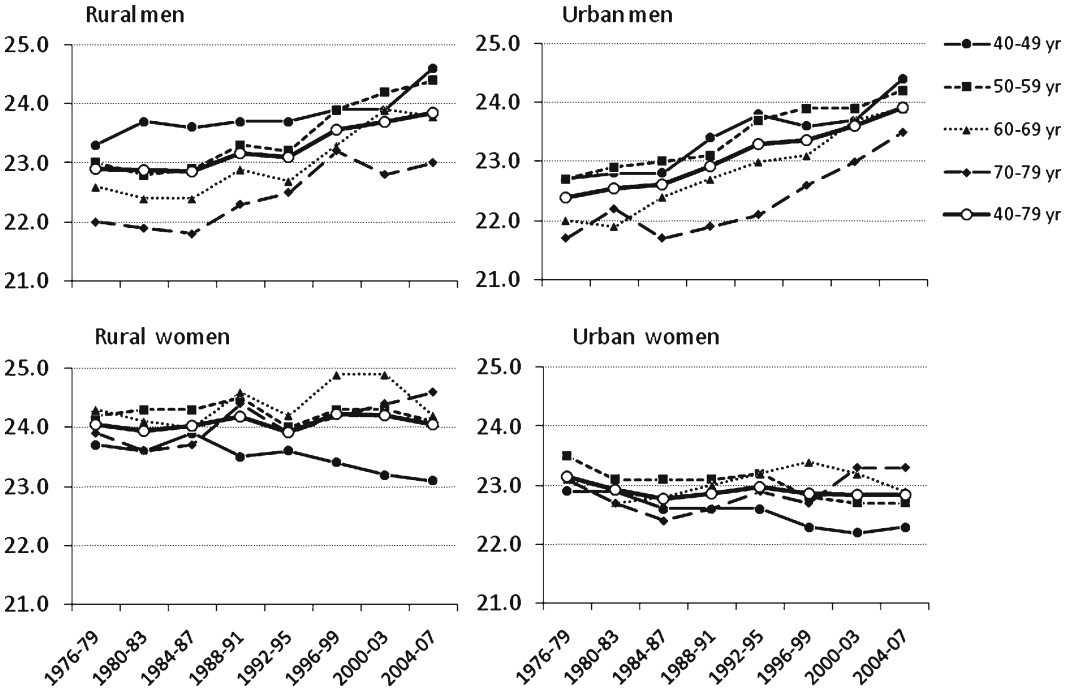

Fig. 166.1 Age- and sex-specific trends for body mass index (kg/m^2) in rural and urban communities. Mean body mass index (BMI) did not change from 1976–1979 to 1984–1987 and increased thereafter for men of each age group in both rural and urban communities. There were no remarkable changes in BMI levels for women of all age groups, except for rural women aged 40–49 and urban women aged 40–59 whose mean BMI declined gradually over time

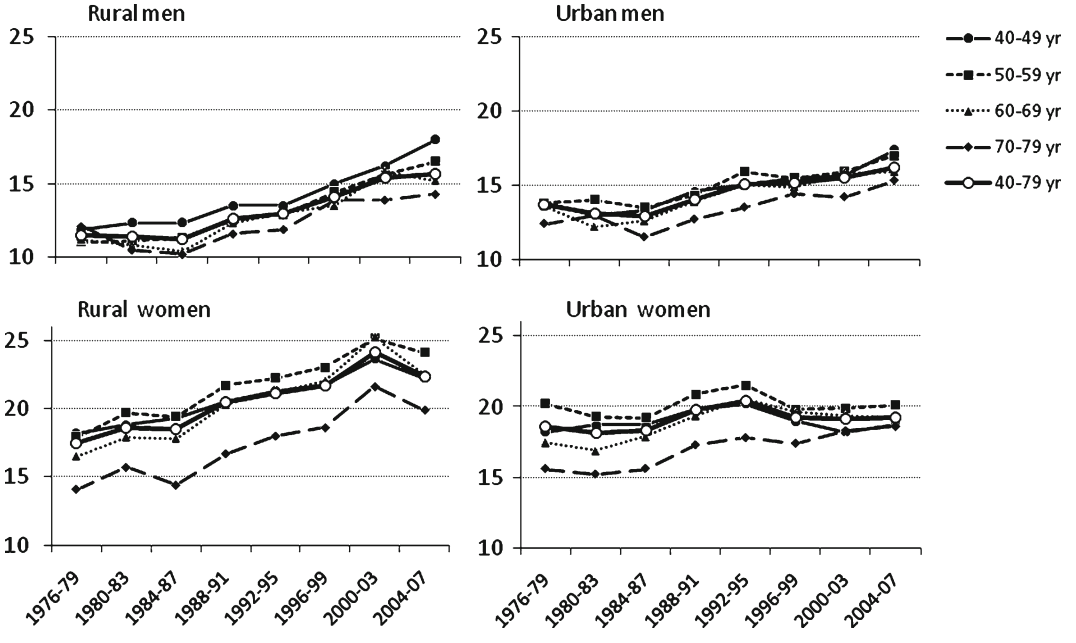

Fig. 166.2 Age- and sex-specific trends for subscapular skinfold thickness (mm) in rural and urban communities. Mean subscapular skinfold thickness (SSF) did not change from 1976–1979 to 1984–1987 and increased thereafter for both men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean SSF did not change materially over time

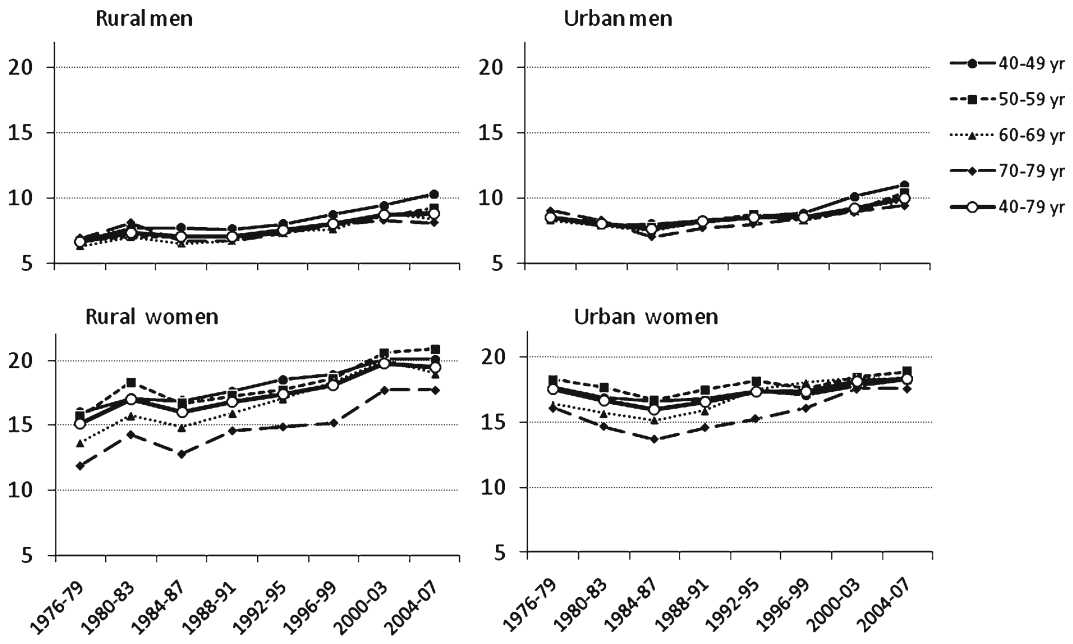

Fig. 166.3 Age- and sex-specific trends for triceps skinfold thickness (mm) in rural and urban communities. Mean triceps skinfold thickness (TSF) did not change from 1976–1979 to 1984–1987 and increased thereafter for men and women of every age group in both rural and urban communities, except for urban women aged 40–59 whose mean TSF did not change materially over time

166.4 Correlations of BMI, SSF, and TSF with Cardiovascular Risk Factors

Sex-specific Spearman correlations of BMI, SSF, and TSF with systolic blood pressure, diastolic blood pressure, serum total cholesterol, and serum glucose for men and women aged 40–79 in rural and urban communities are shown in Table 166.7. BMI, SSF, and TSF correlated positively with systolic and diastolic blood pressure and serum total cholesterol for both men and women in rural and urban communities in every survey period. BMI and SSF appeared to correlate positively with serum glucose levels for rural men and women and for urban women from 1992–1995, when means of these indices for the general population started to increase. Correlations between TSF and serum glucose levels for either men or women were weak or non-existent in every survey period. When we limited the analysis to fasting samples, the trends for the correlations of BMI, SSF, and TSF with serum glucose levels were essentially the same, but they became stronger than for total subjects.

Putting it all together, consistent correlations of BMI, SSF, and TSF with systolic and diastolic blood pressures and serum total cholesterol for both men and women aged 40–79 in the rural and as well as in the urban community throughout almost the entire study period. The correlations of BMI, SSF, and TSF with serum glucose were weak between 1976–1979 and 1988–1991, but increased thereafter for rural men and women and for urban women.

Skinfold thickness measurement is useful to obtain a clearer picture of long-term trends for body-fat distribution which would be difficult to obtain with BMI measurement only. An accumulation of central body fat, represented by an increase in mean SSF, may increase the likelihood of abnormal glucose levels in the general population.

Table 166.7 Sex–specific Spearman correlations of body mass index (BMI) and subscapular and triceps skinfold thickness (SSF and TSF) with cardiovascular risk factors among men and women aged 40–79 in rural and urban communities

	Rural																Urban													
	BMI					SSF					TSF						BMI					SSF					TSF				
	SBP	DBP	TC	GL	FGL	SBP	DBP	TC	GL	FGL	SBP	DBP	TC	GL	FGL		SBP	DBP	TC	GL	FGL	SBP	DBP	TC	GL	FGL	SBP	DBP	TC	GL	FGL
Men																															
1976–1979	.08*	.22‡	.13‡	–.07	.02	.07	.09	.19‡	.06	.12	.07	.12†	.11†	.02	.08		.15‡	.19‡	.22‡	.15†	.26‡	.14†	.20‡	.30‡	.17‡	.14	.13†	.19‡	.24‡	.17†	.13
1980–1983	.01	.18‡	.19‡	–.05	–	.05	.17‡	.21‡	.04	–	.11‡	.22‡	.10*	.09	–		.13‡	.19‡	.16‡	.04	.36	.14‡	.18‡	.21‡	.002	–.01	.15‡	.21‡	.08*	–.01	.24
1984–1987	.06	.24‡	.19‡	.00	–.08	.03	.19‡	.16‡	.03	–.08	.03	.15‡	.14‡	.03	–.01		.16‡	.23‡	.18‡	.07	.20	.11†	.17‡	.20‡	.06	–.03	.07*	.15‡	.18‡	–.01	–.18
1988–1991	.03	.17‡	.21‡	.02	.24*	.02	.13‡	.21‡	.02	.22	.01	.11‡	.17‡	.01	.02		.16‡	.28‡	.21‡	.09†	.39*	.18‡	.27‡	.23‡	.09†	.10	.12‡	.16‡	.17‡	.04	.04
1992–1995	.09†	.19‡	.17‡	.14‡	.18‡	.07*	.13‡	.18‡	.17‡	.15†	.08*	.11†	.10†	.15‡	.15‡		.11†	.21‡	.16‡	.14‡	.20*	.10†	.16‡	.15‡	.10†	.15†	.07*	.12‡	.12‡	–.01	.07
1996–1999	.12‡	.23‡	.16‡	.15‡	.14†	.14‡	.17‡	.19‡	.18‡	.18‡	.14‡	.17‡	.15‡	.10†	.09*		.16‡	.26‡	.10†	.14‡	.18‡	.16‡	.24‡	.12‡	.11†	.14†	.15‡	.16‡	.11†	.06	.10*
2000–2003	.14‡	.24‡	.16‡	.12‡	.10*	.11†	.22‡	.19‡	.11†	.08	.10†	.15‡	.16‡	.03	.02		.18‡	.21‡	.16‡	.10†	.14†	.15‡	.15‡	.11†	.11†	.13†	.13‡	.07*	.12‡	.04	.04
2004–2007	.09†	.21‡	.16‡	.13‡	.16†	.07	.15‡	.19‡	.12‡	.13†	.06	.12†	.12†	.09*	.07		.09†	.15‡	.06	.05	.06	.05	.06*	.07*	.06*	.12†	.01	.00	.06	.00	.05
Women																															
1976–1979	.25‡	.29‡	.18‡	.20‡	.12	.14‡	.20‡	.11†	.12	.19	.09†	.16‡	.08*	.10	.19		.26‡	.26‡	.13‡	.16‡	.08	.18‡	.20‡	.14‡	.15‡	.07	.12‡	.19‡	.10†	.09*	.00
1980–1983	.21‡	.29‡	.18‡	.20‡	–	.13‡	.23‡	.16‡	.17‡	–	.10‡	.27‡	.13‡	.06	–		.22‡	.28‡	.15‡	.13‡	.53*	.15‡	.22‡	.10†	.07*	.27	.06*	.16‡	.08†	.02	–.29
1984–1987	.21‡	.29‡	.16‡	.19‡	.67†	.15‡	.25‡	.13‡	.20‡	.48	.12‡	.22‡	.11‡	.07*	.58*		.25‡	.28‡	.14‡	.08‡	.08	.16‡	.24‡	.10‡	.05*	.10	.09‡	.20‡	.08†	.00	–.07
1988–1991	.21‡	.29‡	.15‡	.14‡	.21	.11‡	.24‡	.10‡	.10‡	.14	.07†	.22‡	.11‡	.09†	.04		.24‡	.31‡	.16‡	.10‡	.07	.16‡	.23‡	.18‡	.10‡	.04	.10‡	.13‡	.13‡	.04	–.13
1992–1995	.23‡	.27‡	.06*	.19‡	.20‡	.17‡	.26‡	.09†	.12‡	.14‡	.09†	.21‡	.06*	.08†	.13†		.27‡	.29‡	.12‡	.12‡	.14‡	.20‡	.24‡	.15‡	.12‡	.15‡	.13‡	.15‡	.09‡	.04	.07
1996–1999	.26‡	.30‡	.07†	.19‡	.25‡	.17‡	.23‡	.11‡	.12‡	.18‡	.10‡	.18‡	.06*	.06*	.13‡		.28‡	.28‡	.11‡	.16‡	.20‡	.21‡	.25‡	.08‡	.11‡	.12‡	.14‡	.16‡	.06†	.06†	.06*
2000–2003	.26‡	.27‡	.06*	.22‡	.27‡	.19‡	.28‡	.12‡	.18‡	.24‡	.14‡	.24‡	.10‡	.09†	.17‡		.31‡	.28‡	.11‡	.20‡	.21‡	.23‡	.24‡	.11‡	.16‡	.19‡	.16‡	.17‡	.06*	.09‡	.08†
2004–2007	.22‡	.19‡	–.01	.17‡	.16‡	.11‡	.17‡	.01	.11‡	.11†	.09†	.19‡	.02	.05	.06		.28‡	.24‡	.04	.21‡	.28‡	.24‡	.21‡	.05*	.15‡	.22‡	.18‡	.16‡	.03	.10‡	.14‡

Body mass index (BMI) and subscapular and triceps skinfold thickness (SSF and TSF) correlated positively with systolic and diastolic blood pressures and serum total cholesterol for both men and women in rural and urban communities in every survey period. BMI and SSF appeared to correlate positively with serum glucose levels for rural men and women, and for urban women from 1992–1995

*$p < 0.05$; †$p < 0.01$, ‡$p < 0.001$

SBP systolic blood pressure; *DBP* diastolic blood pressure; *TC* serum total cholesterol; *GL* serum glucose; *FGL* fasting serum glucose

Summary Points

- Mean body mass index (BMI) increased for both rural and urban men between the 1980s and early 2000s.
- Mean BMI of either rural or urban women did not change, except for a decline in middle-aged women.
- Subscapular skinfold thickness (SSF) increased consistently for both men and women in rural and urban communities between the 1980s and early 2000s.
- The correlation between SSF and serum glucose started to become stronger in the 1990s.
- Measurement of skinfold thickness is useful for identifying long-term trends for fat distribution and its influence on cardiovascular risk factors.

Acknowledgements The authors wish to thank Emeritus Professors Yoshio Komachi and Takashi Shimamoto (University of Tsukuba), Dr. Minoru Iida (Osaka Medical Center for Health Science and Promotion), Late Emeritus Professor Masamitsu Konishi (Ehime University School of Medicine), Professor Yoshihiko Naito (Mukogawa Women's University), Dr. Tomoko Sankai (University of Tsukuba) and Professor Tomonori Okamura (Keio University) for their support for long-term cohort studies. We also thank the research staff of the Osaka Medical Center for Health Science and Promotion and health professionals in the survey communities.

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Chapter 167
Socioeconomic Status, Anthropometric Status and Developmental Outcomes of East-African Children

Amina Abubakar and Fons van de Vijver

Abstract The aim of the current review is to critically evaluate existing evidence on the relationship between socio-economic status, anthropometry and child development. We observed that socio-economic variables (e.g. maternal and paternal educational level, occupation and income, and wealth index, which is a composite of various wealth indicators) were positively associated with anthropometric status. Additionally, it was observed that children who had poor anthropometric status (i.e. stunted or underweight) performed more poorly on measures of child development compared to peers with proper growth. Relationships between SES and developmental outcomes are consistently found; with some studies reporting a direct and others an indirect relationship. We propose a mediation model in which SES has an influence on developmental outcomes through various more proximal variables, such as maternal caring capacity, anthropometric status, and ill-health. Potential pathways of the influence of SES on anthropometric status include inadequate food intake, ill health and sub-optimal parenting behaviour. Anthropometric status also influences developmental outcomes through multiple pathways, such as potential brain damage and lowered activity levels. It is concluded that parental SES influences child's physical growth which in turn affects their developmental outcomes. Implementing intervention measures to improve the anthropometric status of children living in poverty can be expected to improve developmental outcomes.

Abbreviations

BSID	Bayley Scales of Infant Development
Hb	Haemoglobin
HAZ	Height-for-Age *Z*-scores
HIV	Human Immunodeficiency Virus
KDHS	Kenya Demographic and Health Survey
KDI	Kilifi Developmental Inventory
MDGs	Millennium Development Goals
SEM	Structural Equation Modelling
SES	Socio-Economic Status
SSA	Sub-Saharan Africa

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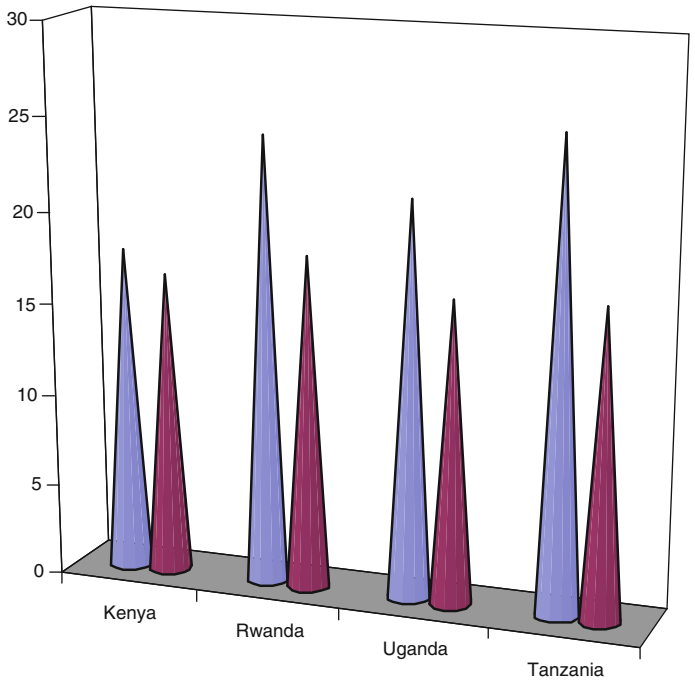
V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_167,

UNICEF United Nations Children's Fund
WAZ Weight-for-age *Z*-scores
WHZ Weight-for-height *Z*-scores

Poor physical growth is rampant in developing countries where approximately 27% and 32% of children under the age of 5 years are underweight and stunted, respectively (Stephenson et al. 2000). Given the high human cost (mortality, morbidity and disability) associated with malnutrition, tackling this problem has been a key aspect of the first millennium development goal (MDG). One of the targets of the first MDG was to reduce malnutrition by at least half from their 1990s proportion, by 2015 (De Onis et al. 2004). Unfortunately, a combination of several factors, such as slow economic growth and the spread of human immunodeficiency virus (HIV), have challenged the development of East-African countries (defined here as the members of the East African Community: Tanzania, Kenya, Uganda, Rwanda and Burundi) and they are unlikely to meet their millennium targets. In a review of progress, it was noted that prevalence rates of underweight children have either stagnated or decreased very slowly in all East-African countries (De Onis et al. 2004); Fig. 167.1 presents relevant summary statistics from different countries in East Africa.



	Kenya	Rwanda	Uganda	Tanzania
Underweight (percentage) 1990	17,6	24,3	21,5	25,3
Underweight (percentage) 2000	16,5	18	16,4	16,7

Underweight (percentage) 1990 Underweight (percentage) 2000

Fig. 167.1 Prevalence of underweight in East-African countries. The prevalence of underweight children in four East-African countries is presented, based on data collected in 1990 and 2000. Burundi has only data for 2000, hence its exclusion. The figure was generated based on data extracted from the WHO database on child growth and malnutrition

Table 167.1 Key features of developmental outcomes and their assessment

1. Developmental outcomes as referred to in this chapter entail several interdependent domains of child development, including sensorimotor, cognitive and social–emotional outcomes
2. Developmental outcomes can be assessed by three main approaches: (a) naturalistic observations; (b) standardised assessments that involve child participation in a variety of tasks and (c) assessment made through parent or caregiver reports
3. Approaches to and the complexity of the assessment will largely be determined by a child's age

A definition of developmental outcomes is provided alongside a discussion on how developmental outcomes can be assessed and how the child's age influences the type and complexity of developmental assessment

Poverty and its co-occurring factors place children at an elevated risk of experiencing growth failure (Walka and Pollitt 2000), with poor developmental and cognitive outcomes (Walker et al. 2007). Furthermore, children who are experiencing growth failure have been found to perform poorly on measures of developmental and cognitive outcomes (Grantham-Mcgregor 2002), independent of their SES. The current review aims at critically evaluating the existing evidence from East Africa on the relationship (and possibly, pathways) between socioeconomic indicators, anthropometrics status and developmental outcomes (Table 167.1 presents a brief description of developmental outcomes and its assessment). Specifically, the review aims at answering the following research questions:

1. What is the relationship between SES and anthropometric status among East-African children?
2. What are the relationships between SES and anthropometric status and between SES and developmental outcomes among East-African children?
3. Does existing evidence from East Africa provide support for the pathways suggested in the literature?

167.1 SES and Anthropometric Status

SES has traditionally been and still remains a subject of great interest in the social sciences; yet, there is no consensus on how it should be conceptualised and measured (Bradley and Corwyn 2002). In Europe and North America, the most common approach to assessing SES involves developing an index based on parental educational levels, income and/or occupation. However, numerous challenges in developing countries, such as limited variability in income, difficulties in estimating income in subsistence-based economies and limited variability in educational level or massive differences in educational quality across schools (challenging the adequacy of years of schooling as a useful measure) have rendered Western indicators inadequate. Several alternative approaches have been proposed, including the evaluation of assets owned by the family. Our review employs various SES indicators. Table 167.2 presents a summary of identified studies on SES and anthropometric status, highlighting some of the key findings in each study.

Maternal and paternal educational levels have been associated with anthropometric status in various studies in East Africa. Children of mothers and fathers with low educational status were more likely to be stunted or underweight compared to those whose parents had high educational levels (Kikafunda and Tumwine 2006). Vella et al. (1995) investigated the effects of parental education; in a stepwise regression, they found that parental education was associated with anthropometric outcomes. Fathers' education was positively associated with weight-for-age z-scores (WAZ) ($\beta = .03$, $p < 0.01$) and weight-for-height z-scores (WHZ) ($\beta = 0.02$, $p < 0.05$), while maternal education was positively associated with height-for-age (HAZ) ($\beta = 0.04$, $p < 0.05$). Several studies have consistently reported the influence of parental characteristics on children's anthropometric status, although

Table 167.2 Summary of studies and results from East Africa

Author	Country	Sample size (n)	Age range	Prevalence	Main findings
Abubakar (2008)	Kenya	204	24–35 months	19.6%[a] 49.0%[b]	Maternal education and a wealth Index were both associated with WAZ and HAZ
Bloss (2004)	Kenya	175	0–60 months	30.0%[a] 47.0%[b]	Mothers' education and family size were associated with poor nutritional outcomes
Chesire et al. (2008)	Kenya	384	6–12 years	14.9%[a] 30.2%[b]	Anthropometric status was predicted by monthly household income and food prices among other factors
Kikafunda et al. (2006)	Uganda	41	3–6 years	29.3%[a] 46.0%[b]	Fathers' education predicted anthropometric status, with better educated parents having children with better outcomes. Children from higher-income families had lower prevalence of growth restriction
Kikafunda et al. (1998)	Uganda	261	0–36 months	24.1%[a] 23.8%[b]	Rural residence, lack of access to clean water, poor personal hygiene, low SES and low maternal education predicted growth restriction
Kogi-Makau (1992)	Kenya	1,042	0–19 years	62%[c]	Amount of land owned, size of the household and monthly expenditure on food predicted anthropometric status
Kulwa et al. (2006)	Tanzania	100	6–24 months	22%[a] 43%[b]	Numbers of hours mothers worked outside the house negatively predicted child's anthropometric status
Nyaruhucha (2006)	Tanzania	250	0–59 months	31.0%[a]	Maternal education predicted the relative risk of being underweight
Ogden (1993)	Rwanda	965	0–59 months	16%[a] 43.8%[b]	Poor anthropometric status was associated with maternal education and female-headed households
Tumwine (2002)	Uganda	932	6–59 months	17.0%[a] 49.8%[b]	Low maternal and paternal education significantly increased the risk of growth restriction
Vella et al. (1992)	Uganda	1,178	0–59 months	24.8%[a] 42.4%[b]	Poverty, low parental education and lack of sanitation were found to be significant predictors of poor anthropometric status

Details on studies from East Africa investigating the relationship between socioeconomic indicators and anthropometry are presented alongside key findings from these studies

[a] Prevalence of underweight

[b] Prevalence of stunting

[c] Presents the number of households with at least one stunted member

different studies have shown slightly differing patterns of relationships. For instance, Kikafunda and Tumwine (2006) reported that neither maternal age nor maternal education had a significant association with WAZ and HAZ. The education of the father, however, had a significant ($p = 0.017$) association with WAZ; children whose fathers had lower than tertiary-level education showed WAZ values below the median.

Other parental characteristics, such as marital status (Nyaruhucha et al. 2006), occupational status (Kamau-Thuita et al. 2002) and income (Bhargava 2000), have also been found to influence anthropometric status. The influences of socioeconomic factors have also been described at the household level. Kogi-Makau (1992), working among a population living in a semi-arid area in Kenya, found that anthropometric status was predicted by household characteristics, such as household size, size of owned land, labour shortage and monthly cash food expenditure.

Assessing family assets has been widely used to evaluate the SES of families in East-African studies. These studies have consistently reported a positive association between children's anthropometric status and family assets. Ownership of land and types of vegetables and other foods harvested are also positively associated with anthropometric status. Quality of housing, access to clean water and access to adequate, clean latrines have also been positively associated with anthropometric status in all East-African countries (Vella et al. 1995; Bloss et al. 2004; Abubakar et al. 2008).

In summary, socioeconomic variables, whether measured as parental education, parental occupational status, family assets or living conditions, have been found to consistently predict childhood outcomes in East Africa. Regardless of the method by which SES was estimated, its influence on child's anthropometric status was significant and consistent in that children from less advantaged home environments were more likely to experience growth restriction (i.e. stunting and being underweight). Yet, in several cases, there were differences in the factors that predicted being underweight and those that predicted stunting. Variation in results could also be expected, given that the various studies had different methodologies. This variation arises because of the use of different, not interchangeable, measures of SES and, conversely, the use of both HAZ and WAZ as indicators of anthropometric status. HAZ and WAZ represent different forms of nutritional deprivation and potentially different aetiology (Frongillo et al. 1997); HAZ scores reflect chronic malnutrition, while WAZ scores reflect acute malnutrition.

167.2 SES, Anthropometric Status and Developmental Outcomes

Compared to the number of studies investigating the relationship between anthropometric status and SES, fewer studies have addressed the relationship between both anthropometric status and socioeconomic variables and psychological outcomes (Table 167.3 presents a description of some of the developmental and cognitive measures used in the studies reviewed here). In a series of studies in Embu, Kenya, the relationship between SES, anthropometric status and cognitive abilities among a largely lower-middle-class community has been investigated over a long period of time (Sigman et al. 1989a, b, 1991; Whaley et al. 1998). The authors evaluated the manner in which anthropometric status, family characteristics and toddler characteristics influence performance on cognitive tasks at 5 years of age. Anthropometric measures taken at toddlerhood influenced performance at the initial assessment (weight: $r(81) = 0.28$, $p < 0.05$; height: $r(81) = 0.21$, *ns*) and correlated with cognitive scores at 30 months of age (weight: $r(84) = 0.25$, $p < 0.05$; height: $r(81) = 0.23$, $p < 0.05$) and at 5 years. When the same sample was assessed at school age (age 7–8 years), cognitive scores were significantly related to SES and anthropometric status (Sigman et al. 1989a). Bhargava et al. (2005) collected data from Tanzanian schoolchildren aged 6–9 years. Using regression, the children's cognitive test scores (composite score of digit span, matrices, arithmetic and word meaning) were predicted by SES and income. In summary, the results obtained in these studies indicate that children with poor anthropometric status came from poorer homes and had lower scores in cognitive tasks.

In a study carried out among preschool children in two low-income settings in Kenya, we set out to investigate if anthropometric status mediates the relationship between SES and psychomotor outcomes (Abubakar et al. 2008). The study involved 204 children aged 24–35 months and two indicators of SES (an index of wealth and maternal education) were used. The wealth-index measure was developed using an adapted version of the Kenya Demographic and Health Survey (KDHS) SES measure (Central Bureau of Statistics 2004), which lists features, such as ownership of land, quality of housing and electric goods among others. Maternal education was operationalised as the number of years of formal schooling the mother attended. Developmental outcomes were assessed using a

Table 167.3 Key features of developmental and cognitive tests used in studies in East Africa

Name of the test	Purpose	Target age group	How it is administered
Raven's Progressive Matrices	Evaluate cognitive abilities by assessing abstract reasoning	Several versions appropriate for both children and adults	This is a multiple-choice test in which an individual is presented with a picture with a missing part and an option of four choices to complete the missing portions
Bayley Infant Development Scales	Evaluate mental, sensorimotor and behavioural development of children	0–42 months	This test involves the exposure of a child in a standardised manner to a series of tasks aimed at eliciting their developmental functioning in a several domains including motor, language, and memory
Kilifi Developmental Inventory	This is a locally developed and standardised measure of psychomotor functioning	6–35 months	This test involves the exposure of a child in a standardised manner to a series of tasks aimed at eliciting their developmental functioning in two main domains: gross-motor and fine-motor functioning

The key features of psychological measures used in the studies discussed here are presented. These include the purpose of the assessment, target age groups and how the measures are administered.

locally developed measure of psychomotor functioning, the Kilifi Developmental Inventory (KDI). We found that both SES indicators were positively associated with HAZ and WAZ, which, in turn, were associated with psychomotor development. Using path-analytic procedures, we fitted a model which indicated that the influence of SES on psychomotor outcomes in this population was fully mediated by the influences of anthropometric status on psychomotor development. We evaluated the influence of being underweight and being stunted separately and observed that being stunted was the stronger predictor of psychomotor outcome. In younger children ($N = 95$, age 2–10 months) from Kilifi, Kenya, we found similar patterns of results across different developmental domains including motor, language and personal–social development (see Fig. 167.2). The results from this younger population indicate that there is a robust relationship between SES, anthropometric status and developmental outcome.

Relatively few studies have examined the relationship between SES, anthropometric status and developmental outcomes. However, those studies that have addressed the issue have consistently found that anthropometric status is associated with developmental outcomes. Children with better physical growth show better developmental outcomes. These East-African findings are in agreement with those from other regions, as a similar pattern of results has been observed in two studies in Ethiopia. Among children aged 16–42 months, SES was found to be significantly associated with cognitive test score; moreover, anthropometric status predicted scores on the Bayley Scales of Infant Development (BSID) (Aboud and Alemu 1995). In this study, SES was not strongly related to the mental scale, but it was related to motor skills. Drewett et al. (2001) did not report correlations between SES and anthropometric status. However, they did find that anthropometric status influenced performance on the BSID and that SES influenced performance on the mental scales of the BSID but not on the psychomotor scales. Pollit and colleagues showed that among malnourished Indonesian children, SES was associated with anthropometric status which itself was associated with motor skills (Walka and Pollitt 2000). Results by Abubakar et al. (2008) indicate that the effects of SES on psychomotor outcome are fully mediated by anthropometric status. If this finding could be replicated across different studies, intervention efforts would focus on the mediating variables, anthropometric status, which is easier to influence than SES and the massive poverty burden.

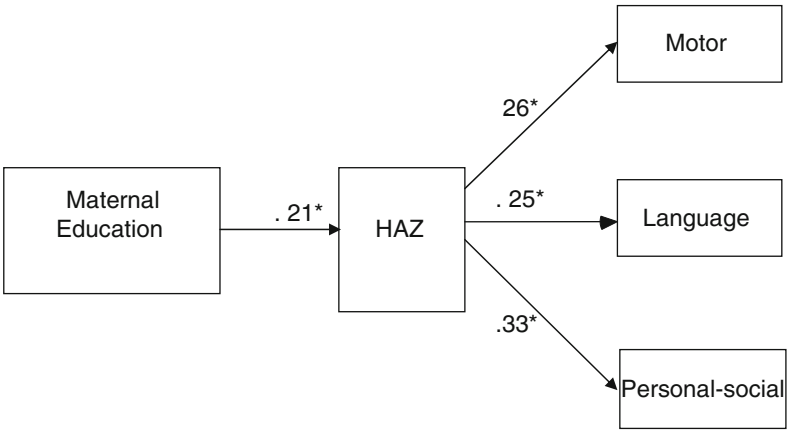


Fig. 167.2 Results of path analysis of the relationship between SES, anthropometry and developmental outcomes. The intervening role of anthropometric status on the relation between socioeconomic status (SES- maternal education) and developmental outcomes is shown in this figure. The results show that the model presented here fits properly with the data. The fit statistics: χ^2 (1, $N = 95$) = 3.43, $p = 0.32$, χ^2/df = 1.15, Tucker Lewis index = 0.97, root mean square error of approximation = 0.04, goodness-of-fit index = 0.98, and adjusted goodness-of-fit index = 0.92. The numbers presented are standardised path coefficients. Higher maternal education positively predicts height-for-age, which indicates that children from better educated mothers had a better anthropometric status. Height-for-age positively predicts all developmental outcomes. * $p < 0.05$

167.3 Potential Pathways of the Influences of SES on Anthropometric Status and Child Development

The statistical links that have been observed between SES, anthropometric status and developmental outcomes require a conceptual explanation. There are methodological problems in disentangling the interrelated causes of growth failure and impaired developmental outcomes; as a consequence, it is difficult to ascertain a causal link between poverty, growth and outcome. The aim of the present section is to present an overview of the existing evidence regarding the link between the three variables. The presentation and subsequent discussion are guided by the United Nations Children's Fund (UNICEF) extended framework (developed by UNICEF in 1990) on causes and consequences of malnutrition. The aim of this framework was to provide a set of guiding principles on how scientists and practitioners can conceptualise and approach intervention in the area of malnutrition. The main principle of the framework is that poor nutritional status is the manifestation of a complex, multilevel chain of causes. According to the framework, these causes can be placed under three strata:

1. Immediate causes: These causes manifest themselves at the individual level in the forms of ill health and inadequate nutrient intake.
2. Underlying causes: They manifest themselves at the household level. Three factors have been classified in this category: lack of finances, inadequate care for mothers and children (care here refers to provision of time, attention and support to meet the needs of both mother and child) and lack of access to health services.
3. Basic causes: These manifest themselves at the community and national level. Basic causes of malnutrition largely entail issues related to access to potential resources.

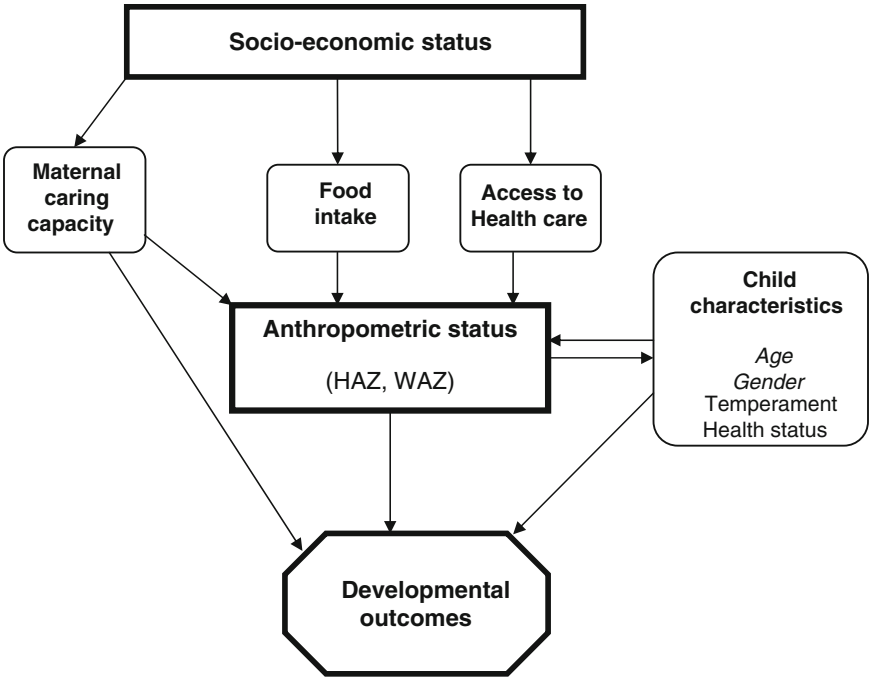


Fig. 167.3 Probable pathways regarding the relationship between SES, anthropometric status and developmental outcomes. The hypothesised potential pathways by which SES effects are transmitted to developmental outcomes through anthropometry are presented. As can be observed, this is a complex relationship that goes through several indirect pathways (maternal caring capacity, food intake and access to health). The relationships are further complicated by the fact that some of these factors, such as maternal caring capacity, may have a direct, independent influence on developmental outcomes. A bi-directional relationship is indicated for anthropometry and child characteristics. This bi-directionality is expected to hold true of all child characteristics, with the exception of gender and age; that is why they are italicised

Recently, Wachs (2008) proposed an extension of the UNICEF model with a view to providing a more detailed picture of the mechanisms by which underlying factors may contribute to poor anthropometric status. Specifically, the presentation aimed at highlighting the role of maternal contributions and child characteristics, such as temperament, age and gender, in the discussion about causes of malnutrition. The UNICEF framework and the proposed extension by Wachs guide the presentation here. The next section reviews studies which provide evidence or suggestions on pathways that link the observed relationship between anthropometric status, SES and developmental outcomes.

The numerous studies discussed in the subsection on SES and anthropometric status all underscore the fact that poverty is a major underlying cause in the high rates of malnutrition observed across East-African countries. Inadequate social, economic and human resources all seem to contribute to growth restriction. There is ample research evidence to show that SES indicators are pathways to poor anthropometric status. In Fig. 167.3, we present a simplified model of our hypothesised potential pathways from poverty to impaired developmental outcomes via anthropometric status. In the following subsections, we evaluate evidence for our model.

Limited material resources limit a family's capability to acquire food, which, in turn, limits a child's dietary intake. Studies in Kenya by Sigman et al. (1991, 1989a, b) indicate that families with limited economic resources have inadequate dietary intake, especially of animal proteins. This deficiency in intake of animal protein, which is not compensated for by intake of similar nutrients from

other sources, has been observed to contribute to both poor anthropometric and developmental outcomes, because of the absence of vital micro- and macronutrients for physical and cognitive development. Moreover, the lack of material resources contributes to inadequate access to health services and a healthy environment, which may also contribute to poor growth and development due to a lack of timely preventive and interventional health measures.

The contribution of maternal caring behaviour to a child's anthropometric status and cognitive abilities has been addressed in studies in East Africa. In a study among toddlers aged 18–30 months, it was observed that children who experienced a less supportive home environment were more frequently ill, which, in turn, led to poorer anthropometric and developmental outcomes. Follow-up data indicated that, at 5 years of age, children with relatively poor outcomes during their toddler days still had relatively poor cognitive outcomes (Sigman et al. 1991; Whaley et al. 1998). The negative effects reported in this study seemed to be moderated by gender, with girls showing worse outcomes. Girls who were lighter and shorter were more likely to experience more days of morbidity, to show poorer cognitive outcomes and to come from homes with mothers who did not provide enough stimulation. Results on the contribution of maternal care-giving behaviour on cognitive and anthropometric outcomes are consistent with what has been observed in Kilifi, Kenya (Abubakar 2008). Scores on a measure of quality and quantity of stimulation received at home (Bradley and Corwyn 1996) correlated positively with HAZ, WAZ and cognitive outcomes. Additionally, there was also a significant, positive relationship between SES and stimulation provided at home. Bhargava and Fox-Kean (2003) evaluated how different maternal characteristics may influence food and calorie intake. Although maternal education did not predict calorie intake, maternal scores on an IQ test had a positive influence on intake (and hence, nutritional and anthropometric status). These findings are in line with Wachs' hypothesis on the saliency of maternal characteristics as a pathway to poor outcome.

Wachs proposes the inclusion of four child characteristics in the conceptual model on undernutrition: health, age, gender and temperament. Children's *health status* has been associated with compromised anthropometric status across different studies in East Africa. Illnesses, such as HIV, malaria, parasitic infections and diarrhoeal disease, have all been associated with poor anthropometric status (Stoltzfus et al. 1997; Nyakeriga et al. 2004; Abubakar et al. 2009; Olney et al. 2009). The relationship between ill health and poor anthropometric status is complex. Existing evidence points to the increased risk for growth failure in most of the common childhood illnesses (e.g., malaria, HIV and parasitic infections); however, it is difficult to ascertain a causal link (see section on disease for further elaboration). Several studies have observed that a *child's age is* a significant, positive predictor of both stunting and being underweight. The prevalence of underweight and stunted children starts to dramatically increase at the age of 3–6 months (which coincides with the inception of weaning) (Stoltzfus et al. 1997; Kwena et al. 2003; Bloss et al. 2004) and seems to peak at between 12 and 24 months (see Fig. 167.4). The role of *gender* as a potential risk factor for poor anthropometric status has been highlighted. Based on data from the global database on malnutrition, we present a summary of rates of prevalence of underweight among boys and girls aged 0–60 months (see Fig. 167.5). The data indicates that boys had higher prevalence rates of underweight than girls in all East-African countries, with the exception of Burundi where the rates for both genders were similar.

Of the four proposed child characteristics likely to impact on nutritional status, the least studied is *temperament*, though there have already been early studies on the role of temperament in growth and development of East-African children. Among the Maasai of Kenya (De Vries 1994, 1999), it was observed that fussy children had better growth outcomes and survived longer compared to those who were mostly quiet. It was hypothesised that in conditions of extreme poverty and need, fussy children forced caregivers to pay more attention to their needs, which increased and improved their chances for survival. The opposite effect was observed among the Digos of Kenya, where children with 'difficult temperaments' were less likely to thrive. These differential effects were attributed to

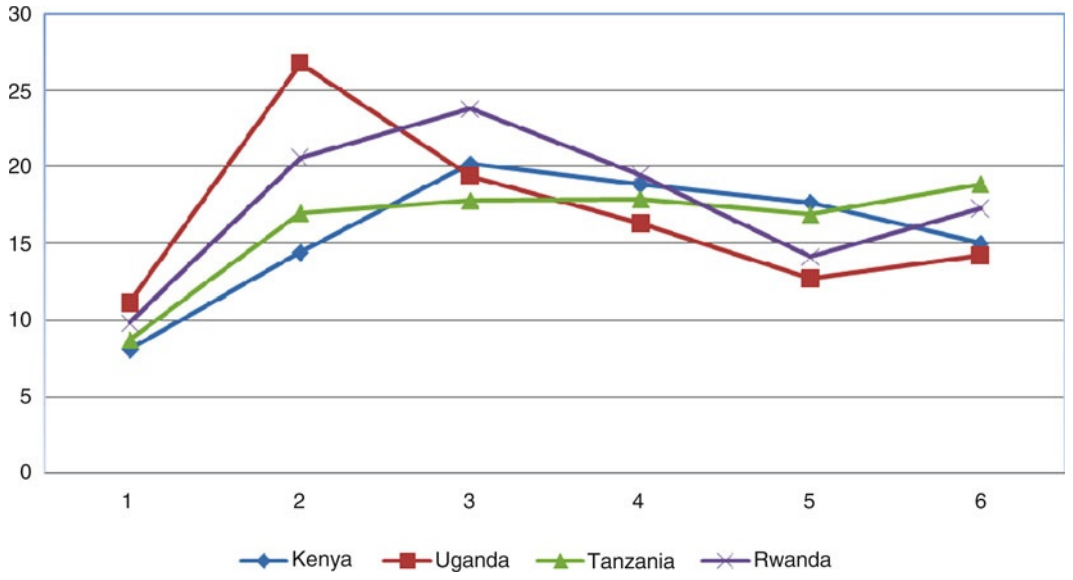


Fig. 167.4 Rates of underweight children by age group in different countries of East Africa. Children aged 0–5 months have the lowest rates of underweight, and then a drastic increase is seen in the next age group before stabilisation although not a return to the low rates observed in the first months of life. Key to different age groups: (*1*) 0–5 months of age, (*2*) 6–12 months, (*3*) 12–24 months, (*4*) 24–36 months, (*5*) 36–48 months and (*6*) 48–60 months. The figure was generated based on data extracted from the WHO database on child growth and malnutrition

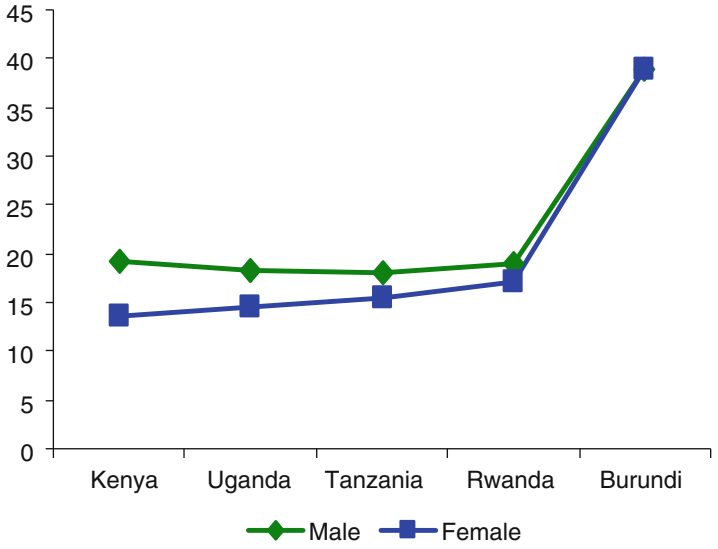


Fig. 167.5 Rates of malnutrition by gender in the five East-African countries**.** Other than in Burundi, boys are at an elevated risk of being underweight in all East-African countries. In the case of Burundi, the prevalence of underweight is similar for boys and girls. The figure was generated based on data extracted from the WHO database on child growth and malnutrition

the fact that how a child thrived could be related to the 'goodness of fit' between the child's characteristics and the environment.

Our review has produced consistent evidence for the existence of statistical associations between poverty/SES, anthropometric status and developmental outcomes. It is less clear, though, which developmental pathways underlie the statistical associations. We were not able to identify any East-African study, which aimed to identify pathways by which SES affects anthropometric status or anthropometric status influences cognition. However, using the UNICEF extended care model and Wachs' recent extension, we were able to collate existing evidence and illustrate some potential pathways to poor outcome in the undernourished East-African population. Our summary of potential pathways in the East-African data is consistent with existing literature from elsewhere, which shows that poverty (low SES) influences anthropometric status by limiting food intake, lowering maternal caring capacity and lowering child's general health. As a consequence, children are more susceptible to infections, and the negative influence of these infections on developmental outcomes is more likely, given the unfortunate accompanying lack of access to vital services (e.g., healthcare and clean water). How does anthropometric status influence cognitive outcomes? There are two potential pathways. The first is through damage to brain structure. Data from other regions of the world indicate that malnutrition is associated with structural and functional abnormalities in the brain. Malnutrition has been associated with reduced brain cells, damage to the hippocampus, delayed myelination and alteration in neurotransmitter systems, among others (Levitsky and Strupp 1995). The resulting brain damage may contribute to poor developmental or cognitive outcomes. Second, ill health may limit the degree to which children are able to get and attract stimulation and experience new things that contribute to their cognitive development.

167.4 SES, Common Diseases, Anthropometric Status and Developmental Outcome

Risk factors tend to cluster together. Children living in poverty are more likely to experience poor health compared to those from high socioeconomic backgrounds. Sub-Saharan Africa (SSA) is the poorest region of the world and many children tend to be exposed to multiple health risks. Not surprisingly, this part of the world carries a disproportionate portion of the global disease burden.

HIV has been associated with both poor anthropometric status and cognitive impairments. In a study carried out in Kilifi, Kenya, it was observed that HIV-infected children who had poor anthropometric status (i.e. underweight) performed significantly more poorly on measures of psychomotor development compared to HIV-exposed but uninfected peers without growth failure (Abubakar et al. 2009). In this rural population, anthropometric status provided an indicator to identify which HIV-positive children needed psychomotor monitoring and rehabilitation that are relatively cheap and easy to administer.

Various studies have shown that malaria, especially in its severe form, is detrimental to developmental and cognitive outcomes. Additionally, malaria has been associated with poor anthropometric status. In a sample of more than 1,862 children, it was observed that a higher proportion of stunted children had more malaria parasetemia (odds ratio = 1.98, $p < 0.001$), indicating that being stunted puts children at an elevated risk of malaria-related morbidity. SES and poor anthropometric status have been suggested as potential pathways explaining the poor neurocognitive outcomes of children surviving severe malaria; however, these have yet to be investigated (Kihara et al. 2006). Children with a heavy helminth infection load are at a higher risk of both poor anthropometric status and cognitive impairment. Jukes et al. (2002) reported that children with heavy worm infestation and

poor nutritional status suffered cognitive impairments. Olney et al. (2009) studied more than 800 children in Zanzibar to investigate the effects of malaria, anthropometric status and anaemia on developmental outcomes. Using structural equation modelling (SEM), Olney and colleagues examined the relationships between malaria, stunting, anaemia and child developmental outcome. It was found that children with higher malaria parasite densities had significantly lower Hb and HAZ. Moreover, HAZ was a significant, positive predictor of developmental outcome (motor activity and motor and language development). Additionally, children with higher Hb had higher motor development and activity scores. Malaria was directly and indirectly related to motor activity in the 10–14-month-old group [standardised total effects: -0.14; direct: -0.10 ($p = 0.015$) and indirect: -0.04]. It can be concluded that major health risks, such as HIV, malaria and anaemia, can contribute significantly to impaired developmental outcomes. The available evidence tentatively suggests that the influence of the disease on developmental outcomes can be both direct and indirect through the influence of the disease on anthropometric status.

167.5 Implication for Practice and Policy

Our review suggests that frequent anthropometric measurements and surveillance of children living in poverty can be used to identify children at risk of developmental or cognitive delay or impairments. The implementation of such a programme in resource-constrained countries would be feasible, given that those anthropometric measures are relatively cheap and easy to administer.

The relationship systematically found between anthropometric status and cognition implies that the implementation of combined nutritional and psychosocial intervention measures is likely to give the best results in terms of improving childhood cognitive outcomes. The value of combined programmes has been evaluated and confirmed in a series of studies in Jamaica (Grantham-Mcgregor et al. 1991; Walker et al. 2005). Although interventions aimed at reducing poverty levels are underway (and badly needed), implementing combined nutritional and psychosocial interventions could be a cheaper way of reducing developmental delays among children living in poverty.

167.6 Application to Other Areas of Health and Disease

Among children living in poverty, improved anthropometric status through combined nutritional and psychosocial intervention has been observed to lead to enhanced performance on developmental and cognitive tasks. Therefore, in diseases where anthropometry is negatively affected, similar intervention measures should be put in place to enhance both anthropometric and developmental status.

167.7 Practical Methods and Techniques

Issues in developmental assessments in East Africa

(a) There are numerous measures of cognitive, language and social–emotional functioning that are commercially available for children of all ages.
(b) Most of the available measures have been developed for and standardised for use in Europe and North America. However, the transfer of tests developed for Western populations to a non-Western

context is frequently accompanied by test bias (Greenfield 1997; Vijver 2002). This bias may arise from a lack of familiarity with the demands of taking formal psychological tests in non-Western children (Mulenga et al. 2001), poor translation of test items (Vijver 2002) and unfamiliarity with test material (Sigman et al. 1988; Sonke et al. 1999) among many other difficulties.

(c) Two approaches, adaptation and assembly, seem to provide an adequate solution to the shortage of assessment measures in East Africa and other developing regions of the world (Malda and Van De Vijver 2005). Adaptation involves retaining some and changing other features of a Western instrument to increase the suitability of the instrument for the new context; assembly involves the construction of a new assessment measure. Recent efforts in East Africa and surrounding regions indicate that such efforts can lead to the development of culturally appropriate and valid assessment procedures.

(d) Systematic approaches and guidelines for adequate test adaptation that can be used in East Africa and other developing regions of the world have been developed.

Summary Points

- Children from families with low SES in East Africa are at an elevated risk of poor anthropometric status (i.e. being underweight or stunted).
- Poor anthropometric status (i.e. being underweight or stunted) is significantly associated with poor developmental outcomes.
- Several factors in the day-to-day life of children in low SES families may contribute to their poor anthropometric status. These factors include suboptimal maternal caring behaviour, inadequate access to food and a lack of access to adequate health services.
- Anthropometric status is linked to poor developmental outcomes through several mechanisms including potential brain damage and inability to attract and receive adequate stimulation and learning opportunities from the environment.
- Anthropometric measurements are an important target of intervention among children living in poverty. Intervention efforts aimed at improving the anthropometric status of children living in poverty are likely to lead to improved developmental and cognitive outcomes.

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Chapter 168
Body Mass Index and Mortality in India

Catherine Sauvaget

Abstract The paper reviews the current nutritional situation of India. The country is still facing childhood and adult under-nutrition, 28% of adult men and 33% of adult women have a body mass index (BMI) lower than 18.5 kg/m^2. Recently, due to demographic, epidemiological and nutritional transitions, going along with economic changes, the country is also facing a dramatic increase in the prevalence of overweight and obesity. Consequently, India is currently suffering from the coexistence of both chronic energy deficiency and obesity. Disparities in terms of nutritional status are observed: populations from East and Central states suffering more frequently from malnutrition, while people living in urban areas, highly educated, or from a high socio-economic level suffering more often from overweight and obesity. Although the association between mortality and body mass index in India has been scarcely addressed, studies on morbidity related to overweight and obesity report a growing prevalence of type 2 diabetes mellitus (31 million patients in 2005) and cardiovascular diseases (36 million patients in 2004). It is estimated that within a decade, the number of cases of these two diseases will double. The body composition of Indians has specific features such as excess body fat and great abdominal fat. Persons may be classified as "normal" by BMI criteria are actually "metabolically-obese" when body fat or abdominal obesity are considered. Attempts have been made for lowering BMI cut-off points for Asian ethnic groups; increased risk of diabetes and cardiovascular diseases is likely to start from a BMI of 23 kg/m^2, and high risk of these diseases at 25 kg/m^2.

Abbreviations

BMI	Body mass index
NFHS	National Family Health Survey
WHO	World Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_168,

168.1 Introduction

India is the second most populous country in the world with 1.2 billion inhabitants, representing 17% of the world's population (Fig. 168.1, drawn with Statistical Analysis Software, GMAP procedure) (SAS Institute Inc. 2002).

Based on the World Health Organization (WHO), in 2005, the mean body mass index (BMI) values in India were low (men: 21.1 kg/m^2, women: 21.6) as compared to values from Western countries such as UK (men: 26.8 kg/m^2, women: 26.7) or USA (men: 28.4 kg/m^2, women: 28.8) (World Health Organization 2008b). Consequently, the BMI distribution tends traditionally to shift toward the low level, with a high proportion of underweight and a small proportion of overweight and obese persons.

Over the past two decades, however, there has been a clear rightward shift in the distribution, thereby suggesting an improvement in the adults' rates of underweight over this period. This has been accompanied with a concomitant increase in the obesity rates in certain urban areas (Pednekar et al. 2008). India is currently facing the double burden of undernutrition as well as overnutrition (Table 168.1).

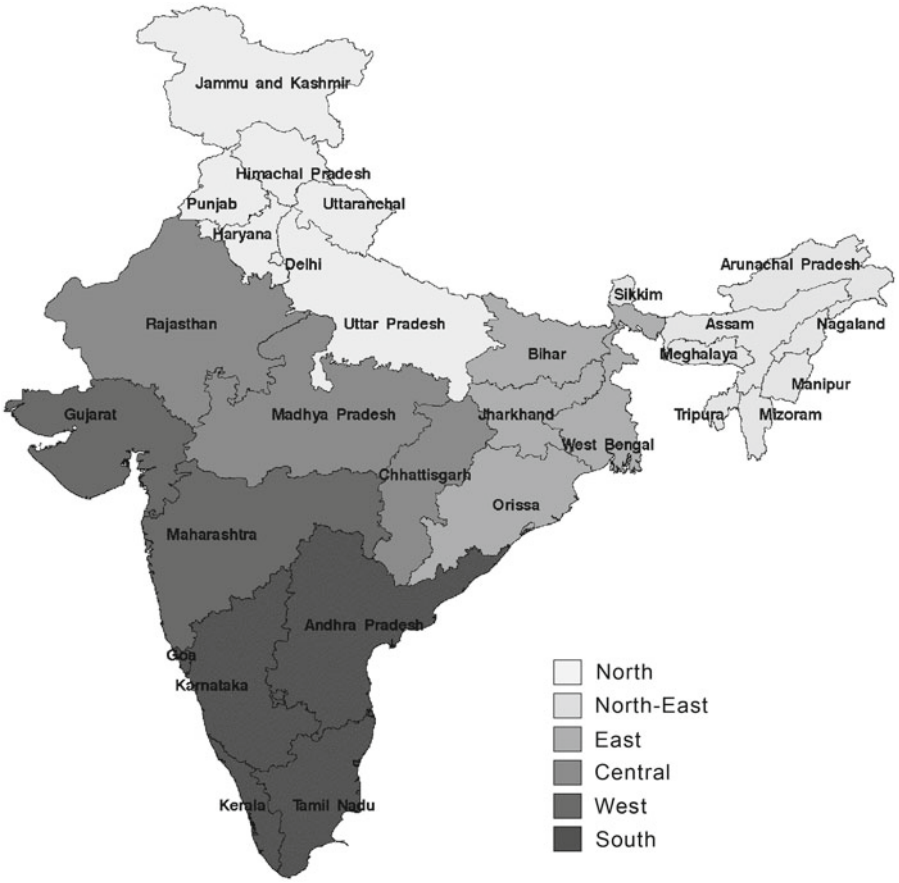


Fig. 168.1 Map of India with states and regions. This map shows the states and main regions of India

Table 168.1 Key features of the twin burden of under- and overweight in India

1. India is still suffering from undernutrition with half of the children aged less than 3 years old and one-third of adults being underweight.
2. At the same time, prevalence of overweight is increasing, especially in urban areas, among those educated and those from high socioeconomic status.
3. Overweight and obesity are known risk factors of diabetes and cardiovascular disease.
4. It is likely that the prevalence and the mortality from cardiovascular disease is becoming a major public health problem in the country.

The table shows the current nutritional situation in India with the double burden of under- and overweight. Short-term consequences of overweight and obesity are an increase in the prevalence and mortality from cardiovascular disease

168.2 Predictors of Body Mass Index

Within the country, large differences in nutritional status are observed between the regions, the living area, the gender, the education level, and the socioeconomic status. Certain regions show extremely high rates of childhood undernutrition (ranging from 20% to 80%), others have a high prevalence of adult undernutrition (more than 50%), while some have both (Pednekar et al. 2008). As shown in Table 168.2, those living in East and Central India had a low mean BMI as compared to those from North and South India. Persons living in urban areas had a greater BMI than those living in rural areas, and women presented a higher BMI than men. The average value of BMI in Asian Indians appears to increase with urbanization and migration (Misra and Vikram 2004).

It has been hypothesized that the causes of rural–urban differences may include the effects of urbanization, processed and fast food, and dependence on TV and radio, leading to less physical activity and the consumption of a diet rich in calories and poor in nutrients (Bharati et al. 2007). In many urban areas of India, increased consumption of energy and fat in conjunction with reduced levels of physical activity was found to be associated with escalation of adolescent and adult obesity (Bharati et al. 2007). Similarly, when people living in rural areas migrate to metropolitan cities and settle in urban slums, they tend to become obese, glucose intolerant, and dyslipidemic, as a result of changes in their activity pattern and dietary profile (Misra 2003).

Education is one of the most important regulatory factors; it enhances awareness of health and hygiene in the society. Higher educational level has been associated with healthier dietary patterns and decreased prevalence of obesity in Western countries (Sundquist and Johansson 1998). The standard of living is another important factor. A strong association between BMI and socioeconomic status, particularly income and standard of living, has been found in developing countries (Nube et al. 1998). However, in contrast to high-resource countries where poverty is associated with greater obesity, in India increasing education level and socioeconomic status are associated with increasing prevalence of obesity. Figure 168.2 shows the relationship between income and overweight in each Indian state: the higher the per-capita income, the higher the prevalence of overweight.

Indeed, overweight is becoming a serious problem in urban India, particularly in the upper-middle class, while rural-based populations in India have a low prevalence (nearly half or less compared to urban ones) of obesity, hypertension, diabetes, dyslipidemia, and coronary heart diseases. One of the important reasons could be that the latter have a physically vigorous lifestyle and consume low-calorie, low-saturated-fat diets (Misra 2003).

The comparison of data between two major nation-wide surveys performed in 1998 and 2005 (Table 168.3) shows that, for the whole country and in a majority of states, the prevalence of underweight in women (BMI <18.5 kg/m^2) has hopefully declined (in 1998: 35.8%, in 2005: 33%). However, the prevalence of overweight and obesity in women has also increased (in 1998: 10.6%,

Table 168.2 National and state-wise mean body mass index and prevalence of underweight and obesity in the National Family Health Survey 2 (NFSH-2 1998–1999), women only (Source: Ministry of Health and Family Welfare 2000)

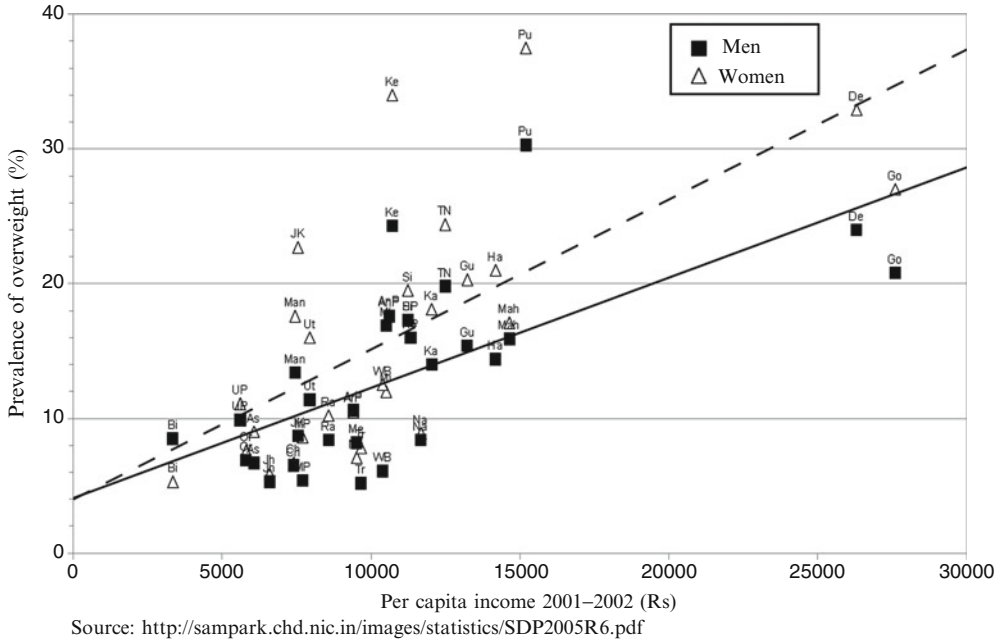
	Mean BMI (kg/m^2)				
	Urban	Rural	Total	% BMI <18.5 kg/m^2	% BMI ≥30 kg/m^2
All India	**22.1**	**19.6**	**20.3**	**35.8**	**2.2**
North					
Delhi	23.7	22.8	23.7	12.0	
Haryana	23.4	20.4	21.3	25.9	
Himachal Pradesh	23.1	20.5	20.8	29.7	
Jammu & Kashmir	23.3	20.4	21.0	26.4	
Punjab	24.9	22.2	23.0	16.9	
Uttar Pradesh	21.8	19.5	20.0	35.8	
Uttaranchal	22.6	19.5	20.3	32.4	
North-East					
Arunachal Pradesh			21.0	10.7	
Assam	21.6	19.9	20.1	27.1	
Manipur			21.1	18.8	
Meghalaya			20.3	25.8	
Mizoram			20.4	22.6	
Nagaland			20.9	18.4	
Sikkim	22.5	21.9	22.0	11.2	
Tripura			20.3	35.2	
East					
Bihar	20.5	19.3	19.4	39.3	
Jharkhand	20.3	19.1	19.3	41.1	
Orissa	20.7	19.0	19.2	48.0	
West Bengal	22.0	18.9	19.7	43.7	
Central					
Chhattisgarh	20.6	18.9	19.2	48.1	
Madhya Pradesh	21.1	19.4	19.8	38.2	
Rajasthan	21.3	19.5	19.9	36.1	
West					
Gujarat	22.5	19.4	20.7	37.0	
Maharashtra	21.9	19.0	20.2	39.7	
South					
Andhra Pradesh	22.3	19.6	20.3	37.4	
Goa	22.4	21.1	21.6	27.1	
Karnataka	22.3	19.3	20.4	38.8	
Kerala	22.6	21.9	22.0	18.7	
Tamil Nadu	22.4	20.2	21.0	29.0	

Women living in the East and Central parts have a lower mean BMI than those living in the North and South parts. Those from urban areas have a higher BMI than those from rural areas

in 2005: 14.8%). Again, in the 2005 survey, the prevalence of overweight as well as the prevalence of underweight in women was higher than in men (Ministry of Health and Family Welfare Government of India 2000; 2008).

In Table 168.4, the results being based on several large-scale cross-sectional studies, the prevalence of overweight in rural areas shows an increase with time, in both men and women. However, no specific trend is observed in those living in urban areas.

According to WHO, in 2015, one-third of the Indian adult population will be overweight and the prevalence of obesity will double in 10 years, from 2005 to 2015 (World Health Organization 2008b).



Source: http://sampark.chd.nic.in/images/statistics/SDP2005R6.pdf

Fig. 168.2 State-wise income and prevalence of overweight. Per-capita income and prevalence of overweight (BMI ≥25 kg/m^2) for each state are plotted and the correlation line is drawn. It shows the higher per-capita income and the higher prevalence of overweight, in both men and women (Source: http://sampark.chd.nic.in/images/statistics/SDP2005R6.pdf)

According to another prediction, 20% of Indian females and 16% of males will be overweight by the year 2020 and therefore the incidence of chronic diseases is expected to increase (Dasgupta et al. 2008). What are the chronic diseases associated with overweight and obesity in India?

168.3 Obesity-Related Morbidity

The increasing prevalence of overweight and obesity in India is concomitant to the growing prevalence of obesity-related comorbidities, such as hypertension, metabolic syndrome, dyslipidemia, type 2 diabetes mellitus, and cardiovascular diseases. India is now facing an epidemic of diabetes and coronary heart diseases (Gupta et al. 2007). It has been predicted that, within the coming 15 years, these diseases will increase rapidly and the country will be host to more than half the cases of heart diseases in the world. So far, prevalence of coronary heart disease and stroke are increasing in both urban and rural areas, at all age groups (Fig. 168.3) (Ministry of Health and Family Welfare National Commission on Macroeconomics and Health 2005).

This fact is explained by the substantial rise, over the past decades, of their risk factors: tobacco use, obesity with high waist/hip ratio, high blood pressure, high LDL cholesterol, low HDL cholesterol, diabetes, low consumption of fruits and vegetables, high fat intake, and sedentary lifestyles (Gupta 2008).

Cardiovascular disease is the leading cause of death in India, representing 26% of all causes with 2.7 million deaths in 2004 (among them: 1.5 million deaths from ischemic heart diseases and

Table 168.3 National and state-wise prevalence of underweight (BMI <18.5 kg/m^2) and overweight/obesity (BMI ≥25 kg/m^2) in the National Family Health Surveys 2 and 3 (NFHS-2, NFHS-3) (Sources: Ministry of Health and Family Welfare Government of India 2000; Ministry of Health and Family Welfare National Commission on Macroeconomics and Health 2005)

	NFHS-2 (1998–1999)				NFHS-3 (2005–2006)			
	% BMI <18.5 kg/m^2		% BMI ≥25 kg/m^2		% BMI <18.5 kg/m^2		% BMI ≥25 kg/m^2	
	Men	Women	Men	Women	Men	Women	Men	Women
All India	**35.8**		**10.6**		**28.1**	**33.0**	**12.1**	**14.8**
North								
Delhi	12.0		33.8		10.4	10.6	24.0	32.9
Haryana	25.9		16.6		26.8	27.8	14.4	21.0
Himachal Pradesh	29.7		13.1		19.8	24.3	16.0	17.3
Jammu & Kashmir	26.4		13.8		19.9	21.3	8.7	22.7
Punjab	16.9		30.2		12.0	13.5	30.3	37.5
Uttar Pradesh	35.8		7.3		32.7	34.1	9.9	11.1
Uttaranchal	32.4		9.2		21.8	25.7	11.4	16.0
North-East								
Arunachal Pradesh	10.7		5.1		13.6	15.5	10.6	10.5
Assam	27.1		4.2		33.4	36.5	6.7	9.0
Manipur	18.8		10.8		12.2	13.9	13.4	17.6
Meghalaya	25.8		5.8		8.0	13.7	8.2	7.1
Mizoram	22.6		5.3		6.0	15.3	16.9	12.0
Nagaland	18.4		8.2		10.8	15.9	8.4	8.9
Sikkim	11.2		15.7		7.2	9.6	17.3	19.5
Tripura	35.2		8.4		38.3	35.1	5.2	7.8
East								
Bihar	39.3		3.9		28.7	43.0	8.5	5.3
Jharkhand	41.1		3.2		33.4	42.6	5.3	5.9
Orissa	48.0		4.4		32.1	40.5	6.9	7.6
West Bengal	43.7		8.6		31.6	37.7	6.1	12.5
Central								
Chhattisgarh	48.1		4.1		31.8	41.0	6.5	6.7
Madhya Pradesh	38.2		6.8		36.3	40.1	5.4	8.6
Rajasthan	36.1		7.1		33.8	33.6	8.4	10.2
West								
Gujarat	37.0		15.8		28.2	32.3	15.4	20.3
Maharashtra	39.7		11.7		24.9	32.6	15.9	17.1
South								
Andhra Pradesh	37.4		12.0		24.8	30.8	17.6	17.7
Goa	27.1		21.2		16.8	20.5	20.8	27.0
Karnataka	38.8		13.6		25.5	31.4	14.0	18.1
Kerala	18.7		20.3		11.9	12.5	24.3	34.0
Tamil Nadu	29.0		14.7		18.5	23.5	19.8	24.4

This table shows the time trend of prevalence of under- and overweight, by states. In majority of states, the prevalence of underweight in women is decreasing; however, the prevalence of overweight is increasing. Women present a higher prevalence of both underweight and overweight, as compared to men

0.7 million deaths from stroke) and an age-standardized death rates of 382/100,000 (World Health Organization 2008a). In 2005, 36 million patients were diagnosed with coronary heart diseases, the number is expected to double in 2015 (Ministry of Health and Family Welfare National Commission on Macroeconomics and Health 2005; Ministry of Health and Family Welfare Government of India 2006).

Table 168.4 Prevalence of overweight in large studies according to gender, area (urban or rural), and year (Source: WHO, WHO Global InfoBase 2008)

		Men		Women	
	Study level	Sample size	% BMI ≥25 kg/m^2	Sample size	% BMI ≥25 kg/m^2
Urban					
1985	Subnational	6,143	21.3	7,271	33.4
1998	National	14,236	5.8	21,385	6.1
2000	National	5,275	25.4	5,904	35.8
2005	National	23,304	15.9	36,366	23.5
Rural					
1975	Subnational	19,157	2.3	19,986	3.4
1988	Subnational	9,447	2.6	11,914	4.1
1996	Subnational	12,751	4.1	18,022	6.0
1998	National	60,993	4.0	81,227	4.1
2005	National	42,438	5.6	75,416	7.4

This table lists the results of large national and subnational surveys on nutritional status. In rural areas, prevalence of overweight is increasing with time. Specific time trend is not observed in urban settings

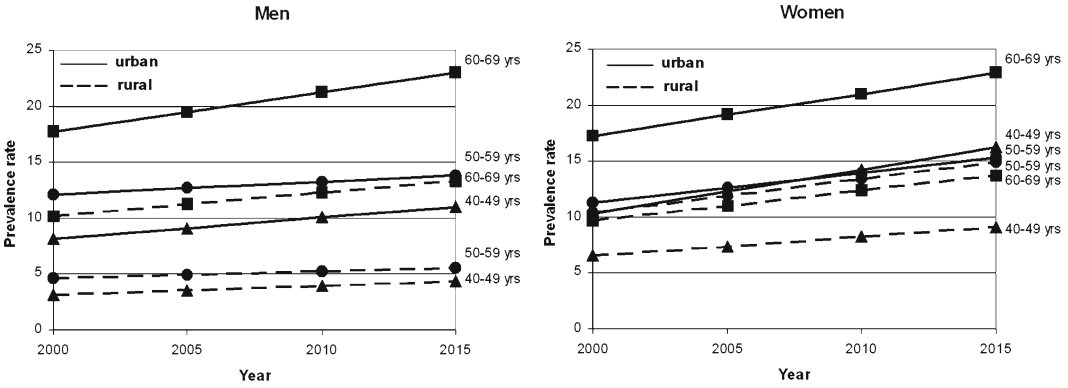


Fig. 168.3 Estimation and prediction of prevalence rate of coronary heart disease according to age group and place of living, in men and women. In men and women, at all age groups, the prevalence of coronary heart disease is increasing with time. This is observed in both urban and rural areas (Source: Ministry of Health and Family Welfare National Commission on Macroeconomics and Health 2005)

In 2004, 160,000 persons died from diabetes (age-standardized death rate: 22.4/100,000) (World Health Organization 2008a), and in 2005, 31 million Indians were suffering from diabetes – there are expected to be more than 79 million persons in 2030 suffering from diabetes (World Health Organization 2004; Ministry of Health and Family Welfare Government of India 2006).

Moreover, low birth weight followed by increased obesity could lead to the insulin resistance syndrome during adulthood (Pradeepa and Mohan 2002). A large proportion of children is still born undernourished; they represented 46% in the last national nutritional survey (Ministry of Health and Family Welfare Government of India 2008). If these children are later exposed to high-fat diets and sedentary lifestyles and develop into obese adults, then it is likely that they will suffer severe consequences in the form of early heart disease, hypertension, and diabetes (Gill 2001).

168.4 Body Mass Index and Mortality

The association between BMI and overall mortality in India has been scarcely addressed. A previous study reported that, in 800 men, with 40% being categorized as normal BMI (BMI ≥18.5 kg/m^2) and 60% being undernourished, the mortality rates increased with decreased BMI (Satyanarayana et al. 1991). More recently, two large-scale studies performed in adults aged 35 years and over, one in the main city of Mumbai (former Bombay) and the other in a rural area of Trivandrum (Kerala State), reported very similar results (Pednekar et al. 2008; Sauvaget et al. 2008). Both studies had a prospective design, and they had a similar methodology: vital status information and cause of death actively assessed: exclusion of the first years of follow-up to eliminate existing medical conditions at baseline with potential effects on both BMI and mortality, and adjustment for tobacco use and other potential confounding factors in the statistical analyses. The two studies reported that the thin and very thin persons were at increased risk of death, while those overweight or obese were not. A similar inverse-J-shaped association was observed in men and women (Fig. 168.4). The detrimental consequence of overweight and obesity observed in high-resource countries was not supported by these two studies. However, the Mumbai study reported that obese subjects had a 40% increased risk of dying from diseases of the circulatory system (especially cardiovascular diseases), while overweight and obesity had no effect on mortality from cardiovascular diseases in the Trivandrum study. Unfortunately, the

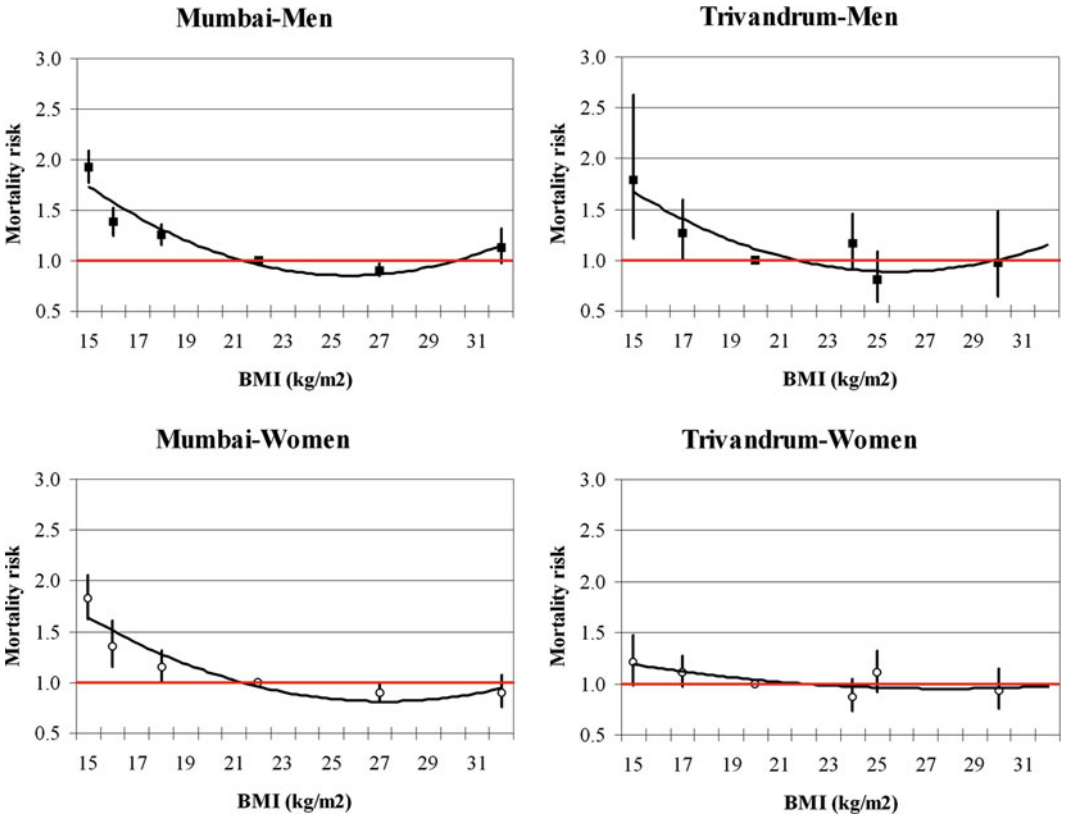


Fig. 168.4 BMI and mortality risks in the Mumbai and Trivandrum studies. An inverse-J-shaped relationship is observed between BMI and all-cause mortality risk; subjects with low or very low BMI are at increased risk of death, while those with BMI greater than 25 kg/m^2 do not show any increase in risk. The two studies report similar results (Sources: Pednekar et al. 2008; Sauvaget et al. 2008. With permission)

two studies addressed solely the effect of BMI and did not consider body fat and excess body weight. However, body composition needs to be considered when studying the Indian ethnic group.

168.5 Body Composition

The body composition of Asian Indians presents several specificities: (1) an excess body fat in relation to body mass index, (2) a lesser lean body mass, and (3) a greater abdominal adiposity with (i) high waist/hip ratio, (ii) normal waist circumference, and (iii) high intra-abdominal fat, as compared to other Asian ethnic groups or Caucasians (Deurenberg-Yap et al. 2000; Misra and Vikram 2004). Indeed, some Indians classified as 'non-obese' by the WHO criteria are actually obese when *body fat* is used to define obesity. Moreover, the prevalence of *abdominal adiposity* is high even in people who are otherwise considered non-obese, these normal-weight persons being described as 'metabolically obese' (Ruderman et al. 1998; Misra 2003). Even among relatively thin urban men with a mean BMI of 22.4 kg/m^2, body fat content was found to be as high as 28% (Misra and Vikram 2004). Also, among overweight subjects (BMI ≥ 25 kg/m^2) from the metropolitan area of New Delhi, abdominal fat – measured with the waist/hip ratio – was found in 68% of men and 58% of women (Gill 2001) (Fig. 168.5).

The relevance of the definition of normal range of BMI (18.5–25 kg/m^2), because it is associated with a high proportion of body fat in Asian ethnic groups, is questioned. The concern that the current BMI cutoff points actually in use – which were originally based on data from European Caucasian populations – were not applicable to Asian populations, has motivated a group of experts to propose a specific classification for Asian ethnic groups (World Health Organization 1995; WHO Expert Consultation 2004). Alternative trigger points for public health action were identified as 23 kg/m^2 or higher, representing increased risk of cardiovascular diseases and diabetes, and 25 kg/m^2 or higher as representing high risk of these diseases (Table 168.5) (WHO Expert Consultation 2004).

Lowering the BMI cutoff points, especially in Asian populations, may be beneficial in identifying individuals at risk for developing overweight-associated comorbidities and their complications (Raji et al. 2001). However, as explained earlier, although BMI is the most commonly used anthropometric indicator of nutritional status, it is not a perfect marker because it does not take into account the proportion of body fat as well as abdominal adiposity. Increased central or visceral fat independent of relative body weight is known to be associated with a variety of metabolic disorders and increased cardiovascular mortality (Gupta et al. 2007).

168.6 Conclusion

Transition is defined in terms of *demographic* transition through its increased longevity and change in the age structure, *epidemiological* transition by way of its decreasing prevalence of infectious diseases and increasing rate of chronic diseases, and *nutritional* transition with the receding famine and malnutrition and rising prevalence of diet-associated non-communicable diseases (Popkin 2002). India is experiencing the three transitions due to economic changes, although this is mostly observed in urban areas. Some of the major consequences of these transitions are the twin burden of under- and overnutrition, where chronic energy deficiency is still a major problem for large parts of the population, associated with an epidemic of cardiovascular diseases and other diet-associated non-communicable diseases, making some experts warn that India is sitting on a diabetes time bomb (Unknown 2009).

Fig. 168.5 Men enjoying a shower under a waterfall in Tamil Nadu state

Table 168.5 International classification and BMI cutoffs for Asian population (Sources: World Health Organization 1995, 2008a)

	BMI cutoffs		Risk of comorbidity	
	International classification	Asian populations	International classification	Asian populations
Severe thinness	<16.00	<16.00	Low	Low
Mild and moderate thinness	16.00–18.49	16.00–18.49		
Normal range	**18.50–24.99**	**18.50–22.99**	**Average**	**Average**
Mild overweight		23.00–24.99		Increased
Pre-obese class I	25.00–29.99	25.00–27.49	Increased	
Pre-obese class II		27.50–29.99		Moderate
Obese class Ia	30.00–34.99	30.00–32.49	Moderate	Severe
Obese class Ib		32.50–34.99		
Obese class II	35.00–39.99	≥35.00	Severe	
Obese class III	≥40.00		Very severe	

International classification refers to the current WHO classification in use. The classification for Asian populations was established by a group of experts for populations specifically from Asia. Risk of comorbidity appears at a lower level in Asia (from BMI 25 kg/m^2 in Asia and 30 kg/m^2 in other populations)

168.7 Practical Methods and Techniques

- WHO BMI cutoff points for Asian populations should be used.
- Besides height and weight, hip:waist ratio and markers of abdominal fat should be measured.
- Training of field workers is necessary.
- Two measurements per subjects are needed.

Summary Points

- Burden of underweight is high in India (46% of children aged <3 years old, 28% of adult men, and 33% of adult women).
- Burden of overweight and obesity is increasing (12% in men, and 15% in women).
- Obesity is more often reported in urban areas, among highly educated subjects and among wealthy populations.
- Prevalence of hypertension, metabolic syndrome, dyslipidemia, type 2 diabetes mellitus, and cardiovascular diseases is dramatically increasing.
- Cardiovascular disease is the leading cause of death (26% of all causes) with 2.7 million deaths and an age-standardized death rate of 382/100,000.
- The body composition of Indians differs from other ethnic groups, with excess body fat and great abdominal fat leading to 'metabolically obese' subjects with 'normal' body mass index (18.50–24.99 kg/m^2).
- Alternative cutoff points of body mass index for Indian populations were identified as ≥23 kg/m^2 for overweight, and ≥25 kg/m^2 for obesity.

Key Points – Twin Burden of Under- and Overweight in India

- India is facing a twin burden of under- and overweight.
- Large discrepancies in nutritional status are observed between regions, living areas, education level, and socioeconomic status. Those living in urban areas, highly educated, or from a high socioeconomic level are suffering more often from overweight and obesity.
- Obesity is associated with metabolic disorders, such as diabetes mellitus, and increased risk of cardiovascular diseases. Prevalence and mortality rates of diabetes and cardiovascular diseases are expected to double within the next decade.
- The body composition of Asian Indians presents specificities: an excess body fat, a low muscle mass, and a high abdominal adiposity. These specificities should be taken into consideration in classifying subjects at risk of diabetes or cardiovascular diseases.

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Part XXIV
Anthropometry and Nutrition: General Aspects

Chapter 169
Anthropometric Measurements and Nutritional Status in the Healthy Elderly Population

Lilia Castillo-Martínez, Carmen García-Peña, Teresa Juárez-Cedillo, Óscar Rosas-Carrasco, Claudia Rabay-Gánem, and Sergio Sánchez-García

Abstract Anthropometric evaluation is an essential part of the nutritional assessment in geriatrics to determine conditions of malnutrition, overweight and obesity, as well as the loss of muscle mass, gain of fat mass and redistribution of adipose tissue. These anthropometric indicators have been used to evaluate the prognosis of acute and chronic diseases, and to guide medical intervention in the elderly.

It has been demonstrated that anthropometric measurements are highly reliable in determining nutritional status in comparison with other, more sophisticated methods (hydrodensitometry, dilution techniques, radio-labeled potassium and electronic bioimpedance), the use of which is restricted by their complexity and cost.

Changes in body composition at different stages of life differ in men and women, and are reflected in anthropometric measurements. There is a certain consensus in which the values of the body mass index (BMI) currently in use in the elderly underestimate deficit and overestimate the condition of being overweight, and that the critical points of waist circumference probably underestimate metabolic risk.

The nutritional needs of older adults with a good level of health vary little in relation to the needs of adults in general. Nevertheless, some special recommendations are indicated for groups at special risk; their application to all the population is still a motive for discussion.

Nutritional evaluation in the elderly is especially difficult because many of the signs related to malnutrition are also related to the ageing process itself. Currently, a series of rapid application scales have been developed for nutritional evaluation in geriatrics. The selection of instruments for said evaluation should consider the intended objective (screening of the population at risk or care and follow-up), the profile of the population and the available resources, including the trained personnel and time required.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_169,

Abbreviations

2C	The 2-component (2C) model
4C	The 4-component (4C) model
ANOVA	Analysis of variance
BMI	Body mass index
BOD-POD	Body composition assessment
BS	Bicipital skinfold
BW	Body weight
Cc	Cubic centimeter
CCG	Calf circumference corrected
Cm	Centimeter
CS	Calf skinfold
CTG	Thigh circumference corrected
DEXA	Dual-Energy X-Ray Absorptiometry
DNA	Deoxyribonucleic acid
FAO	Food and Agriculture Organization
FG	Uncorrected forearm circumference
FFM	Fat free mass
FM	Fat mass
G	Grams
Ht	Height (cm)
IR	Intake reference
kcal	Kilocalories
kg	Kilograms
mg	Milligrams
mg/day	Milligrams per day
ml/min	Milliliters per minute
ml/kg	Milliliters per kilograms
MM (g)	Muscle mass
MNA	Mini Nutritional Assessment
MNA-SF	Mini Nutritional Assessment-Short Form
MUST	Malnutrition Universal Screening Tool
NSI	Nutritional Screening Initiative
RDI	Reference Daily Intake
S	Sex
SD	Standard deviation
SGA	Subjective Global Assessment
SIRT 1–7	Sirtuin 1–7
SIRT 2	Silent information regulator 2 or Sirtuin 2
μg/day	Micrograms per day
TBW	Total Body Water
WHO	World Health Organization
WHR	Waist-Hip Ratio

169.1 Introduction

Anthropometry and nutrition are interrelated and include genetic and environmental characteristics, sociocultural conditions, lifestyle, functional status, and health. Anthropometric evaluation is an essential part of nutritional assessment in geriatrics, to determine conditions, such as malnutrition, overweight, and obesity, as well as loss of muscle and gain of fat mass and the redistribution of adipose tissue. These anthropometric indicators have been used to evaluate the prognosis of acute and chronic diseases and also to guide medical intervention in the elderly.

The changes in body composition at the different stages of life differ in men and women, as is reflected in anthropometric measurements. Consequently, different anthropometric indicators are used to evaluate nutritional status. However, there are few studies in a population over 60 years of age directed toward understanding the changes in anthropometric measurements and nutritional status in a healthy elderly population.

169.2 Aging and Body Composition: Physiological and Nutritional Changes

169.2.1 Molecular Changes Involved in Nutrition

Human aging is a progressively deleterious process, which inevitably occurs over time through the interaction of multiple factors. These include multiple molecular changes that have recently been reported, which we will describe later.

One of these factors is oxidative stress, which has been shown to play a fundamental role in harming DNA, promoting apoptosis and inducing cellular death (Guarente 2007).

The sirtuins (disacetylases of histones) are enzymes that, upon being activated, regulate metabolic processes that retard aging and contribute to preventing diseases, such as obesity, diabetes, and cardiovascular disease. To date, seven types of sirtuins have been established in humans (SIRT 1–7), formed by a domain of approximately 237 amino acids. Alterations in these proteins through acetylation have the important functions of activating transcription, stabilizing proteins, and modulating the affinity of histone proteins for DNA, the transport of proteins between the nucleus and cytoplasm, and the activity of chaperone proteins (Wenzel 2006).

A relationship between the sirtuins and nutrition (Fernandez et al. 1976) was indicated when the authors showed that a reduction of food intake (caloric restriction) prolonged life expectancy in various animal models. In recent years, the effect of a hypocaloric diet upon the specific activation of sirtuins has been demonstrated. One of these studies (Civitarese et al. 2007) was performed to determine the response of muscle cell mitochondria to caloric restriction alone or in combination with exercise in 36 overweight young people. Two groups were included: one with 25% caloric restriction and the other with 12.5% restriction but with an increase in energetic spending of 12.5% through exercise. Both groups exhibited an increase in the genetic expression of sirtuin 1 (SIRT1); after 6 months, the cellular consumption of oxygen was diminished and damage to DNA had occurred via free radicals.

In another clinical study, it was demonstrated that caloric restriction of 48 overweight men and women reduced two markers of longevity (fasting insulin levels and core body temperature) at 6 months (Heilbronn et al. 2006). In obese subjects, it was also demonstrated that, after 8 weeks, caloric restriction provoked the direct activation of sirtuins and resulted in both weight loss and a reduction of oxidative stress in the patients (Crujeiras et al. 2008).

Before these findings, questions had arisen with regard to possible interventions that could be used to prolong life, as well as to retard the appearance and/or modify the clinical of different diseases that include oxidative stress in their physiopathology. Among these treatments are antioxidants; one of the most studied recently is resveratrol, a polyphenol found in the skin of red grapes, raspberries, blueberries, peanuts, and pine nuts. In different studies, the positive effects of these treatments have been shown, such as antiaggretory, antineoplastic, and anti-inflammatory effects as well as a stimulating effect on SIRT-2. Therefore, there is a possible benefit for aging, longevity, and neurodegenerative diseases, such Parkinson's disease and the dementias (Milne and Denu 2008).

169.2.2 Changes in Body Composition

Weight: Over a lifetime, weight is constantly modified. In adults, in general some amount of weight increase is seen until 60 years, after which, in certain studies a gradual reduction has been reported of up to 0.5% of the body per year.

Height: Height diminishes proportionately with age. On average, there is the loss of 1 cm per decade of age. This could be due to a shortening of the height of the vertebral bodies through a reduction in calcium in the bone tissue and a reduction in the hydration of the intervertebral disks. In addition, there is also a modification of the axis, and dorsal kyphosis often develops. These abnormal mechanical loads deform the vertebral diameter and osteophytes frequently appear (Gutiérrez et al. 2006).

Changes in body composition: Associated with age, there is an increase in fat tissue. The distribution of this tissue is presented both peripherally and centrally (perivisceral), as well as the intrahepatic and intramuscular accumulation of fat that accompanies disorders, such as insulin resistance. The muscle tissue (lean tissue) is reduced up to 30% due to replacement with fat tissue because of physical and molecular metabolic factors (Chapman 2006).

A reduction of the water compartment of the organism has been described as being associated with difficulties in maintaining fluid balance. This reduction predominates in the intracellular space and is one of the causes of loss of weight in older people.

169.2.3 Changes Due to Progressive Aging in Different Organs Related with Nutrition

Oral changes: Multiple changes in the stomatognathic apparatus are related with aging, such as anatomic modification of the temporomandibular joint through variations in weight and increase in fibrous muscle tissue, which can cause pain associated with movement, limitation of the oral opening and crepitation of articulation. There can also be weakness of the chewing muscles. There is a reduction of the tongue epithelium, atrophy of the taste buds, and especially phyloforms, with fissures and presence of sublingual varices.

With regard to the teeth, these acquire a yellowish color, become fragile, and undergo a reduction in water content and organic matter in the enamel; and there are phenomena of attrition and abrasion. Caries become more frequent; the radicular type brings a series of consequences including dental extraction (D'Hyver de las Deses and Gutiérrez Robledo 2006).

Periodontal disease is characterized by inflammation and destruction of the supporting tissues of the tooth. Gingivitis and periodontitis come to present dental mobility along with the loss of teeth. Frequently, a reduction of salival production is encountered (less than 500 cc a day or salival flow less than 0.2 ml/min and a sensation of dry mouth [xerostomy]). Swallowing is often characterized

by a longer duration. When related to neurodegenerative diseases, cancer, etc., there can be upper and/or lower dysphagia (D'Hyver de las Deses and Gutiérrez Robledo 2006).

Sense organs: Reduction of visual acuity can bring about changes in nutritional intake patterns and is caused by such diseases, such as cataracts, glaucoma, macular degeneration, and retinopathy, which hamper the person physically from engaging in a pattern of good nutrition (D'Hyver de las Deses and Gutiérrez Robledo 2006).

Digestive system: Presbyesophagus is sometimes evident. Often, reduction is found in the secretion of gastric juices compensated for by a retardation in gastric emptying. At the level of the small intestine, a retardation in digestion is brought about by atrophy of the intestinal cilia, reduction in the cellular renovation of the intestinal epithelium, proliferation of conjunctive tissue, and vascular arteriosclerosis, which carries with it a consequent deficiency in the absorption of various nutrients and vitamins.

At the level of the colon, smooth muscle weakness and replacement of the original cells with collagen results in major weakness and the appearance of diverticula. Alteration in the motility associated with immobility can contribute to constipation (D'Hyver de las Deses and Gutiérrez Robledo 2006).

Respiratory system: Kyphosis promotes restrictive respiratory insufficiency due to reduction of the alveolar surface, pulmonary distension, and eventually diminution of vital capacity, which, in turn, negatively influences tolerance of exercise.

Cardiovascular system: Systolic dysfunction both limits the tolerance of exercise and reduces appetite (D'Hyver de las Deses and Gutiérrez Robledo 2006).

169.3 Anthropometric Evaluation in the Elderly

169.3.1 Nutritional Assessment of the Elderly

Anthropometric evaluation is an essential part of nutritional assessment in geriatrics because it allows the determination of conditions of malnutrition, overweight and obesity, loss of muscle mass, gain or loss of fat mass, and the redistribution of adipose tissue. It can be performed by trained health personnel, is low in cost, noninvasive, and very sensitive to the different components of body structure, such as muscular and fat components.

In addition to height and weight, which were mentioned previously, the anthropometric measurements most commonly used in the elderly are as follows.

Circumference of body segments, abdominal and hip circumference, and cutaneous folds. The circumference of certain body segments (arm, thigh, and calf), the abdominal and hip circumference, as well as the cutaneous folds (tricipital and subscapular) are all used to indicate the respective fat and muscle levels.

Given the reduction of muscle mass and the accumulation of fat (at the intra-abdominal level), the measurement of cutaneous folds is not an accurate reflection of total fat. Therefore, the reliability of these anthropometric parameters for detecting malnutrition and predicting morbimortality is relatively limited, but they can be used, together with weight and a physical examination, as complementary measurements.

Longitude or body segments: heel–knee length. In the elderly population, there are typically a great many confounding pathologies; hence, serious difficulties are often encountered in determining height. For this reason, other means have been developed to estimate as exactly as possible the height of elderly individuals with these confounding elements. Measurement of the heel–knee length is therefore the optimal procedure to determine the height of the elderly.

Due to the fact that the large bones maintain the adult length at maturity, simple formulas have been developed that allow a fairly accurate estimation of height (Chumlea et al. 1985).

Body mass index (BMI). BMI is most frequently used in nutritional and epidemiological studies as an indicator of body composition and to evaluate patterns of nutritional status. It is a less reliable indicator to evaluate changes in adiposity in older adults because it is affected by both reduction in height and increase in fat, even in subjects with otherwise stable weight.

Waist–hip index (WHI). Aging is associated with a redistribution of adipose tissue with an increase in visceral fat. Measurement of these circumferences (waist and hip) and their combination in the waist–hip index allows a simple approximation of the distribution of body fat. The use of the waist circumference can have limitations in older adults due to the fact that, with age, said circumference could reflect a shortening of the trunk; therefore, the diameter of the abdomen increases accordingly as the trunk is reduced. This is supported by the inverse as well, that is, there is a significant association between abdominal circumference in the elderly and height taken in a sitting position.

169.3.2 Anthropometric Measurements and Nutritional Status in Healthy Elderly Population by Age and Sex

In the study reported by Sánchez-García et al. (2007), an analysis was performed to determine the sex and age differences in anthropometric values (Table 169.1).

Differences were observed among the measurements of the anthropometric values obtained from the elderly in weight, height, BMI, mid-brachial circumference, waist–hip ratio, waist circumference, hip circumference, and elbow amplitude (ANOVA, $p < 0.05$). Among the men, differences were found in weight, height, CMI, mid-brachial circumference, and elbow amplitude (ANOVA, $p < 0.05$).

Measurements of weight, height, waist–hip ratio, waist circumference, elbow amplitude, and knee–heel length were superior in men ($p < 0.05$), while the measurements of BMI and hip circumference were superior in women ($p < 0.05$). For the body mass index, a difference was observed in the group of 70–74 years of age; the mean was greater for women in comparison with men ($p < 0.05$). For calf circumference, a difference was found in the group of over 80, with the greater mean value being in men ($p < 0.05$).

Regarding hip circumference, it was observed that in the groups of 60–64, 65–69, and 70–74 years, the mean values are greater for women ($p < 0.05$). No differences were observed in the mean of the mid-brachial circumference, waist circumference, or elbow amplitude between men and women in any of the age groups.

169.3.3 Distribution of BMI in Healthy Elderly Population Using Different Criteria as Cutoff Points to Determine Nutritional Status

Evaluation of nutritional status is essential to determine the health of the elderly, both at the individual and collective levels. There is a consensus that the BMI values currently in use underestimate deficits and overestimate the condition of being overweight, and, perhaps, the critical point of waist circumference underestimates metabolic risk in the elderly.

If one considers the high prevalence of obesity, especially the abdominal type, in this age group, it is indispensable to have cutoff points to identify groups at risk that would allow putting into practice

Table 169.1 Anthropometric values according to age and gender in participating subjects (Source: Sánchez-García et al. 2007)

	Women Mean ± S.D.	Men Mean ± S.D.	Total Mean ± S.D.		Women Mean ± S.D.	Men Mean ± S.D.	Total Mean ± S.D.
Weight (kg)[a,b,c]				Waist to hip ratio (WHR)[c]			
60–64[d]	64.3 ± 11.7	71.8 ± 12.5	67.8 ± 12.6	60–64[d]	0.89 ± 0.08	0.95 ± 0.06	0.92 ± 0.08
65–69[d]	63.6 ± 10.4	71.8 ± 11.9	68.6 ± 12.0	65–69[d]	0.90 ± 0.07	0.94± 0.05	0.93 ± 0.06
70–74[d]	61.9 ± 11.1	69.6 ± 12.2	66.6 ± 12.3	70–74[d]	0.91 ± 0.10	0.95 ± 0.06	0.93 ± 0.08
75–79[d]	58.2 ± 11.7	67.7 ± 12.9	64.1 ± 13.2	75–79[d]	0.89± 0.07	0.95 ± 0.06	0.93 ± 0.07
80 and more[d]	57.4 ± 12.2	66.1 ± 10.4	62.8 ± 11.9	80 and more[d]	0.91 ± 0.10	0.96 ± 0.07	0.94 ± 0.09
Total[d]	62.7 ± 11.6	70.3 ± 12.3	66.9 ± 12.6	Total[d]	0.90 ± 0.08	0.95 ± 0.06	0.93 ± 0.07
Height (cm)[a,b,c]				Waist circumference (cm)[c]			
60–64[d]	153.9 ± 7.2	163.8 ± 7.5	158.5 ± 8.8	60–64	93.8 ± 13.8	95.5 ± 11.6	94.5 ± 12.9
65–69[d]	152.6 ± 7.6	163.8 ± 8.1	159.4 ± 9.6	65–69	95.3 ± 14.0	96.1 ± 10.8	95.8 ± 12. 2
70–74[d]	151.3 ± 7.1	163.3 ± 8.7	158.6 ± 10.0	70–74	93.2 ± 11.9	95.4 ± 10.8	94.5 ± 11.3
75–79[d]	150.5 ± 7.4	161.3 ± 10.1	157.3 ± 10.5	75–79	91.1 ± 11.5	94.1 ± 12.5	93.0 ± 12.2
80 and more[d]	150.4 ± 8.2	162.0 ± 9.4	157.5 ± 10.6	80 and more	92.8 ± 15.1	95.7 ± 12.2	94.6 ± 13.4
Total[d]	152.6 ± 7.5	163.2 ± 8.5	158.5 ± 9.6	Total[d]	93.7 ± 13.4	95.5 ± 11.4	94.7 ± 12.4
IMC (kg/m^2)[a,b,c]				Hip circumference (cm)[a,c]			
60–64	27.1 ± 4.5	26.8 ± 4.4	26.9 ± 4.4	60–64[d]	104.8 ± 12.8	100.4 ± 10.3	102.8 ± 11.9
65–69[d]	27.3 ± 4.2	26.7 ± 3.9	26.9 ± 4.1	65–69[d]	105.3 ± 13.0	101.1 ± 9.6	102.8 ± 11.2
70–74	27.0 ± 4.4	26.0 ± 4.1	26.4 ± 4.3	70–74[d]	102.5 ± 11.5	100.1 ± 9.6	101.1 ± 10.5
75–79	25.5 ± 4.2	26.0 ± 5.0	25.8 ± 4.8	75–79	101.6 ± 10.9	98.8 ± 10.4	99.9 ± 10.6
80 and more	25.2 ± 4.4	25.3 ± 5.0	25.3 ± 4.7	80 and more	101.6 ± 14.5	98.8 ± 10.2	99.8 ± 12.1
Total[d]	26.8 ± 4.4	26.4 ± 4.4	26.6 ± 4.4	Total[d]	104.0 ± 12.6	100.2 ± 10.0	101.9 ± 11.4
Mid-brachial circumference (cm)[a,b,c]				Elbow amplitude (cm)[a,b,c]			
60–64	30.5 ± 4.0	30.8 ± 4.0	30.7 ± 4.0	60–64	27.8 ± 12.3	29.4 ± 11.5	28.6 ± 11.9
65–69	29.8 ± 4.5	30.4 ± 4.1	30.1 ± 4.3	65–69	28.6 ± 11.8	28.6 ± 12.5	28.6 ± 12.2
70–74	30.1 ± 4.2	29.5 ± 3.8	29.7 ± 4.0	70–74	24.6 ± 10.3	26.0 ± 13.7	25.4 ± 12.5
75–79	29.2 ± 4.7	28.6 ± 3.7	28.8 ± 4.1	75–79	25.3 ± 13.7	25.8 ± 14.1	25.6 ± 13. 9
80 and more	27.3 ± 5.7	28.8 ± 3.9	28.2 ± 4.7	80 and more	23.9 ± 11.9	24.5 ± 12.0	24.3 ± 11.9
Total	29.9 ± 4.4	29.9 ± 4.0	29.9 ± 4.2	Total[d]	27.0 ± 12.1	27.6 ± 12.7	27.3 ± 12.5
Calf circumference (cm)[a]				Knee–heel length (cm)			
60–64	35.2 ± 8.1	35.8 ± 8.0	35.5 ± 8.1	60–64[d]	46.2 ± 4.4	50.0 ± 5.6	47.9 ± 5.3
65–69	34.8 ± 9.2	35.6 ± 8.6	35.3 ± 8.8	65–69[d]	46.3 ± 3.5	49.5 ± 5.9	48.2 ± 5.4

(continued)

Table 169.1 (continued)

	Women Mean ± S.D.	Men Mean ± S.D.	Total Mean ± S.D.		Women Mean ± S.D.	Men Mean ± S.D.	Total Mean ± S.D.
70–74	33.7 ± 7.4	34.9 ± 9.1	34.4 ± 8.5	70–74[d]	46.4 ±4.1	50.0 ± 4.1	48.6 ± 4.5
75–79	34.1 ± 9.2	33.6 ± 8.7	33.8 ± 8.9	75–79[d]	46.6 ± 4.0	50.2 ± 5.0	48.8 ± 4.9
80 and more[d]	31.3 ± 4.2	34.7 ± 8.7	33.4 ± 7.5	80 and more[d]	46.3 ± 4.9	50.0 ± 3.9	48.6 ± 4.6
Total	34.5 ± 8.3	35.2 ± 8.6	34.9 ± 8.4	Total[d]	46.3 ± 4.1	49.9 ± 5.2	48.3 ± 5.1

Changes in body composition at different stages of life differ in men and women and are reflected in anthropometric measurements

[a] Significant differences between age range in women ($p < 0.05$)

[b] Significant differences between age range in men ($p < 0.05$)

[c] Significant differences between age range ($p < 0.05$)

[d] Significant differences between women and men ($p < 0.05$)

Table 169.2 Body weight classification by BMI (kg/m^2) according to different criteria

Weight classification	WHO (1995)	Reidpath et al. (2002)	Perissinotto et al. (2002)	Douketis et al. (2005)
Malnourished	<18.5	<20	<20	<21.9
Normal	18.5–24.9	20–25	20.0–29.9	22.0–29.9
Overweight	≥25	> 25	≥30	≥30

There are disagreements among the different cutoff points used to classify the health status based on body mass index

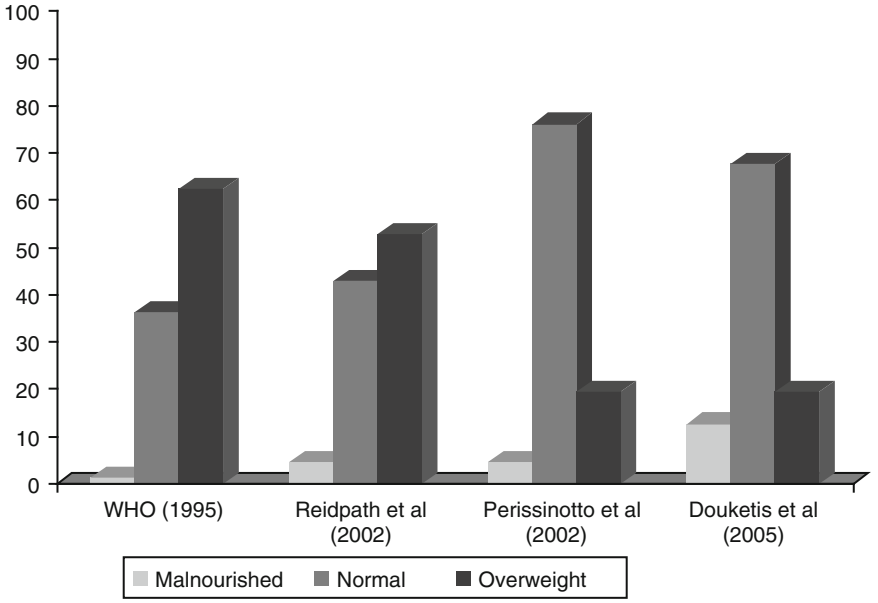

Fig. 169.1 The distribution of the BMI using various criteria proposed in the literature for the elderly population. WHO cutoff points underestimate the deficit and overestimate the degree of being overweight; therefore, it is necessary to validate these measures in a more extensive way with different cutoff points

programs with a sharp focus. It has been suggested that if the same BMI cutoff points are used for adults and the elderly, it would lead to a misclassification of nutritional risk in the latter and that the waist circumference is a better predictor of metabolic risk than BMI in older adults. Furthermore, the critical points are different from those proposed in the literature to determine the response required.

Table 169.2 and Fig. 169.1 depict the distribution of the BMI using different criteria proposed in the literature for the elderly population.

The ratio of waist circumference and hip circumference, or WHR, is used more and more frequently in estimating a possible increase regarding abdominal fat, with the purpose of identifying those individuals at risk of incurring non-insulin-dependent diabetes mellitus, dyslipidemias, arterial hypertension, and/or coronary problems. WHR values of <1.00 for men and <0.85 for women are considered desirable (World Health Organization 1997); values above these points identify individuals at risk for morbidity and mortality of cardiovascular disease.

The joint use of BMI and waist circumference could better orient health professionals toward making the proper decisions regarding the nutritional status of the elderly to control those with problems of weight and distribution of adipose tissue (Fig. 169.2).

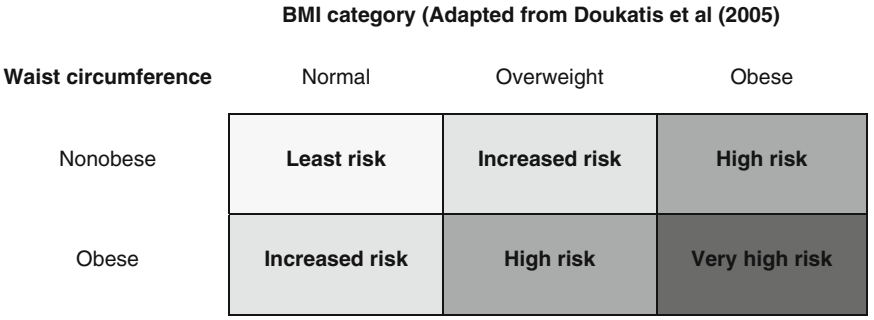

Fig. 169.2 Applying BMI and waist circumference measurements to assess a patient's risk of health problems. The BMI and waist circumference reflect a person's risk status at a single time point. The pattern of BMI and waist circumference over the long term may provide additional information. The need for weight-loss interventions should be determined not only on the basis of a person's BMI and waist circumference, but also on the presence or absence of concomitant disease and other patient characteristics

It must be stressed that the reference ranges for evaluating the nutritional status of elderly adults either have been extrapolated from younger adults, or are based on statistical cutoff points, more than on the actual results of morbidity, mortality, and quality of life from population studies in older adults.

169.4 Anthropometry and Evaluation of Body Composition in the Elderly

169.4.1 Prediction of Total Body Fat and Skeletal Muscle

The three most commonly used methods to obtain criteria for estimating body composition are: hydrodensitometry, total body water, and count of the d ^{40}K level. They may not be valid in the elderly who might have total body water, bone mineralization, or concentrations of potassium in the fat-free mass (FFM) other than the normal values. Specifically, hydrodensitometry or underwater weight, which uses a model with two compartments (2C), divides the body into fat mass (FM) and fat-free mass (FFM). It considers constant densities (FM = 0.0900 kg/l and FFM = 1.100 kg/l at 37°C), the fixed hydration for the FFM (72–74%), and the relative quantities of the three components of FFM (aqueous, mineral and proteins), which are known, additive, and progressive in all ages, genders, and ethnic groups (Huerta et al. 2007).

The reliability of the equations used to estimate body composition depends on the precision of the method in question and the ethnicity. Precision also depends on changes in elasticity, hydration, and the compressibility of the tissues. Studies that utilize anthropometry need to take into consideration a variety of possible measurements that are not confounded by changes related with age. Furthermore, the equations have to be designed and validated for specific groups, using as a reference the four-compartment model (4C) (Huerta et al. 2007).

The 4C model combines the measurement of the total body water (TBW) with diluted isotopes; total bone mineral mass obtained by DEXA and total body density by underwater weight. The advantage of this method is that it uses minimum suppositions and is based on direct measurements of the main compartments of body composition. In addition, the measurement of bone mineral mass and TBW is independent, allowing a more exact, accurate estimate of body composition in older adults by considering the effect of age on these components (Huerta et al. 2007).

Differences between the 2C and 4C models in the estimation of percentage of fat in elderly people have been associated with either variation in the aqueous fraction or hydration in FFM, mainly in men. Equations have been developed based on cutaneous folds to estimate body fat in older adults using the multiple-compartment method as the method of reference (Huerta et al. 2007).

In one study, an equation was generated that included only anthropometric data in 202 Mexican individuals from 60 to 89 years old. A cross-validation with a 4C model was performed, with body density determined by plethysmography by displacement of air (BOD-POD), total body water by the dilution with deuterium oxide method, and total body bone ash through bone densitometry. The equation selected to estimate fat mass in kilograms was

$$\mathrm{FM(kg)} = (0.165 \cdot \mathrm{CS}) + (0.355 \cdot \mathrm{BS}) + (0.521 \cdot \mathrm{BW}) - (6.054 \cdot \mathrm{S}) - 13.171,$$

where FM = fat mass expressed in kg, CS = calf skin fold in mm, BS = bicipital skinfold in mm, BW = body weight in kg, and S = sex (women = 0 and men = 1).

In the cross-validation application, an equivalency was observed between the methods. It is worth remembering that, by subtracting the fat mass already obtained from the total body weight, the FFM can be obtained (Huerta et al. 2007).

There are a few studies that have evaluated muscle mass by anthropometry in the elderly population. One is derived from the Brussels Cadaver Study, where prediction formulas were developed through anthropometry for total skeletal muscle mass. Anthropometric dimensions were quantified and 12 elderly male cadavers were dissected to obtain the following equation:

$$\mathrm{SM(g)} = \mathrm{Ht} \cdot (0.0553 \cdot \mathrm{CTG}^2 + 0.0987 \cdot \mathrm{FG}^2 + 0.0331 \cdot \mathrm{CCG}^2) - 2445,$$

where Ht = height (cm); CTG = corrected circumference of the muscle according to the thickness of the cutaneous skinfold of the anterior thigh (cm); FG = uncorrected forearm circumference; and CCG = corrected calf circumference by the thickness of cutaneous skinfold. This model had a random error of approximately ±2 kg in comparison with other models which have been shown to consistently underestimate muscle mass by 5–10 kg (Lee et al. 2000).

Therefore, the equations to predict the body composition of the elderly from anthropometric measurements should have access to estimation criteria obtained through a multicompartment model. A representative sample should be taken with internal and external cross-validation and with the measurement of an independent sample using the same techniques.

169.4.2 Distribution of Adipose Tissue

The accumulation of visceral fat without the corresponding changes in weight in the elderly can cause the waist circumference and sagittal diameter parameters to be less sensitive to the identification of health risks attributable to being overweight or the distribution of abdominal fat in comparison with young people. Indeed, data obtained in two studies that compared visceral adipose tissue valued through computerized axial tomography with anthropometric indices (waist circumference, sagittal diameter, waist–thigh ratio, and cutaneous skinfolds) demonstrate that these are not good prognostic factors of visceral adipose tissue in men and women of advanced age and that they are related with total body fat (Sardinha and Texeira 2007).

169.4.3 Estimation of Changes in Body Composition

Anthropometric measurements do not detect any level of intramuscular adiposity; therefore, this method only gives an estimate of muscle mass. In addition, reduction in muscle volume only explains half of the reduction in muscular strength that is produced with aging; this could be due to a modification of muscle composition, since data based on magnetic resonance have shown that, in the sedentary elderly, there is progressive replacement of muscle tissue with intramuscular fat (Arroyo et al. 2007). This change is not reflected in subcutaneous fat and, therefore, anthropometry fails to record this change.

169.5 Anthropometric Indicators for Prognosis and Intervention in Older Adults

169.5.1 Association Between the Indicators of the Percentage of Fat and Muscle Mass and Health Risks

Functional limitations, defined as the restriction of the physical or mental capacities required to carry out the tasks of an independent life, are important predictors of mortality, morbidity, and incapacity in the older adult. Sarcopenia (progressive reduction of muscle mass) contributes to the presence of functional limitations and incapacity in aging. The reduction of muscle mass negatively impacts physical output and limits mobility (Arroyo et al. 2007).

Various epidemiological studies have demonstrated a direct association between BMI and functional limitations and report that overweight subjects have a loss of movement and functional limitations. Nevertheless, Arroyo et al. (2007), in 377 subjects of 65 years or more, found that neither BMI, nor waist circumference, nor percentage of fat is associated with functional limitation, but muscle mass measured through dynamometry is (women <15 kg; men <27 kg); only on multivariate analysis was it found that a greater BMI in women means a greater risk of limitation.

By contrast, Houston et al. (2009) found that, in subjects aged 70–79 years for whom BMI was calculated, with self-reported weight at 25 and 50 years along with current weight, those with overweight and obesity had a greater risk of limited mobility on follow-up (4.2 years on average) compared those with normal weight.

On the other hand, there is evidence in elderly populations that, being obese or overweight (BMI = 24.6–29.8), does not increase the risk of mortality and might even be protective (Arnold et al. 2010). However, if only weight in old age is taken into account, this association might be distorted by the preexistence of chronic degenerative diseases and/or smoking, which are related to reduced BMI and increased risk of death. More studies are needed that evaluate the effects on health of weight-loss therapies in the elderly who are obese or overweight that minimize the loss of muscle and bone mass.

169.5.2 Changes in Weight and Mortality

Weight fluctuations in older adults can indicate difficulties in maintaining homeostasis and, therefore, might be an early indicator of deterioration in health and physical function (Arnold et al. 2010).

In a 6-year follow-up of participants in the Cardiovascular Health Study of 3,278 individuals over 65 years, there was an evaluation performed between the average weight change per year and evidence

of functional difficulty, including physical incapacity and deterioration in mobility and mortality. The participants were classified into groups of weight loss (≥5%), stable weight, weight gain (≥5%), or 'weight cycling' (gain and loss of ≥5% in the same year). It was found that more men remained stable in comparison with women, and of the latter, Afro-Americans were those who least frequently lost weight or experienced fluctuations. On the other hand, the participants who experienced weight loss or fluctuations in weight were older and had the more deteriorated health, smoked more, and had either diabetes or cardiovascular disease, compared with those who remained stable or gained weight, including after adjustment for age, sex, race, height, education, diabetes, cancer, and self-reported health. The categories of weight gain, variability in weight, and weight cycling are associated with deterioration in the activities of daily life. Those with weight cycling had a 20% greater risk of mortality. In addition, when using patterns of weight change (loss–gain, stable–loss, gain–loss, and loss–loss), it was found that the greater the variability in weight, the greater the relative risk of physical incapacity and mortality in the following 7 years.

A higher average weight was associated with a greater incidence of events indicating physical limitation. Weight loss, low weight, and very high weights increased the risk of mortality (Arnold et al. 2010).

Part of the relationship between the weight dynamic and such events might reflect the presence of simultaneous diseases in these participants. It should be remembered that the elderly form a group in which there are commonly multiple pathologies, handicaps and poor nutritional status, as well as persistent edema. For example, patterns of weight gain–loss could be explained by the presence of chronic heart failure, which produces weight gain through edema and volume overload as well as weight loss due to treatment with diuretics. In the pattern of weight loss, one could suspect cachexia, which is a complication of many diseases, such as the arthritis, cancer, heart failure, and chronic pulmonary obstruction disease, which are frequently present in elderly people.

Also, it is recommended not to evaluate only on current weight, but rather history (weight in early adulthood) and the weight dynamic in recent months and years, and to consider any history of smoking and/or simultaneous diseases.

169.5.3 Relationship Between Nutrition and Anthropometric Measurements in a Healthy Elderly Population

Loss of weight is related to an inadequate nutriment intake and digestive system changes (Villarino-Rodríguez et al. 2002). Several authors have reported that increases in body fat can be caused by a decreased capacity for free fat acids, to a lower tissue capacity to oxidize free fat acids, or a combination of both. These conditions would contribute to higher level of accumulation (Toth and Tchernof 2000).

The role of diet in age-related changes in body composition remains unclear. Although research indicates that age-related changes in body composition may be modifiable by environmental variables, particularly physical activity, the role of diet remains unclear. Despite experimental evidence in support of a direct relationship between energy and/or protein intakes and muscle mass, many observational studies of diet and sarcopenia report null effects. The role of nutrition in age-related increases in body fat has so far been limited to decreases in energy expenditure. Age-related increases in body fat are primarily attributed to declines in physical activity and basal metabolic rate, rather than to dietary intake.

The relationship between diet and age-related changes in lean and fat mass may become clearer if concurrent changes were studied together. Considerable evidence indicates that patterns of change in body composition over the short term are explained by particular profiles of energy and protein intake.

Clinical studies of obesity (overfeeding studies), starvation, and the treatment of obesity-controlled feeding studies, as well as the treatment of malnourished individuals (refeeding studies), demonstrate that energy and protein intakes, relative to dietary requirements, predict simultaneous change in both the lean and fat compartments. Longer-term, age-related changes in body composition may thus be associated with long-term dietary intake profiles (Stookey et al. 2001).

In a study that used longitudinal data on 608 healthy, non-obese Chinese (aged 50–70 years) from the 1993 and 1997 China Health and Nutrition Surveys, the subjects were described in terms of the changes in the mid-arm muscle area and body fat (waist circumference). Patterns of change involving gains in arm muscle and lost of fat were associated with increased protein intake, urban residence, and moderate or heavy levels of physical activity at baseline. Variation in protein intake, physical activity, and urban residence were also differentiated between the groups that gained fat and those that gained muscle mass. They also found that taller subjects appeared more likely to lose muscle, and this may be accounted for by the fact that any given level of energy or protein intake is more likely to fall short of requirements among larger individuals than among smaller individuals. In conclusion, the patterns of age-related change in body composition appear to be associated with modifiable variables, including income, urban residence, activity level and protein, and energy intake (Stookey et al. 2001).

Data from Castaneda et al. (1995) show that feeding healthy elderly women 0.4 g/k of protein (half the recommended dietary allowances), compared to 0.8 g/k for 9 weeks produces a marked reduction in cell mass, muscle mass, and nitrogen balance, as well a weakness by electrical stimulation testing. Thus, in just a few months, nutrition can make a dramatic difference in muscle function and mass.

Bernstein et al. (2002) hypothesized that consumption of a more diverse diet would predict better nutritional status in frail elderly persons. In a study that included elderly people (72–98 years), they found that, in women, high dietary variety score was associated with higher BMI ($p < 0.001$) and higher total body potassium ($p = 0.02$); high fruit and vegetable variety score was associated with higher BMI, mid-arm circumference, and mid-arm muscle area.

By contrast, in a cross-sectional study, Roberts et al. (2005) found that healthy older adults (≥61 years) with low BMI (<22 kg/m^2) consumed a lower variety of energy-dense foods compared with older adults with higher BMIs ($p < 0.05$). Another result of this study was that the percentages of the participants who consumed the recommended dietary allowances for protein and the estimated average requirements for micronutrients were particularly low among older persons who had a low BMI and low micronutrient-dense variety: only 65.4% for protein (compared with 97.6% for older adults who consumed a wide variety of micronutrient-dense foods and had a BMI <22 kg/m^2) and 0.0% for the estimated average requirements for all 14 micronutrients (compared with 9.2% for older adults who consumed a wide variety of micronutrient-dense foods and had a BMI <22 kg/m^2). These results may help to explain both unintentional weight loss and the maintenance of undesirably low body weight in old age. Taken together, these findings suggest that consuming a wide variety of micronutrient-rich foods tended to counterbalance the reduced micronutrient intakes associated with old age, with positive associations of micronutrient-dense variety with the intake of vitamins A, E, C, folate, B12, magnesium, and zinc.

169.6 Nutritional Recommendations for Healthy Aging

Aging can and should be a healthy, pleasant, productive life process if the risks are diminished and the protective factors increased. It is important to know how changes in dietary behavior over the course of time can provide aging people the knowledge to select, preserve, and prepare their foods so as to consume balanced, healthy diets.

Table 169.3 Daily needs of vitamins for older adults

Riboflavin	Men 1.3 mg/day Women 1,1 mg/day
Vitamin B12	2.5 μg/day
Vitamin A	600–700 μg/day
Vitamin C	60–100 μg/day
Vitamin D	10–15 μg/day
Vitamin E	100–400 UI/day
Vitamin K	60–90 mg/day

Nutritional needs for older adults in good health vary little in terms of basic needs. Essential nutrients for which there are reliable data for older adults include proteins, carbohydrates, lipids, vitamins, minerals, phytochemicals, and water.

Source: Organización Panamericana de la Salud. Universidad Tufts. Facultad de Ciencias y Políticas de Nutrición. Mantenerse en forma para la vida. Necesidades nutricionales de los Adultos Mayores. Publicación Científica y Técnica no. 595. Washington: PANO; 2004. p 2.

Healthy eating offers all the essential nutrients and energy each person needs to remain robust. Nevertheless, there are a large number of different gastronomic cultures and cuisines; hence, WHO and FAO (1985) established a culturally acceptable method that considers the relationships between dietary regimen and health.

169.6.1 Recommendations for the Intake of Nutrients in Older Adults

The nutritional needs of older adults in good health vary little in terms of the basic necessities. However, special recommendations are indicated for groups at special risk, although this is still a subject of controversy as regards the general population. The essential nutrients about which there are reliable data for older adults are: proteins, carbohydrates, lipids, vitamins, minerals, phytochemicals, and water (Table 169.3).

Energy: Research from various countries indicates that energy consumption in older adults commonly diminishes due to a reduction in physical activity, and that is an important factor in efforts to prevent weight gain and/or obesity. As a general guideline, various authors point out that the intake level should be equivalent to 1.5 times the basal metabolism (Kritchevsky 2001).The intake of foods necessary to balance higher energy expense should be increased so as to ensure an adequate intake of essential nutrients.

It is important that older adults with low energy intake consume foods abundant in nutrients, instead of those with low nutrient density such as are afforded by sugars, fats, and alcohol. The recommended dietary intake (RDI) is 2.100 and 2.500 kcal for women and men, respectively, although the quantity can be lower in accord with co-morbidities, physical activity, and height.

Calcium: It has been demonstrated that a lower absorption of calcium is related with age, due to changes in the metabolism of vitamin D. Intervention studies have been performed on an extensive scale for the purpose of calculating the requisite calcium requirement of older people, based on the level of intake of this substance to protect against bone mineral loss, mainly in older women. One study performed by Lundberg (2008) demonstrated that although vitamin D consumption was not adequate to meet the requirements of 800–1,200 mg/day of calcium, there was a beneficial effect on bone mineral density in the femur, spinal column and lumbar, and a reduction in the rate of fractures, besides maintaining arterial pressure and lowering the risk of colon cancer.

Iron: Aging does not affect the absorption of heminic iron, nor have changes been observed in the elderly compared with healthy young people. Some studies have demonstrated an increase in non-heminic iron in ferritin in older men, but the ferritin serum concentration is difficult to interpret in the elderly because inflammation can increase it. Due to the fact that iron is a pro-oxidant nutrient, it is necessary to investigate if there is a progressive accumulation in the body during aging and whether there is a relationship between the status of iron and chronic disease due to the increase in oxidative stress (Vaquero 2002). Therefore, it is recommended that 10 mg/day be construed as an adequate intake level for both older men and women.

Magnesium: Magnesium plays an important role in the prevention of cardiovascular diseases, hypertension, osteoporosis and diabetes. The greatest losses of magnesium are found in alcoholics, diabetics, and in patients undergoing treatment with certain diuretics (Vaquero 2002). In addition, hypocalcemia and hypopotasemia are associated with hypomagnesemia. It is estimated that the intake of magnesium should be 225–280 mg in older adults.

Copper: Copper participates in the formation of hemoglobin and is fundamental for the development and maintenance of bones, tendons, connective tissue, and the vascular system. The recommended copper intake, according to WHO, for persons over 60 years of age is 1.3 mg/day (Bunker et al. 1984).

Chromium: Chromium acts as a co-factor for insulin and is necessary for normal metabolism of lipids and glucose; for persons over 60, a dosage of ~50 μg/day is recommended (Vaquero 2002).

Selenium: A micromineral which protects against cardiovascular disease, selenium stimulates the immunological system and is associated with the prevention of cancer. Beck et al. (2007), in a study performed in Baltimore, Maryland, in a community of handicapped women, demonstrated that selenium participates in muscular function, mainly in grip strength, since selenoenzymes protect the muscle against oxidative effects. Selenium is reduced in older adults; hence, the daily recommendation for this age group is 50–70 μg/day.

Zinc: Zinc is extremely important in older adults, because it helps to maintain optimal immunocompetence. Prasad et al. (2007) administered zinc supplements to older adults in a controlled, randomized clinical trial. They had observed that a deficiency of zinc caused immune dysfunction, susceptibility to infections and increased oxidative stress. After administering zinc supplements, the incidence of infections was significantly lower. Therefore, zinc is an effective antioxidant and anti-inflammatory agent. The daily intake recommended for healthy elderly is 5.8–12.8 mg/day. As a supplement, 45 mg/day is recommended.

Proteins: Older people are less efficient in metabolizing proteins. They commonly exhibit a reduction in lean mass. With a good level of caloric intake, most of the elderly do not exhibit a deficit in protein intake. Some authors consider it reasonable to increase the recommended intake to 0.9–1 g/kg/day (RI = 0,8 g/kg/day) (World Health Organization 1985). All this suggests the need for an adequate intake of proteins, which is recommended to not be less than 12% of the total caloric intake, although the renal function of the patient must also be taken into account.

Carbohydrates: Recommendations for carbohydrates are estimated as being between 50% and 60% of the total value of the diet, and it should be stressed that an inadequate intake results in the appearance of alterations in protein metabolism as well as in the loss of sodium and in dehydration.

Lipids: It is recommended that the proportion of lipids in the diet not surpass 30% of the total energetic intake or 35% if olive oil is consumed habitually without frying. Less than 10% should be saturated fatty acids and less than 10% should be polyunsaturated fatty acids. It is important to ensure the administration of essential fatty acids and to avoid the consumption of trans-fatty acids, such as hydrogenated vegetable oil in foods.

Table 169.4 Key facts on anthropometric measurements and aging

There are a variety of molecular changes that indicate a close relationship between aging and nutrition.
The changes which come with aging may directly impact the nutritional status of older adults.
The joint use of BMI and waist circumference better orients the decision-making process regarding nutritional status of the elderly.
The greater the variability in weight, the greater the physical incapacity and mortality.
Changes in body composition in the elderly differ between men and women and are reflected in anthropometric measurements.
Nutritional needs for older adults in good health vary little in relation to the needs of other adults.
Adequate intake of antioxidants, fiber, and water has a positive effect on nutrition and health in the elderly.
The choice of instruments to evaluate nutritional status should consider the intended objective.

This table summarizes the most important points discussed in this chapter regarding nutrition in healthy elderly

Table 169.5 Key antioxidant facts

Antioxidants have the critically important function of eliminating (the) free radicals from the organism.
Free radicals are produced as a result of cellular oxidation and are related to degenerative diseases, such as cancer, cardiovascular disease, premature aging, and diseases of the nervous system.
Selenium, zinc, copper, magnesium, vitamin E (alfa-tocoferol), vitamin C (ascorbic acid, and beta-carotene (provitamin A) are some of the antioxidants that help protect cells against the toxic effect of free radicals.
Antioxidants are found in almost all fruits and vegetables.
Some of the fruits and vegetables with a high antioxidant value are: carrots, spinach, potatoes, tomatoes, garlic, squashes, cabbages, peppers, oranges, lemons, apples, apricots, almonds, pecans, green tea, and soya.
Foods with antioxidant value must be consumed daily for an effect on healthy aging.

This table presents the importance of the consumption of fruits and vegetables with antioxidants in order to maintain healthy nutrition

Fiber: The RDI suggests a consumption of 20–30 g/day, in equal parts of soluble and insoluble fiber. A greater amount can result in flatulence and digestive discomfort, in addition to deleteriously affecting the absorption of some micronutrients.

Vitamins: Vitamins are of special importance because of the effects their lack provokes. The most important vitamins include the following.

Vitamin D: Due to the fact that older persons have less capacity to synthesize this micronutrient from exposure to solar light, in many cases a supplement is necessary.

Vitamins E and C: These are antioxidant vitamins par excellence. They should be present in the diet because they maintain proper functioning of the immune system as well as the antioxidant pathways which have been associated with a slowed process of aging. Their immunomodulating effect has been demonstrated in older persons (75–80 years).

Vitamins B6, B12, and folic acid: A deficit in these vitamins provokes alterations in the levels of highly toxic homocysteine in the blood, which can eventually lead to the appearance of cerebrovascular disease and dementia.

Tables 169.4 and 169.5 indicate the daily requirements for vitamins in older adults, whether based on diet or supplements and the key facts on antioxidants.

Water: The necessary amount of water in older adults is 30 ml/kg day, but this amount is insufficient in older adults of lower weight, who should consume 1,500 ml/kg a day if they afflicted with renal disease (Table 169.6).

Table 169.6 Key hydration facts

After 60 years of age, it is recommended that water consumption per day should be approximately one and a half liters for a person with 70 kg.
In old people, a lack of proper hydration produces bone frailty, constipation, kidney problems, and even behavior problems.
The sensation of thirst may diminish as a person ages. Therefore, there is a risk of not drinking enough liquids in older people.
A balanced diet provides 700 ml of fluid intake per day, but it may be necessary for older people to consume an additional liter.
It is known that alcohol consumption increases the dehydration risk because of the increment in urinary loss and interferes with an adequate of liquids at the intravascular level

This table presents the daily recommendations of liquids for persons older than 60 years. It also includes the risks and benefits of the intake of liquids

169.7 Practical Methods and Techniques for Assessing Nutritional Status

The elderly are vulnerable to a number of nutritional risks because of associated multiple pathologies and the frequent changes in body composition and nutritional needs which they undergo. Furthermore, nutritional assessment in the elderly is especially difficult because many of the signs of malnutrition are also associated with the aging process.

Recently, rapid-application scales have appeared for the purpose of allowing nutritional assessment in geriatrics; these instruments can be classified according to their objective and scope of application.

Nutritional Screening Initiative, Level I and II Screening (NSI). This is a set of instruments well suited to community screening. It incorporates a simple nomogram to determine body mass index and a questionnaire of laboratory data (albumin and serum cholesterol), clinical characteristics, eating habits, living environment, and mental and cognitive states. Level II adds skinfold measurements and biochemical indicators. The objective of these instruments is to estimate the magnitude and causes of malnutrition (Montorio and Lázaro 1996). The questionnaire, applied separately, can be used as an indicator of high, medium, or low risk of malnutrition.

Mini Nutritional Assessment (MNA). This is a questionnaire created for the elderly population and can be applied in cases of ambulatory or hospitalized care. It qualifies the condition of the malnourished patient, the risk of malnutrition, and the general nutritional status. It can be performed in approximately 10 min, consists of 18 questions which comprise an anthropometric evaluation (weight, height, and magnitude of weight loss over time), general assessment (lifestyle, medication and mobility), dietary assessment (number of meals, self-directed food, and liquid intake), and a brief questionnaire for a subjective evaluation (self-perception of health and of nutritional status).

One of its advantages is that there is the possibility of studying each section separately. The total score possible is 30 points. A score above 23.5 classifies the individual as well-fed; scores between 17 and 23.5 indicate a situation of risk, in spite of no evidence of loss or biochemical alteration; and scores below 17 express a situation of malnutrition (Guigoz et al. 1996).

Mini Nutritional Assessment-Short Form (MNA-SF). This abbreviated form was created to reduce the time of administration to 10 min without losing diagnostic power and thus simplifying and generalizing implementation in clinical practice. Among its characteristics, the followings stand out: good correlation with the MNA, adequate sensitivity and specificity, and good internal consistence. This form presents false positives when compared with customary dietary assessment due to the fact that it detects not only malnourished individuals but also those at risk of malnutrition. This version consists of six questions that

can be effectively asked in approximately 3 min. The questionnaire should be used in two phases: the first consists of filling out the short form; if a risk of malnutrition is detected (score lower than or equal to 11 points), the entire questionnaire is then administered (Rubenstein et al. 2001).

Malnutrition Universal Screening Tool (MUST). Initially, this tool was developed for non-institutionalized individuals, but currently its use has been validated in various contexts including the hospital environment, external consultation, and home residences (Stratton et al 2004). Its fundamental objective is to identify individuals at risk for malnutrition, including an assessment of BMI, changes in weight and any disease that affects food intake for more than five days. With regard to BMI, the cutoff points are based on clinical and physiological observations that indicate minor functional deterioration with a BMI of 20. This is the cutoff for which modifications are made for the elderly population. In terms of prognostic value, in hospitalized individuals the results can predict length of stay and the likelihood of mortality. In non-institutionalized individuals, it is related to the likelihood of future hospitalization. It allows the establishment of three risk categories: low, medium, and high, which enable making a series of recommendations. Its limitations include not incorporating any measure of functionality and a focus on acute disease.

Subjective Global Assessment (SGA). This method was designed by Detsky et al. (1987) to estimate nutritional status through clinical history and physical exploration. It has greater sensitivity and specificity than assessment with measurements of albumin, transferrin, cutaneous sensitivity, anthropometry, height-creatinine, or the prognostic nutritional index. The SGA can be used to determine which patients require nutritional intervention and which would benefit from intensive nutritional support.

The data obtained from the clinical history include the evolution of weight, current dietary intake in relation with customary dietary intake, digestive symptoms present in the last 2 weeks, functional capacity, and metabolic requirements. Within the scope of the physical examination are evaluations of: loss of subcutaneous fat, musculature and the presence of edema or ascitis. Each of the elements is evaluated as light, moderate, or severe and patients are classified into three groups: (a) adequate nutritional status; (b) suspicion of malnutrition or moderate malnutrition; and (c) severe malnutrition. One of the limitations is that it depends on an assessment by the professional who administers it. It has been used in both hospitalized and non-hospitalized patients. It has also demonstrated to have utility in patients with severe disease. Given the simplicity of its use, it is frequently used for multicenter studies (Detsky et al. 1987).

The selection of these instruments should be considered from the perspective of the objective that is desired (sifting of the population at risk or in follow-up), the profile of the population or individual, and the available resources, especially personnel and time.

There are other instruments, such as *indices of nutritional prognosis*, designed to improve the sensitivity and specificity to detect risk or morbidity and mortality associated with malnutrition, combining various assessment parameters in formulas derived from regression analysis. These are often used in surgery patients, but currently the results suggest certain variations in their prognostic value in other groups.

169.8 Conclusions

It is important to note that, although there are different patterns of reference, tests, or anthropometric measurements that can be useful for determining the nutritional status of the older adult, considerably more research is needed in this field. This population is heterogeneous and presents with physiological and pathological changes that affects their nutritional status and needs. The objective is to be able to determine from the nutritional status insights into the prognosis of both and chronic diseases, as well as to guide appropriate medical intervention in the elderly, both individually and collectively.

Summary Points

- There are molecular changes that reflect a close relationship between aging and nutrition. One of them is the activation of sirtuins (histone desacetylases) that delay aging, promote longevity, and contribute to the prevention and/or amelioration of chronic diseases.
- The changes that occur with aging at the level of the oral cavity and the cardiovascular, respiratory, sensory, and gastrointestinal systems can directly impact the nutritional status of older adults.
- Evaluation of body composition should consider changes in FFM related with age, whether they occur either as the result of an increase in TBW or as a reduction of mineral mass.
- It is recommended that, in addition to current weight, the history and dynamic of weight in recent months and years be considered, in addition to any history of smoking and simultaneous diseases.
- Anthropometric values by sex are higher in men. Upon comparing groups by age, in both sexes there is a tendency toward reduction of the average values with greater age.
- The joint use of BMI and waist circumference can help to orient health professionals in making decisions regarding nutritional status of the elderly in order to properly manage those with excess weight and/or distribution of adipose tissue.
- There is a certain consensus that the values of BMI currently in use in the elderly tend to underestimate weight deficits and to overestimate the condition of being overweight and, that, probably the critical point of waist circumference underestimates metabolic risk in the elderly.
- Nutritional needs for older adults in good health vary little in basic needs. Essential nutrients for which there are reliable data for older adults include proteins, carbohydrates, lipids, vitamins, minerals, phytochemicals, and water.
- The selection of instruments to assess nutritional status should consider the objective which needs to be met (e.g., sifting the population at risk or care and follow-up), the profile of a given population or individual, and the available resources, especially personnel and time.

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Chapter 170
Anthropometry of Leg Lean Volume: Application to Nutrition in Systemic Disorders

Débora Villaça and J. Alberto Neder

Abstract Depletion of leg lean mass has been progressively recognised as an important clinical outcome in disease populations, being related to early disability, impaired health-related quality of life, and even mortality. Estimation of leg lean volumes (LLV) from circumferences and skinfold thicknesses, in particular, have long been used as these techniques are inexpensive and widely-available in clinical settings. The truncated cones method proposed by Jones and Pearson (1967) might be particularly useful for clinical populations in which loss of leg lean mass is common, usually as part of the cachexia syndrome (e.g., chronic heart failure, chronic obstructive pulmonary disease (COPD), chronic renal failure, liver failure, sepsis, rheumatoid arthritis, AIDS and cancer). The method divides the leg into six segments which are assumed to represent truncated cones. Summation of the volume of each cone, determined from the circumferences and the height of each individual cone, gives an estimate of total LV. By subtracting the skinfold thicknesses from the circumferences, a lean volume of each cone can be derived, thereby providing an estimate of LLV. Despite its obvious advantages compared to more sophisticated and costier approaches, the method is time-consuming, needs careful standardization and a trained observer. Moreover, it is technically difficult to be performed in bed-bound patients, being influenced by oedema and obesity. More importantly, however, skinfold thickness measurements are obtained only at few selected locations and it is assumed that they are invariant across the lower limbs and not influenced by gender-specific patterns of fat tissue deposition. Notwithstanding these limitations, there is limited evidence that the method might be highly sensitive to indicate depletion of metabolic active tissue and its functional consequences in specific clinical populations, such as those with chronic obstructive pulmonary disease (COPD). Additional studies are warranted to extrapolate these findings for other disease populations with different levels of nutritional impairment.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ATS	Anterior thigh skinfold
BMI	Body mass index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_170,

CI	Confidence interval
CSA	Cross-sectional area
CT	Computed tomography
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
DEXA	Dual energy X-ray absorptiometry
FEV_1	Forced expiratory volume in one second
LBM	Lean body mass
LLV	Leg lean volume
MC	Mid-thigh circumference
MRI	Magnetic resonance imaging

170.1 Introduction

Sarcopenia (from the Greek *sarx* (flesh) and *penia* (poverty)) refers to the progressive decline in muscle mass, force-generating capacity and quality that frequently accompanies the aging process (Cruz-Jentoft et al. 2010). By contrast, cachexia (*kakòs* (bad) and *héxis* (condition)) is as a multifactorial syndrome characterized by severe loss of body weight, fat, and muscle associated with increasing protein catabolism due to underlying disease(s), such as chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic renal failure, liver failure, sepsis, rheumatoid arthritis, AIDS, and cancer (Table 170.1) (Anker et al. 2006). The *Cachexia Society* (Evans et al. 2008) proposed the following definition of the syndrome which was recently (Muscaritoli et al. 2010) endorsed by the 'cachexia-wasting syndromes' and 'nutrition in geriatrics' Special Interest Groups of the *European Society for Clinical Nutrition and Metabolism*: "*cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia.*

Table 170.1 Objective criteria for cachexia diagnosis. Diagnostic criteria for wasting disease (cachexia) in adults according to the European Society for Clinical Nutrition and Metabolism (2010) (Based on Muscaritoli et al. 2008)

Weight loss of at least 5% (edema free) in 12 months or less in the presence of underlying illness,[a] plus three of the following criteria:

- Decreased muscle strength (lowest tertile)
- Fatigue (defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity)
- Anorexia [Limited food intake (i.e., total caloric intake less than 20 kcal/kg body weight/day; <70% of usual food intake) or poor appetite]
- Low fat-free mass index[b]
- Abnormal biochemistry
  - increased inflammatory markers CRP (>5.0 mg/l)
  - IL-6 >4.0 pg/ml
  - Anemia (<12 g/dl)
  - Low serum albumin (<3.2 g/dl)

[a]In cases where weight loss cannot be documented, a BMI <20.0 kg/m^2 is sufficient

[b]Lean tissue depletion (i.e., mid-upper-arm muscle circumference <10th percentile for age and gender; appendicular skeletal muscle index by DEXA (kg/m^2) <5.45 in females and <7.25 in males

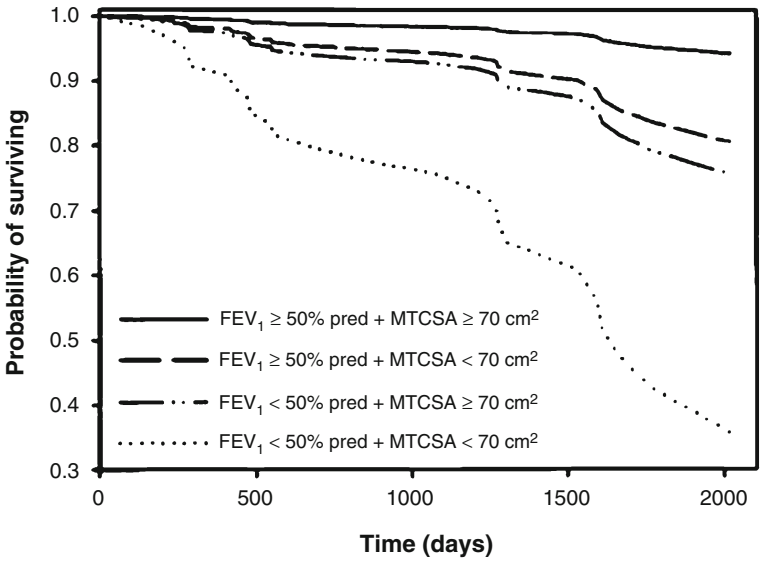

Fig. 170.1 Survival as a function of leg muscle depletion and lung function in patients with COPD. Marked reduction in survival in COPD patients with decreased leg muscle mass (mid-thigh muscle cross-sectional area by computed tomography (*MTCSA*) <70 cm^2) and worse airflow obstruction (forced expiratory volume in one second (FEV_1) <50% predicted). Note the better survival rates of patients with similar degrees of airflow obstruction but with preserved MTCSA values (Extracted from Marquis et al. (2002). With permission)

Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity."

In this context, it has been well established that depletion of lean body mass (LBM) has important deleterious consequences to different clinical populations (Schols et al. 1993; Fiori et al. 1999; Mafra et al. 2008). Loss of appendicular LBM is particularly relevant to decrease patients' mobility and health-related quality of life. In addition, fat-free tissue depletion increases the likelihood of negative clinical outcomes, such as osteoporosis and frequency of falls (Fiori et al. 1999; Evans et al. 2008; Muscaritoli et al. 2010). There is also evidence that LBM depletion and its functional consequences tend to be more pronounced in the lower compared to upper limbs, suggesting that at least part of the wasting process might be ascribed to physical inactivity (see also *Pathophysiology of lean tissue depletion in clinical populations*) (Fransen et al. 2002). In fact, exercise tolerance, especially in patient populations, is strongly influenced by the amount of metabolic active tissue and vice versa (Baarends et al. 1997; Anker et al. 1997).

Interestingly, recent data demonstrated a significant association between decreases in appendicular LBM and long-term survival in patients with COPD (Fig. 170.1) (Marquis et al. 2002) and subjects at risk of dying from cardiovascular disease (Heitmann et al. 2009) suggesting a prognostic role for segmental body composition estimates in these patients. Unfortunately, however, simple indices of whole-body LBM depletion, such as the body mass index (BMI), are poorly sensitive to indicate abnormalities in appendicular composition, making its direct measurement clinically relevant.

It is not surprising, therefore, that there is a renewed interest in measuring appendicular LBM in patients with chronic diseases. For this purpose, several methods have been used, ranging from expensive and sophisticated laboratory techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), and dual energy X-ray absorptiometry (DEXA) to simpler and widely available methods, such as anthropometry. Anthropometric segmental measurements, in particular,

have long been used to estimate leg lean volume (LLV) from circumferences and skinfold thickness in children (Davies et al. 1972) and adults (Jones and Pearson 1969). Although such techniques would be expected to be particularly useful in clinical settings due to their simplicity and low cost, most of the extant literature on this topic is based upon measurements performed in young and healthy subjects, frequently in the sports science arena (Winter et al. 1991; Doré et al. 2001; Howden et al. 2002; Temfemo et al. 2007).

This chapter, therefore, will present some key technical aspects of the more relevant anthropometric methods of segmental body composition assessment with special attention to LLV and its role in the evaluation of nutritional status in clinical populations.

170.2 Pathophysiology of Lean Tissue Depletion in Clinical Populations

It has been recognized that the 'fat-free' (i.e., muscle and bone) compartment is frequently reduced as disease progress in systemic disorders. In the context of lean tissue assessment by anthropometric techniques, much more attention has been paid to loss of appendicular muscle mass compared to decrease in bone mass, as the latter contributes to only a fraction of the whole limb volume. Nevertheless, decrease in bone mineral density is an important correlate of LBM depletion and both share similar etiological and pathophysiological mechanisms in clinical populations.

170.2.1 Mechanisms of Impaired Protein Balance in Chronic Diseases

The prevailing view is that nutritional depletion in chronic, systemic, non-malignant disorders results from a disturbed energy balance, which mainly affects body fat mass, and an impaired protein balance, resulting in predominant loss of metabolic active lean tissue (Fransen et al. 2002; Evans et al. 2008; Muscaritoli et al. 2010).

Although most of the available literature pertains to chronic cardiopulmonary and inflammatory diseases, it is likely that similar mechanisms are operant in other systemic, non-malignant disorders. For instance, cardiac cachexia affects 12–15% of CHF patients being diagnosed if, over 6 months or more, there is weight loss of more than 6% (in the absence of edema) compared to previous weight (Anker et al. 2006). Patients with cardiac cachexia have increased resting energy expenditure and a chronic state of neuroendocrine and immunological disturbances, which predisposes to an imbalance between anabolism and catabolism. More specifically, muscle atrophy is the final result of sympathetic overactivation associated with increased cortisol, aldosterone, and rennin levels under the influence of a pro-inflammatory status. Loss of appetite (anorexia) plays a significant role in only 10–20% of all cases of cardiac cachexia (Anker et al. 2006).

Similar alterations have been described in 25–40% of the patients with advanced COPD (Schols et al. 1993). Clinically relevant weight loss (5% of actual weight within 3 months or 10% within 6 months) is linked to tissue hypoxia, aging, physical exercise, increased resting metabolic rate, low-grade chronic inflammatory activity, and certain drugs, such as corticosteroids. Different from CHF, however, a pronounced loss of appetite (anorexia) and decreased food intake are common. Disease exacerbations worsen the nutritional status and intake is further reduced due to difficulties in chewing and swallowing secondary to the altered mechanics of breathing. Moreover, severe hypoxia might reduce the appetite via the neurohormonal actions of leptin and additional pro-inflammatory cytokines' burden (Anker et al. 2006). Regardless of the precise mechanism(s), disease exacerbations are associated with further decreases in LBM and deterioration of the health-related quality of life.

170.2.2 Muscle Morphological and Functional Abnormalities

In addition to decreases in the muscle mass bulk, there is a relative shift in fiber-type distribution in patients with COPD and CHF. The percentage of type I oxidative muscle fibers is decreased, and the proportion of type II (mainly type IIX) glycolytic fibers is increased. In addition, muscle fibers seem to be smaller in patients compared to healthy controls (Fransen et al. 2002). There are also striking similarities in terms of alterations in activities of metabolic enzymes, as well as bioenergetic abnormalities indicative of impaired oxidative metabolism in these diseases. Such alterations are associated with variable decreases in muscle strength and endurance which seem to affect primarily the lower limbs in COPD but might be more generalized in CHF. In patients with chronic renal failure, the muscle weakness is also more pronounced in the lower than in the upper limbs and is particularly present in the proximal muscles (Mafra et al. 2008).

A controversial issue on this topic is the putative structure–function relationship, as both mass and performance are concomitantly reduced. Using an allometric approach, Malaguti and co-workers (2006) found that the coefficients for correction of isokinetic strength and endurance by leg muscle mass (DEXA) were significant higher in COPD patients than in controls. In other words, more muscle mass was needed to generate a given functional output in patients than in normal subjects. These data seem to indicate that factors other than simple atrophy (i.e., mass-independent mechanisms) might play a role in explaining the COPD-related skeletal muscle dysfunction.

170.2.3 The Role of Deconditioning and Aging in Muscle Atrophy

Reduced physical activity is a ubiquitous finding in clinical populations. In fact, skeletal muscle alterations in patients with CHF, COPD, and renal failure do resemble those occurring during disuse. However, there is a trend for disease-related atrophy to affect type II fibers, while disuse-induced atrophy disproportionately involves type I fibers (Fransen et al. 2002). Moreover, muscle atrophy and qualitative alterations remain present long after organ transplantation, especially in patients with COPD. Therefore, despite deconditioning seeming to constitute an important contributing factor for the observed loss of lean tissue in systemic disorders, it is clear that this is not the main mechanism behind muscle atrophy in patients with more advanced disease.

Aging per se is also associated with decrease in appendicular muscle mass and impaired oxidative capacity. However, there is a relative increase in proportion of type I muscle fibers, that is, a pattern not identical to that observed in disease (Cruz-Jentoft et al. 2010). More importantly, however, most studies investigating disturbances in peripheral skeletal muscle in patients involved age-matched control groups that did not depict the same extensive abnormalities found in patient populations.

170.3 Practical Methods to Determine LLV

170.3.1 The Truncated Cones Method of Jones and Pearson (1969)

The method consists in dividing the non-dominant leg into six segments (Fig. 170.2), which are assumed to represent truncated cones. Summation of the volume of each cone, determined from the circumferences and the height of each individual cone, gives an estimate of total LV. By subtracting

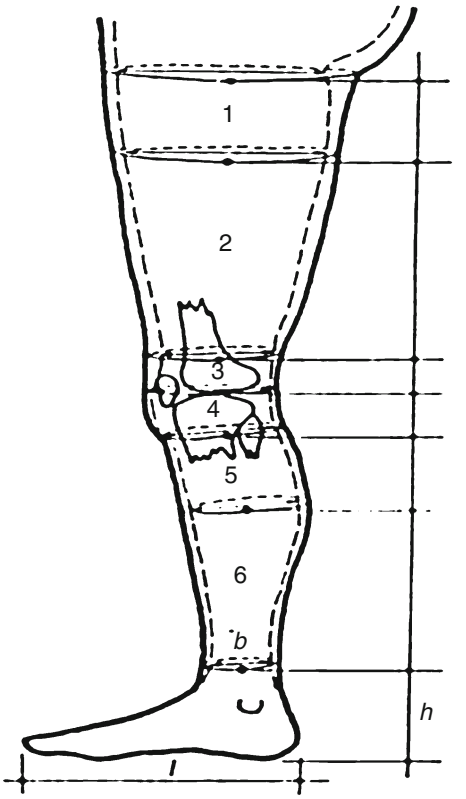

Fig. 170.2 Reference markers for anthopometric measurements of leg lean volume. Schematic illustration of the sites from which the anthropometric measurements should be taken in order to obtain the six truncated cones for leg lean volume (*LLV*) estimation, according to the method proposed by Jones and Pearson (1969) (Extracted from Jones and Pearson (1969). With permission)

the skinfold thicknesses from the circumferences, a lean volume of each cone can be derived, thereby providing an estimate of LLV. The cross-correlation coefficients of total leg (thigh and calf) and total leg fat according to this method and those obtained by water displacement and soft-tissue roentgenogrammetric readings were highly significant ($r = 0.86$–0.99). Despite the method has been originally applied to a sample consisting of only 32 male and 15 female young adults, LV estimates demonstrate acceptable levels of accuracy for most practical uses in different healthy populations (Winter et al. 1991; Doré et al. 2001; Howden et al. 2002; Temfemo et al. 2007) and, more recently, in patients with COPD (Villaça et al. 2008).

In this method, seven circumferences are taken with a metric tape at predetermined sites (Fig. 170.2) with the patient standing erect and the feet slightly apart:

1. The gluteal furrow (C1),
2. One-third of the subischial height up from the tibial–femoral joint space (C2),
3. The minimum circumference above the knee (C3),
4. The maximum circumference around the knee (C4),
5. The minimum circumference below the knee (C5),
6. The maximum calf circumference (C6), and
7. The minimum ankle circumference (C7).

The heights (h) above the floor level for each circumference are obtained by using a stadiometer. In addition, anterior and posterior skinfold thicknesses are measured at C2 (thigh) and medial

and lateral skinfold thicknesses are measured at C6 (calf) using a caliper following standard techniques.

In order to obtain the volume of a truncated cone (Vc), the following standard equation should be used:

$$\mathrm{Vc} = \frac{1}{3h}\left(a + \sqrt{(ab)} + b\right) \tag{170.1}$$

where a and b are the areas ($0.785 \times C^2$) of two parallel surfaces. The volume of the foot (Vf) is also calculated by assuming the foot to be wedge shaped:

$$\mathrm{Vf} = \frac{1}{2l \times b \times h} \tag{170.2}$$

where l is the foot's length and b is the diameter calculated from C7. LLV (L) is then calculated by summing up the volumes of the six lean cones (i.e., by subtracting the skinfold reading from their respective diameters) *plus* Vf. In addition, LLV might be expressed as a function of leg height (m) in order to further correct for interindividual differences in leg dimensions (Villaça et al. 2008). It is recommended that these equations be incorporated on a software for faster and more accurate results.

170.3.2 The Thigh Muscles' Cross-Sectional Area (CSA)

Although this method does not aim to estimate LVs, its practicality and similar rationale make it potentially useful for clinical populations. The method proposed by Housh et al. (1995) aims to estimate the area of specific muscle groups from mid-thigh circumference (MC) and anterior thigh skinfold (ATS) measurements. In this study, MRI was used to measure the CSA of the thigh muscles, which were separated into three groups: (1) the *quadriceps* (*vastus intermedius, vastus lateralis, vastus medialis*, and *rectus femoris*), (2) the hamstrings (*semimembranosus, semitendinosus*, and *biceps femoris*), and (3) *adductor* (*adductor longus, adductor magnus*, and *gracilis*). The CSA of the *sartorius* was measured individually and added to others to determine the total thigh muscle CSA. The following multiple linear regression equations were then derived to estimate individual muscle group CSA from the anthropometric measurements:

$$\text{Quadriceps CSA} = (2.52 \times \text{MC in cm}) - (1.25 \times \text{ATS in mm}) - 45.13. \tag{170.3}$$
$$R = 0.86; \quad \text{SEE} = 5.2\ \text{cm}^2$$

$$\text{Hamstrings CSA} = (1.08 \times \text{MC in cm}) - (0.64 \times \text{ATS in mm}) - 22.69. \tag{170.4}$$
$$R = 0.75; \quad \text{SEE} = 3.5\ \text{cm}^2$$

$$\text{Total thigh muscle CSA} = (4.68 \times \text{MC in cm}) - (2.09 \times \text{ATS in mm}) - 80{,}99 \tag{170.5}$$
$$R = 0.86; \quad \text{SEE} = 9.5\ \text{cm}^2$$

Data obtained on a derivation group ($N = 30$) indicated better results for the *quadriceps* CSA ($r = 0.85$) though there was a substantial intra-subject disagreement between predicted and criterion CSA.

170.4 Advantages and Shortcomings of LLV Estimation in Patients

Anthropometric-based methods for the estimation of LLV (and mass) are particularly attractive in clinical settings, as they are inexpensive and widely available, being therefore suitable for bedside applications. However, there are some inherent limitations that should be carefully considered (Table 170.2):

1. These methods are time consuming and need careful standardization and a trained observer.
2. They are technically difficult to be performed in bed-bound patients, being clearly influenced by edema and obesity.
3. The bulk of the evidence demonstrates that leg muscle mass tends to be overestimated (12–48%) and subcutaneous adipose tissue underestimated (25–47%) (Buckley et al. 1989; Fuller et al. 1999; Elia et al. 2000) though better results have been described in younger and leaner subjects (Holmes et al. 2005; Burkhart et al. 2008).
4. LLV might be a particularly weak estimate of 'fat-free' volume, as intermuscular adipose tissue infiltration (Ruan et al. 2007), a finding associated with impaired functional performance and metabolic consequences, is more prevalent in older and diseased populations (Hilton et al. 2008).
5. Skinfold thickness measurements are obtained at few selected locations and it is assumed that they are invariant across the lower limbs and not influenced by gender-specific patterns of fat tissue deposition. In fact, Tothill and Stewart (2002) found that this source of error was the central mechanism to explain the substantial underestimation of adipose tissue by the truncated cones method (Jones and Pearson 1969), as the central anterior measurement was poorly representative of the non-uniform thickness distribution around the limb (Fig. 170.3).

170.5 LLV and Nutritional Status in Chronic Diseases

Decline in muscle mass commonly occurs with the aging process and it is closely related to physical disability. Loss of lean body mass per year in elderly persons has been estimated to reach 0.1–0.3 kg (Cruz-Jentoft et al. 2010). As mentioned, however, a number of chronic conditions which are more

Table 170.2 Anthopometry of leg lean volume in practice. Recommendations for using leg lean volume measurements according to the Jones and Pearson method (1969) in clinical populations

Factor	Recommendations
Subject	Extra caution in interpretation of data from obese subjects due to low accuracy and reproducibility
	Eedema as a potential confounding factor
Body position	Subjects should stand on a platform with a stadiometer 150 cm high parallel to the non-dominant leg
	Members slightly apart.
	Limited experience with bed-bound patients
Skinfold thickness	Posterior skinfold thickness at C2 particularly difficult to be obtained in women and overweight subjects
	Record in triplicate and use the average.
Circumferences	Variations in C2 and C6 are the main source of variability for the calculation of the volume of the cones
	A plastic metric tape should be used.
	Record in triplicate and use the average.
Data calculation	Computer calculation is advisable.

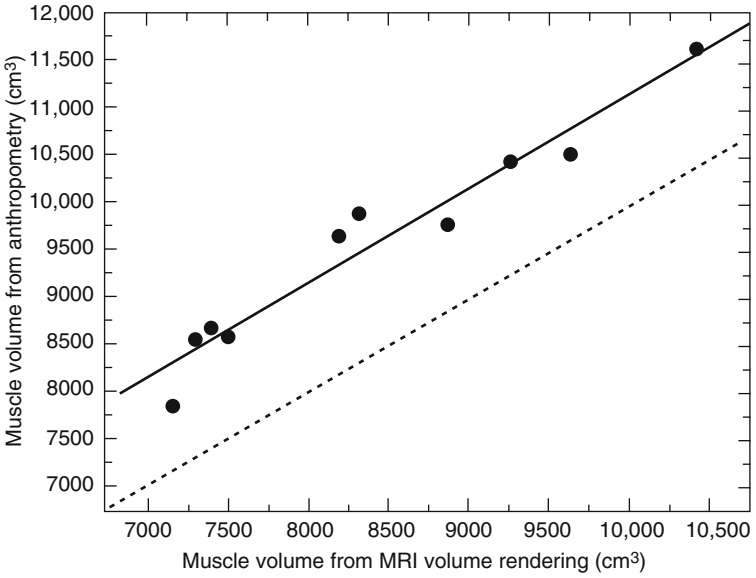

Fig. 170.3 Anthropometry versus magnetic resonance imaging for the estimation of leg muscle volume. Muscle volume derived from anthropometry (Jones and Pearson 1969) as a function of magnetic resonance imaging in healthy adults. The *dashed line* is the line of identity. Note the consistent, and apparently linear, overestimation of the readings by anthropometry (Extracted from Tothill and Stewart (2002). With permission)

prevalent in this age group further contribute to accelerate muscle wasting and weakness, including cancer, chronic kidney, liver and heart failure, and COPD (Evans et al. 2008; Muscaritoli et al. 2010).

The truncated cones method (Jones and Pearson 1969) has been recently used by Villaça and co-workers (2008) to investigate the usefulness of LLV estimates in identifying nutritionally depleted (BMI ≤ 21 kg/m^2 and/or fat-free mass index by DEXA ≤15 kg/m^2 in females and ≤16 kg/m^2 in males) (Schols et al. 1993) from non-depleted (N = 21) patients with moderate to severe COPD. The authors found that anthropometric and DEXA-based estimates of LLV agreed within 0.4 L (95% CI: 0.59, 1.39) and 0.5 L (95% CI: 1.08, 2.08) in depleted and non-depleted patients, respectively (Fig. 170.4). Leg-height-corrected LLV values also showed acceptable sensitivity and specificity to identify systemic depletion (area under a receiver operating characteristics curve = 0.93 (range 0.86–1.00); P < 0.001) (Fig. 170.5). In fact, the 'best cutoff' value of 9.2 L/m was 95% sensitive and 80% specific to indicate depletion of metabolic active muscle. Also important, patients with LLV ≤9.2 L/m had significantly lower exercise capacity and muscle function than their counterparts. These data provided novel evidence that the truncated cones method can be clinically useful in predicting the presence of nutritional depletion and its functional consequences in COPD.

Mathur et al. (2008) tested the performance of the thigh muscles CSA method developed by Housh et al. (1995) in establishing lean leg tissue depletion in 19 patients (10 females) with COPD. In contrast with the results of Villaça and co-workers (2008), they found that anthropometrically determined *quadriceps* and hamstrings CSAs (170.3 and 170.4) overestimated those determined by MRI to an extent that there were no significant between-group differences in these measurements. However, the sample presented with a forced-expiratory volume in one second (FEV_1, an index of airflow obstruction) and BMI values quite similar to the 'non-depleted' group of Villaça´s study (1.38 ± 0.48 L *vs.* 1.34 ± 0.41 L and 26.6 ± 4.7 kg/m^2*vs*. 25.6 ± 2.6 kg/m^2, respectively). These numbers contrast sharply with those found in the 'depleted' group of the latter study (0.99 ± 0.39 L and 19.3 ± 2.1 kg/m^2). Consequently, Marthur et al. (2005) seemed to have evaluated a group of COPD

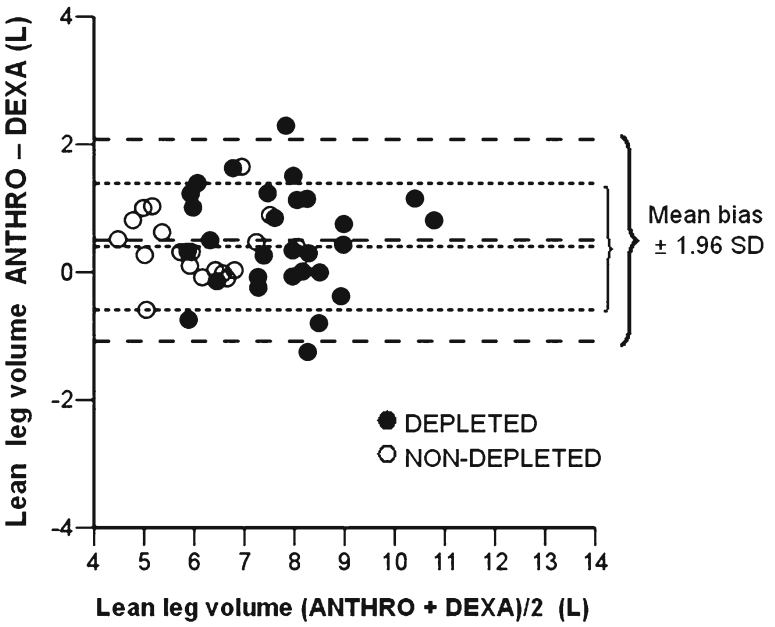

Fig. 170.4 Leg lean volume according to anthopometry and DEXA in patients with COPD. The limits of agreement between anthropometry and DEXA in estimating leg lean volume (*LLV*) in nutritionally depleted and non-depleted patients with COPD (Villaça et al. 2008). Note the homocedastic overestimation of LLV by anthropometry in both groups (Extracted from Villaça et al. (2008). With permission)

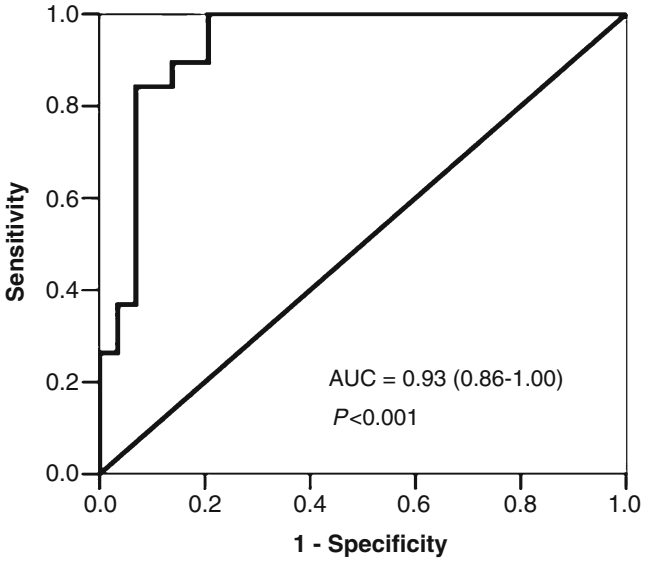

Fig. 170.5 Leg lean volume to establish nutritional depletion in patients with COPD. A ROC curve analysis of the diagnostic performance of anthropometric estimates (leg lean volume/leg height, L/m) in identifying patients with nutritional depletion. Notice that a threshold of 9.2 L/m presented with the best combination of sensitivity and specificity (95% and 80%, respectively). Depletion was defined according to the following criteria: body mass index ≤21 kg/m^2 and/or fat-free mass index ≤15 kg/m^2 in females and ≤16 kg/m^2 in males (Schols et al. 1993). AUC is the area under the curve (Extracted from Villaça et al. (2008). With permission)

patients with low prevalence of nutritional depletion, making difficult the assessment of the actual performance of anthropometry in this specific setting.

Unfortunately, despite the widespread recognition of the relevance of segmental body composition abnormalities in systemic diseases, there is a lack of information regarding the usefulness of anthropometric estimates of LLV in determining nutritional depletion in other clinical populations.

170.5.1 Future Research

There are several important gaps in the current knowledge on the sources of variability of anthropometric estimates of LVs in clinical populations. There is an urgent need to validate the Jones and Pearson method (1969) in the elderly and develop more comprehensive technical approaches, probably by using additional sites of skinfold thickness and circumference measurements. Moreover, little is known about the sensitivity of anthropometry to early detect subtle reductions in leg lean volumes before the development of cachexia and its negative metabolic and functional consequences. There is also a lack of data on accuracy, reliability, and external validity of these measurements in specific patient population groups, such as those with cancer and AIDS. Finally, it is likely that there are important ethnical and racial variations in the relationship between LLV and leg height (Villaça et al. 2008), an issue which remains largely unexplored.

170.5.2 Application to Other Areas of Health and Disease

Measurements of LLV have been previously used in applied research in sports sciences (Winter et al. 1991; Doré et al. 2001; Howden et al. 2002; Temfemo et al. 2007). However, there is a large potential for these estimates to be used as a screening and follow-up tools in selected sport modalities in which the muscle mass of the lower limbs is particularly relevant for performance. LLV could be useful to estimate the risk of negative clinical outcomes in the general population, such as the risk of cardiovascular and metabolic disease. Large-scale, longitudinal evaluations of LLV might also prove to be relevant for screening sarcopenia in the aged population. These potential developments, however, depend on multinational studies to establish reliable reference values for LLV across age groups in both males and females.

170.6 Conclusions

Contemporary methods for body composition assessment rely on highly sophisticated and expensive equipment despite the progressive curtailment of healthcare resources. By contrast, inexpensive and widely available anthropometric methods to estimate segmental body composition, especially the Jones and Pearson's (1969) approach to measure LLV, are potentially useful to identify nutritionally depleted subjects with systemic diseases. In the specific context of COPD, there is limited evidence that leg-height-corrected LLV (≤9.2 L/m) is highly sensitive to indicate depletion of metabolic active tissue. There is, however, no published experience in other disease groups which calls for additional validation studies in wider clinical settings.

Summary Points

- Patients suffering from chronic diseases which affect the major organs (e.g., heart, lungs, liver, and kidney) frequently present with loss of fat-free ('lean') tissue, a finding that impairs quality of life and leads to disablement and early death.
- These abnormalities seem to disproportionately affect the lower limbs, making clinically important the measurement of leg lean mass.
- The methods available to measure leg lean mass are cumbersome and expensive. Anthropometric techniques to estimate leg lean volume, however, are easily performed with a minimum of equipment.
- The techniques are based on a series of measurements of circumferences, girths, and the thickness of subcutaneous ('fat') tissue, which allows the estimation of the leg volumes.
- There are some research findings indicating that a particular method of measuring leg lean volume developed in 1967 by Jones and Pearson is useful to establish if patients with a chronic lung disease (COPD) are nutritionally depleted and functionally impaired.
- Despite these encouraging results, very few studies have looked at these aspects in other disease populations and there is large room for future investigations before these techniques actually reach the clinical practice on a larger scale.

Key Features

Table 170.3 Key points on leg lean volume to indicate nutritional depletion in patients. Key points on clinical value of leg lean volume in estimating nutritional status in disease populations

Depletion of lean body mass is a relevant clinical outcome in several disease populations, being related to increase disability and mortality.
The lower limbs are particularly affected in this process, thereby making the anthropometry of the legs of special interest.
Although there have been several attempts to develop techniques to measure leg lean volumes, the truncated cones method of Jones and Pearson still provides a more comprehensive evaluation of the whole limb.
Preliminary evidence suggests that this method might be highly sensitive and specific to indicate fat-free tissue depletion in selected groups, such as those suffering from chronic obstructive pulmonary disease.
There is a need for further research on different clinical populations presenting with varied degrees of nutritional impairment.

Acknowledgments The authors would like to thank CAPES (Coordenadoria de Aperfeiçoamento do Pessoal de Nível Superior, Brazilian Government), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq, Brazilian Government), and FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo, Brazil) for contínuous research funding.

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Chapter 171
Nutritional Anthropometry for Amputees: Challenges for Clinicians

Elaine Bannerman, Jolene Thomas, and Michelle Miller

Abstract Anthropometric measurements pose interesting challenges for clinicians when attempting to perform and interpet these in individuals with a lower extremity amputation. With little evidence to guide best practice, when clinicians do incorporate anthropometry into their practice they tend to apply measures with demonstrated validity in other populations. Following a comprehensive literature review, very few studies challenging the application of anthropometric measurements in those with a lower extremity amputation were identified. Largely the literature makes recommendations to continue to utilise body mass index, with complex equations developed to enable estimation of weight for the amputated limb. Alternatively the literature advocates for adopting measurements of the upper body while acknowledging that while these have correlation with measures such as body mass index, there is yet no information on whether these measures have any predictive ability in terms of health outcomes. The ideal approach is thus still controversial and research should focus on evaluating the ease and validity of various anthropometic measurements amongst those with a lower extremity amputation with a view to establish best practice recommendations for this group.

Abbreviations

BMI	Body mass index
CAMA	Corrected Arm Muscle Area
HRQoL	Health Related Quality of Life
MAMC	Mid Arm Muscle Circumference
MUAC	Mid Upper Arm Circumference
NHS QIS	National Health Service Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
UK	United Kingdom
WHO	World Health Organisation

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_171,

171.1 Introduction

171.1.1 Statistics

In 2005, the prevalence of individuals with amputations in USA was approximately 1.6 million individuals. Nearly all (97%) amputations were of a lower limb, of which approximately one-quarter were above the knee. Incidence rates of amputations due to trauma have shown a decline in recent years; however, the risk remains high in those over 85 years (National Limb Loss Information Centre 2008). The main cause was vascular complications associated with chronic diseases, such as diabetes mellitus (38%), these being more common in males and also in African-Americans (Zeigler-Graham et al. 2008). With the growing prevalence of diabetes, it is projected that the number of those individuals with vascular complications and thus need for amputation will also increase.

The National Amputee Statistical Database for the UK (NHS NSS 2009) reported approximately 5,000 new referrals to prosthetic services for the period 2006/2007. Of these, 28% were over the age of 75 years and less than 3% were under 16 years. The gender ratio of new referrals remained relatively constant over the 10 years (1997–2007), with approximately two-thirds being male (2006/2007, 3506 males: 1,451 females). Over 90% of referrals were for lower-limb amputations.

The National Hospital Morbidity Database Procedure Data cubes as classified by the ICD-10-AM Australian Classification of Health Interventions (ACHI), 5th Edition allows identification of the number of lower-limb-amputation procedures that were performed in Australian hospitals for the period 2006–2007 to 2007–2008 (Australian Institute of Health & Welfare 2009). In terms of procedures on the musculoskeletal system, amputations below the knee (1505 – 44367-02) reported 2,589 cases, of which 71% were male and 61% were >65 years. Amputation above the knee (1484 – 44367-00) reported 1,950 cases, of which 63% were male and 79% were >65 years. Neither specific details of diagnoses for related procedures nor prevalence data are available. Differences in statistics reported may, in part, be related to different definitions for procedures.

Key features of lower-limb amputees are outlined in Table 171.1.

Table 171.1 Key features of lower-limb amputees

1. Amputation is the removal (often by surgical operation) of a limb, or part of a limb, of the body.
2. Individuals who are most likely to need to undergo an amputation are individuals who have developed significant problems with their blood circulation as a result of chronic diseases, such as diabetes mellitus. The other key group of individuals who have an amputation are individuals who have injured a limb through a traumatic event.
3. The most common part of the body where amputations are performed is on the lower limbs (legs). This may be surgical removal of a foot or of the lower leg (below the knee) or the full leg.
4. Many individuals who undergo a lower-limb amputation will have an artificial limb (prosthesis) made to improve their everyday functioning.
5. Being overweight or obese can add complications for individuals with lower-limb amputations, including affecting their mobility and can increase wear and tear of their prosthetic device meaning it may need to be replaced more frequently.
6. Being able to accurately monitor weight status and nutritional status of individuals with lower-limb amputations has important implications for the management and health outcomes for the individual.
7. However, many of the tools used for nutritional screening and assessment purposes include weight and height, which can be difficult to measure or interpret in individuals with an amputation.

This table lists the key features of individuals who undergo amputations, how this is generally managed and how this can impact on an individual's quality of life and their health

171.1.2 Health-Related Quality of Life and the Importance of Nutritional Well-Being

Assessment of individuals after a lower-extremity amputation has shown varying factors that predict health-related quality of life (HRQoL), including depression, the use of prosthetic devices, presence of other comorbidities and social functioning (Asano et al. 2008). Research has shown significant reductions in health-related quality of life in individuals with diabetic neuropathy who undergo amputation (Happich et al. 2008).

The importance of nutritional well-being post-amputation has been a largely neglected area of research as much focus has been on diet as a causative factor. Neuropathy and vascular complications of the lower limbs of individuals with diabetes is one of the leading causes of amputation, particularly of the lower limb. Overweight and obesity increase the risk of individuals developing type 2 diabetes and other metabolic complications, including hypertension and abnormal blood lipid profiles. This is especially evident in those with poorly managed blood glucose levels, increasing the risk of diabetic neuropathy, and therefore the risk of amputation as well as increasing the risk of cardiovascular disease.

Post-amputation, obesity has been noted as a complication for some individuals with lower-extremity amputation (Kurdibaylo 1996). While it is well known that obesity increases the risk of chronic disease as highlighted earlier, obesity can also pose practical problems for use of the prosthetic device. An audit of repairs to lower-extremity prosthetic devices of amputees ($n = 113$) in the UK showed that even after controlling for length of use of device, increasing body weight was significantly related to increased need for prosthetic repairs (Haboubi et al. 2001). Thus, in addition to the metabolic complications, the weight status of individuals with lower-limb amputations requiring prosthetic limbs brings economic implications, considerations of maximum body weight for use of specific devices as well as negative effects on an individual's psychological, physical and social quality of life. Being able to accurately monitor weight status and nutritional status of individuals with lower-limb amputations has important implications for their management and the health outcomes for the individual.

171.1.3 Measurement of Nutritional Well-Being

It is well recognised that nutritional screening to identify individuals with nutritional risk should be routinely performed in acute, primary and rehabilitation settings (Council of Europe 2003; NHS QIS 2003; Watterson et al. 2009) and is considered to be a cost-effective method in low-mortality-risk individuals (NICE CG32 2006). While most prominently recognised for its ability to assess risk of undernutrition, nutrition screening is also capable of identifying those individuals who are at increased risk of overweight and obesity (NICE CG 43 2006). A key challenge for clinicians working with individuals post-amputation, however, is that many of the tools used for nutritional screening purposes contain measures of anthropometry, including weight and height. Nutritional assessment poses an even greater challenge for clinicians as all methods of assessment will require some measurement of body size and/or composition.

Measurements of body size and composition (anthropometry) are recognised as a core part of the nutritional assessment of an individual, which are then interpreted in conjunction with medical and diet history, physical examination and various laboratory data. These assessments contribute to determining individuals' nutritional health status and can be used to indicate appropriate care pathways,

clinical management of an individual as well as monitoring the impact of therapeutic interventions and changes in nutritional status. Measurements need to be valid and reliable and have prognostic value in terms of health outcomes; however, they need to be simple to perform to ensure that they are administered when necessary. However, the assessment of either the weight or the nutritional status of an individual with an amputation brings with it a number of complications. The aim of this review is to present a summary of the literature reporting recommendations for measuring nutritional anthropometry in amputees and to provide some practical guidelines for clinicians.

171.2 Search for Relevant Studies

The studies in this review were obtained through electronic databases. The electronic databases MEDLINE, PubMed, CINAHL, Cochrane Library and SportDiscus were searched using the following terms: amputation, artificial limbs, above knee amputation, below knee amputation, transfemoral amputation, transtibial amputation, amputee, limb, anthropometry, measurement, circumference, girth, skinfold, weight, body mass index, body weight or body mass, overweight, underweight, nutritional assessment, diet, assessment and nutritional status. The databases were searched for the period up until September 2009. Titles and abstracts were examined by the authors and if the abstracts met the inclusion criteria, the full text of the article was retrieved. A total of 45 abstracts was screened as worthwhile for retrieval and, of these, ten resulted in being appropriate for the purpose of this review.

171.3 Summary of the Evidence

One of the key points that this review has uncovered is the lack of research performed regarding the use of nutritional anthropometry amongst amputees and the resultant lack of suitable data for contributing to a review of this kind. While ten studies were located that were deemed suitable for inclusion, the samples across this scant literature are extremely heterogeneous, making overall recommendations difficult.

The literature is global, covering such diverse populations as those in India (Monzumdar and Roy 2004), Australia (Miller et al. 2008) and Brazil (Innocencio da Silva Gomes et al. 2006). Baseline nutritional health and healthcare following amputation are likely to be very different; hence, pooling of this data would be inappropriate. Likewise, pooling of data is questionable when the samples surveyed in the literature span from elite athletes (Innocencio da Silva Gomes et al. 2006) (Table 171.2) to frail older people (Miller et al. 2008) (Table 171.3), where nutritional health, comorbidities and risk factors for further decline are vastly different. It is also important to consider the level of amputation undertaken, with many studies choosing to select transtibial (Eneroth et al. 1997) or transfemoral (Boonstra et al. 1995) but some choosing to pool data for both groups (Innocencio da Silva Gomes et al. 2006; Miller et al. 2008). With these issues in mind, the following discussion attempts to highlight where and what nutritional anthropometry has been reported for amputees and any implications or recommendations worthy of consideration for clinicians.

The most commonly performed anthropometric measurements are weight and height, which allow the determination of a relative body mass index (BMI: kg/m^2). Internationally accepted classification of weight categories has been developed by the WHO (1995). The BMI and this classification system have been shown to have a strong relationship with body fat and significant prognostic

Table 171.2 Anthropometric parameters of the Brazilian Amputee Soccer Team players, with respect to the positional role on the team (Reprinted by permission from Elsevier Innocencio da Silva et al. 2006)

	Positions				
Variables as mean (SD)	Goalkeepers ($n = 2$)	Fullbacks ($n = 4$)	Midfielders ($n = 3$)	Forwards ($n = 6$)	All groups ($n = 15$)
Stature (cm)	177.1 (5.9)	177.0 (2.1)	172.5 (3.9)	172.9 (5.2)	174.5 (4.5)
Body mass (kg)	76.5 (5.0)	64.5 (3.6)	73.9 (7.6)	62.5 (7.5)	67.2 (8.1)
Corrected body mass (kg)	78.3 (5.1)	76.4 (8.6)	90.6 (9.4)	74.9 (9.4)	78.9 (10.0)
Skinfold thickness (mm)					
Tricipital	9.0 (0.3)	9.7 (2.7)	16.6 (2.7)	11.3 (3.6)	11.6 (3.8)
Abdominal	19.8 (4.1)	20.8 (9.4)	28.8 (6.4)	22.0 (8.7)	22.7 (8.0)
Thoracic	11.3 (0.42)	12.7 (5.8)	19.6 (1.5)	10.8 (4.7)	13.1 (5.2)
Thigh	11.1 (6.4)	12.2 (4.1)	14.0 (1.7)	11.5 (3.2)	12.0 (3.4)
Sum of skinfold thicknesses	51.2 (1.6)	55.5 (20.6)	74.4 (4.0)	55.6 (18.1)	58.7 (16.7)
Circumference (cm)					
Thigh	56.3 (0.5)	56.4 (2.0)	60.9 (3.8)	55.6 (2.9)	57.0 (3.2)
Right arm	31.5 (0.7)	32.6 (1.8)	34.3 (2.2)	31.0 (2.4)	32.2 (2.3)
Left arm	26.3 (3.8)	30.8 (1.4)	33.8 (1.9)	31.1 (2.9)	30.9 (3.1)
Arm muscle (mm)	286.7 (6.2)	295 (11)	291 (30)	275 (19)	285 (19)
Arm muscle area (mm^2)	6,547 (282.3)	6,950 (511)	6,802 (1,405)	6,031 (854)	6,499 (881)
Arm fat area (mm^2)	1,354.6 (71.8)	1,519 (470)	2,610 (207)	1,668 (596)	1,775 (616)

Selected anthropometric measurements amongst athletes with lower-limb amputation

Table 171.3 Selected anthropometric data available from an Australian observational study of 64 amputees attending a prosthetics clinic

	Below-knee amputee ($n = 42$)	Above-knee amputee ($n = 22$)
Body weight, no prosthesis (kg)	72.9 (15.0)	71.4 (18.4)
Standing height (cm)	169.4 (12.1)	168.3 (7.3)
Knee height (cm)	53.5 (5.9)	52.9 (2.8)
Demispan (cm)	86.5 (7.6)	-
Mid-arm circumference (cm)	28.0 (4.0)	28.8 (5.5)
Triceps skinfold thickness (mm)	15.8 (7.1)	15.9 (7.1)
Calf circumference (cm)	33.3 (3.4)	36.8 (6.8)

Comparison of selected anthropometric measurements between above and below knee amputees

value in terms of morbidity and mortality at both extremes of weight status (underweight and obesity) in a variety of patient groups. Use of the BMI in the assessment of individuals with amputations is complicated not only regarding how to compensate for the missing limb in the weight measurement but also regarding difficulties in being able to get an accurate measurement of height or estimate of stature.

Body weight is a routine measure conducted in the general population to assess and monitor nutritional health. In the general population, this measure is relatively simple to obtain and has considerable predictive ability in terms of poor health outcomes. However, the same cannot be said for the amputee population. There is a great deal of debate in the clinical setting surrounding the issue of which body weight to utilise. Pre-amputation weight is difficult to determine without weighing either the individual pre-surgery or the amputated limb. As a pragmatic approach to this challenge, for many years clinicians have been recommended to determine body weight in amputees using results from cadaver studies (Osterkamp 1995) in which body segments were weighed to determine the % body

weight attributable to particular segments. However, it is important to note that these data were derived from old studies with small samples, and there was no consideration of differences between gender, age or ethnic background. Also, since these data were collected, there have been changes in body size and body composition; hence, the data may no longer be applicable to the population of today. Given these issues, it is not unreasonable to suggest that tracking post-amputation weight alone might in fact be a sufficient marker of change in nutritional health. However, practical considerations include the need for a calibrated chair, bed or hoist scales to make weight measurements.

Giving support to this suggestion is the complexity of measurements and calculations proposed for estimation of pre-amputation weight by Mozumdar and Roy (2004) (Fig. 171.1). In this study, 102 male unilateral lower-limb amputees from India were enrolled, and data from the unaffected lower limb used to predict the proportion of weight loss from the amputated limb. While the formulae were well developed, the measurements and calculations required result in this method being difficult to implement in clinical practice. Furthermore, there does not appear to be any evidence to suggest that prediction of pre-amputation weight and the ability to calculate BMI is any more meaningful in terms of health outcomes than simply monitoring change in post-amputation weight. This is an area that requires further research

While BMI, obtained through measurement of standing height and body weight, is a common index of nutritional health used in the general population, there are considerable complexities involved in obtaining these measures in the amputee population. The complexities of body weight measurement have, while briefly, been acknowledged in the literature and are described above, there has not yet been acknowledgement in the literature that ability to accurately measure height in the amputee population may be compromised. Certainly, for bilateral amputees measurement of standing height is not possible. For unilateral amputees, however, it may be possible to measure standing height, but the contribution that the prosthesis might make would need to be considered. An alternative for standing height in unilateral amputees may be knee height (or, a more consistent approach for all lower-limb amputees might be to recommend a measure such as demispan (Bassey 1986) or arm span). Furthermore, the reference ranges available are based on the non-amputee population (Lehmann et al. 1991); clinicians should therefore question the feasibility and reliability of this index in this population.

A small number of studies have attempted to establish methods for assessing BMI in the amputee population (Mozumdar and Roy 2004; Tzamaloukas et al. 1994; Tzamaloukas et al. 1996). Both studies clearly demonstrate that using actual post-amputation weight significantly underestimates BMI and consequently leads to inaccurate assessment of nutritional health. To overcome this issue, it is suggested that an adjusted weight would be more appropriate for use in the standard BMI equation. The methods employed in these studies were based on mathematical determination of body weight based on pre- and post-amputation weights and the proportion of weight attributable to the amputated body segment, which could then be used in the standard BMI equation. Comparisons could then be made to the standard BMI reference ranges to determine BMI status in the amputee. Again, the formulae were well developed, but the method would be difficult to implement in the clinical setting. Also, no evidence was provided to support the use of BMI in these health settings over the use of monitoring changes in body weight in terms of subsequent health outcomes.

Other indices used in the evaluation of nutritional health are calculated based on upper-limb anthropometric measures or indices, common ones being mid-arm muscle circumference (MAMC) and corrected arm muscle area (CAMA) (Friedman et al. 1986). Miller et al. (2008) evaluated the use of BMI and CAMA as measures of nutritional health in 58 unilateral amputees. Comparisons were made between BMI (corrected and uncorrected) and CAMA with the conclusion that there was a moderate–high correlation between them. CAMA was also predictive of quality of life.

$$W_E = W_O / (1 - \Delta W / W_E)$$

where,

$\Delta W/W_E = W_S/W_E + W_T/W_E\ (1 - L_{Stp}/L_{Kn})$ (for individuals with below-knee amputation)

$\Delta W/W_E = W_S/W_E + W_T/W_E + W_F/W_E\ (1 - L_{Stp}/L_{BtK})$ (for individuals with above-knee amputation)

where, W_E is the body weight to be estimated, W_O is the observed body weight, $\Delta W = (W_E - W_O)$, L_{Stp} is the length of the stump (remaining portion of the limb from its nearest distal bone-joint) and W_S, W_T and W_F are weight of sole/foot, knee and thigh, respectively.

Based on Osterkamp (1995), $W_S/W_E = 1.5\%$, $W_T/W_E = 4.4\%$, $W_F/W_E = 10.1\%$, L_{Kn} = knee height and L_{BtK} = buttock knee length.

Measurements

Knee height: The subject sits erect, with foot resting on a surface so that the knee is bent at right angle. The vertical distance from the floor to the top of the patella is measured.

Buttock knee length: The subject sits erect, with foot resting on a surface so that the knee is bent at about right angle. The horizontal distance from the rear-most point of the buttock to the front of the kneecap is measured.

Therefore,

$\Delta W/W_E = 0.015 + 0.044\ (1 - L_{Stp}/L_{Kn})$ (for individuals with below-knee amputation)

$\Delta W/W_E = 0.015 + 0.044 + 0.101\ (1 - L_{Stp}/L_{BtK})$ (for individuals with above-knee amputation).

Here are two examples:

Patient 1 (with below-knee amputation):

$W_O = 67.5$ kg

$L_{Stp} = 26.5$ cm

$L_{Kn} = 50.8$ cm

$\Delta W/W_E = 0.015 + 0.044\ (1 - 50.8\ \text{cm}/24.0\ \text{cm}) = 0.015 + 0.044\ (1 - 0.472) = 0.038$

Patient 2 (with above-knee amputation)

$W_O = 67.5$ kg

$L_{BtK} = 58.5$ cm

$L_{Stp} = 26.5$ cm

$\Delta W/W_E = 0.015 + 0.044 + 0.101\ (1 - 58.5\ \text{cm}/26.5\ \text{cm}) = 0.015 + 0.044 + 0.101\ (1 - 0.453) = 0.114$

Therefore, $W_E = 79.5\ \text{kg}/(1 - 0.114) = 89.75$ kg

Fig. 171.1 Formulae for estimating weight for adults with above- or below-knee amputation. Formulae for estimating body weight from anthropometry in lower-limb amputees

Table 171.4 Descriptive statistics of anthropometric measurements in individuals with lower-extremity amputation (Reprinted by permission from Macmillan Publishers Ltd Mozumdar and Roy 2006)

	Above-knee amputees (n = 32)		Below-knee amputees (n = 70)	
	Mean	SD	Mean	SD
Stature (cm)	164.47	6.16	161.22	7.41
Body weight (kg)	66.79	13.58	57.54	12.30
Body mass index (kg/m^2)	24.51	3.89	22.02	3.74
Upper arm circumference (cm)	29.34	3.14	26.63	3.15
Waist circumference (cm)	90.04	10.72	83.07	12.76

Selected anthropometric data for 103 lower-limb amputees in India

Skinfolds are also commonly used anthropometric measures. Innocencio da Silva Gomes et al. (2006) investigated the nutritional profile of Brazilian amputee soccer players. The sum of three skinfolds (abdominal, thoracic and thigh) was calculated in 15 subjects on the non-amputated side of the body. They found that subjects had a higher level of subcutaneous fat compared to non-amputee athletes, particularly around the abdomen; however, as prediction equations were developed in non-disabled individuals, the results should be treated with caution. Innocencio da Silva Gomes et al. (2006) cited another study (Kurdibaylo 1996) that found higher rates of obesity, particularly relating to increased subcutaneous fat, in amputees when compared to non-amputees.

Triceps skinfold thickness has been used by Eneroth et al. (1997) to describe the nutritional status of postoperative amputees. It was reported that 37% of subjects had a triceps skinfold thickness below the 10th percentile, hence indicating nutritional depletion in the population. While commendable, the studies described above made no or limited comparisons between their results and results in non-amputees, and where Innocencio da Silva Gomes et al. (2006) did, comparisons were made to athletes and not to the general population.

Girths or circumferences of body parts are also commonly used anthropometric measures, and there have been some attempts to use these to describe and monitor nutritional well-being amongst amputees. Innocencio da Silva Gomes et al. (2006) measured brachial and thigh circumference on the non-amputated side of 15 Brazilian amputee soccer players. The main findings related to the differences in measurements according to position played, rather than to any key recommendations for use of these measures for assessment of nutritional well-being amongst amputees. By contrast, Miller et al. (2008) evaluated the use of upper-arm anthropometric measures and BMI as measures of nutritional health in 58 lower-limb amputees. Mid-upper arm circumference (MUAC) was compared to uBMI and cBMI, resulting in a moderate–high positive correlation between the two measures. The correlation between BMI and upper-limb anthropometric measures was also found by Mozumdar and Roy (2004) in 102 unilateral, male amputees in India (Table 171.4). They found that MUAC was significantly positively correlated with both observed BMI (r = 0.846, P = 0.01) and estimated BMI (r = 0.872, P = 0.01). It is important to recognise that changes in upper-body strength, as a result of lower-limb amputation, can lead to problems in the interpretation of upper-arm anthropometric measurements as these may not reflect whole body status.

As noted, individuals who require lower-limb amputations are often those with advanced diabetic neuropathy. It is clearly documented that individuals with diabetes are at increased risk of morbidity and mortality from cardiovascular disease and metabolic complications (Wilson et al. 2002). It is well recognised that waist circumference measurement provides prognostic value in terms of central obesity and associated metabolic health risks (NICE 2006). Although there is no specific evidence for its use in individuals with lower-limb amputations, support for its use comes from the practicalities for its measurements compared with limiting factors for using body mass index in this patient group, as outlined above. Further research in this area is needed.

171.4 Conclusion

Assessment of the weight and nutritional status of individuals with lower-limb amputations should be a standard component of the health management of this group of individuals. Upper-arm anthropometrics appear to be a useful and reliable measure in determining nutritional health in the amputee population and also enable simple, repeated measuring for monitoring purposes. While using body weight as a monitoring tool, actual body weight is probably adequate to monitor change over time. The current classification system for BMI has limited use in this population group. While using BMI to assess nutritional health, an adjusted/corrected BMI should be employed to allow comparison to available reference ranges, as unadjusted BMI underestimates BMI due to the weight associated with the absent limb. It is recommended that future research is carried out to determine the prognostic value of various nutritional indices that can be performed relatively easily within amputee populations.

171.5 Applications to Other Areas of Health and Disease

Inability to accurately measure nutritional anthropometry is not limited to the area of amputees. Elderly, those with skeletal deformity or individuals who are bed or chair bound are other groups where anthropometric assessment is difficult and fraught with inaccuracies. Precise and reliable measures of nutritional anthropometry that are meaningful have use outside the amputee population. Upper-arm anthropometry therefore has broad applicability and potential.

171.6 Practical Methods and Techniques

Performing anthropometric measurements takes significant skill. Anatomical landmarks require accurate identification and proficient use, and understanding of measurement error is mandatory. Training programmes are available at many universities and it is highly recommended that either these or equivalent training programs are undertaken prior to undertaking these measurements in clinical practice (see http://www.isakonline.com/). Standard protocols should be adhered to, including regular calibration of any necessary equipment.

Summary Points

- Obesity or increasing weight following amputation poses challenges for the clinician with increasing risk of metabolic disturbances and also the physical complications for prosthetic fit and longevity.
- Nutrition screening and assessment for identification of nutritional risk (over- and undernutrition) mostly require accurate measurement of body size, commonly stature and/or weight; however, these measures are complex in those with a lower-extremity amputation.
- There is little data available to guide recommendations for measurement of body size in those with a lower-extremity amputation. Weight, BMI, skinfold thickness and upper-arm girths have all been reported.
- Weight monitoring post-amputation is feasible and informative.

- BMI is underestimated if weight is not corrected to account for the amputated limb. Equations to estimate the weight of the amputated limb are complex and rely heavily on either old data or difficult-to-obtain anthropometric measurements.
- Girths and skinfolds have not been measured widely, but there is some preliminary evidence to suggest that upper-arm anthropometry could be a suitable alternative for BMI in those with a lower-extremity amputation.

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Chapter 172
Anthropometry of Malnutrition in End Stage Liver Disease

E.T. Tsiaousi and A.I. Hatzitolios

Abstract One of the most common encountered clinical complications in end stage liver disease (ESLD) is macro- and micronutrient deficiency. Clinically evident malnutrition is strongly correlated with the degree of the disease progression reflected in the Child Pugh classification. The pathogenesis of malnutrition in ESLD is multifactorial. The use of anthropometry has provided us with an efficient but simple method for the assessment of malnutrition in cirrhosis. Most common anthropometric indices are triceps skinfold thickness (TST) and mid arm muscle circumference (MAMC). Both parameters are of great prognostic value and are recommended, along with subjective global assessment (SGA), by the European Society for Clinical Nutrition and Metabolism (ESPEN) for the evaluation of malnutrition in cirrhotic patients and patients awaiting liver transplantation.

Abbreviations

BCM	Body Cell Mass
BMI	Body Mass Index
CP CLASSIFICATION	Child Pugh classification
ESLD	End Stage Liver Disease
ESPEN	European Society for Clinical Nutrition and Metabolism
FFM	Free Fat Mass
MAA	Mid Arm Area
MAC	Mid Arm Circumference
MAFA	Mid Arm Fat Area
MAMA	Mid Arm Muscle Area
MAMC	Mid Arm Muscle Circumference
PEM	Protein Energy Malnutrition
REE	Resting Energy Expenditure
SGA	Subjective Global Assessment
TST	Triceps Skinfold Thickness

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_172,

172.1 Introduction

Protein–energy malnutrition is a common feature of end-stage liver disease (ESLD) and is by far regarded as one of the most important prognostic factors regarding the final course of the disease. Collective evidence points to the fact that malnutrition is considered a severe complication of ESLD and merits the same attention as the presence of hepatic encephalopathy, esophageal varices, or ascites. It may adversely affect quality of life and most importantly the outcome of liver transplantation (Kondrup 2006).

The prevalence of malnutrition in cirrhosis is considered universal although not always evident. Deficits in micro- and macronutrients are present from the very early stages of the disease. The severity of malnutrition ranges from subclinical micronutrient deficiencies to protein–calorie malnutrition with obvious muscle wasting and depletion of fat tissue (Figueiredo 2005).

Screening the majority of patients with ESLD for nutritional abnormalities has therefore emerged as a necessity in order to identify those at greater risk for complications that could emerge as a direct effect of protein–fat depletion. The modified Child–Pugh classification that has substituted the original Child–Turcotte classification after 1973 has replaced nutritional status with prothrombin time. Nevertheless, the specific guidelines on enteral nutrition that were issued in January 2006 (updated 2009) by the European Society for Clinical Nutrition and Metabolism (ESPEN) emphasize the importance of the correction of the nutrient deficit in patients with ESLD, stressing that it reduces complications and prolongs survival. The original ESPEN guidelines propose the use of simple anthropometric parameters in the evaluation of malnutrition in cirrhotic patients and patients awaiting liver transplantation. In particular, the measurement of mid-arm muscle circumference (MAMC) or mid-arm circumference (MAC), and triceps skinfold thickness (TST) which are not affected by the presence of ascites or peripheral edema provide sufficient information regarding the loss of protein and fat tissue, respectively (Plauth 2006, 2009).

172.2 Most Common Causes of End-Stage Liver Disease

The most frequent causes of ESLD are reflected in the major indications for liver transplantation. Alcoholic liver disease and chronic hepatitis C represent more than 40% of all cases reported. Other less common liver diseases with an ominous prognosis are chronic hepatitis B, cryptogenic cirrhosis (a majority of which may represent non-alcoholic steatohepatitis-related cirrhosis), primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, hepatic malignancy, acute liver failure, and metabolic diseases. In the pediatric populations, α1-antitrypsin deficiency and metabolic disorders are more common (Table 172.1) (Martin 2006).

172.3 Pathophysiology of Malnutrition in ESLD

Hypermetabolic state. The contribution of hypermetabolism, which is often present in liver cirrhosis, to the extent of malnutrition is still debated. Systematic vasodilation, which leads to an expanded intravascular blood volume, is a direct effect of the hyperdynamic circulation of cirrhosis (Guglielmi 2005). An increase in the resting energy expenditure (REE) of 120% of the expected value is observed in 34% of patients with cirrhosis of any degree (Kondrup 2006). Hypermetabolic patients exhibit

Table 172.1 Most common liver diseases in patients with ESLD

Chronic hepatitis C
Alcoholic liver disease
Chronic hepatitis B
Cryptogenic cirrhosis (NASH?)
Primary biliary cirrhosis
Primary sclerosing cholangitis
Autoimmune hepatitis
Acute liver failure
Hepatic malignancy
Metabolic diseases

Chronic hepatitis C and alcoholic cirrhosis represent more than 40% of all cases
ESLD End-Stage Liver Disease; *NASH* Non-Alcoholic Steatohepatitis

greater losses in muscle mass, free-fat mass (FFM), and body cell mass (BCM) and have a better chance to be transplanted than normometabolic patients (Matos 2002). In the post-transplant era, hypermetabolism is corrected. Apart from these, the frequent infections observed in cirrhotic patients due to the compromised gut-barrier function raise the REE. Elevated pro-inflammatory and anti-flammatory cytokines, such as tumor necrosis factor (TNF), point to a cytokine-driven hypermetabolic state (Plauth 2002).

Poor nutrient intake. Although hepatic synthetic function may be preserved even in the late stages of the disease, a low caloric diet that the majority of the cirrhotic patients follow may compromise their nutritional status. Patients often complain about loss of appetite, which has been attributed to the elevated levels of TNF (cytokine-mediated anorexia), presence of ascites, altered taste, and early satiety (Plauth 2002). Patients may experience gastrointestinal symptoms, such as abdominal pain, nausea, and bloating, which are associated with diminished food intake and subsequent weight loss. Diet restrictions regarding sodium, fluids, and protein in the circumstance of ascites, peripheral edema, and hepatic encephalopathy make the diet unpalatable and may reduce even more the ingested calories and micro- and macronutrients. Nevertheless, unjustified diet restrictions of protein for the fear of hepatic encephalopathy are still imposed, despite the strict guidelines issued by ESPEN (Plauth 2002; Tsiaousi 2008).

Malabsorption and maldigestion. Utilization of the ingested nutrients is often hindered by the presence of portal hypertension and its effects on gut function. Mucosal congestion and villus atrophy, bacterial overgrowth, pancreatic insufficiency, and diminished digestive enzyme production and secretion impair the absorption of nutrients. Apart from these, reduced intraluminal bile salt concentrations, especially in cholestatic diseases, inhibit the absorption of fat and fat-soluble vitamins. The toxic effect of alcohol on the gut mucosa is another cause of malabsorption (Matos 2002).

Inadequate hepatic synthesis. The diminished synthetic ability and storage capacity of the cirrhotic liver in combination with the accelerated loss of body protein, due to infections and episodes of gastrointestinal bleeding, often lead to protein depletion. In the late stages of the disease process, the liver has lost most of its capacity to synthesize protein, glycogen, and very low density lipoproteins. Owen et al. made evident that, after an overnight fasting, patients exhibit a metabolic state similar to that of healthy individuals after a three days' fast (Owen 1981, 1983) (Table 172.2).

Table 172.2 Main causes of malnutrition in end-stage liver disease

Hypermetabolic state	Poor nutrient intake	Malabsorption and maldigestion
Systematic vasodilation	Loss of appetite (TNF driven?)	Portal hypertension
Expanded intravascular blood volume	Abdominal pain, nausea, and bloating	Mucosal congestion and villus atrophy
Increase in the resting energy expenditure (REE)	Diet restrictions (sodium, protein, and those for diabetes mellitus)	Pancreatic insufficiency and diminished digestive enzyme production and secretion
Infections	Altered taste	Bacterial overgrowth
Elevated pro-inflammatory and anti-inflammatory cytokines	Unjustified diet restrictions	Reduced intraluminal bile salt concentrations
Decreased hepatic synthetic ability	Ascites (early satiety and discomfort)	Alcohol

The pathogenesis of malnutrition is multifactorial. Diminished hepatic synthetic ability, portal hypertension, and overexpression of cytokines are the principal causative factors
TNF Tumor necrosis factor

172.4 Body Composition and Redistribution of Somatic Fluids in Liver Cirrhosis

Proper understanding of the alterations in body composition in liver cirrhosis could help healthcare physicians to assess and manage malnutrition in patients with ESLD. Protein–calorie malnutrition is ideally measured by body cell mass (BCM) depletion. BCM is the metabolically active compartment of lean tissue.

Protein depletion. Peng et al. have found significant protein depletion in 51% of their patients measured by in vivo neutron activation analysis (INVAA), which is the gold standard for the measurement of protein loss. The degree of protein depletion correlated with the Child–Pugh (CP) grade, with increased protein loss in grades B and C. It is noteworthy to mention that >40% of patients with CP grade A presented with increased protein losses and malnutrition (Peng 2007). An interesting observation that was made is that hydration of the free-fat mass (FFM) was higher in protein-depleted patients, a fact which was also observed by Heymsfield et al. in postmortem examinations. Increased hydration of wet muscle tissue can mask the losses of muscle functional protein (Heymsfield 1982). Clear evidence of the increased catabolism of protein are plasma amino-acid accumulation, skeletal-muscle wasting, and increased urinary excretion of nitrogen and 3-methylhistidine (a byproduct of myofibrillar protein) (Matos 2002).

Fat metabolism. The greater dependence on lipids as a fuel source, because of the impaired synthetic ability and storage capacity of glycogen, results in marked lipolysis and reduction of fat tissue. Figueiredo et al. quantified body-composition changes and found that BCM and body fat were significantly reduced mainly in patients with moderate and severe disease. In CP grade A, body-fat loss predominated (Figueiredo 2005).

Somatic fluids. Fluid retention is a common feature of liver cirrhosis. The presentation of ascites and peripheral edema are hallmarks of decompensated cirrhosis and a major therapeutic burden. Fluid shifts to the extracellular compartment as a result of portal hypertension and the hyperdynamic circulation. Total body water (TBW) and extracellular water are measured using dilution techniques (tritium dilution). Up to 64% of patients are over-hydrated even in the absence of clinically evident ascites. Greater hydration correlates with the severity of liver disease (Peng 2007).

Bone metabolism. In cholestatic and non-cholestatic liver diseases, bone density is affected with lower levels as the disease progresses and malnutrition is established.

172.5 Assessment of Malnutrition with the Use of Anthropometric Measurements

172.5.1 Common Anthropometric Indices Used in ESLD

Among the anthropometric parameters best studied and evaluated for the recognition of the presence of malnutrition among patients suffering from liver decompensation, triceps skinfold thickness (TST) and mid-arm muscle circumference (MAMC) correlate better with the actual loss of lean body tissue. The extreme catabolic effects of liver decompensation are attributed to the poor nutritional intake and to the hypermetabolism which characterizes liver cirrhosis. Since fluid tends to accumulate in the lower extremities as peripheral edema, measurement of the mid-arm circumference (MAC), mid-arm muscle circumference (MAMC), triceps skinfold thickness (TST), mid-arm area (MAA), mid-arm muscle area (MAMA), and mid-arm fat area (MAFA) is not affected by fluid retention. Fluid tends to accumulate to a lesser extent in the upper extremities, even in the late stages of the disease process. The presence of ascites precludes other anthropometric indices most commonly used in different states of malnutrition. In the setting of generalized edema, careful correction of fluid retention is required in order to deduct correct conclusions using anthropometry. Body mass index (BMI) has also been extensively used for the assessment of malnutrition but in combination with the previously mentioned anthropometric measurements, since the accumulation of fluid cannot ensure proper results using only this parameter.

BMI is calculated from the estimated weight or dry weight and height. MAC and TST are measured in the dominant side of the body using skinfold calipers and a steel tape measure. MAC is measured to the nearest centimeter with the arm hanging relaxed midway between the tip of the acromion and olecranon. TST is measured to the nearest millimeter at the back of the arm at the same height as the mid-arm circumference, using a skinfold caliper, having a pressure of 10g/mm^2 of contact surface area. The mean of three calculations is enough to provide accurate results. MAMC, MAA, MAMA, and MAFA are then calculated using the previous parameters. MAMC and TSF measurements are compared with published standards and expressed both in relation to the 5th percentile and as a percentage of the 50th percentile (relative MAMC) with correlation to age and gender (Table 172.3) (Frisancho 1981; Heymsfield 1982; Morgan 2006).

Table 172.3 Anthropometric measurements used for the identification of malnutrition in ESLD

Weight (kg)	BMI (kg/m^2) = weight (or estimated dry weight)/[height]^2
Height (cm)	MAMC (cm) = MAC – [TSF × π]
MAC (cm)	MAA (mm^2) = (π/4) × (MAC/π)
TST (mm)	MAMA (mm^2) = [MAC – (π × TST)]^2/4π
	MAFA (mm^2) = MAA – MAMA

TST and MAMC are of great prognostic value regarding the evaluation of malnutrition in cirrhosis. MAMC, MAA, MAMA, and MAFA are derived from the measurements of TST and MAC (MAC converted to millimeters)

BMI Body mass index; *MAMC* mid-arm muscle circumference; *MAC* mid-arm circumference; *TST* Triceps skinfold thickness; π 3.142; *MAA* Mid-arm area; *MAMA* mid-arm muscle area; *MAFA* Mid-arm fat area

Table 172.4 Anthropometric parameters in cirrhotic patients according to the degree of nutrition

		Well nourished	Moderately nourished	Moderately malnourished
Campillo et al. (2005)	BMI (kg/m^2)	27.2 ± 5.0	23.5 ± 3.7	20.3 ± 3.2
	TST (mm)	12.5 ± 6.4	8.0 ± 4.2	4.2 ± 2.0
	MAMC (cm)	24.3 ± 2.6	21.2 ± 2.1	18.5 ± 2.1
Guglielmi et al. (2005)	BMI (kg/m^2)	22 ± 3	NA	17 ± 2
Gunsar et al. (2006)	BMI (kg/m^2)	26	22	19
	TST (mm)	15	14	6
	MAMC (cm)	25	22	20
Riggio et al. (2003)	BMI (kg/m^2)	27.5 ± 0.4	NA	23.3 ± 0.6

The level of malnutrition is reflected in simple anthropometric measurements
NA not applicable

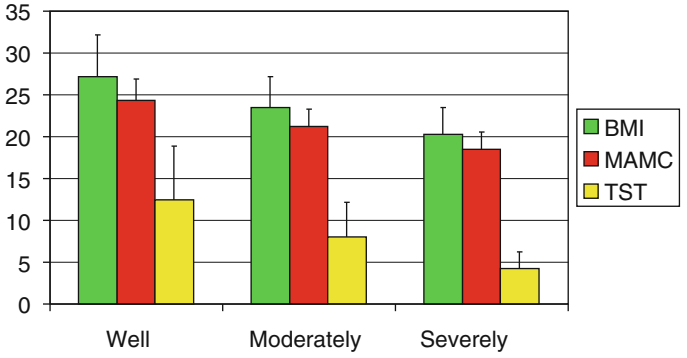
172.5.2 Evaluation of Anthropometry as a Significant Diagnostic Tool for the Detection of Malnutrition in Cirrhosis

The methods which are used universally for the evaluation of the nutritional status are subjective global assessment (SGA) and anthropometric parameters. Assessment of protein–energy malnutrition (PEM) severity and evaluation of the outcome of nutritional therapeutic intervention are crucial in order to differentiate patients with good or bad prognosis. Proper therapeutic intervention should be given to the ones who actually need it in order to improve their clinical status (Table 172.4).

PEM is best measured by body cell mass (BCM) depletion. BCM is the heat producing or metabolically active cell mass representing the compartment of the body which utilizes and produces energy. It has been identified as an important parameter of nutritional status with strong correlation with the clinical outcome. Figuiredo et al. have attempted to investigate which nutritional parameter best correlates with BCM depletion (Figueiredo 2000). They conducted a thorough nutritional assessment of 69 patients awaiting liver transplantation. The parameters that were assessed, apart from BCM analysis, using isotope dilution (bromide) with correction for extracellular water were SGA, handgrip dynamometry, laboratory tests, body composition measured by dual-energy X-ray absorptiometry (DEXA) and anthropometric measurements. In multivariate analysis, the most interesting finding was that anthropometry and handgrip strength were the best predictors of BCM depletion. The anthropometric data that were collected were weight, height, triceps skinfold thickness (TST), mid-arm circumference (MAC) and mid-arm muscle circumference (MAMC). MAC correlated better with BCM. It is astonishing that more sophisticated and time-consuming methods for the evaluation of PEM and BCM are not superior to simple, inexpensive, bedside methods, such as anthropometry and handgrip dynamometry.

Anthropometric parameters that are more often used in the evaluation of nutritional deficit in patients with terminal liver diseases or in patients awaiting liver transplantation are TST and MAMC (Table 172.5). Malnutrition seems to be an independent risk factor and predictor of survival, according to Alberino et al. (Alberino 2001). In fact, it was shown that the inclusion of MAMC and TST improved the prognostic accuracy of the CP score. This evidence confirmed the findings of a previous study, which showed that the inclusion of MAMC improved the predictive outcome of the CP classification (Abad-Lakruz 1993). On the other hand, Chang et al. found that only triceps skinfold fat thickness correlated with the etiology and the severity of liver disease (Chang 2003). Similar results were deduced in a cross-sectional study among 42 cirrhotic children aged three months to 18 years in Brazil. The index with the highest prognostic value was TST. The parameters that were measured

Table 172.5 Malnutrition and changes in anthropometric measurements (Data taken from Campillo et al. 2006)



The degree of malnutrition is reflected by anthropometric parameters. Gradual loss of soft tissue is typical as the disease progresses

were weight/age, height/age, BMI, TST, and MAMC, and they were compared with the CP classification score that was given for each child (Schneider 2007). Perhaps the addition of anthropometric parameters to the CP classification could improve its prognostic value (Abbott 2001). The diminished muscle status and loss of functional tissue among liver disease patients with differences in etiology and pathogenetic mechanism or liver disease are associated with advanced CP classification and early postoperative morbidity (Abbott 2001).

Taking into account the accumulating evidence regarding the importance of the nutritional status with the use of simple and subjective anthropometric measurements, Gunsar et al. evaluated a modified SGA. The Royal Free Hospital (RFH)-SGA index combines subjective assessment of nutritional status with BMI, TST, MAMC, and a subjective override. The RFH-SGA index adds body mass index (BMI), TST, and MAMC to the standard SGA. According to this index, patients are easily classified into three groups: well nourished, mild or moderately malnourished, and severely malnourished. The RFH-SGA index may provide additional information to CP or model for end-stage liver disease scores regarding nutritional indices (Gunsar 2006) (Fig. 172.1).

Anthropometric parameters have been associated with survival. Merli et al. showed that patients with a MAMC below the 5th percentile, which reflects marked muscle tissue depletion, were expected to have poorer survival rates since malnutrition is considered a bad prognostic value (Merli 1996).

Therefore, the inclusion of anthropometry in the guidelines issued by the European Society for Clinical Nutrition and Metabolism (ESPEN) on January 2006, regarding the evaluation and therapeutic intervention of the nutritional deficit in end-stage liver diseases along with SGA, was not a surprise. *The use of simple bedside methods, such as SGA and anthropometry, to identify patients at risk of undernutrition* makes the evaluation of malnutrition fast and easy to perform. The ESPEN guidelines recommend the use of MAMC or mid-arm circumference (MAC) and TST (Plauth 2006). Diagnosis of undernutrition is established on values of MAMC and/or TST below the 5th percentile in ages 18–74 years or the 10th percentile in patients over 74 years (Campillo 2005).

It is very interesting to mention that the measurement of BMI can prove to be sufficient enough for the evaluation of the nutritional deficit. Campillo et al. used a simple method for the evaluation of the nutritional status of cirrhotic patients. The use of different BMI cutoff values according to the presence or not of ascites and its severity can prove reliable enough for the detection of malnutrition. Malnourishment was confirmed when patients had a BMI below 22 without the presence of acsites, below 23 with the presence of mild ascites, and below 25 with tense ascites (Campillo 2005).

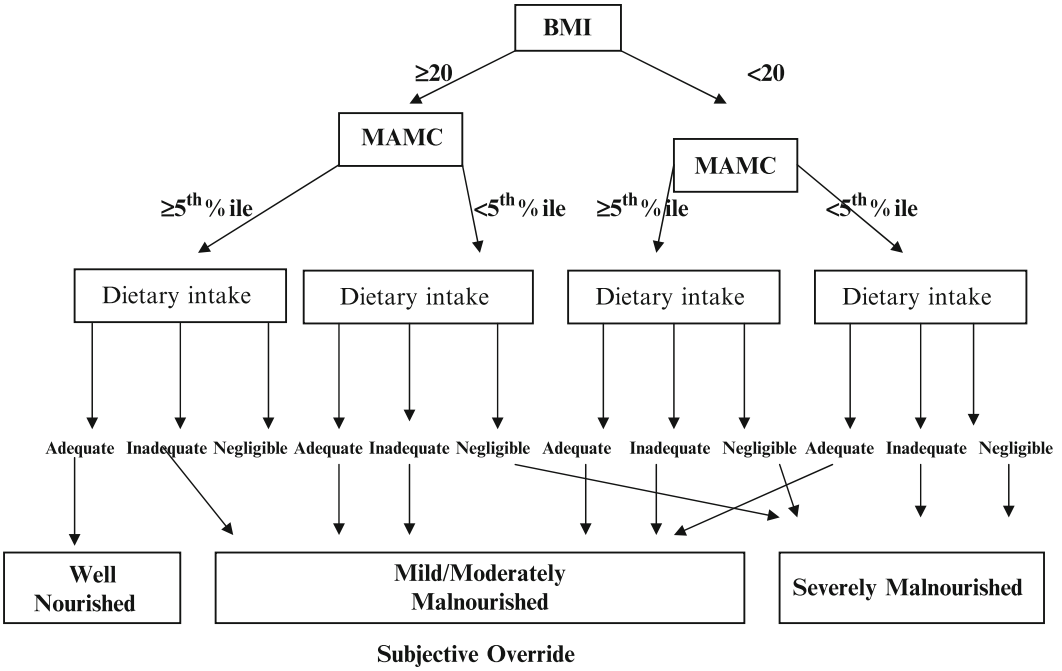


Fig. 172.1 Royal Free Hospital-Subjective Global Assessment (RFH-SGA) scheme for the assessment of the nutritional status in patients with ESLD as proposed by Gunsar F et al. Patients are divided in three categories: adequately nourished, moderately nourished (or suspected to be), and severely malnourished, with the use of simple anthropometric measurements

For long, BMI was not and perhaps is still not considered a reliable anthropometric parameter for the evaluation of malnutrition in the setting of liver cirrhosis since it can be falsely affected by the extreme accumulation of fluids in cirrhotic patients. Fluid retention, which is quite often encountered in liver decompensation, may inhibit the use of body weight and BMI for the identification of malnutrition since false negative results will be deduced. Since almost two-thirds of all cirrhotic patients exhibit overhydration, even in the absence of ascites, due to the shift of fluids to the extracellular compartment, the measurement of body weight and BMI certainly calculates much of all these fluids instead of the actual lean body mass (Tsiaousi 2008).

172.5.3 Limitations of Anthropometric Measurements

Despite the fact that anthropometric measurements are considered simple and reliable tools in the evaluation of the nutritional deficit in patients with liver cirrhosis, there are several factors that affect the precision of the measurements in this special group. In several cases, it seems extremely difficult to assess subjectively the nutritional state because of the gross maldistribution of bodily fluids among the various compartments. Marked fluid retention and overhydration of the peripheral tissues including the muscle tissue are the major factors that could interfere with the accuracy of the results taken from anthropometric measurements (Peng 2007).

Weight and BMI, which are widely used for the identification of malnutrition in several diseases, are not a reliable indicator of malnutrition in decompensated cirrhosis since the surplus body water will increase body weight but the actual lean body tissue might be significantly reduced. The presence of ascites and peripheral edema prohibit the use of common anthropometric parameters apart from body weight and BMI. For instance, subscapular skinfold thickness, suprailiac skinfold thickness, and waist circumference cannot be used in cirrhotic patients even without the obvious presence of fluid retention because more than two-thirds of this special population exhibit overhydration of body tissues.

Another potential limitation of anthropometry is the poor inter-observer reproducibility and intra-observer variability, especially among physicians inexperienced with this method. Possible means of receiving more accurate measurements are the repeated measurements on different occasions in the same hospital stay or visit and by more than one experienced physicians.

172.5.4 Diagnostic Accuracy of Anthropometry in Comparison with Other Applied Techniques

One of the parameters that should be estimated in the effort to assess the nutritional status is the degree of depletion of BCM. Morbidity and mortality among patients with markedly depleted lean tissue are significantly higher before and after liver transplantation (Muller 1992; Selberg 1997). BCM, which represents the active metabolic compartment of the body, can be quantified by various techniques. Whole-body potassium, in vivo neutron activation analysis, and isotope dilution are considered the most precise methods in the evaluation of the body compartments. These techniques are not available in the routine clinical assessment of malnutrition because they are costly and labor intensive. Perhaps, they should be limited to specialized units with sufficient clinical experience. Bioelectrical impendance analysis is a more readily available technique. Unfortunately, its diagnostic accuracy is affected by the retention of fluids.

Evaluation of resting energy expenditure (REE) with indirect calorimetry is also a practical method in the evaluation of malnutrition. Since hypermetabolism in cirrhosis drives many cirrhotic patients to protein and fat depletion due to the increased energy consumption, the evaluation of the status of energy metabolism is considered important (Henkel 2006).

Handgrip examination dynamometry has emerged to be a simple method in the detection of malnutrition. Alvares-da-Silva and Reverbel da Silveira have shown that handgrip examination is a reliable and easy-to-perform method with comparable results (Alvares-da-Silva 2005). Handgrip strength and MAMC have proved to be important nutritional assessment parameters for the detection of depleted BCM, which has been associated with adverse outcomes in patients with ESLD (Figueiredo 2000).

Anthropometric measurements may be the most practical objective indices of nutritional deficiency. They are simple, easy to perform, costless, and easily reproducible. They should be used routinely for the assessment of malnutrition in cirrhotic patients, along with SGA. The combination of a subjective assessment of nutritional status with BMI, TST, MAMC, and a subjective override (The Royal Free Hospital (RFH)-SGA index) can identify those malnourished patients in need of therapeutic intervention. The use of these two simple methods (anthropometry and SGA) in routine hospital visits is adequate in the screening for malnutrition (Gloro 2006; Gunsar 2006). The original guidelines of ESPEN propose the use of anthropometry and SGA since liver decompensation is an ongoing process with multiple complications, which require repeated evaluations of the liver function and the nutritional state (Tables 172.6 and 172.7).

Table 172.6 Methods of evaluation of the nutritional status in ESLD

BMI
Anthropometry
Serum Albumin
DEXA
Electrical impendance
Creatinine Index
Indirect calorimetry

Anthropometry provides sufficient data regarding the nutritional status in cirrhotic patients without being time consuming and labor intensive
BMI Body Mass Index; *DEXA* Dual-Energy X-ray Absorptiometry

Table 172.7 Key features of anthropometry in malnutrition in ESLD

1. Malnutrition is an independent predictor of survival in ESLD.
2. Anthropometry and SGA should be preferred to more sophisticated techniques in the routine examination of the nutritional state.
3. Common anthropometric indices used in ESLD: mid-arm circumference, triceps skinfold thickness, and mid-arm muscle circumference.

The table lists the key features of anthropometry in ESLD and emphasizes its prognostic value regarding the levels of malnutrition

172.6 Applications to Other Areas of Health and Disease

The evaluation of malnutrition in ESLD, in particular among patients awaiting liver transplantation, is of foremost importance. The outcome of liver transplantation in the early and late post-transplantation period depends, among others, on the nutritional state of the patient. The use of an inexpensive and practical method for the assessment of malnutrition in these patients is preferred to other more sophisticated but labor-intensive techniques. Apart from this, since anthropometry, along with SGA, provides sufficient information to categorize patients into the various degrees of malnutrition, it could be incorporated into the classifications used for the staging of the severity of end-stage liver disease.

172.7 Practical Methods and Techniques

- Assessment of the nutritional state should be performed in every hospital visit or stay in patients with end-stage liver disease since malnutrition is an independent predictor of survival.
- Measurement of anthropometric parameters and SGA should be preferred to more sophisticated techniques in the routine examination of the nutritional state.
- Measurement of mid-arm circumference (MAC) with the use of a simple or steel tape measure and the triceps skinfold thickness (TST) with skinfold calipers of the dominant arm will provide sufficient information regarding nutritional deficit.
- The mean of three measurements should be taken into account.
- Diagnosis of undernutrition is established on values of MAMC and/or TST below the 5th percentile in ages 18–74 years or the 10th percentile in patients over 74 years.
- Body mass index (BMI) will not provide sufficient data because of the fluid retention in cirrhosis and should not be used without the measurement of TST and MAMC for the evaluation of malnutrition.

Summary Points

- Malnutrition is almost universal in patients with decompensated liver cirrhosis and is an independent predictor of survival.
- Malnutrition is considered a severe complication of ESLD with adverse effects on the outcome of the disease before and after liver transplantation.
- The methods which are used universally for the evaluation of the nutritional status are subjective global assessment (SGA) and anthropometric parameters.
- Most common anthropometric parameters that are measured in cirrhotic patients are mid-arm circumference (MAC) and triceps skinfold thickness (TST).
- The anthropometric parameters with the greatest diagnostic and prognostic value are TST and mid-arm muscle circumference (MAMC).
- Possible limitations of anthropometry in ESLD are the fluid retention and the overhydration of tissues observed in liver cirrhosis, which may lead to false negative results and the intra- and inter-observer variability.
- Diagnosis of undernutrition is established on values of MAMC and/or TST below the 5th percentile or the 10th percentile.

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Chapter 173
Anthropometry in Anorexia Nervosa

Antonella Diamanti and Fabio Panetta

Abstract Anorexia Nervosa (AN) is a disorder characterized by a refusal to maintain body weight at or above a minimally normal level for age and height. Two subtypes of the disorder have been identified by the American Psychiatric Association: restricting and binge-eating/purging types. In the former, weight control is attained by a marked reduction in food intake only; in the latter, the occasional food consumption is followed by some forms of compensatory behaviours, such as self-induced vomiting, laxative or diuretic misuse, or strenuous physical exercise. This psychiatric disease mainly involves adolescent girls and young women. Their incidence is increasing in adolescent girls, but first symptoms sometimes appear in childhood. Malnutrition is the prominent feature of AN, requiring a careful and complete medical surveillance, based on anthropometry and body composition assessment.

Anthropometric evaluation in AN patients includes the direct determination of some anthropometric parameters (height, weight, skin fold thickness and mid-upper arm circumference) and the calculation of nutritional indices derived from these (BMI and Weight-for-Height). Most single anthropometric measurements, indeed, in themselves may partially assess the nutritional status. Nutritional indices are derived either by combining two or more anthropometric measurements, or by comparing the anthropometric measurements with reference to values of healthy, well-fed populations.

The evaluation of body composition completes the anthropometric evaluation and is relevant in these patients, because it gives an objective measure of their malnutrition. These patients, indeed, overevaluate their shape and weight and then have limited motivation to change, which results in unreliable self-evaluation and anamnestic assessment. A wide variety of methods are available to measure body composition. Anthropometry, based on the evaluation of skin fold thickness and mid-upper arm circumference, represents the simplest method of estimating body composition and, as such, are often used. More sophisticated techniques to study body composition are represented by bioelectric impedance analysis and dual-energy X-ray absorptiometry, both employed in clinical practice as well as in research settings. Other methods, employed only in research settings, are represented by total body imaging techniques (magnetic resonance imaging and computed tomography), underwater weighing, isotope dilution techniques and neutron activation analysis.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_173,

Abbreviations

AMA	Upper Arm Muscle Area
AN	Anorexia Nervosa
BIA	Bioelectric Impedance Analysis
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CT	Computed Tomography
DSM-IV	Diagnostic and Statistical Manual for Mental Disorders-IV
DXA	Dual-energy X-ray Absorptiometry
FFM	Fat Free Mass
FM	Fat Mass
ICD-10	International Classification of Diseases and Related Health Problems 10th Revision
LBM	Lean Body Mass
MRI	Magnetic Resonance Imaging
MUAC	Mid-Upper Arm Circumference
MUAMC	Mid-Upper Arm Muscle Circumference
SFT	Skin Fold Thickness
UWW	UnderWater Weighing
WHO	World Health Organization

173.1 Introduction

Anorexia nervosa (AN) is the visible eating disorder, universally associated with emaciation and usually accompanied by marked increase of physical activity. AN typically arises in adolescence but often persists into adulthood. Patients with AN lose weight by restricting their food intake and by exercising a lot; several AN patients also self-induce vomiting after meals and take laxatives, diuretics, or diet pills. Individuals with AN are unable to maintain a normal healthy body weight, often dropping well below 85% of their ideal weight. Despite increasing cachexia, individuals with AN have an obsession about gaining weight, feel frustrated about the perceived largeness of their bodies, and engage in an array of behaviors designed to perpetuate weight loss. Table 173.1 shows the key features of AN.

Table 173.1 Key features of Anorexia Nervosa

- Eating disorder, universally associated with emaciation and usually accompanied by marked increase of physical activity.
- Typically arises in adolescence but often persists into adulthood.
- Patients with AN lose weight by restricting their food intake and by making high exercise
- Patients self-induce vomiting after meals and take laxatives, diuretics, or diet pills.
- Individuals with AN are unable to maintain a normal healthy body weight, often dropping well below 85% of their ideal weight.
- Despite increasing cachexia, individuals with AN have an obsession about gaining weight, feel frustrated about the perceived largeness of their bodies, and engage in an array of behaviors designed to perpetuate weight loss.

This table lists the key facts of AN including clinical and psychological features of this disease
An annorexia nervosa

Table 173.2 DSM IV-TR criteria for anorexia nervosa

(a) Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected, or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
(b) Intense fear of gaining weight or becoming fat, even if underweight.
(c) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
(d) In postmenarcheal females, amenorrhea, that is, the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen administration.)
Restricting type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or misuse of laxatives, diuretics, or enemas).
Binge-eating/purging type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or misuse of laxatives, diuretics, or enemas).

This table lists the diagnostic criteria of anorexia nervosa by DSM-IV, a manual published by the American Psychiatric Association that provides diagnostic criteria for mental disorders
DSM-IV Diagnostic and Statistical Manual for Mental Disorders-IV

Table 173.3 ICD-10 criteria for anorexia nervosa (F50.0)

(a) The patient's body mass index (BMI) is 17.5 or less, or body weight is maintained at least 15% below the expected or average body weight for the patient's age and sex. If the patient is prepubertal, then the expected weight gain does not occur during the growth period.
(b) Weight loss is self-induced and/or sustained through the avoidance of 'fattening' foods and through the utilization of other weight-loss tactics.
(c) Body-image distortion and a morbid dread of fatness, such that the patient imposes an unhealthy and unreasonably low weight threshold on themselves.
(d) There is evidence of endocrine disorder in the form of amenorrhea among women and loss of sexual desire and potency among men. There may also be elevated levels of growth hormone and cortisol, alterations to the metabolism of thyroid hormone, and abnormal insulin secretion.
(e) In prepubertal patients, puberty is delayed but is often completely normal after recovery.

This table lists the diagnostic criteria of anorexia nervosa by ICD-10: a coding of diseases and signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases, as classified by the World Health Organization (WHO)
ICD-10: International Classification of Diseases and Related Health Problems 10th Revision

173.1.1 Diagnostic Criteria of AN

The clinical features of AN are easily recognized, and the diagnosis is usually made by highly reliable clinicians. The diagnostic criteria of the two major classification systems currently used, Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV) and World Health Organization's (WHO) ICD 10th edition (ICD-10), are very similar (Tables 173.2 and 173.3). Both diagnostic criteria currently use a % ideal body weight equivalent to 85% of expected body weight or a failure to achieve expected growth during a growing period. The ICD provides an additional index utilizing body mass index (BMI) of <17.5 kg/m^2, which is below the WHO and CDC (Centers for Disease Control and Prevention) definitions of underweight (BMI < 18.5 kg/m^2). DSM-IV, however, distinguishes between two subtypes of AN, restricting and binge-eating/purging, based on the presence or absence of bulimic symptoms. It happens more often that individuals with the binge-eating/purging type present comorbidity, impulsivity, as well as substance use disorders, mood lability, and suicidality, compared to those with the restricting type. Tables 173.2 and 173.3 report diagnostic criteria for AN by DSM-IV and ICD-10.

173.1.2 Epidemiology

In the large-scale population, prevalence of AN is estimated at 1%.

About 90–95% of patients with anorexia are females. Data gathered from two recent, large population-based studies, one in USA and one in Scandinavia, found lifetime prevalence rates of 0.9% and 1.20%, respectively, for women and 0.3% and 0.29%, respectively, for men (Bulik et al. 2007). Researches suggest that prevalence of AN has increased in recent years. AN typically first manifests in adolescence; midlife onset is rare. Age at onset for AN ranges from preteen to adult, with bimodal peaks at ages 13–14 and 17–18 years. Prepubertal AN may be associated with a more severe profile, and onset at adolescence is associated with a better prognosis than are prepubertal and adult ones. AN is no longer predominantly a disorder of the middle class, as it may have been 50 or 100 years ago. In developed societies today, it is distributed fairly equally between the social classes; it is also found in developing countries. Some evidence indicates that women immigrating to more industrialized countries from countries in which the prevalence of AN is low may be at greater risk of assimilating thin body ideals.

173.1.3 Clinical Features

Adolescent patients often appear physically younger than their chronological age, whereas those with chronic AN may look considerably older than they actually are. Cachexia and breast atrophy are apparent. Often, the skin is dry and yellow tinged due to carotenemia. Physical signs commonly include bradycardia, hypotension, lanugo, alopecia, and edema. Patients who self-induce vomiting present dental erosion and dorsal-surface hand lesions.

AN patients may complain of cold intolerance, dizziness, constipation, and abdominal discomfort. Despite malnutrition, these patients are often hyperactive; lethargy may indicate fluid and electrolyte imbalance, dehydration, cardiovascular compromise, or severe depression.

Table 173.4 reports clinical complications of AN.

173.1.4 Differential Diagnosis of Eating Disorders

In the absence of behavioral or cognitive indicators of AN, the clinician may suspect a somatic cause of weight loss. However, it is not advisable to encourage extensive and invasive clinical investigations if the patient's symptoms can be explained adequately by making a diagnosis of either AN or another eating disorder. Main diseases that can mimic eating disorders and that, therefore, should be ruled out during the diagnostic work-up of AN are: Addison's disease, hyperthyroidism, inflammatory bowel disease, and celiac disease.

173.1.5 Course of Illness

Although the course of the disorder varies, it is often marked by chronicity and relapse. A comprehensive meta-analysis of 119 studies including 5,590 patients with anorexia indicated that over long-term follow-up (up to 29 years; mode = 5–10 years), less than one-half of the surviving patients

Table 173.4 Clinical features of anorexia nervosa

Metabolic	Electrolyte disturbances (hypoglycemia, hypophosphoremia, hypocalcemia, and hypomagnesemia)
Cardiovascular	Orthostatic hypotension
	Bradycardia
	Arrhythmia
	Attenuated response to exercise
	Atrial Fibrillation and Flutter
	A-V Blocks
Neurological	Pseudoatrophy of the brain
	Abnormal electroencephalogram and seizures
	Peripheral neuropathy
	Psychomotor slowing
Hematological	Anemia
	Leukopenia
	Thrombocytopenia
	Hypocellular bone marrow
	Infectious complications
Renal	Partial diabetes insipidus
	Acute and chronic renal failure
Endocrine	Amenorrhea
	Pubertal delay
	Low T3 syndrome
	Growth delay
	Raised growth hormone
Musculoskeletal	Cramps, tetany, and muscle weakness
	Osteopenia, osteoporosis, and stress fractures
Gastroenterological	Dental caries and erosion of enamel (with vomiting)
	Superior mesenteric artery syndrome
	Delayed gastric emptying, severe constipation, and bowel obstruction
	Irritable bowel syndrome and melanosis coli (from laxative misuse)
Skin	Acrocyanosis
	Lanugo
	Hypertrichosis
	Brittle nails
	Sparse and brittle hair

This table lists main clinical features of AN according to the different body organs involved

achieved full recovery (Steinhausen 2002). Even among those who achieve full recovery, up to one-third are likely to experience relapse. The majority of individuals with AN engage in bingeing and purging behaviors during the course of the disorder; thus, diagnostic migration from the restricting type of AN to the binge/purge type or to bulimia nervosa is common, particularly within the first 5 years of illness (Eddy et al. 2002). In spite of diagnostic and treatment advances, the prognosis of AN does not seem to have improved during the twentieth century (Steinhausen 2002). The mortality rate for women with AN, at 0.56% per year, is more than 12 times higher than that for age-matched women in the general population (Sullivan 1995). The rate of suicide is also high, with one study reporting a 57-fold increase in death by suicide among individuals with AN (Keel et al 2003). In a survey of 14 outcome studies, Herzog et al. (1988), found that 24% of the deaths reported were due to suicide. Although death is commonly due to suicide, it is also frequently ascribed to inanition and cardiac failure. Table 173.5 summarizes the main prognostic, reported factors in AN outcome.

Table 173.5 Prognostic factors of Anorexia nervosa

Favorable factors	Unfavorable factors	Predicting death factors
• Absence of severe emaciation (i.e., body mass index >17)	• Presence of vomiting in very malnourished patients, particularly vomiting that has become so frequent as to be almost automatic	• Abnormally low serum albumin levels and low weight at intake
• Absence of serious clinical complications	• Later age of onset	• Poor social functioning,
• Motivation to change present behavior	• History of neurotic and personality disturbances	• Longer duration of illness
• Presence of supportive family and friends	• Disturbed family relationships	• Bingeing and purging
	• Longer duration of illness	• Comorbid substance abuse • Comorbid affective disorders

This table lists the prognostic factors in AN that were subdivided into favorable, unfavorable, and predicting death

With recovery from AN, physical health can be regained. Patients can live a long and normal life. Fertility is not impaired, and pregnancy and normal childbirth can be achieved. There is no evidence of permanent brain, heart, or kidney injury in recovered patients who did not present a too serious form of the disorder. Possible permanent physical complications are loss or erosion of teeth, Korsakoff's syndrome (the permanent clinical syndrome of impaired short-term memory that results if Wernicke's encephalopathy is not treated), and, perhaps, osteopenia. Whether bone density can return to 'normal' is not known, but recovery to 'within normal limits' is possible.

The most common long-term symptoms after recovery from AN are those related to the bowel. Constipation, bloating, and abdominal pain may last for decades or may even be permanent. The most common complaint that endangers health is osteoporosis. Recurrent bone fractures can cause chronic pain and lead to chronic disability. Those patients who do not recover suffer from progressive weakness, decreased exercise tolerance, bone pains and fractures, episodes of faintness, tiredness, stress incontinence of the bladder, bowel pain, cramping, and bloating, and decreased ability to recover from bacterial infections or for wounds to heal following surgery.

With regard also to the psychiatric outcome, the recovered AN patients can live a normal life. They can return to work and have families; however, they will always have a greater concern than others about their body weight and shape and might respond to a life trauma with recurrent anorexia behavior. Patients who are chronically anorexic become reclusive, have low self-esteem, and remain obsessional and depressed (Bulik et al. 2005).

173.2 Malnutrition in AN

Malnutrition is the prominent feature of AN, requiring a careful and complete anthropometrical evaluation. AN is different from other forms of malnutrition because it is voluntary, resistant to nutritional treatments, accompanied by increased physical activity, without an initial organic cause (such as malignancy or surgery) and without associated infections. Due to the fact that AN is a state of mere malnutrition without associated increase of energy expenditure due to fever, immune response, or tissue reconstruction, these patients have a lowered metabolic rate and do not tend to develop opportunistic infections. In AN, a very low weight is achieved through weight loss as the result of a

severe and selective restriction of food intake. In most instances, there is no true anorexia as such. Many patients engage in a driven type of overexercising, which can contribute to their weight loss. Self-induced vomiting and misuse of laxatives or diuretics are practiced by a few individuals (restrictive vs. purgative patterns). AN is a self-imposed starvation. The term 'anorexia' is a misnomer since (at least initially) these patients are hungry. The exact mechanism by which these patients are able to control their hunger is unknown. Disturbed brain neurotransmitter activity may be implicated primarily or secondarily.

The psychiatric illness of AN, which occurs mainly in adolescent girls and young women, is characterized by strict dieting, a morbid fear of fatness, maintenance of an abnormally low weight, and amenorrhea. The obsession of losing weight leads AN patients to adopt some distorted attitudes toward food and an altered pattern of food consumption which, in some cases, produce in the patients such a serious state of malnutrition as to require their hospitalization. It seems extremely difficult to correct the psychic aspect of the illness without first improving the nutritional status.

173.3 Anthropometry and Body Composition

Anthropometric evaluation in AN patients includes the direct determination of some anthropometric parameters and the calculation of nutritional indices derived from these. Most single anthropometric measurements, indeed, in themselves may partially assess the nutritional status. Nutritional indices are derived either by combining two or more anthropometric measurements, or by comparing the anthropometric measurements with reference to values of healthy, well-fed populations.

The main anthropometric measurements employed in AN patients are height, weight, skinfold thickness (SFT), and mid-upper arm circumference (MUAC). Among all the nutritional indices available, a relevant role in diagnosing and monitoring the nutritional status of these patients is attributed to BMI and to weight-for-height ratio.

Regarding the reference values of all these parameters, many countries have developed their own reference standards for weight and height of children and adolescents. In USA, the CDC published, in the year 2000, growth charts for people 0–20 years of age. UK, France, and several other countries have developed reference growth curves based on national data sets. Although growth rates differ across countries, there is, in general, a consensus that, in a healthy population, these differences are encompassed within the boundaries of acceptable percentile ranges, usually the 5th and 95th. A new reference data set, derived from mostly cross-sectional studies undertaken between 1978 and 1990 of 23,000 British people aged 0–20 years, has been developed by the Human Measurements Anthropometry and Growth Research Group. Growth charts from these data have been produced by sex for weight-for-age, height-for-age, length-for-age, head circumference-for-age, and BMI-for-age (http://www.cdc.gov/growthcharts/).

In the clinical management of AN, some anthropometric measurements are also employed to estimate body composition. The evaluation of body composition completes the anthropometric evaluation and is relevant in these patients, because it gives an objective measure of their malnutrition. These patients, indeed, overevaluate their shape and weight and then have limited motivation to change, which results in unreliable self-evaluation and anamnestic assessment. A wide variety of methods are available to measure body composition. Anthropometry represents the simplest method of estimating body composition and as such is often used.More sophisticated techniques to study body composition are represented by bioelectric impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA), both employed in clinical practice as well as in research settings.

Other methods, employed only in research settings, are represented by total body imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT), underwater weighing (UWW), isotope dilution techniques, and neutron activation analysis.

173.4 Anthropometry

173.4.1 Anthropometric Measurements

173.4.1.1 Height

Height indicates attained size or growth of adults and children. Long periods of inadequate food intake, as in AN patients, result in a slowing of skeletal growth and individuals being short for their age, or stunted. Consecutive measurements of height every three to six months should be adopted to assess growth velocity in prepubertal AN subjects. Growth velocities are useful to monitor growth and assess the response to therapy including nutritional supplementation. In AN patients, the duration of hospitalization, a marker of disease severity and chronicity, seems to strongly influence growth velocity, with negative influence on the target height at adulthood for a given individual (Rozé et al. 2007).

173.4.1.2 Weight

The initial assessment of weight is a good time to inquire about the greatest weight the patient has ever attained, the lowest weight (at the current height), the weight trajectory over the past few years, the patient's desired weight, and the weight the patient would settle upon to achieve good health. Along with obtaining a careful history, a treatment team member should measure weight and height and, during the course of treatment, should continue to measure weight in a consistent manner, under similar conditions, for example, at the same time of the day, postvoiding, and with the patient in similar garb. Occasionally, some patients with AN may try to make themselves appear heavier than they really are either by strapping weights close to their body, or by carrying heavy objects in their pockets, or by drinking excessive amounts of water and avoiding urinating before weighing. If possible, for purposes of accurately comparing repeated weights, the weight should be obtained at the same time each day, preferably in the morning, immediately after voiding. Excess clothing, such as coats, scarves, shoes, belts, and watches, should be removed.

Consecutive measurements of weight can be used to monitor the effects of treatment, such as either weight loss on reduction diets or weight gain with nutritional interventions and supplementation.

This anthropometric marker is important in diagnosing, monitoring, and predicting the outcome of AN. Both the diagnostic criteria employed for the diagnosis of eating disorders include the weight. Both schema currently use either a % ideal body weight equivalent to 85% of expected body weight or a failure to achieve expected growth during a growing period, as diagnostic criteria of AN.

Indications to hospitalization take also into account the weight. In-patient brief hospitalization (7–14 days) is sometimes possible for patients with the following: weight loss of either 10–15% from normal weight if relapsed or 16–20% if first episode. Extended hospital treatment (14–60 days)

is often necessary for patients who have weight loss >20% of normal for age, height, and bone structure (Yage and Powers 2007).

As a prognostic factor, in a well-documented sample of 84 female patients with anorexia, who had been followed up after an average of 21.3 years following first in-patient treatment, it was shown that an inadequate weight gain during the first hospitalization was an additional risk factor for a poor outcome (Zipfel et al. 2000).

173.4.1.3 SFT

Precision SFT calipers are used to measure the double fold of skin and subcutaneous fat to the nearest millimeter. SFT is not useful for monitoring short-term change in fat stores but can have great importance in chronic situations, such as AN. The study of body fat distribution can have important implications for the treatment of AN because of the patients' intense fear of gaining weight and becoming fat, which is enhanced by the belief that this would be accompanied by fat distribution in the abdominal region. Hence, the amount of body fat at discharge may influence the further evolution of the disease (Krahn et al. 1993). In addition, plicometry seems to have a prognostic value in the clinical assessment of AN: a trend to revert to the restricting habits once the patients leave the hospital seems to exist; therefore, there is a critical time with a high risk of relapse around the end of the first year of follow-up. The decrease in the intake of energy and macronutrients at this time of treatment seems to be related to fat replenishment (Nova et al. 2001).

There are various measures of skinfold thickness:

- *Triceps*: at a point equidistant from the tip of the acromion and the olecranon process;
- *Subscapular*: just below the tip of the inferior angle of the scapular;
- *Biceps*: at the midpoint of the muscle with the arm hanging vertically; and
- *Suprailiac*: over the iliac crest in the midaxillary line.

In AN, triceps SFT seems to be the most significantly correlated with percentage of body fat (Kerruish et al. 2002).

173.4.1.4 MUAC

MUAC is assessed on the non-dominant arm, midway between the tip of the acromion process and the olecranon, and it measures upper-arm fat and muscle in adults and children. It is a useful surrogate of weight when weighing is impossible. This parameter represents a simple, objective, and reproducible marker of nutritional status that correlates with BMI in adolescents with AN. Lack of consistency between longitudinal measurements of BMI and MUAC in individuals with AN should be viewed suspiciously and prompt a more detailed nutritional assessment. Since the rate of change of arm circumference is slow, it cannot be used to assess short-term changes in nutritional status as response to therapy. Longitudinal measurements of MUAC, instead, provide an unbiased and truly objective picture of the trend in nutritional status over time.

This measure seems to have an important role not only in monitoring the nutritional status of these patients but also in indicating the hospitalization due to malnutrition. Indeed, it is suggested that adolescents with AN who have a MUAC $\geq$ 20 cm rarely require hospitalization for malnutrition (Martin et al. 2009).

173.4.2 Nutritional Indices

173.4.2.1 BMI

In addition to determination of the patient's weight and height, calculation of BMI has gained increasing attention in both research and clinical settings. The use of the simple measure of body weight as an indicator of body protein and triceps skinfold thickness as an indicator of percentage of body fat obviates the need for more sophisticated, expensive, and hazardous techniques.

This index has high value in the diagnosis of eating disorders (ICD-10) and in the assessment of protein malnutrition in these patients: a BMI >16.5, indeed, is likely to be indicative of a normal protein status. In addition to diagnosis, BMI of 13 seems to have great importance as a prognosis factor in these patients. BMI of less than 13 entails a strongly elevated mortality risk (Hebebrand et al. 1997).

Furthermore, in a well-documented sample of 84 female patients with anorexia, followed up for about 21 years, low BMI, inadequate weight gain during first hospitalization, and severe psychological or social problems resulted risk factors for a poor outcome (Zipfel et al. 2000). It is also shown that a BMI percentile range of 14th–39th is generally associated with the resumption of menses and, therefore, can be used to assign a treatment goal weight (Hebebrand et al. 1997), while a persistently low BMI predicts for delayed menarche (Rozé et al. 2007). A low BMI is also considered the most important predictor for a disturbed bone turnover (Weinbrenner et al. 2003).

173.4.2.2 Weight-for-Height

In children aged 1–10 years, this index seems to be more reliable than BMI. The BMI criterion based on a BMI less than 17.5 is indeed only applicable to adults; for example, in 10-year-old girls, this BMI is above the 50th centile, thus clearly documenting its inapplicability in children and young adolescents.

Children with weight-for-height less than 85% of the median reference are considered wasted.

173.5 Body Composition

173.5.1 Changes in AN

In the underweight state, although patients may feel 'huge', studies have documented that all components of body are severely diminished (Krahn et al. 1993; Kerruish et al. 2002).

Therefore, AN patients, adults, and adolescents have less FM and LBM. However, in the starvation that accompanies AN, although both FM and LBM decrease, FM is preferentially depleted (Soh et al. 2009).

With weight recovery, AN subjects had increases in FM and LBM (Vaisman et al. 1988).

However, reduced % of FM is maintained also in recovered AN patients, probably due to the fact that former AN patients are more physically active than control ones (Frey et al. 2000).

Regarding the fat distribution, in contrast to adults with AN, percentage extremity fat is not significantly different in AN subjects compared with control subjects. In addition, adolescent girls with

Table 173.6 Anthropometrical evaluations in Anorexia Nervosa

Measurement	Clinical practice	Scientific purpose	Diagnosis	Longitudinal evaluation	Prognosis
Stature	*Yes*	*Yes*	*Yes*	Not	*Not*
Weight	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
SFT	*Yes*	*Yes*	*Yes*	*Yes*	Not
MUAC	*Yes*	*Yes*	Not	*Yes*	Not
BMI	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Weight for height	*Yes*	*Yes*	Not	*Yes*	Not
MRI/CT	Not	*Yes*	Not	Not	Not
Isotope dilution techniques	Not	*Yes*	Not	Not	Not
BIA	*Yes*	*Yes*	Not	*Yes*	Not
DXA	*Yes*	*Yes*	Not	*Yes*	Not
Hydrodensitometry	Not	*Yes*	Not	Not	Not
Neutron activation analysis	Not	*Yes*	Not	Not	Not

This table reports the clinical application of the single anthropometry and body-composition measurements in diagnostic work-up of malnutrition in AN patients
SFT skinfold thickness; *MUAC* mid-upper arm circumference; *BMI* body mass index; *MRI* magnetic resonance imaging; *CT* computed tomography; *BIA* bioelectric impedance analysis; *DXA* dual-energy X-ray absorptiometry

AN had lower percentage trunk fat than did control subjects. Weight recovery led to an increase in trunk fat relative to extremity fat and thus led to central fat accumulation, as in adult patients (Misra et al. 2003).

Boys with AN had lower fat and lean mass than did control subjects. However, in addition and in contrast with findings in girls with AN, percentage trunk fat was higher than in control subjects, particularly after adjustment for weight and fat mass. LBM in boys with AN also resulted lower in control subjects than reported in girls with AN. These findings are consistent with a sex-specific dichotomy and are likely mediated by low concentrations of testosterone. To summarize, boys with AN have preferentially lower FM and LBM in the extremities and higher FM in the trunk than do control subjects. In contrast, girls with AN have much lower FM in the trunk than in the extremities than do control girls (Misra et al. 2008).

The changes in body composition may have a clinical significance for the prognosis. The amount of FM may indeed affect the clinical outcome. Menses return with refeeding when patients reach higher percentages of body fat (18%); however, the changes in FM and the return of menses may also enhance the psychological stress in patients, increasing the likelihood of relapse (Probst et al. 2001).

Additionally, in weight-restored women, lower percent of FM is associated with poor long-term outcome (Mayer et al. 2007).

173.5.2 Assessment of Body Composition

Various direct and indirect methods for estimation of body composition have been developed, all of which are imperfect and require several assumptions and age- and gender-specific considerations. For research purposes, body composition has been determined using techniques, such as total body water, DXA, total body imaging techniques, UWW, neutron activation analysis, and isotope dilution techniques. In clinical studies, bioelectrical resistance and skinfold measurements are most frequently employed. Table 173.6 summarizes the potential application of all anthropometry and body composition measurements in the diagnostic work-up of AN patients.

173.5.3 Assessment of Body Composition Direct Methods

173.5.3.1 Anthropometry

Body composition by anthropometry is potentially a very accurate, reliable, and inexpensive way of estimating total body fat. Anthropometry is based on the evaluation of SFT and MUAC. SFT measures subcutaneous body fat. Durnin and Womersley made measurements of SFT and body density using UWW and produced tables to enable calculation of the percentage of body-fat weight from skinfold measurements (Durnin and Womersley 1974). MUAC measures the totality of mid-upper arm tissues (bone, muscle, fluid, and fat).

Mid-upper arm muscle circumference (MUAMC) and upper-arm muscle area (AMA) are estimates of upper-arm muscle and, therefore, body composition. They can be used as indicators of muscle mass and protein stores. Both MUAMC and AMA can be compared with reference values by age and sex (Caballero et al. 2005).

173.5.3.2 MRI/CT

The use of CT has had limited application in body-composition research primarily due to radiation exposure. Its use has mainly been limited to single-slice acquisitions in the abdomen and mid-thigh, whereby information on adipose-tissue distribution and muscle cross-sectional area has been derived. The use of MRI has resulted in important advances in body-composition phenotyping. MRI studies are safe, and instruments are available in most hospitals or related facilities. Expense is a limiting factor. The importance of both CT and MRI is that both methods acquire cross-sectional images of the body at pre-defined anatomic locations. These methods are used for research purposes, to evaluate the regional body-fat distribution in AN patients and in controls.

173.5.3.3 Isotope Dilution Techniques

Examples of commonly used tracers for these studies include deuterium oxide for total body water, sodium bromide for extracellular water, and total body potassium for body cell mass. These studies, reported only in research settings, showed that stable female patients with AN have more body water and more body potassium per kilogram body weight than age-matched healthy female controls (Dempsey et al. 1984).

173.5.4 Assessment of Body Composition by Indirect Methods

173.5.4.1 BIA

BIA is a simple, inexpensive, noninvasive body-composition measurement method. It is based on the electrical conductive properties of the human body. Measures of bioelectrical conductivity are proportional to the total body water and to the body compartments with high water concentration, such as fat-free and skeletal muscle mass. BIA assumes that the body consists of two compartments, FM and fat-free mass (FFM).

This method seems to be a promising tool for the assessment of changes in nutritional status and of body composition in AN patients during refeeding. This is of particular clinical importance in the planning of adequate energy and nutrient intake to support restoration of weight and proportionate body composition to normal nutritional status in the patients (Mika et al. 2004).

Both anthropometry and BIA are tools to estimate FFM and FM. Although there was a good linear correlation between the two methods, when BMI declines below 15, a progressive disagreement between methods is documented, being a (threshold) function of BMI in the estimation of FM and FFM. Below BMI 15 kg/m^2, BIA equations progressively underestimated FM (overestimated FFM) compared with skinfold. Hence, BIA equations should not be used in anorexic patients with a BMI of 10–15 (Piccoli et al. 2005).

173.5.4.2 DXA

DXA represents the most commonly used technique today, with good reproducibility in children and adults. There are no known factors, including hydration effects, which significantly influence the validity of DXA body-composition estimates, unlike BIA. The radiation exposure is minimal, and the technique can be used in children and adults of all ages. Significant correlations between BMI and percentage of body fat evaluated by DXA are found (Kerruish et al. 2002).

Assessment of bone density represents the main goal of this procedure. The studies performed with DXA in this field showed that girls with AN had reduced bone mineral accrual and progressive spinal osteopenia over the years, compared with their healthy counterparts. Change in FFM was the most significant determinant of change in lumbar BMD in both AN and healthy girls (Soyka et al. 2002).

However, AN patients at the early stage do not show significant differences in bone mineral status when compared to healthy controls (Diamanti et al. 2007).

173.5.4.3 UWW

UWW is considered to be the method of reference for body-composition assessment and is estimated to have excellent reliability and validity. The correlation between UWW and SFT measures ranges from 0.65 to 0.93 (Zipfel et al. 2000). Because there was sufficient agreement among the results obtained by UWW and SFT measurement, for AN patients with relatively little body fat, simple SFT measurements are as useful as this more sophisticated measure for the estimation of body composition (Mayer et al. 2007).

173.6 Neutron Activation Analysis

The advantage of using this method over other techniques for estimating protein nutritional status is that it measures body protein directly and is not affected by other factors, such as hydration status, renal function, and catabolism. Neutron activation analysis has been shown to provide safe, accurate, and precise measurements of total body nitrogen in children and adolescents. It is employed, however, only in few research settings (Kerruish et al. 2002).

Summary Points

- Individuals with AN are unable to maintain a normal healthy body weight, often dropping well below 85% of their ideal weight.
- The American Psychiatric Association identified two subtypes of the disorder: restricting and binge-eating/purging.
- Prevalence of AN is estimated at 1%.
- Measurements of height every 3–6 months should be adopted to assess growth velocity in prepubertal AN subjects.
- Weight during the course of treatment should be measured in a consistent manner, under similar conditions, for example, at the same time of the day, postvoiding, and with the patient in similar garb.
- An inadequate weight gain during the first hospitalization is an additional risk factor for a poor outcome.
- SFT is useful for monitoring long-term change in fat stores.
- MUAC is a useful surrogate of weight when weighing is impossible.
- BMI >16.5 is likely to be indicative of a normal protein status.
- BMI <13 entails a strongly elevated mortality risk.
- Weight-for-height ratio seems to be more reliable than BMI <10 years.
- BIA seems to be a promising tool to assess changes in nutritional status and in body composition during re-feeding.
- BIA equations should not be used in anorexic patients with a BMI 10–15, because they underestimate FM.
- DXA is a good technique used to estimate the body composition in children and adults. However, the main goal of this procedure is the assessment of bone density.

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Chapter 174
Clinical Practice of Body Composition Assessment in Female Subjects with Anorexia Nervosa

Michel Probst and Marina Goris

Abstract Anorexia Nervosa (AN) is characterised by a refusal to maintain a minimally normal body weight and by the distorted perception of one's own body (weight, size, shape) as a negative interpretation of their appearance as too fat, resulting in the intense fear of weight gain, even when severely underweight. Both from a physiological and psychological viewpoint, weight, weight restoration and body composition are crucial elements for the treatment of AN. AN patients have unrealistic ideas about body fat and the influence of food intake and dieting on body weight and shape.

Over the last ten years, body composition in female anorexia nervosa has become an important topic in treatment as well as in research. Increasingly, body composition is integrated into the assessment of the evolution of AN in patients.

A wide variety of methods have been used to measure body composition in anorexia nervosa. The skinfold measurements and the bio impedance analysis are most often used in clinical practices. However, clinicians have to be careful with the use of the bio impedance analysis BIA for the estimate of body fat in AN. Additionally, the body mass index (BMI) does not predict the body composition or reveal the change in body composition.

There are a number of available equations to estimate the percentage of body fat from the available body density. The Siri-Formula (In: Lawrence JH, Tobias CA, editors. Advances in biological and medical physics. New York: Academic Press, p. 239–280, 1956) is recommended, with some restrictions.

A weight gain program for patients with anorexia nervosa lead to a significant increase in body weight and body fat. More than half (55%) of the weight increase is attributed to the increase of fat mass. The body composition results had to be communicated and explained to the AN patients in psycho-education sessions.

Here, guidelines for a standard protocol of anthropometric assessments in the clinical practice are proposed. Despite an increase in knowledge about the body composition of patients with anorexia nervosa, more fundamental research is necessary in regard to the limitations of the techniques and equations for these specific group of underweight patients.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_174,

Abbreviations

AN	Anorexia nervosa
BIA	Bio impedance analysis
BMI	Body mass index
CS	Control subjects
D	Density
DXA	Dual energy X-ray absorptiometry
DSM	Diagnostic statistical manual
FFM	Fat free mass
FM	Fat mass
NM	Not mentioned
PBF	Percentage body fat
r	Correlation coefficient
SFT	Skinfold thickness
TBW	Total body water
UWW	Underwater weighing

174.1 Introduction

Anorexia nervosa (AN) is characterised by a refusal to maintain a minimally normal body weight. A subgroup of AN is characterised by fasting, followed by inappropriate compensatory behaviours, such as self-induced vomiting, misuse of laxatives (or other medications), fasting or excessive exercise. A distorted attitude towards one's own body shape and weight is an essential feature of eating disorders. The disorder primarily affects female adolescents. Weight restoration is one of the important goals in the treatment of patients with anorexia nervosa. For the diagnostic criteria, see Diagnostic Statistical Manual (DSM-IV; American Psychiatric Association (APA) 1994).

These diagnostic features of AN could be accompanied by somatic, psychic, behavioural and social disturbances (APA 1994). For a more detailed description of the somatic features of AN, see chapter 174. Furthermore, in AN, many psychic symptoms are typically well developed, such as a distorted body experience, sexual problems, an attempt to prolong childhood and to escape the responsibilities of adulthood, perfectionism, feelings of ineffectiveness, inflexible thinking, limited social spontaneity, overly restrained initiative and emotional expression, a strong control over one's own environment, a denial of illness and mood changes with marked lability. Additionally, obsessive–compulsive features, both related and unrelated to food, are often prominent. The anorectic patient quickly develops a repertoire of behaviours in the pursuit of weight loss, including caloric restriction, refusal to eat food, adoption of special diets or vegetarianism, calorie obsession, hyperactivity, vomiting and laxative abuse. Moreover, unusual eating rituals are frequently described. These behaviours create a vicious cycle with behavioural and psychological sequelae that perpetuate the disorder. In a social context, patients become isolated and numerous conflicts arise with family members.

174.2 Clinical Manifestations of Body Experience in Eating Disorders

The distorted perception of one's own body (weight, size and shape) and the intense fear of weight gain, even when severely underweight, indicates how patients with anorexia nervosa experience their bodies. These characteristics are included in the current diagnostic criteria for AN (APA 1994).

Persons suffering from anorexia evaluate their body structure, their size or certain body parts in an unrealistic way. Even when clearly underweight, some patients experience their appearance as either normal, or even too fat. The discrepancy between the way they see themselves and the way they see others is striking; in most cases, AN patients can give a fairly accurate estimate of another patient's body size, while they do not realise that they themselves look the same or even worse. Furthermore, they have misconceptions about the consequences that eating will have on their body structure. After a meal, they feel their stomach is 'bulging' or that their belly is 'swelling'. In general, most patients with eating disorders maintain a very negative attitude towards their own bodies and their physical appearance. They are constantly watching their body, criticising it relentlessly or fighting it. Others avoid seeing themselves (naked) and often hide in loose clothing. Generally, they are dissatisfied with certain body parts (usually their belly, thighs or bottom). This dissatisfaction can also apply to body parts that are not related to weight (wide hips, short height, short legs and narrow shoulders). A minority of patients with anorexia seems to be proud of their emaciation (which they seem to show in an almost 'exhibitionistic' manner), but, for most of them, the weight loss does not increase their satisfaction at all. Along with frequent weighing or mirror inspections, some develop their own standards, such as 'my ribs must show' or 'the inner part of my thighs shouldn't touch when I am standing'.

Patients suffering from an eating disorder show a lack in confidence in their own bodies; they experience it as something annoying, and they do not feel "at home" in their bodies. The patients dislike being touched and have trouble with physical closeness, in general. The way that they think others regard them often plays an important role in their self-perception, and they generally anticipate a negative opinion. It is as if they looked at themselves through the eyes of someone very critical. This way, the opinion they have of themselves is constantly subject to conflicting points of view: 'how do I see myself' (the internal lens), 'how do others see me' (the external lens), 'how do I really look' (the unbiased or neutral lens) and 'how would I like to look' (the ideal lens). As the four lenses increasingly diverge, the self-perception becomes more problematic. The core problem resides in the absence of self-esteem and a negative self-perception, which is expressed in the negative body image.

174.3 The Importance of Body Composition Assessment in Anorexia Nervosa

This description of the disorder clearly illustrates why body-composition research is more and more important in the evaluation of subjects with AN.

1. The body composition of subjects with AN is influenced by the eating behaviour and is different from the body composition of a normal female population. In comparison to non-clinical subjects, patients with AN and athletes have a lower fat mass (FM). Athletes have a higher fat-free mass (FFM) than AN patients and non-clinical subjects.
2. The body composition in AN is important in regard to the female triad and fertility.
3. The body composition represents the state of (mal-) nutrition and the net results of metabolic processes and the structural contribution of ingested nutrients and is closely related to an organism's biochemical, metabolic and mechanical function (Heymsfield et al. 1995).
4. From both a physiological and psychological viewpoint, weight and body composition are crucial elements in the treatment of AN because the patients are dissatisfied with their body appearance and have unrealistic ideas about the influence that food intake and dieting have on body weight and shape. To educate the patients about their poor physical condition, information concerning body composition and consequence of weight gain/loss can help motivate the patients to change their way of thinking.

5. The study of body composition and body-fat distribution can have important implications for the treatment of AN; AN patients have an intense fear of weight gain and of becoming fat, and this is enhanced by the belief that this would be accompanied by fat distribution in the abdominal region. Hence, there is a possibility that the level of body fat upon discharge from clinic may influence the further progress of the patient.
6. The estimation of body composition over time is difficult. Therefore, body-composition studies that include an assessment of the changes after weight gain in large groups of patients are necessary.

174.4 Methods to Assess Body Composition in Anorexia Nervosa

A wide variety of methods have been used to measure body composition in anorexia nervosa. Table 174.1 reviews the most important studies in the field of body composition in anorexia nervosa. The mean search term, 'body composition (or related terms) in anorexia nervosa', was used. The studies had to mention percentage body fat (PBF).

The lowest value of PBF is 6.6% and the highest value is 18%. In 19 studies, PBF was found to be lower than 15%. In 11 studies, PBF was higher than 15%.

Body composition is primarily measured by anthropometry (skinfold thickness (SFT; Rusell et al. 1983; Charest-Lilly et al. 1987; Vaisman et al. 1988, 1991; Mayo Smith et al. 1990; Casper et al. 1991; Rusell et al. 1994; Probst et al. 1996, 2001; Orphanidou et al. 1997; Scalfi et al. 2002; Haas et al. 2009) and dual-energy X-ray absorptiometry (DXA; Mazess et al. 1990; Orphanidou et al. 1997; Pagliato et al. 2000; Grinspoon et al. 2001; Kerruish et al. 2002; Scalfi et al. 2002; Misra et al. 2003; Mayer et al. 2005; Haas et al. 2009; Yamashita et al. 2010).

The bioimpedance method (BIA) was used by Casper et al. (1991), Haas et al. (2005) and Probst et al. (2006). Casper et al. (1991) used the total body water method.

Probst et al. (1996, 2001, 2006) and Polito et al. (1998) applied the underwater weighing (UWW) method, which is considered as the method of reference of body-composition measurement.

The starting point for categorisation is based on how the body weight is divided. In the two-component model, body weight is simply partitioned into fat mass (triglycerides, FM) and fat-free mass (FFM), assuming that an individual only differs from the reference individual in terms of fat mass and has a constant composition of fat-free mass with a density of 1.1 g/cm³ (fat = 0.90 g/cm³) (Siri 1956). The assumptions of this traditional model may be sufficiently accurate for determining body composition in the general adult population, but this is not the case in deviations from the 'normal' body composition. Within this body-composition model, the SFT and the BIA methods are the mainly used. The difference between both methods is that, in the SFT method, PBF is estimated by density. Density is calculated by a regression formula using different SFTs.

BIA estimates the FFM, and percentage body fat is calculated from body weight minus FFM.

These methods are inexpensive, non-invasive, reasonably valid and easy to use in clinical practice for measuring body composition.

UWW is a gold standard but is related to a laboratory setting and difficult in clinical practice.

Other methods, such as DXA, total body water and neutron activation analysis, and other more invasive techniques, are based on a tissue-system component. In the three-component model, body weight is divided into three compartments (FFM, FM and bone). In the four-component model, body fat can be calculated from body weight, protein, water and body minerals. Although the methods are more valid, they are very expensive and more invasive. These methods are used as in-depth research, to overcome the limitations of simple techniques. Technical details of the different methods have been described elsewhere in this book.

Table 174.1 Chronological review of the percentage body fat (PBF) assessed by different methods in female subjects with anorexia nervosa

Authors	Method[a]	*N*	Age (years)	Duration (years)	Weight (kg)	Height (cm)	BMI (m/kg²)	PBF (%)	Equation[b] Density/PBF
Rusell et al. (1983)	SFT	6	23.8	4.3	38.3	166		14.0	Durnin/Siri
Charest-Lilly et al. (1987)	SFT	16	25.4 ± 6.6	> 4				15.5 ± 7.4	Jackson/Brozek
Vaisman et al. (1988)	SFT	13	15.4 ± 1.2		38.6 ± 6.1			16.4 ± 3.9	Durnin/Siri
Mayo Smith et al. (1989)	SFT	15	24 ± 5.8		42.6 ± 7	164 ± 8		13 ± 5	Durnin/Siri
Mazess et al. (1990)	DXA	11	21 ± 3	>1	44 ± 5	161 ± 7		7.7 ± 5.4	
Vaisman et al. (1991)	SFT	18	15.8 ± 1.5		38.2 ± 5.6	159.6 ± 7.1		17.2 ± 4.0	Durnin/Siri
Casper et al. (1991)	BIA	6	24.5 ± 2.8[c]		42.5 ± 3.8[c]	165 ± 3[c]	15.7 ± 1.2[c]	14.2 ± 3.3[c]	
Casper et al. (1991)	SFT	6	24.5 ± 2.8[c]		42.5 ± 3.8[c]	165 ± 3[c]	15.7 ± 1.2[c]	10.8 ± 2.6[c]	Jackson/Siri
Casper et al. (1991)	TBW	6	24.5 ± 2.8[c]		42.5 ± 3.8[c]	165 ± 3[c]	15.7 ± 1.2[c]	16.1 ± 2.9[c]	
Rusell et al. (1994)	SFT	32	18.8 ± 4.1	2.3 ± 2.3	42.0 ± 4.9	165 ± 5.7	15.4 ± 1.3	15.2 ± 5.0	Durnin/Siri
Probst et al. (1996)	UWW	200	22.7 ± 6.3	5.6 ± 4.8	40.3 ± 5.7	164.0 ± 7	14.9 ± 1.7	13.5 ± 4.3	–/Siri
Probst et al. (1996)	SFT	200	22.7 ± 6.3	5.6 ± 4.8	40.3 ± 5.7	164.0 ± 7	14.9 ± 1.7	13.4 ± 4.8	Durnin/Siri
Orphanidou et al. (1997)	DXA	26	27.6 ± 6.6	10.6 ± 6.4	43.6 ± 5.4	162.3 ± 5.7	16.5 ± 1.9	18.8 ± 6.2	
Orphanidou et al. (1997)	SFT	26	27.6 ± 6.6	10.6 ± 6.4	43.6 ± 5.4	162.3 ± 5.7	16.5 ± 1.9	10.2 ± 2.2	Jackson/Siri
Polito et al. (1998)	UWW	20	23.6 ± 5.5		40.7 ± 5.2	162.8 ± 7.6	15.3 ± 1.6	17.1 ± 5.9	–/Siri
Pagliato et al. (2000)	DXA	32	23.5 ± 4.4		34.5 ± 5.2	160.8 ± 7.2	13.2 ± 1.8	7	
Grinspoon et al. (2001)	DXA	20	27.0 ± 1.3[c]				16.1 ± 0.3[c]	18.2 ± 1.6[c]	
Probst et al. (2001)	UWW	130	20.1 ± 4.3	3.7 ± 3.3	40.7 ± 5.1	165.2 ± 6.2	14.9 ± 1.5	12.8 ± 3.6	–/Siri
Probst et al. (2001)	SFT	130	20.1 ± 4.3	3.7 ± 3.3	40.7 ± 5.1	165.2 ± 6.2	14.9 ± 1.5	12.8 ± 4.0	Durnin/Siri
Kerruish et al. (2002)	DXA	23	15.5 ± 1.3	10 ± 9[d]	40.2 ± 4.6	161.9 ± 6.2	15.3 ± 1.2	13.8 ± 5.8	
Scalfi et al. (2002)	DXA	10	19.7 ± 5.8		37.8 ± 6.2		14.8 ± 1.3	6.6 ± 4.2	
Scalfi et al. (2002)	SFT	10	19.7 ± 5.8		37.8 ± 6.2		14.8 ± 1.3	13.1 ± 3.6	Durnin/Siri
Misra et al. (2003)	DXA	21	15.9 ± 1.6	14.4[d]	44.1 ± 4.0	163.9 ± 6.2	16.4 ± 1.0	17.2 ± 6.0	
Haas et al. (2005)	BIA	57	25 ± 7		42.5 ± 4.5	167 ± 6	15.2 ± 1.5	12 ± 6.8	
Mayer et al. (2005)	DXA	29	23.5 ± 4.9	7.4 ± 4.4	42.0 ± 4.5		15.9 ± 1.6	9.3 ± 6.4	
Probst and Goris (2006)	BIA	24	20.1 ± 4.3				14.9 ± 1.5	9.7 ± 4.8	
Probst and Goris (2006)	UWW	24	20.1 ± 4.3				14.9 ± 1.5	13.8 ± 3.8	–/Siri
Haas et al. (2009)	SFT	50	15.2 ± 1.5		44.4 ± 5.5	163 ± 7	16.7 ± 1.6	17.3 ± 4.7	Slaughter
Haas et al. (2009	DXA	50	15.2 ± 1.5		44.4 ± 5.5	163 ± 7	16.7 ± 1.6	15.5 ± 6.3	
Yamashita et al. (2009)	DXA	97	23.2 ± 8.7	5.7 ± 6.5	34.3 ± 6.3	156.4 ± 6.3	13.9 ± 2.1	12.8 ± 5.2	

This table shows a review of the mean percentage body fat of anorexia nervosa assessed by different methods in different studies.
N number; *BMI* body mass index; *PBF* percentage body fat
All values are expressed in mean and SD except
[a]BIA = bioimpedance analysis; DXA = dual-energy X-ray absorptiometry; SFT = skinfold thickness; TBW = total body water;UWW = underwater weighing
[b]Durnin and Womersley (1974); Jackson et al. (1980); Siri (1956); Slaughter et al. (1988); Wilmore and Behnke (1970)
[c] SEM
[d] In months

174.5 Equations to Convert Density to Percentage Body Fat

A clinically useful formula is important for the estimation of body composition in specific age categories. Clinicians need a formula that can be used in the extreme conditions of severe underweight, as well as in the normalised conditions after weight restoration. There are different formulas available to convert the density (*D*) into percentage of body fat (Tables 174.2 and 174.3).

Probst et al. (2008) compared the Siri equation (1956), the age-specific Lohman's equation (1989), the Duerenberg-Westraete equation (1989) and the Heyward equation (1996) in 238 female adolescent AN patients. The relationship between the results of the four formulas in each different age category is higher than $r = 0.97$. Despite the high relationship, the authors found a significantly large difference in mean fat percentages within the different age categories. The differences between the mean fat percentages, when applying the four formulae, ranged from 0.021% to 6.33%; the average difference between the four formulae for all of the age categories was 2.6%. Negative fat percentages were found in the elder category with the Heyward and the Lohman formula. For that reason, Probst et al. (2008) recommended, with some restriction, to apply the Siri formula in AN patients. This formula might lead to an overestimation of the fat percentage in cases of underweight patients, but this overestimation will decrease when weight normalisation occurs.

Heyward and Stolarczyk (1996) stated that the use of the Siri equation for the estimation of per cent fat from density can be questionable in an anorectic population. Siri (1956) assumed that the density of the fat-free mass equals 1.10 g/cm³, that fat has a density of 0.90 g/cm³ and that FFM consists of 72% water ($D = 0.9937$ g/cm³), 21% protein ($D = 1.34$ g/cm³) and 7% mineral ($D = 3.00$ g/cm³). Heyward and Stolarczyk (1996) estimated that, in AN, the FFM components were 76% water ($D = 0.9937$ g/cm³), 6.3% mineral ($D = 2.73$ g/cm³) and 17.7 protein ($D = 1.34$ g/cm³). They proposed the following formula for calculating % fat from density: $\%\ \text{fat} = (5.26/D - 4.83) \times 100$. Compared to this formula, the average body fat of anorectic women will be systematically overestimated by 3–4% when the Siri equations are used to estimate % fat from density. Two problems arise when using the Heyward and Stolarczyk formula: (a) some patients with AN obtain a negative percentage fat and (b) when this formula is applied upon admission, it may not be still valid at discharge, when the test subjects more closely resemble the general population.

The Slaughter equation is also used in anorexia nervosa (Haas et al. 2009), but this equation has proved valid in the USA, but not in the UK (Nicholls et al. 2002).

174.6 Relation Between Different Body-Composition Methods

Seven studies compared two or more body-composition methods (Table 174.1). Body composition measured by skinfold thickness is compared with UWW, DXA and BIA.

174.6.1 Comparing UWW and SFT in AN

There is a sufficient agreement between and among the results obtained by UWW and SFT. UWW and SFT gave approximately the same values for PBF, FFM and FM. Indices from the two methods had good correlations, and there were no significant differences between the values (Probst et al. 1996). The relationship is $r = 0.76$ before and $r = 0.71$ after weight gain.

Table 174.2 Key features of the reference model of Siri to estimate the percentage of body fat from the body density

1. The starting point for the Siri formula is the two-component model where Siri (1956) assumed that body weight is simply partitioned into fat mass (triglycerides, FM) and fat-free mass (FFM).
2. Derived from the formula [body density (D) = mass/volume], the volume can be calculated as [volume= mass/density]. The volume of the body is measured by underwater weight or the water or air displacement of the body. More specifically, the volume is the sum of fat mass divided by the density of fat mass and the fat-free mass divided by the density of fat-free mass.
3. Siri assumed that an individual only differs from the reference individual in terms of fat mass and has a constant composition of fat-free mass with a density of 1.1 g/cm³ and fat with a density of 0.90 g/cm³.
4. Siri assumes that the density of the fat-free mass equals 1.10 g/cm³, that fat has a density of 0.90 g/cm³ and that FFM consists of 72% water (D = 0.9937 g/cm³), 21% protein (D = 1.34 g/cm³) and 7% mineral (D = 3.00 g/cm³).
5. The Siri formula to estimate body fat is the result of 4.95 divided by the density of the body minus 4.50. Percentage body fat is calculated by the same formula multiplied by 100.
6. The difference between methods could be supported by the reference body.

This table lists the key features of the Siri formula to estimate the percentage of body fat from body density

Table 174.3 Formulas to estimate the percentage of body fat from the body density

Author	Equation for percentage body fat
Siri (1956) adults	(4.95/body density) – 4.50
Lohman (1989) 13–15 years	(5.12/body density) – 4.69
Lohman (1989) 15–17 years	(5.07/body density) – 4.64
Lohman (1989) > 17 years	(5.05/body density) – 4.62
Deurenberg and Westraete (1989)	{[5.53–7.3 (age – 10)]/body density} – [5.14 – 8 (age – 10)]
Heyward and Stolararczyk (1996)	(5.26/body density) – 4.83
Specific equations for AN	
Slaughter et al. (1988)	1.33 × (Triceps + subscapular skinfold) - 0.013 (Triceps + Subscapular skinfold)² – 2.5

This table lists the different formulas to estimate percentage body fat from the density

The SFT percentage fat (density estimated from skinfolds by the formula of Durnin and Womersley 1974) was not significantly different from those obtained by UWW either before or after refeeding (Probst et al. 2001).

The findings suggest that, for an undernourished population, such as AN patients with relatively little body fat, simple skinfold measurements are, in clinical practice, as useful as more sophisticated measurements for the estimation of body composition. This is an important finding because SFT can be used more easily as a screening method. Moreover, the skinfold measurements have a lower cost and can reveal subcutaneous fat distribution.

174.6.2 Comparing SFT and BIA in AN

The results regarding the relationship between BIA and SFT are contradictory. Birmingham et al. (1996) found a low relationship (r = -.305), while Haas et al. (2005) and Probst and Goris (2006) found a relationship of 0.75. In the latter study, the PBF of five AN patients could not be determined by BIA. The inability of BIA to detect changes in body composition due to altered hydration and to accurately assess the distribution of water between intracellular and extracellular compartments limits its clinical usefulness in AN (Birmingham et al. 1996). In daily clinical treatment of AN, it appears that SFT measurement is preferable.

174.6.3 Comparing UWW and BIA in AN

Despite significant correlations between UWW and BIA (Maltron Model BF 907), significant differences in PBF were found in AN and in recovered AN patients (Probst 2006).

The same results were found between UWW and BIA (Tanita model TBF-300). Between the two BIA instruments, there was no significant difference. The correlation between both BIA methods was 0.84. Using Maltron and/or Tanita BIA, the body composition of five AN patients could not be determined, which shows the inability to measure the body composition in a certain group. Moreno et al. (2008) compared DXA with various impedance methods (a foot-to-foot impedance meter and Xitron 4200). In comparison with DXA, they found 7.8% (measured by the foot-to-foot impedance) and 4.5% (Xitron 4200) lower FFM. The results of the foot-to-foot impedance meter were significantly different from that of the Xitron 4200 in AN subjects, but not in control subjects.

This result suggests that the pre-programmed body-composition equations used in the BIA body-composition analyser have not been adjusted accurately by the company to provide accurate body-measuring instruments for different target groups.

174.6.4 Comparing SFT and DXA in AN

Orphanidou et al. (1997), Scalfi et al. (2002) and Haas et al. (2009) compared skinfold thickness and DXA. They found a significant difference in PBF between the skinfold methods and the DXA method. Contrary to the first study, both other studies found lower PBF with DXA.

174.7 Specific Topics in Body-Composition Assessment in Anorexia Nervosa Related to Clinical Practice

174.7.1 Percentage Body Fat and BMI

The relationship between BMI and PBF, estimated by SFT and UWW, was high (r = 0.75). Nevertheless, only 56.2% of the variance (r^2) in PBF could be predicted by BMI. The variation in PBF at any given BMI was great. For instance, with a BMI of 13, the PBF varied from 7% to 17% (Probst et al. 1996).

BMI reflects real changes in ratio of weight to height, but, despite the high correlation with PBF, it is not a direct indicator or predictor of relative body fatness. Changes in fat mass and fat-free mass are clinically important and may occur without a change in BMI or weight.

Hannan et al. (1993) stated that the target values for FFM may be more appropriate than BMI for assessing the severity of the disorder and its response to treatment.

In the light of these results, one may question some recent attempts to define AN in terms of BMI (APA 1994). Trocky and Shephard (2000) also questioned the use of weight gain alone for reinforcement in a behaviour therapy for anorexia nervosa.

Soh et al. (2009) assessed the relationship between skinfold and body mass index in North-European Caucasian and East-Asian young women with and without AN. For the same BMI, women

with AN had significantly smaller sums of skinfolds than did women without AN. East-Asian women both with and without AN had significantly smaller sums than their North-European Caucasian counterparts, after adjusting for BMI.

174.7.2 The Influence of a Refeeding Programme on Body Composition in Anorexia Nervosa

A refeeding programme led to a significant increase in body weight and body fat. More than half (55%) of the weight increase was attributed to the increase of fat mass (Probst et al. 2001). The low to very low PBF findings before refeeding are similar to other studies (Kerruish et al. 2002; Scalfi et al. 2002; Mayer et al. 2005). There is a general consensus in the literature about the 'normal percentage of body fat' for the general female population; the results of the refeeding program are in the normal range (BMI > 18; % fat > 22.5). Patients with a low PBF upon admission usually have a low PBF at discharge as well, and vice versa.

The length of treatment or the duration of illness has no effect on body composition after treatment and a rapid weight gain does not change the amount of fat.

The amount of body fat may also affect the clinical outcome. Menses returned with refeeding when patients reached higher levels of body fat (18%); however, the changes in body fat and the return of menses may also enhance psychological stress in the patients, increasing the likelihood of relapse.

The changes in body fat are also in contradiction with what patients want themselves, at least as long as they are anorectic. In the different studies, the mean percentage of body fat after refeeding was still lower than in normal-weight females, although most patients believe they are too fat and are afraid to become overweight. However, the results of body-fat percentage at discharge were still lower than in a normal female population (23–25%). Therefore, it could be important to include some sort of body-oriented therapy in the latter part of the treatment, in addition to a refeeding programme. The aim of this therapy is to educate the patients about their poor physical condition and to help them accept the physical and psychological changes as a result of increasing weight. A fitness-training programme (20 sessions; 2 times a week) during refeeding, supervised by a therapist who is familiar with the physical consequences of undernutrition, could increase the fat-free mass, redirect the patients' hyperactivity in a healthy way, allay the fears of weight gain and improve their sense of self-control. The possible influence of an adapted fitness-training programme on body composition and body experience of AN patients has not yet been assessed in detail and will be an interesting topic for future research.

174.7.3 Changes in Subcutaneous Fat

A skinfold analysis indicated that all of the skinfolds were significantly greater after weight gain. The greatest increase of skinfold thickness is not situated in the abdominal region, as many patients believe, but instead on the thighs, the waist and side (Probst et al. 2001). Orphanidou et al. (1997) found a larger increase of fat in the abdominal region and less in the arms and calves. Other studies (Orphanidou et al. 1997; Scalfi et al. 2002) have mentioned that relative increases in SFT during weight gain may not be the same at various sites. The lowest relative increase of subcutaneous thickness (less than 100%) was situated at the biceps, subscapula, chin and the lateral and medial calf. Changes

in SFT were highly correlated with weight gain. The highest correlation (Probst et al. 1996) was found for the chin ($r = 0.66$) and the sum of the 12 skinfolds ($r = 0.69$), and the lowest correlation was found for the medial calf ($r = 0.35$). SFT showed a small correlation with FFM ($r = 0.20$) but was moderately to highly correlated with PBF (before weight gain: $r = 0.51$, for abdomen to 0.74, for triceps; after weight gain: $r = 0.31$ for medial calf to 0.54 for the side). These correlations did not differ markedly among the common sites.

The relationship between PBF before and after treatment (Probst et al. 2001), measured by rank correlation, was $r = 0.44$ ($P < 0.0001$). This indicates that the ranking order before therapy was at least partially maintained after therapy.

174.7.4 Other Specific Elements in Body-Composition Research in Anorexia Nervosa

The level of physical activity, eating behaviour, stage of refeeding and maturity level influence body composition in anorexia nervosa.

Older and more chronic AN patients (>30 years) have a higher PBF than younger patients. This is not due to a difference in the duration of illness, which does not influence PBF. A detailed analysis did not reveal differences between adolescents (<19 years) and young adults (20–29 years) nor between the subgroup of ages (14–19).

The PBF of the mixed type of anorexia differed significantly from that of the restricting type using UWW. SFT differed significantly between the types, except for the abdomen SFT.

AN patients of the restrictive type had lower values and differed significantly from the binging–purging type for the variables, weight percentage body fat, fat mass and fat-free mass measured by UWWW. After treatment, no significant differences were found between the subtypes (Probst et al. 1996).

AN patients are sometimes compared to athletes. However, athletes have higher fat-free mass value when compared to AN patients and healthy controls (Iacopino et al. 2003).

174.8 Guidelines for a Standard Protocol of Anthropometric Assessments in Clinical Practice

1. The assessment of body composition has to be executed upon admission and at the end of treatment. If possible, it is recommended to repeat a regular body-composition assessment during the therapy.
2. For the standardisation of the assessment, it is advised that the assessment is done by the same highly experienced investigator and at the same time of the day.
3. Height is measured to the nearest completed 0.5 cm using a stadiometer. Body weight is measured, with the subject wearing only a swimsuit, on a beam balance to the nearest 100 g. The Quetelet or body mass index (BMI, kg/m²) is calculated. Although body mass index has been recommended as a measure for nutritional status in anorexia nervosa, BMI does not predict the body composition or the change in body composition. Body mass index has been shown to be an imprecise measurement of fat-free and fat mass.
4. At least three, but if possible 12, skinfolds should be measured: biceps, triceps, subscapular, suprailiac, chin, side, waist, abdomen, anterior and posterior thigh and lateral and medial calf on the left side of the body, using a well calibrated skinfold calliper (Probst et al. 1996).

5. The calculation of trunk fat and extremity fat percentages and the trunk/extremity ratio are useful. From skinfold measurements, the following formulae are proposed: percent trunk fat = sum of upper body skinfolds (subscapula, suprailiac, side, waist, abdomen and chin)/sum of 12 skinfolds; percent extremity fat = sum of extremity skinfolds (biceps, triceps, thigh anterior and posterior and calf lateral and medial)/sum of 12 skinfolds; trunk/extremity ratio = percent trunk fat/percent extremity fat (Probst et al. 2001).
6. From a clinical point of view, the two-component model using the skinfold technique is acceptable and is the most useful. This model proposes that the density of the fat and the fat-free mass is known and is constant, that the density and proportions of the components of the fat-free mass between individuals are relatively constant and that the individual only differs from the reference body in terms of the amount of fat mass.
7. Until now, and with some restrictions, the Siri formula is recommended to estimate PBF from body density.
8. If possible, the use of more than one method to measure body composition is advised in clinical practice. Clinicians should be careful with the use of BMI and the BIA. In fundamental research, more sophisticated models and methods are recommended.
9. In choosing their method, investigators must balance a host of issues including precision, bias, expense and safety. Body composition (research) in anorexia nervosa has to fulfil some conditions. The method and the equations used in anorexia nervosa can influence the results. Researchers have also taken into account age and maturation level, duration of illness and amenorrhea, level of physical activity and compensatory behaviour (purging behaviour and use of laxatives and other pills). In the anamnesis, a previous history of being overweight has to be checked.
10. The *therapeutic implications* of body-composition assessment are that patients with AN have to be informed about the physiological meaning of body fat. The therapist has to emphasise the importance of body fat for the return of menses and normalisation of the reproductive functions. Not only the implications of low body fat have to be addressed, but also the implications of low weight on maturation, growth and osteoporosis, certainly in young patients. On the other hand, therapists should be aware that a normalisation of body fat might also increase the patient's 'fat phobia', which has led to her pursuit of thinness.

174.9 Summary

Body composition has become an important topic in the treatment and research of anorexia nervosa. Table 174.4 lists clinical key points with regard to body-composition assessment in subjects with anorexia nervosa.

More fundamental research is necessary regarding the limitations of the techniques and equations for these underweight patients.

Table 174.4 Summary: Key points in clinical practice of body composition in subjects with anorexia nervosa

1. Body composition has become an important topic in the treatment and research of subjects with anorexia nervosa.
2. The results from different studies are difficult to compare because of the small groups, the different methods and the different equations for deriving percentage body fat (PBF).
3. Simple skinfold measurements are, in clinical practice, as useful as other instruments for the estimation of body composition.
4. The use of the bioimpedance analysis (BIA) in subjects with underweight has limitations.
5. Body mass index (BMI) is not a direct indicator or predictor of body fatness.

This table lists clinical key points with regard to body-composition assessment in subjects with anorexia nervosa

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Chapter 175
Perceived Body Image and Actual Anthropometric Indices in Eating Disorders

Dieter Benninghoven

Abstract A disturbed body image is a main characteristic of patients with eating disorders and plays an important role in the development and maintenance of eating disorders. The construct of body image comprises two different components: an attitudinal and a perceptual component both of which need to be taken into consideration when body image distortions are addressed in research and in clinical settings. Attitudinal body image covers a global subjective, an affective, a cognitive, and a behavioral dimension. Mainly questionnaire instruments have been developed to assess body image attitudes. Distortions in body image perception are assessed by measuring discrepancies between actual, perceived and ideal body images. Again, a number of different methods are available in this context. Discrepancy calculations must be based on adequate anthropometric indices. They vary according to the body image assessment method. Traditional methods apply body calipers for measuring body width at specific body sites to compare these measurements with how subjects model their perceived body image. The same principle is applied when subjects are asked to morph their perceived and ideal body images on video or computer screens. Researchers or clinicians are then able to compare the results with actual images captured through video or digital photographs. These methods are basically unidimensional. In recent years more sophisticated multidimensional methods have been developed. They require more elaborate anthropometric techniques such as an assessment of body composition to depict distributions of body fat and muscularity. Both skinfold thickness and measurement of bioimpedance analysis have proven reliable methodologies in this context. An assessment of body movement patterns is needed to describe a dynamic body image.

Perceived body image and actual anthropometric indices in eating disorders.

Abbreviations

ICD-10	International Classification of Diseases (ICD-10)
DCM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EDI-BD	Eating Disorder Inventory-Body Dissatisfaction Scale
BCQ	Body Checking Questionnaire
DVT	Distorting Video Technique
BMI	Body Mass Index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_175,

PAR Perimeter-Area Ratio
FFMI Fat Free Mass Index
BIA Bioimpedance Analysis
VDU Visual Display Unit

175.1 Introduction

Two different types of risk factors are involved in the development and the maintenance of anorexia and bulimia nervosa, each of which are severe mental disorders with growing incidence rates during the past decades. Risk factors can be divided into general and specific factors. General factors are those risk factors relevant not only for the development of eating disorders but also for other psychiatric diseases. Specific factors, however, are risk factors specific for eating disorders. In a meta-analysis, Stice (2002) found that single risk factors have minimal predictive power for the pathogenesis of eating disorders except for one finding: the internalization of a very thin ideal body and the subsequent dissatisfaction with one's own body has been summarized under the term 'body image disturbance'. A negative body image seems indeed to be a single and relatively clear delimitable risk factor relevant for dieting, negative affect, and for distortions of eating behavior and food intake. The conviction that a more attractive, that is, a thinner body leads to more satisfying interpersonal relationships and to more positive feelings makes it likely to start with and to maintain a restrictive eating behavior. Restrictive eating behavior again is typical for each form of eating disorders at least at some point in the development of the disorder.

Body-image disturbances are relevant not only for the development of eating disorders, but they also became prominent parts of the definition of eating disorders in the two most commonly used classification systems: the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Both consider dysfunctional body image an important symptom of eating disorders (see Table 175.1).

The diagnostic criteria for anorexia nervosa in DSM-IV include "intense fear of gaining weight or becoming fat, even though underweight" and "disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight." Diagnostic criteria for bulimia require that "self-evaluation is unduly influenced by body shape and weight."

Table 175.1 Key features of dysfunctional body image in eating disorders according to ICD-10 and DSM-IV

	Anorexia nervosa	Bulimia nervosa
DSM-IV	– Intense fear of gaining weight or becoming fat, even though underweight – Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight	– Self-evaluation is unduly influenced by body shape and weight.
ICD-10	– Body-image distortion in the form of a specific psychopathology, whereby a dread of fatness persists as an intrusive, overvalued idea and the patient imposes a low weight threshold on him- or herself.	– Morbid dread of fatness; – Sharply defined weight threshold, well below the pre-morbid weight that constitutes the optimum of healthy weight in the opinion of the physician.

This table lists key features of dysfunctional body image as they are included in the diagnostic criteria for anorexia and bulimia nervosa according to DSM-IV and ICD-10

The diagnostic criteria in ICD-10 list a "body-image distortion in the form of a specific psychopathology whereby a dread of fatness persists as an intrusive, overvalued idea and the patient imposes a low weight threshold on him- or herself" for anorexia nervosa and "a morbid dread of fatness" and "a sharply defined weight threshold, well below the pre-morbid weight that constitutes the optimum of healthy weight in the opinion of the physician" for bulimia nervosa.

The importance of the body-image construct in eating disorders is reflected not only by its meaning for the development and by the fact that it is included in the diagnostic criteria but also by its clinical meaning. Hilde Bruch (Bruch 1962) is considered the first author who described body-image disturbance as a core feature of eating disorders. At least some form of body-image therapy is included in most treatment programs. Body-image disturbance also has prognostic value; persistence of severe body-image disturbance after treatment has negative prognostic value for long-term outcome.

175.2 Main Text

When defining body image, it is widely accepted that the construct of body image generally comprises two different components (Thompson and van den Berg 2002):an attitudinal component and a perceptual component (see Fig. 175.1).

The attitudinal component is generally divided into four dimensions:

- A global subjective satisfaction or dissatisfaction;
- An affective distress regarding appearance;
- A cognitive dimension of body image; and
- A behavioral dimension.

175.2.1 Attitudinal Body Image

The global subjective dissatisfaction refers to an overall satisfaction–dissatisfaction continuum as regards one's appearance. The easiest but necessarily most limited way of assessing body dissatisfaction is a single-item question such as "I am satisfied with the appearance of my body." The item can be adapted to weight, size, shape, or specific body features. More sophisticated are schematic figural methods. These methods use figures ranging in size from thin to overweight. Participants select figures representing their perceived current and their ideal body image. The discrepancy is a measure of dissatisfaction (see Fig. 175.2). An example of this technique is the Figure Rating Scale by Stunkard et al. (1983).

Subjective global satisfaction with body image can also be assessed through questionnaire measures. The most widely used instrument is the Body Dissatisfaction Subscale of the Eating Disorder

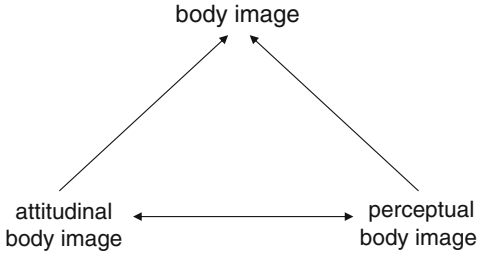

Fig. 175.1 The components of the body-image construct. The construct of body image comprises both an attitudinal and a perceptual component

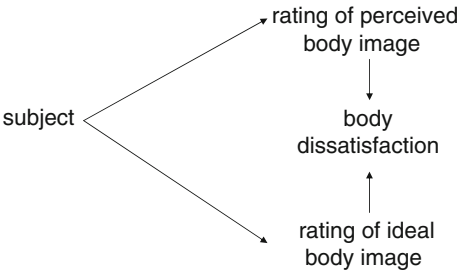

Fig. 175.2 Assessment of body dissatisfaction through figure rating scales. Body dissatisfaction is defined as the discrepancy between a subject's perceived and ideal body image

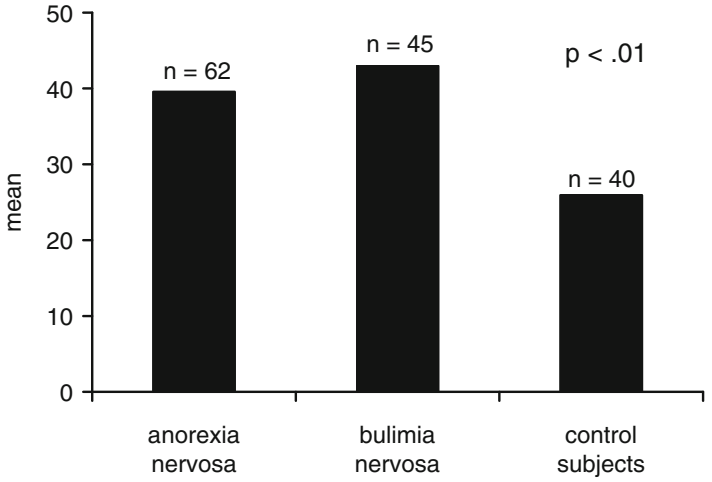

Fig. 175.3 Body dissatisfaction assessed through the Eating Disorder Inventory-2 – subscale Body Dissatisfaction within three female groups. Body dissatisfaction is significantly higher in patients with eating disorders than in healthy female control subjects

Table 175.2 Instruments for the assessment of attitudinal body image (examples)

Dimension	Assessment instrument	Author
Global subjective satisfaction or dissatisfaction	Figure Rating Scale	Stunkard et al. (1983)
	Body Dissatisfaction Subscale of the Eating Disorder Inventory (EDI-BD)	Garner et al. (1983)
Affective distress regarding appearance	Situational Inventory of Body-Image Dysphoria	Cash (1994)
Cognitive dimension	Appearance Schemas Inventory	Cash and Labarge (1996)
Behavioral dimension	Body Checking Questionnaire (BCQ)	Reas et al. (2002)

This table lists common instruments for the assessment of attitudinal body image

Inventory (EDI-BD; Garner et al. 1983). It discriminates reliably eating-disordered patients from female control subjects (e.g., Benninghoven et al. 2007, see Fig. 175.3).

Affective distress regarding appearance is often found in patients with eating disorders and can also be systematically assessed. The Situational Inventory of Body-Image Dysphoria (Cash 1994) measures how often a person experiences negative emotions about body image in different situations. Different questionnaires and subscales target cognitive aspects of body image, such as beliefs, thoughts, or attributions about or toward one's own body. For example, the Appearance Schemas Inventory (Cash and Labarge 1996) addresses dysfunctional appearance-related assumptions.

The behavioral dimension can be seen as the completing part in a picture of the attitudinal component of body image. It has received attention more recently in the field of eating-disorder research. The Body Checking Questionnaire (BCQ, Reas et al. 2002) is an example for this category of instruments. It assesses behavior aimed to control the appearance of one's own body, such as checking one's appearance in a mirror. Examples of scales for the assessment of the four dimensions of the attitudinal body image are given in Table 175.2.

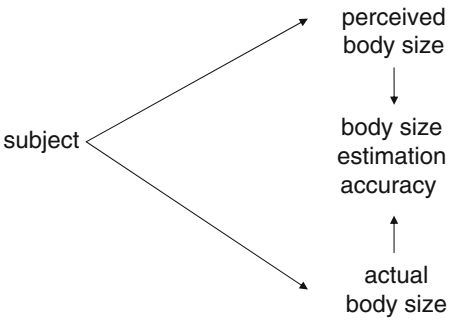

Fig. 175.4 Assessment of body-size estimation accuracy. Body-size estimation accuracy is defined as the discrepancy between a subject's perceived and actual body size

175.2.2 Perceptual Body Image

The perceptual component in body-image research focuses on the ability of individuals to accurately estimate their body dimensions (Thompson and Gardner 2002). This concept was attractive for numerous researchers because it targets so directly one of the main criteria for the diagnosis of eating disorders, that is, the disturbance in the way in which one's body weight or shape is experienced. Methodologies for the assessment of size-estimation accuracy have become more and more sophisticated since the beginning of this research in the 1970s. The basic method in this area is the 'movable caliper technique' (Slade and Russell 1973). Individuals are asked to adjust lights mounted on tracks to reflect their conceptions of their body dimensions at different body sites. Actual body size is assessed using body calipers. The difference between estimated and actual width indexes the estimation accuracy (see Fig. 175.4).

This method inspired a number of variations. A step beyond these body-part size-estimation procedures was the development of whole-body assessment techniques. These techniques enabled researchers to assess whole-image accuracy. Individuals have to modify the size of the entire body in an adjustable mirror, through an anamorphic lens, on a TV screen, on a life-size screen, or on a computer screen. A well-established example is the distorting video technique (DVT, Collins 1986; Freeman et al. 1984). The DVT alters a picture of an individual's body on a screen by distorting it along the horizontal or vertical axis. Again, body-image estimation accuracy is defined as the difference between perceived and actual images.

A more sophisticated methodology for the assessment of the perceptual component of body image is the application of the signal-detection theory on body-image research (Smeets et al. 1999). Subjects are presented with static video images of themselves with size distortion present or absent, with which they judge presence or absence of distortion. The dependent variables are an individual's sensitivity in detecting size distortions (sensory factor) and the response bias (non-sensory factor), that is, a tendency to overreport the body as too wide or too thin. It was found that patients with anorexia nervosa did not differ from control subjects in their ability to detect distorted images of themselves. However, anorexic subjects did show a tendency to report that their image was distorted in size. This result was interpreted as evidence for the theory that distorted size-estimation accuracy in eating disorders is caused rather by non-sensory attitudinal factors than by sensory deficits. Examples of unidimensional instruments for the assessment of perceptual body image are presented in Table 175.3.

175.2.2.1 Mirror-Sized Body-Image Assessment

Beyond what has been summarized so far, some promising new further developments have emerged in body-image research during the last years. Shafran and Fairburn (2002) and Farell et al. (2003)

Table 175.3 Unidimensional instruments for the assessment of perceptual body image (examples)

Assessment instrument	Author
Movable caliper technique	Slade & Russell (1973)
Distorting video technique (DVT)	Collins (1986) and Freeman et al. (1984)
Application of the signal detection theory on body-image research	Smeets et al. (1999)

This table lists common instruments for the assessment of perceptual body image

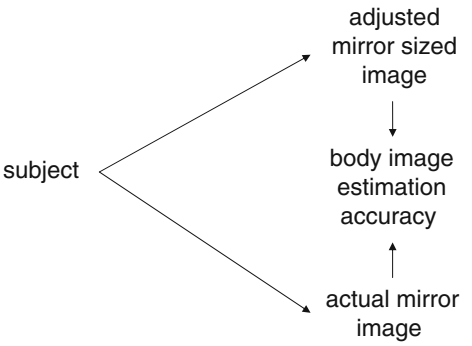

Fig. 175.5 Body-estimation accuracy as the difference between actual mirror image and adjusted mirror-sized image. Body-size estimation accuracy can also be defined as the discrepancy between a subject's actual mirror image and the adjusted mirror-sized image

presented a new ecologically valid method of body-size estimation. Ecologically valid, in this context, means that the authors presented subjects with a mirror-sized image of their own body, and let them compare and adjust this image against what subjects really see while looking in a mirror. A mirror-size image was used because the image with which we are most familiar is our reflection in the mirror and this is half our height, however far we stand from the mirror. The two aspects by which this new method differs from previous similar studies (e.g., Probst et al. 1998) are the size of the images used (mirror size) and the presence of an image for comparison. The latter is important because it ensures that the perception of the participant's body image rather than its memory is assessed (see Fig. 175.5).

175.2.2.2 Assessment of Multidimensional Body Image

Instruments that have so far been presented are limited by the fact that they are unidimensional. They allow subjects to choose among figures of varying sizes or to manipulate the size of a figure by using adequate software programs. The distorting video technique (DVT) has already been described as an example in this domain. However, distorting a body on a screen along the horizontal or vertical axis is not how the shape of a body changes as a person gains or loses weight. The shape changes produced by the DVT do not accurately mimic the pattern of shape change produced by changing body mass. It has been argued that this limitation in validity might be responsible for inconsistencies in the results obtained with this method. This dissatisfaction gave reason for the development of methods that assess body images multidimensionally.

Assessment of Body Size and Shape

To overcome the problem of unidimensional distortions, computer programs have been developed that allow individual body parts to be altered separately (e.g., Tovée et al. 2003). Subjects are photographed

using a digital camera in a standardized pose, wearing a close-fitting leotard. The photograph is entered in a computer program. Individual body parts in the image undergo shape transforms based on template shapes. Subjects are then presented with a distorted picture of their body on a VDU screen. The program allows altering body parts, such as arms, chest, abdomen, hips, thighs, and calf. Subjects are asked to alter their body to make it look like their real and their ideal body. The software then presents the researcher with the apparent body mass index (BMI) of the resulting images. The method used here is the perimeter–area ratio (PAR) (Tovée and Cornelissen 1999). To estimate the BMI of a morphed figure, the PAR needs to be calculated first. The PAR is defined as the area within the perimeter of a figure divided by the path length around the perimeter. The program then reads off the matching BMI value from its internal data bank. Discrepancy between the actual BMI and the estimated BMI of the morphed figure serves as an indicator of size- and shape-perception accuracy. In this context, it is important to mention that an accuracy of self-reported weight and height among women with eating disorders is low. Obtaining objective height and weight data is mandatory both within clinical and research settings (Meyer et al. 2009).

Assessment of Body Image Defined by Body Fat and Muscularity

Another shortcoming of traditional instruments is the fact that they do not allow emulating an apparently visible aspect of body composition, that is, the distribution of body fat versus muscularity. This was not a highly relevant issue in body-image research until colleagues became interested in assessing male body images. The most important body-image dimension for women is that of slimness versus fatness, which can be mapped by enlarging or narrowing body images. Conversely, men evaluate their body image mainly on two dimensions: body fat and muscularity. This gave reason to develop a new instrument for the simultaneous assessment of body fat and muscularity, the somatomorphic matrix (Gruber et al. 2000). Gruber and her colleagues became interested in this field as a result of their involvement with anabolic steroid use in bodybuilders. They found a phenomenon that they named as 'muscle dysmorphia' (Pope et al. 1997). It describes individuals who perceive themselves as less muscular and fatter than they actually are.

The somatomorphic matrix allows an assessment of muscularity and body fat of men's and women's body image. The instrument presents the user with a drawing of a male or a female body that the user can 'morph' through ten levels of muscularity (fat-free mass index, FFMI) and body fat (share of body fat in percent of total body mass). The images were drawn by a graphic artist, according to reference photographs of subjects with quantified levels of body fat and muscularity. Percentage body fat was calculated using skinfold measurements obtained with calipers, using equations developed by Jackson and Pollack (Jackson et al. 1980). Degree of muscularity was quantified by calculating the fat-free mass index with a formula originally developed by Kouri et al. (1995). Estimated body fat of the drawn images varied from 4 to 40 percent; FFMI varied, on the other axis, from 16.5 to 30.0 kg/m^2 for men and from 11.0 to 25.0 kg/m^2 for women (Gruber et al. 2000). Thus, both the male and the female matrices consist of a set of 100 images representing ten levels of body fat and ten levels of muscularity (FFMI). The 100 images for each matrix were then imported into a computer program that allows subjects to navigate among them by clicking buttons to increase or decrease the body fat and FFMI of the image that they are currently viewing. The user of the program is then asked to choose images representing (1) the best estimate of the own body (actual body), (2) the body the user would ideally like to have (ideal body), (3) the body that the user felt represents an average man/woman of her/his age (average body), and (4) the body that he/she felt was most preferred by the opposite sex (society's ideal). A number of studies have used the male version of the matrix (e.g., Mangweth et al. 2004). In applications of the female version, the body-fat dimension of

Table 175.4 Indices of body fat within three female groups assessed through the somatomorphic matrix

	Anorexia nervosa $n = 62$	Bulimia nervosa $n = 45$	Female control $n = 40$	
Body fat in %	M (SD)	M (SD)	M (SD)	p-value
Perceived	15.23 (8.72)	24.80 (9.67)	22.70 (6.92)	<.001
Desired	15.81 (6.08)	16.00 (5.97)	19.30 (4.87)	.007
Average	21.55 (6.12)	20.53 (5.76)	21.50 (5.49)	.636
Men's ideal	19.10 (6.85)	17.16 (5.37)	19.20 (5.14)	.184

Patients with eating disorders differ from female control subjects in terms of perceived and desired body fat
M mean; *SD* standard deviation

the somatomorphic matrix has been found to be most meaningful for defining body images (Benninghoven et al. 2006). As can be seen in Table 175.4, patients with eating disorders differ from female control subjects in terms of perceived and desired percentage of body fat. No differences are found when rating the image of an average woman or of the female body favored by men. This finding supports the theory that body-image disturbances are primarily found in those aspects of body image that directly apply to the patient's own body. Body-image disturbance in patients with eating disorders is not a problem of processing body-image-related information per se but rather a problem of processing self-referential information regarding body image.

For the assessment of dissatisfaction with body image, the somatomorphic matrix requires calculations similar to unidimensional rating scales: namely the difference between perceived and ideal body image, both on the body fat and on the muscularity dimension. A more complex procedure though is required for assessing estimation accuracy. When the accuracy of estimating body size only is the dependent variable, measuring body size is a sufficient methodology. Body size can be measured, for instance, with calipers. The result is then compared with how subjects adjust lights mounted on tracks to reflect their conceptions of their body dimensions. However, when it comes to assessing the accuracy of muscle and body-fat estimation, more sophisticated methods are needed. Skinfold-thickness measurements obtained with calipers for calculating an individual's percentage of body fat and fat-free mass index (FFMI) are appropriate. Estimation accuracy can then be computed as the difference between the objective measurements (actual body fat and FFMI) and the body fat and FFMI of the somatomorphic matrix image representing subject's best estimate of his or her own body (perceived body).

Skinfold-thickness measurement obtained with calipers is a practicable technique in many settings. In terms of reliability, it is comparable to more elaborate methods, such as underwater weighing (Probst et al. 2001). However, it is still invasive, compromising, and potentially traumatizing or retraumatizing, especially for victims of violence because subjects need to undress partly. Bioimpedance analysis (BIA) can be an alternative method in settings where a less invasive technique is required. This is a method for evaluating body composition. It measures the impedance of a small electrical signal as it travels through the body. Because fat has low impedance and muscle and water has high impedance, the impedance a certain body provides indicates what percentage of body mass is fat. Figure 175.6 displays body-estimation accuracy and perceived–ideal difference of patients with eating disorders and female control subjects. Body-estimation accuracy is assessed using BIA as the measure for actual body fat.

Patients with anorexia nervosa clearly overestimate their body fat. Overestimation of body fat can be found with the bulimia nervosa patients, too. Nevertheless, the implications are different for both groups. Overestimation in patients with anorexia nervosa may help patients keeping a subjectively non-pathological image of their body by negating their severe underweight. In women with bulimia though, overestimation contributes to a subjectively pathological image by negating the normality of the body. In anorexia patients, perceived and desired body images are hardly different.

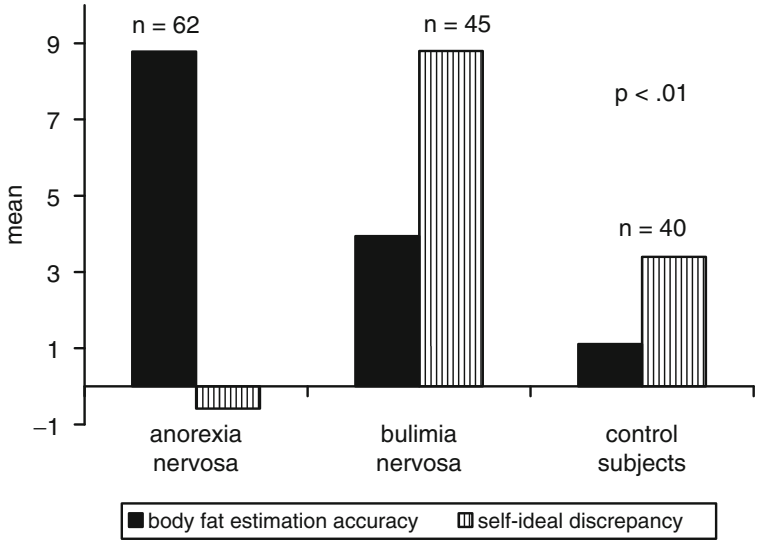

Fig. 175.6 Discrepancy scores within three female groups. Body-fat estimation accuracy and self-ideal discrepancy are significantly higher in patients with eating disorders than in healthy female control subjects. Body fat estimation accuracy: perceived minus actual body fat; perceived–ideal discrepancy: perceived minus desired body fat

Table 175.5 Changes in body-fat estimation accuracy and perceived–ideal discrepancy during a 6-week in-patient treatment

	Anorexia nervosa $n = 41$			Bulimia nervosa $n = 37$		
	adm	disc		adm	disc	
	M (SD)	M (SD)	ES	M (SD)	M (SD)	ES
Body-fat estimation accuracy	9.2 (10.8)	9.0 (7.9)	.03	4.5 (7.7)	1.5 (7.3)	.43
Perceived–ideal discrepancy	–.59 (9.9)	1.4 (9.3)	–.22	9.5 (9.3)	5.8 (9.1)	.40

Patients with bulimia nervosa benefit from in-patient treatment in terms of body-fat estimation accuracy and perceived-ideal discrepancy

M mean; *SD* standard deviation; *Body-fat estimation accuracy* perceived minus actual body fat; perceived–ideal discrepancy: perceived minus desired body fat; *adm* admission; *disc* discharge; *ES* effect size

Body satisfaction, in this respect, is nearly not impaired in spite of severe malnutrition. In patients with bulimia nervosa, body dissatisfaction is relevant in terms of a self-ideal discrepancy. Patients with bulimia nervosa perceive their bodies as too big and desire a thinner body. It seems to be a common feature of both eating disorders to favor a body image thinner than women without an eating disorder do. This results in much bigger self-ideal discrepancies for patients with bulimia than for women with no eating disorder. While perceptual inaccuracy is nearly irrelevant for the female control subjects, they do show a tendency toward a desired body thinner than the perceived body. However, self-ideal discrepancy is less distinct than in the bulimia group. Nevertheless, the desire for a thinner body is not limited to patients with eating disorders but is common also within the at-risk population of young women.

Table 175.5 shows changes in body-estimation accuracy and perceived–ideal difference obtained during a 6-week in-patient psychosomatic treatment for patients with anorexia and bulimia nervosa. Differences between actual and perceived and between perceived and desired body images in anorexia patients are difficult to change during treatment. No correction of the distorted

Table 175.6 New multidimensional instruments for the assessment of perceptual body image

Assessment instrument	Author
Separate alteration of individual body parts in a computer program	Tovée et al. (2003)
Somatomorphic matrix	Gruber et al. (2000)
Dynamic body-image assessment	Vocks et al. (2007)

This table lists three new multidimensional instruments for the assessment of perceptual body image

body-size perception takes place in spite of an increase in weight of 4.85 kg (707 g/week). A correction of body-size overestimation is easier to achieve for patients with bulimia nervosa. At the end of treatment, overestimation can still be found but is less pronounced than at the beginning of treatment. Also, perceived and desired body-image approximate during treatment because the perceived body image becomes more realistic toward the end of treatment. This process is possibly based on the experience of bulimic patients during treatment that their body is quite acceptable, so that there would be no necessity for any manipulation with the help of bulimic eating behavior (Benninghoven et al. 2006).

Assessment of Dynamic Body Image

Another new development is the extension of a traditional static body-image assessment toward an assessment of motion patterns (dynamic body image). Vocks et al. (2007) developed a technique that makes it possible to study biological gait patterns without interference from shape. The technique is based on point-light displays depicting a walking figure in a frontal-view perspective presented on a computer screen. This percept of their own body in motion can be altered by participants along a BMI axis. It was shown that patients with eating disorders not only overestimated their own body dimensions but also perceived their own motion patterns corresponding to a higher BMI than did control subjects. This new method might be an advance in the task of understanding the various dimensions of the complex body-image construct. Examples of methods for the assessment of multidimensional body image are presented in Table 175.6.

175.3 Practical Methods and Techniques

1. A number of different questionnaire methods are available for the assessment of the attitudinal component of body image.
2. Anthropometric techniques are relevant for the assessment of body-estimation accuracy indicating the perceptual component of body image.
3. The movable caliper technique is a basic method for the assessment of body-part estimation accuracy.
4. The distorting video technique is an example of assessing whole-body estimation accuracy.
5. Mirror-sized body-image assessment is an ecologically more valid method.
6. New software programs allow comparing actual and perceived body image in a multidimensional form. The shape of body parts, body fat, muscularity, or motion patterns can be simulated and compared with what has actually been measured.

175.4 Applications to Other Areas of Health and Disease

Most of the body-image methodologies applied in eating disorders can also be useful in other contexts. There are many examples where body-image issues have become of interest. Body dysmorphic disorder is an entity beyond eating disorders in mental health. Dermatology, dental medicine, oncology, and rehabilitation medicine are examples of medical contexts. Cosmetic and reconstructive surgery for acquired disfigurement are areas where changing the body is in the focus of attention. Body image also provides a perspective on developmental issues and cultural differences. A comprehensive overview can be found in Cash and Pruzinsky's (2002) body-image handbook.

Whenever body image is assessed in different areas, attention should be paid to both the attitudinal and the perceptual component. A discrepancy between actual and perceived or ideal body image can only be meaningful when actual body image is assessed by means of reliable anthropometric indices. Measuring body composition through skinfold thickness is an example of such a method.

Summary Points

- The construct of body image comprises an attitudinal component and a perceptual component.
- The four dimensions of the attitudinal component are:
- A global subjective satisfaction or dissatisfaction;
- An affective distress regarding appearance;
- A cognitive dimension of body image; and
- A behavioral dimension.
- The perceptual component focuses the ability of individuals to accurately estimate their body dimensions.
- Anthropometry is necessary to measure the accuracy of body-image estimations.
- Anthropometry in eating disorders should not rely on self-reported data.
- Unidimensional methods have traditionally been applied where body width was measured and compared with subjects' estimations of the same.
- Multidimensional methods that allow morphing of bodies in more than one direction have recently become more attractive.

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Chapter 176
Anthropometry and Nutritional Rehabilitation in Underweight Eating Disorders

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Abstract The restoration of a normal body weight is a key strategy in the treatment of eating disorders, in order to eliminate the adverse effects of starvation on health and on the eating disorder psychopathology. Unfortunately, weight regain is frequently hindered by changes in body shape, in particular a protrusion of the abdomen, which may lead underweight patients to stop their nutritional rehabilitation program. In adult patients with underweight eating disorders, studies using dual-energy X-ray absorptiometry, skinfold thickness, dual photon absorptiometry and circumference measurements found a preferential accumulation of body fat in the central regions rather than the extremities during the process of weight regain. These data, however, were not confirmed in adolescents and in young adults with eating disorders. To date, the mechanism(s) implicated in the preferential accumulation of abdominal fat (e.g., low level of estrogens, fast rate of weight regain) have not been settled by experimental research, nor is it settled whether the preferential accumulation is a transient phenomenon or it persists after complete and stable weight restoration. Available data indicate that weight regain produces an increase in bone mineral density, initially greater in the hip than in the spine, but in the long-term bone recovery is never complete, especially whenever the eating disorder starts during adolescence and peak bone mass has not been attained. As lack of exercising may contribute to decrease bone mass, to increase the risk for atherosclerosis and to decrease compliance with the program, clinicians tend to incorporate healthy and social exercising in the nutritional rehabilitation. Preliminary findings indicate that this procedure helps patients get out of the isolation of their disease, overcome the urge to exercise, accept weight gain and changes in shape, and increase lean body mass, while it does not reduce the short-term gain of body fat or BMI.

Abbreviations

AN	Anorexia nervosa
BIA	Bioelectric Impedance Analysis
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_176,

DXA	Dual-Energy X-Ray Absorptiometry
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDNOS	Eating Disorder Not Otherwise Specified
FM	Fat Mass
LBM	Lean body mass

176.1 Introduction

Eating disorders are conditions characterized by a persistent disturbance of eating or eating-related behavior that result in an altered consumption or absorption of food and that significantly impair physical health or psychosocial functioning. The current DSM-IV classificatory system (American Psychiatry Association 2000) divides eating disorders into the three main diagnostic categories of anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS).

Almost 30% of individuals with eating disorders are severely underweight (i.e., body mass index (BMI) < 17.5 kg/m^2). This group includes all the individuals with AN and a subgroup of individuals with EDNOS (i.e., those with all the diagnostic criteria of AN without either amenorrhea or the overevaluation of shape and weight) (American Psychiatry Association 2000).

The active maintenance of an unhealthy low body weight is harmful and has numerous adverse effects on physical health and psychosocial functioning (Table 176.1). In addition, in individuals with eating disorder psychopathology (i.e., the overevaluation of shape and weight and their control), the symptoms of starvation seem to stimulate further dietary restriction by undermining the person's sense of being in control over his/her eating, shape, and weight, or themselves in general, while other symptoms exaggerate the tendency to use control over eating as an index of general self-control (Dalle Grave et al. 2007; see Table 176.2 for the proposed mechanisms). These observations indicate that the restoration of a normal body weight is a key strategy in the treatment of eating disorders for eliminating the adverse effects of starvation on health and on the eating-disorder psychopathology.

Weight restoration in eating-disorder patients is a complex and difficult task requiring the application of specialized procedures and strategies. The process is principally hindered by the eating-disorder psychopathology, a common difficulty being the change of body shape, in particular the sticking out of the stomach (abdomen) often observed in some patients during the first phase of weight regain, which may lead them to stop the nutritional rehabilitation. Therefore, the study of the changes in fat mass (FM) and body-fat distribution and accumulation during the process of weight regain not only is an interesting phenomenon for physiologists but also has important clinical implications for treatment.

Another important area of research regards the medical complications associated with weight loss, in particular the loss of bone mass. The reversibility of bone mass with the restoration of a normal body weight is a matter of concern, and we need to know whether a few procedures (e.g., associating healthy physical exercising to nutritional rehabilitation) may help improve the restoration of lean body mass (LBM or fat-free mass [FFM]) and the compliance of patients to treatment, without hindering FM gain.

The aims of this chapter are to review the data of the literature on the effect of nutritional rehabilitation on the relative proportion of FM and FFM, as well as on bone mass, and the role of healthy physical exercising in the treatment of underweight eating-disorder patients.

Table 176.1 Starvation effects reported by the Minnesota Study volunteers (Adapted from Keys et al. 1950)

Behavioral effects

- Eating rituals (eating very slowly, cutting the food in small pieces, mixing the food in a bizarre way, and ingesting hot food).
- Reading cookbooks and collecting recipes
- Increasing the coffee and tea consumption
- Increasing the use of salt, spices, gums, hot soup, and water
- Nail biting
- Increase smoking
- Bulimic episodes
- Increasing exercise to avoid the reduction of the caloric content of the diet
- Self-mutilation

Psychological effects

- Impairment of concentration capacity
- Poor insight and critical judgment
- Preoccupation about thought on food and eating
- Depression
- Unstable mood
- Irritation
- Hunger
- Anxiety
- Apathy
- Psychotic episodes
- Personality changes

Social effects

- Social withdrawal
- Loss of sexual appetite

Physical effects

- Abdominal pain
- Gastrointestinal discomfort
- Sleep disturbances and vertigo
- Headache
- Strength reduction
- Hypersensitivity to light and noises
- Edema
- Cold intolerance
- Paresthesia
- Reduction of basal metabolism
- Reduction of heart and respiratory frequency

Table 176.2 Proposed mechanisms through which starvation symptoms maintain the eating-disorder psychopathology

1. Being underweight and dietary restriction increase the need to control eating, shape, and weight, or all of the above in general.
2. Worries with food and eating maintain the eating-disorder mindset permanently in place.
3. Social withdrawal and loss of previous interests prevent the development of other domains of self-evaluation.
4. Maintaining underweight requires the adoption of a hypocaloric diet that favors the worries about food and eating;
5. Uncertainty makes it difficult for patients to decide whether to change or to delay changes (procrastination).
6. Strong need for routine and predictability interferes with change.
7. Sense of immediate fullness makes it difficult to increase the amount eaten.

176.2 Nutritional Rehabilitation and Body Fat in Underweight Adults with Eating Disorders

The effects of nutritional rehabilitation on the relative proportion of FM and FFM have attracted considerable attention. It was demonstrated that a reduction in both lean mass and body fat occurs in underweight eating-disorder individuals. Recovery might involve an increase in both components, but at different rates owing to the higher caloric cost of FM. Clinical observations have shown that the fear of weight gain by AN patients is enhanced by their belief that weight gain during nutritional rehabilitation is accompanied by preferential fat distribution in the abdominal area (Goldner and Birmingham 1994). As a consequence, they are reluctant to be compliant with nutritional treatment, even when it is medically important.

Forbes et al. showed that a satisfactory nutritional rehabilitation and weight regain did not require a high-protein diet (Forbes et al. 1984). Weight regain and changes in anthropometric measurements were similar in patients fed diets providing 20% or 10% energy from protein, but the high-protein diet resulted in higher blood urea nitrogen, suggesting that excess nitrogen may only harm.

The most recent publications on body-fat gain during nutritional rehabilitation are reported in Table 176.3. In female AN patients with a BMI of 16.5 ± 1.9, the accumulation of body fat was tested by dual-energy X-ray absorptiometry (DXA), skinfold thickness, and circumference measurements until they achieved maximum weight gain (Orphanidou et al. 1997). By the end of the observation period and a mean weight gain of 6.7 ± 5.3 kg, FM, LBM, and bone mineral content were all increased, with body fat being the component that increased the most. Fat gain measured by DXA was not significantly different in the three central regions: subscapular, waist, and thigh. In conclusion, 1. fat was the largest component of the weight gained; 2. there was no preferential fat accumulation in any one area of the female gynoid body; and 3. a significantly greater accumulation of body fat occurred in the central regions (i.e., chest, abdomen, hip, and thigh) than in the extremities (i.e., arm and calf), as also observed in studies based on skinfold-thickness measurement (Russell et al. 1983).

Preferential accumulation of body fat in the central regions rather than the extremities under conditions of weight regain seems to be a general phenomenon, being also the norm in individuals without AN (Lapidus et al. 1984), and it was demonstrated by skinfold-thickness measurements at five body sites in AN patients undergoing refeeding (Russell and Mezey 1962) and validated by underwater weighing (Probst et al. 2001) and bioelectric impedance analysis (BIA) (Moreno et al. 2008).

A study using multifrequency BIA (an appropriate tool for monitoring the nutritional status in AN, able to detect even subtle changes (Mika et al. 2004)) showed that, after an initial increase of FM, possibly related to previous depletion or individual variations in the control of energy partitioning, both LBM and FM increased in a parallel fashion until complete recovery (Mika et al. 2004).

176.2.1 Mechanisms Implicated in Fat Distribution During Weight Regain

One potential mechanism explaining the selective increase of FM in the trunk is that weight gain in the initial phase of weight gain in patients with underweight eating disorder occurs in the context of relative estrogen deficiency (Iketani et al. 1999) (Table 176.3). Support to this hypothesis comes from the observation that estrogen administration affects both regional and whole-body composition in estrogen-deficient women. In particular, it has been found that a combination of estrogen and progestin prevented abdominal-fat accumulation in early menopause (Haarbo et al. 1991) and led to significantly smaller overall weight gain in postmenopausal women (Espeland et al. 1997).

Table 176.3 Most recent studies on nutritional rehabilitation and body-fat gain in adults with underweight eating disorders

Study	Sample Size	Methods	Follow-up	Results and Comments
Orphanidou et al. (1997)	26 AN (in- and outpatients; age, 27.6 ± 6.6 y)	DXA and skinfold thickness	Max 6 months	↑↑ FM (78% of weight gain), ↑ LBM (21% of weight gain), and ↑ BMC (1% of weight gain). • Conflicting results between DXA and skinfold thickness
Iketani et al. (1999)	21 AN (both in-patients and outpatients)	DXA	Mean, 1.3 years (range 0.3–3.3)	↑ FM (central regions > extremities) Central adiposity tends to normalize with resumption of menses • Sex steroids might be involved in central adiposity
Probst et al. (2001)	130 AN in-patients	UW, skinfold thickness	113–215 days	↑ BW (55% as FM, LBM/FM = 1:3.4) • Body-fat estimation by skinfold-thickness as accurate as UW
Grinspoon et al. (2001)	27 AN outpatients (14 on estrogens)	DXA	9 months	FM = 68% BW gain; LBM = 32% BW gain Estrogen treatment not protective against ↑ FM in the trunk • The study challenges the estrogen theory of central adiposity
Scalfi et al. (2002)	Ten AN outpatients versus 18 controls	DXA, skinfold thicknesses, and anthropometry	Mean, 1.2 years	↑ FM = 56% BW gain; ↑ FM distributes in abdominal regions Abnormalities persist at follow-up • Nutritional rehabilitation does not restore normal anthropometry
Bertoli et al. (2004)	32 AN outpatients versus eight controls	DXA	3 years of stable recovery	At baseline, FM depletion more severe in limbs than in trunk At follow-up, FM normalized, but deficient LBM and trunk/limb FM ratio > controls • Nutritional rehabilitation does not restore normal anthropometry
Mayer et al. (2005)	29 AN patients versus 15 controls (age, 18–45 y)	DXA, MNR, and hormones	10 weeks	WHR, total trunk fat, and visceral adipose tissue remain > control ↑ cortisol, ↓ estradiol tend to normalize with refeeding (no return within control values) • Nutritional rehabilitation does not restore normal anthropometry
Moreno et al. (2008)	13 AN inpatients versus 17 controls	BIA, DXA	26 weeks	Changes in LBM/FM = 1:5 • BIA underestimates LBM in AN in comparison to DXA

AN Anorexia nervosa; *LBM* Lean body mass; *FM* Fat mass; *BMC* Bone mass content; *BW* Body weight; *DXA* Dual energy X-ray absorption; *UW* Densitometric technique of underwater weighing; *BIA* Bioelectric impedance analysis; *WHR* Waist-to-hip ratio

However, in amenorrheic women with AN randomly assigned to receive or not receive estrogens, treatment was not protective against the central fat accumulation associated with weight gain (Grinspoon et al. 2001).

Fat distribution during weight regain might also be influenced by the rate of accumulation. Most studies typically relied on cohorts predominantly recruited from in-patient populations, where the rate of weight regain is usually greater than that achieved in outpatient cohorts. However, this hypothesis was not confirmed in an outpatient study showing that the central accumulation of body fat was also present in these subjects, who had a slower rate of weight regain (Grinspoon et al. 2001).

176.2.2 Does the Prevalent Central Fat Accumulation Persist After Complete Weight Restoration?

Whether the lipodystrophy characterized by prevalent central-fat accumulation persists, or even worsens, after complete weight restoration is an important unresolved question (Table 176.3). Because healthy individuals tend to gain weight and abdominal fat with increasing age, future studies should control for the effect of time on body composition by serially assessing healthy subjects as well as eating-disorder patients.

In a study where an initial investigation was followed by a second assessment after a 15% weight gain and a third after a stable weight recovery, Bertoli et al. found that AN patients regained completely their FM, whereas LBM remained deficient (Bertoli et al. 2004).

After refeeding above a BMI threshold within the normal range (≥ 18.5 kg/m^2), FM represented on average 56% of the regained mass, being directly related to the extent of weight gain (Scalfi et al. 2002). Skinfolds at biceps and at abdominal sites and the waist-to-hip ratio remained significantly higher, whereas arm muscle circumference remained significantly lower compared to controls. In general, the selective accumulation of fat in the central depots is thus maintained. However, it is possible that a subgroup of these patients did not achieve their pre-morbid habitual body weight. In a large study, waist-to-hip ratio, total trunk fat, visceral adipose tissue, and intramuscular adipose tissue were shown to be significantly greater in patients after weight recovering than in control subjects, without differences in skeletal muscle mass (Mayer et al. 2005). The use of dual-photon absorptiometry has further confirmed the results; after restoring a normal weight, the soft mass of the pelvis and the trunk increased to the levels of controls, and the patients with AN maintained central obesity after weight restoration (Iketani et al. 1999).

176.3 Nutritional Rehabilitation and Body Fat in Adolescents and Young Adult Patients with Underweight Eating Disorders

A study carried out by computed tomography in young females with a short story of AN (on average 12 months) (Zamboni et al. 1997) found a preferential accumulation of fat in the subcutaneous tissue during nutritional rehabilitation (Table 176.4). None of the patients received estrogens during the entire course of the study. Regain of body weight was accompanied by a significant increase in total adipose tissue, but the increase observed in subcutaneous adipose tissue was significantly greater than that observed in visceral adipose tissue (212.6% vs 116.8%, respectively). Another study found that adolescent girls with AN, compared with control subjects matched for age and pubertal stage, had lower trunk fat, without differences in fat at the extremities. Weight restoration resulted in an increased percentage of trunk fat and an increased ratio of trunk to extremity fat; however, this ratio did not exceed that of control subjects (Misra et al. 2003). These results may be difficult to reconcile with the majority of studies on weight restoration in adults with eating disorders (Table 176.3). However, it should be considered that also fat loss in adolescents with underweight eating disorders mainly occurs in the trunk and spares the extremities (Kerruish et al. 2002). Fat accumulation during rehabilitation thus represents the return to normal of fat distribution rather than the development of truncal adiposity.

The pathophysiology underlying the age-related differences in fat accumulation during weight regain is unknown. The longer duration of AN in adults might result in higher cortisol concentrations and longer stimulation of truncal-fat accumulation, producing a different phenotype. These findings, which have important clinical implications for the possible cardiovascular events associated with trunk-fat accumulation, have not been confirmed in another cross-sectional analysis (de Alvaro et al. 2007).

Table 176.4 Nutritional rehabilitation and body fat in adolescents and young adults with underweight eating disorders

Study	Sample Size	Methods	Follow-Up	Results and Comments
Zamboni et al. (1997)	14 AN patients (age, 18–38 y)	TC	12 weeks	↑ total FM; ↑ subcutaneous FM > visceral FM • Normal fat redistribution with rehabilitation in adolescents
Misra et al. (2003)	21 AN adolescents outpatients versus 21 controls	DXA	12 months	At baseline, ↓ trunk fat, without differences in fat at the extremities At follow-up, ↑ trunk percentage FM; ↑ trunk/extremity FM; and trunk/extremity FM = controls • Normal fat redistribution with rehabilitation in adolescents
Mika et al. (2004)	21 young AN inpatients versus 19 controls (14 ± 1.5years)	BIA	15 weeks	Between week 3 and 7, ↑ FM, with only a minor gain in LBM ↑ LBM and ↑ FM increase to a similar extent by week 15 • Central adiposity in the early stages of nutritional rehabilitation
de Alvaro et al. (2007)	42 adolescent AN versus 23 controls	DXA	2 years	At baseline, ↓ trunk/extremity FM in patients with prolonged AN duration. No changes in regional FM in short-term malnutrition (amenhorrea < 1 year). • Fat redistribution during rehabilitation depends on AN duration and prolonged malnutrition

AN Anorexia nervosa; *DXA* Dual energy X-ray absorption; *FM* Fat mass; *LBM* Lean body mass; *TC* Computerized tomography

176.4 Nutritional Rehabilitation and Bone Mass in Patients with Underweight Eating Disorders

Body composition in underweight ED is also characterized by low bone mass and reduced bone mineral density (BMD) when assessed by DXA, with only 15% of AN patients with normal BMD (Compston et al. 2006; Valtuena et al. 2003; Viapiana et al. 2007). This translates into a high risk of fractures (cumulative risk, 57% at 40 years after diagnosis), which increases overall morbidity. In cases when the underweight eating disorder starts during adolescence, a normal peak bone mass is never reached, and the defect is maintained throughout life.

Decreased BMD and bone mineral content (BMC) result from both decreased bone formation and increased bone resorption (Dominguez et al. 2007); their pathogenic mechanism(s), as well as the changes in the homeostatic mechanism(s) during recovery, are largely unsettled. A first phase characterized by the increase of bone formation seems to reflect direct stimulation of nutrients on the osteoblastic activity. This is followed by decreased bone resorption, secondary to a slowing down of the osteoclastic activity, occurring 3–6 months after treatment starts. The initial increase in BMC does not produce an increase in BMD, because of a parallel increased bone area, particularly in adolescents (Tothill et al. 1999). In the long term, bone recovery is never complete in AN patients, even if weight recovery is held for several years (Tothill et al. 1999).

These problems constitute a major challenge during nutritional rehabilitation (Table 176.5). Weight regain produces an increase in BMD (Fig. 176.1), initially greater in the hip than in the spine, possibly due to the skeletal load produced by weight regain (Viapiana et al. 2007). Spine BMD is more affected by menstrual function, with a greater increase after menses restoration. This is confirmed in AN adolescents who restored menses, where the increase of bone mass progressed at higher speed than in AN adolescents with amenorrhea (Soyka et al. 1999). These data indicate a

Table 176.5 Changes in bone mineral parameters and biochemical indices of bone turnover during nutritional rehabilitation in underweight eating disorders

Study	Sample Size	Methods	Follow-up	Results and Comments
Soyka et al. (1999)	19 adolescent AN outpatients versus 19 controls (mean age, 15 years)	DXA, biochemistry, and hormones	12 months	↑ spine BMC and BMD, tBMC, and tBMD ↑ markers of bone turnover (osteocalcin, bone-specific alkaline phosphatase, Dpd, and NTX) • Despite recovery, poor bone mineral accrual persists in adolescent AN girls.
Compston et al. (2006)	26 adolescent AN in-patients (mean age, 16.5 years)	DXA and biochemistry	12 months	↑ tBMC but ↓ tBMD, ↓ NTX ↑ osteocalcin and bone-specific alkaline phosphatase • ↑ BW is associated with linear growth, but BMD does not increase because of a contemporaneous increased of bone area.
Miller et al. (2006)	65 AN outpatients	DXA	6 months	↑ spine BMD in AN who recovered menses ↑ hip BMD in AN who increased BW • Good reproductive function and increased BW, with ↑ LBM, are both necessary for skeletal recovery in AN
Viapiana et al. (2007)	71 AN inpatients	DXA, biochemistry	14 months	Hip BMD related to changes in BW and in bone AP; Spine BMD related to changes in serum osteocalcin • ↑ BW produces ↑ BMD, initially greater in the hip than in the spine possibly due to the skeletal load produced by weight regain
Dominguez et al. (2007)	28 AN inpatients (age, 18–35 y) versus 11 controls	DXA, biochemistry	2,2 months	↑ BMD, ↑ osteocalcin; and ↓ NTX only in subjects who regain menses • Nutritional rehabilitation induces a powerful anabolic effect on bone; full recovery involves a hormonal mechanism and requires a return of menses.

AN Anorexia nervosa; *DXA* Dual energy X-ray absorption; *NR*: Nutritional rehabilitation; *tBMD* total body mass density; *BMD* body mass density; *tBMC* total bone mineral content; *BMC* bone mineral content; *NTX* urinary N-telopeptide/creatinine excretion*; Dpd* deoxypyridinoline, *AP* Alkaline phosphates; *BW* Body weight; *LBM* Lean body mass

main role of the severity and the duration of the eating disorder, as well as of the hormonal status, on bone recovery (Compston et al. 2006). The changes in the bone homeostasis are confirmed by the circulating levels of biomarkers of osteoblastic and osteoclastic activity.

Increased LBM is associated with a more rapid and greater bone recovery than an increase of FM, both in adults and in adolescents (Compston et al. 2006).

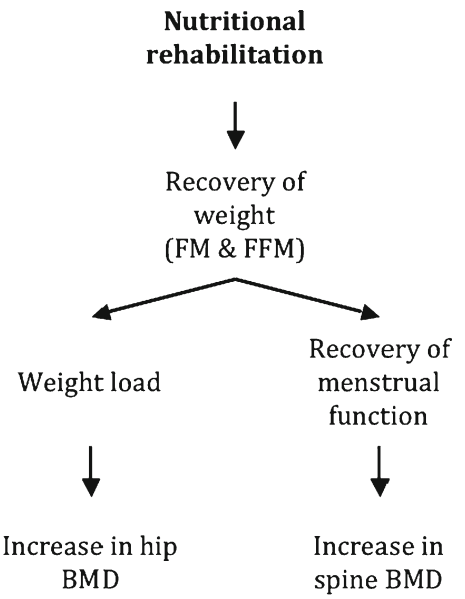

Fig. 176.1 Factors influencing the recovery of bone mineral density at different levels during the nutritional rehabilitation in underweight eating disorders. *Note*: The initial weight gain determines the recovery of bone mineral density in the hip, through the effect of weight load; the recovery in the spine occurs later, favored by the hormonal response

176.5 Physical Exercise and Nutritional Rehabilitation in Patients with Underweight Eating Disorders

Excessive and compulsive exercising in eating-disorder patients has three main general negative consequences. First, it is associated with an increased risk of over-use injuries, bone fractures, and cardiac complications. Second, it has a central role in the maintenance of the eating-disorder psychopathology through several mechanism(s): (1) by reducing the control over eating; (2) by increasing the over-evaluation of shape and weight and their control; (3) by favoring social isolation, which in turn intensifies the over-evaluation of shape and weight; and (4) by modulating mood in a dysfunctional way. Finally, compulsive exercising hinders weight restoration in underweight eating disorders and is a predictor of poor treatment outcome in patients with AN. It is also associated with longer in-patient treatment and a quicker relapse and is a negative predictor of improvement of the eating-disorder psychopathology (Dalle Grave et al. 2008b).

The incorporation of exercise in nutritional rehabilitation of underweight eating disorder patients is a matter of discussion (Table 176.6). In the past, clinicians prescribed AN patients a complete cessation of exercise (i.e., best rest), in order to reduce caloric expenditure and the compulsivity toward exercising. More recently, it has been observed that lack of exercising may contribute to decrease bone mass, to increase the risk for atherosclerosis and to decrease compliance with the program.

These clinical observations lead to incorporate social healthy exercising in the modern treatments of eating disorders (Dalle Grave et al. 2008a). Clinical experience suggests that helping eating-disorder patients, even when underweight, be physically and psychologically in good shape is an effective strategy to overcome excessive and compulsive exercise. Patients are educated to exercise moderately and with friends. In particular, social exercising (e.g., group tennis lessons, yoga classes, and so on) is useful to help patients get out from their isolation, a mechanism implicated in the maintenance of eating-disorder psychopathology. In addition, it may help practice body exposure, control the urge of exercising, and accept weight gain and changes in shape.

Table 176.6 Indication (pros and cons) of physical exercise during the nutritional rehabilitation in patients with underweight eating disorders

Pros	Cons
• Redirect patients' hyperactivity	• Risk of traumatic, over-use injuries
• Restore lean body mass and bone mineral density	• Maintenance of eating-disorder psychopathology
• Allay fears of weight gain	• Hinder weight restoration
• Increase self-control	• Longer in-patient treatment
• Favor compliance	• Risk of cardiac complications

Note that the pros are present with moderate exercise, whereas the cons are observed mainly with exaggerated or strenuous exercise

It has been demonstrated that a fitness-training program (20 sessions, 2 times per week) during refeeding of underweight eating-disorder patients, supervised by a therapist who is familiar with the physical consequences of undernutrition, may increase LBM and redirect the patients' hyperactivity in a healthy way, allay their fears of weight gain, and improve their sense of self-control (Probst et al. 1995). A supervised exercise program increased satisfaction of both staff and patients and was successfully implemented in hospitalized inpatients, with an average weight gain of 1 kg/week (Dalle Grave et al. 2008b). In a randomized, controlled study having change in percent body fat, BMI, and quality of life as outcome measures, Thien et al. tested the effects of a graded exercise program during nutritional rehabilitation in females with AN (Thien et al. 2000). The study showed that both the control and the exercise group increased from their BMI (by 0.8 and 1.0 kg/m^2, respectively) and percent body fat (by 0.5% and 0.9%). However, the exercise group showed an improvement, whereas the control group showed a significant deterioration, in all aspects of quality of life. In summary, although none of the above differences were statistically significant, the study supports the incorporation of a graded exercise program to increase compliance with treatment, without reducing the short-term rate of body fat or BMI increase.

176.6 Conclusions

The study of anthropometry during nutritional rehabilitation in underweight eating-disorder patients is an important research area with several clinical implications. The amount of body fat may indeed affect the clinical outcome. Menses return with nutritional rehabilitation, but both the changes in central body fat and the return of menses may enhance the worries about weight and shape, increasing the likelihood of relapse.

Modern cognitive behavior therapy for eating disorders suggests several strategies to help patients cope with the changes in body-fat distribution during the process of weight restoration (Fairburn 2008). First, eating-disorder patients should be informed that, at least in the initial phase of weight restoration, there is a natural preferential accumulation of body fat in the abdomen and, sometimes, a disproportionate sticking out of the stomach. The phenomenon becomes more prominent by the severe wasting of the abdominal and back muscles, by certain type of clothing (e.g., low-waisted jeans), and by the consumption of a diet rich in fiber and fizzy drinks, and finally by the common tendency of eating-disorder patients to observe their stomach, in particular after eating (Fairburn 2008). Second, they should be helped to disregard the sticking out of their stomach as a sign of overeating or being fat. Third, they should be encouraged to use some simple measures to

reduce this phenomenon (i.e., wearing clothes that do not exaggerate the stomach protrusions, interrupting the checking of their shape in particular after eating, and avoiding the consumption of a diet too rich in fiber and fizzy drinks). Fourth, they should be invited to practice a social healthy exercise that may help both accept weight gain and changes in shape and increase BMD, an important therapeutic target especially in adolescents with eating disorders, who failed to reach a normal peak bone mass.

Future studies should better clarify the physiological mechanisms of body-fat redistribution during weight regain, in particular if some factors (e.g., age, duration of the underweight condition, rate of weight regain, sex, and level of physical exercising) play a role in this process and if the prevalent accumulation of body fat in the abdomen is a transient phenomenon or persists after a complete weight restoration. If the relative increase in abdominal fat is an acute event and it redistributes with stable weight gain, patients should be informed that stomach protrusion is a transient phenomenon and the simple measures described above might be sufficient to help them accept the distorted fat accumulation until redistribution. Alternatively, if no return to normal distribution occurs with time, a targeted and more complex, cognitive approach might be needed to promote the self-acceptance of a different, but healthier, body shape.

176.7 Applications to Other Areas of Health and Disease

The dissemination of the knowledge about the effects of weight regain on body composition in underweight individuals might help improve the assessment and the treatment of the following conditions associated with underweight and low calorie intake (the list is not complete):

- AIDS
- Alcoholism
- Alzheimer's disease
- Anxiety
- Cancer
- Celiac disease
- Chronic heart disease
- Chronic liver disease
- Chronic lung disease
- Chronic renal disease
- Clinical depression
- Cystic fibrosis
- Dementia
- Denture difficulties
- Dysphagia
- Infections
- Inflammatory bowel disease
- Lactose intolerance
- Malabsorption
- Osteoporosis
- Starvation
- Stomach ulcer
- Stomatitis

- Systemic lupus erythematosus
- Schizophrenia
- Tuberculosis
- Uncontrolled diabetes mellitus

176.8 Guidelines

- The body composition of underweight eating-disorder patients should be assessed both at baseline and after weight restoration.
- Fat mass, fat-free mass or lean body mass, and body-fat distribution can be assessed with dual-energy X-ray absorptiometry (DXA), skinfold thickness, circumference measurements, and bioimpedance absorptiometry (BIA).
- Bone mineral density must be assessed by DXA.
- Social and healthy exercising should be incorporated in the nutritional rehabilitation programs of underweight eating-disorder patients.

Summary Points

- Underweight is a key diagnostic criterion for AN, but it is also present in a subgroup of patients with eating disorders not otherwise specified (EDNOS) (e.g., underweight patients who meet all DSM-IV criteria for anorexia nervosa except amenorrhea or the overevaluation of shape and weight).
- The restoration of a normal body weight is a key strategy in the treatment of eating disorders in order to eliminate the adverse effects of starvation on health and on the eating-disorder psychopathology.
- The process of weight regain may be hindered by changes in body shape, in particular a relative protrusion of the stomach (abdomen), which may lead to non-compliance with the treatment program and to stop weight regain.
- During weight regain, there is a preferential accumulation of body fat in the abdomen in adult eating-disorder patients. By contrast, there is a normal fat distribution rather than the development of truncal adiposity in adolescents and young adults with underweight eating disorders.
- The potential mechanism(s) implicated in the preferential abdominal fat accumulation (e.g., low level of estrogens and rate of weight regain) has/have not been definitely settled.
- It is not clear whether the preferential abdominal-fat accumulation is a transient phenomenon or it is maintained after a complete and persistent weight restoration.
- Weight regain is associated with an increase in bone mineral density, initially greater in the hip than in the spine; in the long term, bone recovery is never complete, especially whenever the eating disorder starts during adolescence.
- Social healthy exercising could help patients get out of their isolation, stop their urge to exercise, accept weight gain and changes in shape, and increase lean body mass, without reducing the short-term rate of BMI increase.
- Simple cognitive behavioral procedures and strategies may help compliance to treatment in underweight eating-disorder patients without intensifying the worries about body shape.

Key Points

- Weight regain is associated with a preferential accumulation of body fat in the abdomen, especially in adult eating-disorder patients. It is not yet clear if this is a transient phenomenon or will be maintained after a complete and stable weight restoration. The mechanism(s) proposed to explain this phenomenon have not been fully confirmed by experimental studies.
- Weigh regain is associated with an increased bone mineral density, but, in the long-term, bone recovery is never complete.
- Underweight eating-disorder patients should be educated that, at least in the initial phase of weight restoration, there is a natural preferential accumulation of body fat in the abdomen. Associating social healthy exercising to nutritional rehabilitation increases the compliance to treatment, without reducing the short-term rate of body fat or BMI gain.

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Chapter 177
Anthropometric Nutritional Assessment in Children with Severe Neurological Impairment and Intellectual Disability

Corine Penning and Heleen M. Evenhuis

Abstract This chapter discusses the current evidence and best practices of anthropometric measurements in children with severe neurological impairment and intellectual disability, who both have a severe motor impairment and moderate to profound intellectual disability due to congenital or acquired neurological damage. First the target population is described in detail, with regard to the etiology of the disorder, frequent concomitant medical problems and life expectancy. The necessity of regularly measuring the nutritional state is underlined in the light of these children's nutrition-related problems, such as dysphagia and gastro-esophageal reflux, which are potential causes of malnutrition. In contrast, a subgroup of these children is at risk of developing obesity due to tube feeding.

An overview of the feasibility of commonly used anthropometric measurements in the target population, such as weight, height and skinfold measurements, is presented and where possible, alternative methods are described, such as the use of segmental measures when accurate measurement of standing height is not possible. Outcome of body composition measurement is interpreted by means of specific equations. An overview of frequently applied and, if available, group-specific norm values and equations for interpretation of the outcome is presented, followed by suggestions for future research needed for further improvement of the reliability and interpretation of anthropometric measurements in these children. Based on the current knowledge, practical recommendations are given for applying anthropometry in children with severe neurological impairment and ID.

Abbreviations

BIA	Bioelectric impedance analysis
BMI	Body mass index
CP	Cerebral Palsy
DLW	Doubly labeled water
DEXA	Dual-energy X-ray Absorptiometry
FFM	Fat-free mass
GER	Gastro-Esophageal Reflux
GMFCS	Gross motor function classification scale

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_177,

ID Intellectual disability
KH Knee height
PEG Percutaneous endoscopic gastrostomy
TL Tibia length
UAL Upper-arm length

177.1 Introduction

177.1.1 Children with Severe Neurological Impairment and Intellectual Disability (ID)

Many healthcare professionals will recognize children with severe neurological impairment and ID in their clinical practice as a typical subgroup of wheelchair bound, often spastic children with intellectual disability who have multiple health and nutrition-related problems. Since this is a heterogeneous population by nature, this introduction aims to give a clear description of these children and their health problems before discussing the group-specific methodology of anthropometric recordings.

Internationally, there is lack of consensus for the terminology and definition of this group of children and, as a result, various other descriptions of the disorder have been used in international literature, such as neurodevelopmental disorder, severe (generalized) cerebral palsy, spastic quadriplegic cerebral palsy, or profound intellectual and multiple disabilities. Typically, children with severe neurological impairment and ID are characterized by having both a moderate-to-profound intellectual disability (IQ below 55) and a severe motor handicap (either a hyper- or hypotonic generalized cerebral palsy or a severe motor developmental delay), corresponding with the functional levels of 4 or 5 on the Gross Motor Functional Classification Scale (GMFCS) (Palisano et al. 1997). The disorder is the result of damage to the developing brain that arises before, during, or after childbirth. The most common causes are congenital syndromes or metabolic disorders, prematurity, perinatal asphyxia or trauma, or meningitis, traffic accidents or near-drowning accidents when the disorder is acquired during childhood. Due to the severity of their disabilities, most of these children are wheelchair bound and rely on care from specialized day-care centers, specialized schools, or residential facilities for people with ID. As a result of the availability of multiple forms of specialized daycare in the Netherlands, the majority (approximately 95%) of children with severe neurological impairment and ID live with their parents and only those with severe comorbidity are admitted to residential facilities during childhood. Exact prevalence or incidence numbers are lacking, but, in the year 2000, in the Netherlands the prevalence rate was estimated at 0.6 per 1,000 live births.

177.1.2 Comorbidity

Most children with severe neurological impairment and ID are affected not only with the above-mentioned intellectual and motor disabilities but also with additional health problems that may result from neurological damage. A summary of frequently occurring health problems in these children is given in Table 177.1. As a result of these frequent comorbidities, many of these children use multiple medications, and they are often under treatment by several clinical specialists, such as pediatricians, neurologists, and orthopedic surgeons, and also by several paramedical professionals, such as dieticians,

Table 177.1 Comorbidity in children with severe neurological impairment and ID

General comorbidity	*Nutritional problems*
Epilepsy	Dysphagia
Visual impairment	Gastro-esophageal reflux and vomiting
Reduced pulmonary function	Delayed gastric emptying
(recurrent) Lower respiratory tract infections	Chronic constipation
Low bone mineral density and low-impact fractures	Nutritional status:
Scoliosis	• Malnutrition
Hip displacement	• Obesity
Contractures	Growth retardation

Frequently occurring general and nutrition-related concomitant disorders in children with severe neurological impairment and intellectual disability (ID)

physical therapists, and speech and language therapists. Furthermore, children are frequently admitted to the hospital for either elective surgical procedures or during acute (mostly respiratory) disease. As a result of these health problems, the life expectancy of these children is markedly reduced. Reported predictors of (early) mortality in children with cerebral palsy (CP) are intellectual disability, limited mobility, incontinence, and inability to eat without assistance (Eyman et al. 1990). In most children with severe neurological impairment and ID, typically all of the above are present and, in the early 1990s, presence of these risk factors was linked to a survival rate of 18% reaching the age of 25, with respiratory infections being the most common cause of death (Eyman et al. 1990). However, since then, medical care for this population has markedly improved: between 1983 and 2002, mortality among these children improved at an average rate of 3.4% per year (Strauss et al. 2007).

177.1.3 Nutritional Problems

Table 177.1 shows that many concomitant health problems in children with severe neurological impairment and ID are related to nutrition and food intake. Due to neurological damage, a large proportion of children suffers from severe dysphagia, clinically presenting as difficulties with the reception of food from the spoon or the cup, oral containment of foods, chewing, and oro-pharyngeal swallowing. As a result of dysphagia, feeding the child is often complex and may take a long period of time, while it may also put the child at risk for aspiration of oral contents. Swallowing difficulty may be further deteriorated by episodes of gastro-esophageal reflux (GER): the acidic gastric refluxate may irritate the mucosa of the oro-pharyngeal cavity, further hampering oro-pharyngeal swallowing. It has been suggested that these children may suffer from delayed gastric emptying, a condition that may enhance GER due to gastric stasis and may result in postprandial vomiting. Apart from theses disorders, food intake may also be limited by oro-pharyngeal hypersensitivity, which causes an unpleasant sensation in their mouths during the meals. It will therefore not be surprising that these children may develop negative associations with eating and mealtimes, and, in fact, food refusal is often observed. Since communication is often limited due to their intellectual disability, it may be hard for them to convey feelings of hunger or satiety to their caregivers. Due to all these potential difficulties, attaining a sufficient daily intake of calories is challenging. Indeed, the prevalence of malnutrition in these children is high: when comparing their results of nutritional-assessment tests to reference values for non-handicapped children, approximately 40% of them are undernourished (Sullivan et al. 2000). Since malnutrition increases the risk to develop infections, delays recovery

after surgery, may contribute to growth retardation, and has an overall profound negative effect on health and quality of life, early diagnosis of malnutrition in these children is desirable.

In order to prevent aspiration resulting from severe dysphagia or to assure sufficient daily caloric or medication intake, a considerable number of children are fed through a nasogastric tube or through a gastrostomy. Tube feeding may be administered as an adjuvant, or exclusively to those children with a high risk of aspiration who may receive nil per mouth. Although tube feeding may assure caloric intake, the potential risk of overfeeding should not be ignored. Due to immobility, muscle mass is often reduced, and it has been suggested that energy requirements in these children may be reduced as well; hence, the necessary daily amount of calories may be lower than the amount that is calculated through conventional equations, such as Schofield's pediatric formula. A recent study demonstrated that body-fat percentage was significantly higher in children receiving gastrostomy feeding versus those who were orally fed (Sullivan et al. 2006), while, from clinical practice, it has been reported that several tube-fed children become overweight. Thus, tube feeding may not only lead to a desirable weight gain, but as a result of administering too many calories, a proportion of the children with severe neurological impairment and ID may develop overweight or obesity.

Since nutritional problems leading to an undesired nutritional state are common in this frail population, regular screening and early diagnosis of malnutrition or overfeeding, and evaluation of the effects of surgical procedures, such as gastrostomy or anti-reflux surgery, are highly relevant.

177.1.4 Research in General

During the past decades, professionals have become aware of the multiple health problems in this frail population and of the lack of scientific evidence for specific diagnosis and treatment. Since then, the number of scientific studies, with topics varying from quality of life of their caregivers to the effectiveness of botulinum toxin injections, has gradually increased and, without a doubt, this has resulted in improved medical care and reduced mortality. However, the outcomes of published research projects are, in many cases, hard to interpret. As a consequence of the lack of an internationally accepted definition for the disorder and due to its varying etiology, different subgroups of the target population are being studied, thus hampering extrapolation of the research outcomes to the entire target population. Furthermore, since the prevalence of the disorder is low, most studies have included small groups of children or samples that are not representative, for example, children who are recruited through their pediatricians (many, but not all children with severe neurological impairment and ID are consulting a pediatrician). When interpreting the outcomes of published research, one should keep these potential limitations in mind.

177.2 Measuring Nutritional Status: Pitfalls and Status of Current Research

In clinical practice, growth and nutritional status are conventionally measured using nutritional assessment methods, such as height for age, weight for age, and weight for height. As an alternative measure, body composition (lean body mass or fat-free mass and fat mass) can be determined non-invasively by measuring percentage fat mass from skinfold measurements or from bioelectric impedance

Table 177.2 Equations for estimation of standing height from segmental measures

Segmental measure	*Equation for estimation of standing height (S; cm)*
Knee height (KH)	S = (2.69 * KH) + 24.2
Tibia length (TL)	S = (3.26 * TL) + 30.8
Upper-arm length (UAL)	S = (4.35 * UAL) + 21.8

Equations have been developed in a population of 172 children with severe cerebral palsy and are applicable for children up to the age of 12 years (Stevenson 1995)

assessment (BIA). Measurement of body composition is an accepted measure for the investigation of growth in children and adolescents, irrespective of their standing height and is a valid alternative for the use of growth charts (Sakate 1984). Skinfold measurements and BIA have been previously validated for application in schoolchildren and for several patient groups. Reference values, specified by age, gender, ethnicity, or disease, are available for many populations.

It is known that healthcare professionals involved in the medical care for children with severe neurological impairment and ID, such as pediatricians, intellectual disability physicians, or dieticians working in a hospital or in an ID-care organization, may experience several difficulties when applying these common nutritional assessment methods to the target population. These difficulties, subdivided by feasibility issues, applicability of available equations, and interpretation of the outcome, are discussed below.

177.2.1 Feasibility of Anthropometric Nutritional-Assessment Methods

177.2.1.1 Standing Height

For the determination of height for age or weight for height, an accurate measurement of standing height or stature is required. However, most children with severe neurological impairment and ID are unable to stand upright and, consequently, their height has to be measured while they are in a supine position. Unfortunately, supine measuring boards applicable to children older than infants are, in most cases, not available. The best method to measure their height is therefore with a flexible tapeline, although accurate measurement is hampered by physical deformities, such as the frequently occurring scoliosis or fixed contractures of the limbs. For those children in whom measuring standing height is complicated, the use of segmental measures is advocated. Group-specific equations have been developed for the estimation of standing height from knee height, tibia length, or upper-arm length (Table 177.2) (Stevenson 1995). However, these equations may not apply to all children within the target population, since they have been developed in a subset of children with severe cerebral palsy who were not all intellectually disabled, and, additionally, they can only be applied until the age of 12 years. The developed equation based on knee height showed the best correlation with measured stature and is therefore most accurate, but measuring knee height may not be feasible in children with fixed contractures of the knee and ankle, since these joints have to be flexed in a 90° angle during the recording and, besides that, a special caliper is required which is not available in most clinical offices. By contrast, measurements of tibia length or upper-arm length are not influenced by joint contractures since they do not encompass joints, can be measured with a tape line, and, for both reasons, may be more suitable for these children.

177.2.1.2 Body Weight

Measuring body weight can be challenging as well. In care organizations, the electrical hoists that are used for patient transfers in daily care can, in most cases, be used for measuring body weight. In addition, special wheelchair scales are available that weigh the child while it is sat in its wheelchair, but these specific scales are usually not present in general medical offices. In a clinical setting, smaller children are often lifted by their caregivers and then weighed together on a regular scale, after which the weight of the caregiver is subtracted from the total weight. However, this may be dangerous or even impossible when children are older and heavier and not very accurate.

177.2.1.3 Skinfold Measurements

Body composition can be calculated from indirect measurements, such as skinfold thickness measured at several locations of the body. Measurements are done with a standard caliper that is used for the general population or other patient groups. It is well known that, in general, intra-observer variability of skinfold measurements is considerably high, while it is even higher when comparing the outcome of two separate observers (McRae 2009). Regardless of this variability, regularly measuring skinfold thickness during the clinical follow-up, preferably by the same observer, offers valuable information on changes in the nutritional status of a child. For research purposes involving multiple observers, it is important though to establish acceptable inter-observer agreement by training before the measurements begin.

It is common practice to include either two skinfold measurements, or measurements from four sites, usually the biceps, triceps, suprailiac, and subscapular skinfolds. Measurements at seven or even more sites are mostly applied in research settings only. Since the target population is immobile and is often tube fed, it has been suggested previously that fat distribution may be altered in these children, with less subcutaneous fat on the limbs and a larger internal (abdominal) fat deposit (van den Berg-Emons et al. 1998; Spender et al. 1988). Hence, the use of equations that are based on biceps and triceps measurements only for calculation of fat percentage may lead to an underestimation of body-fat percentage in the target population. Unfortunately, additionally measuring the suprailiac and subscapular skinfolds may be time consuming in clinical practice since many children wear splints and corrective braces for maintaining an optimal body position. For correct measurement of the trunk skinfolds, children will have to be lifted onto an examination bench and have their clothing and braces removed. Since the available time for clinical consults is limited, measuring skinfold thickness at four sites may not always be feasible in clinical practice. Another aspect that limits feasibility is the finding that these children have reduced muscle mass and often also have an altered structure of the skin and subcutaneous tissue, the latter presumably being due to prolonged tube feeding, and, as a result, it may be hard or sometimes impossible to correctly pinch a skinfold for measurement. As a result, outcomes of skinfold measurements may be less reliable in the target population, and the need for an experienced observer is very high.

177.2.1.4 Bioelectric Impedance Analysis (BIA)

Where skinfold measurements aim to determine body composition from a number of local recordings, BIA aims to do so through a recording that involves the whole body or a major segment of it. During recordings, a weak electric current is transmitted through the body and the resistance to its flow through body tissues provides a measure of the amount of total body water, which can be converted into lean body mass, and, by subtraction from body weight, into fat mass. Multiple methods

Table 177.3 Factors influencing outcome of BIA recordings

Factor	*Recommendations for optimal BIA recording*
Fasting conditions	Prior to the test, subjects should have been fasted for at least 4 h
Physical activity	No moderate to heavy physical activity directly preceding the test
Time of the recording	Repeated or multiple tests should be performed on the same time of the day
Body temperature	Subjects should have normal body temperature during the recording (no fever)
Bladder voided	Prior to the test, subjects should have voided their bladder
Rest period	Prior to the test, subjects must have been supine at least 5 min or more
Body position	Subjects should be in a supine position with their arms and legs abducted at a 30–45° angle from the trunk

The optimal conditions for a standardized BIA recording

are available for BIA recordings. Available devices can be subdivided according to placement of the electrodes for transmission and reception, for example, hand-to-hand and foot-to-foot (segmental) recordings versus hand-to-foot (whole body) recordings, where the latter type of measurement is most indicative of lean body mass. Apart from that, BIA devices are available for impedance measurement at either a range of multiple frequencies or a fixed set of frequencies. BIA devices may be expensive and are usually not a part of the standard equipment of medical professionals. In addition, BIA recordings are most reliable when performed under standardized conditions. The most important factors that may influence the outcome of BIA recordings and the optimal recording conditions are listed in Table 177.3.

Since measuring body composition from skinfold measurements may be a challenge in children with severe neurological impairment and ID, a BIA recording may be a viable alternative for this purpose, since it is a quick and noninvasive procedure. In addition, it is hypothesized that the outcome of a BIA recording may be a more reliable estimator of body fat in these children when compared to skinfold measurements, since a BIA recording measures all fat deposits in the body and not only subcutaneous deposits. However, standardization of the recordings may be hard to accomplish, since it may be difficult to adhere to the requirements from Table 177.3. Being in a fasted state for at least 4 h prior to the recording may be complex with regard to medication intake or tube feeding. In addition, infections, such as middle-ear infections, urinary-tract infections, and pulmonary infections, occur often in this population and, as a result, fever is a common condition. BIA recordings in this group should therefore always be preceded by an accurate body temperature recording. Ideally, subjects should void their bladders prior to the recording. Since the majority of children within the target population cannot be toilet trained and wear diapers, varying contents of the bladder may affect the outcome of the recording as well. Finally, achieving and maintaining the prescribed supine position may be troublesome as well, due to lack of cooperation and frequent contractures of the limbs. In some cases, the observer may have to gently fixate the child's limbs using a flannel blanket. Regardless of these possible limitations, it was demonstrated that the influence on the outcome is limited and that BIA is a feasible recording in this population (Veugelers et al. 2006).

177.2.2 Applicability and Validity of Available Equations

When measuring body composition by either BIA or skinfold measurements, the raw outcome (usually the average of 3 recordings) has to be transformed into either fat-free mass or fat mass respectively, using a suitable equation. Most BIA devices have built-in equations and immediately produce

data on fat mass rather than raw outcome, but, in most cases, it may not be clear which equation is used and for which population it was originally developed. For both nutritional-assessment methods, several generic equations have been developed previously, based on outcome in large populations. However, the body compartments that are targeted by these nutritional-assessment recordings may be affected by several medical conditions, for example, altered hydration status and electrolyte balance in dialysis patients, affecting lean body mass and, thus, outcome of the BIA recording. According to the 2004 ESPEN guideline (Kyle et al. 2004), it is therefore important to use population-specific BIA equations for each individual patient group, in order to obtain reliable outcomes. As stated earlier, subcutaneous fat distribution is thought to be altered in children with severe neurological impairment and ID, with lower fat mass on the limbs and a supposed increased internal fat deposit (Spender et al. 1988; van den Berg-Emons et al. 1998), which may result in an underestimation of fat mass percentage when generic equations are applied. Several authors have studied the reliability of generic BIA and skinfold equations in the target population and some have developed population-specific equations. The current knowledge with regard to the available equations is summarized below, in order to help the clinician interpret the nutritional-assessment outcome.

177.2.2.1 Skinfold Measurements

Apart from comparing skinfold thickness or the sum of four skinfold thicknesses to age-related reference values, outcomes can also be converted to percentage body fat. For children, the most commonly applied generic equations for calculation of percentage body fat from skinfold measurements are the equations of Slaughter and Durnin. The equation developed by Slaughter (Slaughter et al. 1988) is based on measurement of the triceps and subscapular skinfolds and also includes gender, race, and pubertal stage. This equation was developed in a population consisting of children aged 8–18 years and, therefore, can only be reliably applied to children of those ages. By contrast, the equation developed by Durnin (Durnin and Rahaman 1967) is applicable to children of all ages, and it is based on the sum of four skinfold thicknesses (biceps, triceps, subscapular, and suprailiac). In addition, it includes gender and pubertal stage, and its outcome, body density, can be converted into percentage body fat by using the formula of Siri (Siri 1961). The above-mentioned equations are listed in Table 177.4.

Until recently, population-specific skinfold equations were not available for children with severe neurological impairment and ID. Several researchers have therefore applied the equations of Durnin and Slaughter to interpret their measurement outcome, but the outcomes raised questions about the applicability of these generic equations to the target population. As a consequence, some validation studies have been performed, in which the outcome of the equations, percentage body fat, was compared to body fat measured by means of a so-called gold standard: a reference method for the determination of body composition, for example, a dual-energy X-ray absorptiometry (DEXA) scan or the doubly labeled water (DLW) technique, which involves the ingestion of stable isotopes of water. Gold-standard methods are more complex measurement techniques that may be either invasive or very expensive and are therefore applied in research settings only. Although agreement with outcomes of a gold-standard method was considerable, it was observed that the generic equations underestimate percentage body fat in the target population (Rieken et al. 2009a; Gurka et al. 2009), which may be the result of the supposed altered2 fat distribution. Therefore, recently, a group-specific equation was developed for interpretation of skinfold measurements. This new equation by Gurka (Gurka et al. 2009) is displayed in Table 177.4 as well, is based on the generic equation by Slaughter,

Table 177.4 Population-specific and generic equations for interpretation of outcome of skinfold measurements in the target population

Generic equations			
1. Slaughter (sum[a] ≤35 mm)[b] (Slaughter et al. 1988)			
Males	Prepubescent[c]	White	% body fat = 1.21*(sum) – 0.008*(sum)^2 – 1.7
		Black	% body fat = 1.21*(sum) – 0.008*(sum)^2 – 3.2
	Pubescent[d]	White	% body fat = 1.21*(sum) – 0.008*(sum)^2 – 3.4
		Black	% body fat = 1.21*(sum) – 0.008*(sum)^2 – 5.2
	Postpubescent[e]	White	% body fat = 1.21*(sum) – 0.008*(sum)^2 – 5.5
		Black	% body fat = 1.21*(sum) – 0.008*(sum)^2 – 6.8
Females	All		% body fat = 1.33*(sum) – 0.013*(sum)^2 – 2.5
Slaughter (sum >35 mm)			
Males	All		% body fat = 0.783*(sum) + 1.6
Females	All		% body fat = 0.546*(sum) + 9.7
2. Durnin[f] (Durnin and Rahaman 1967)			
Males	Prepubescent		Density = 1.1690 – 0.0788*log(sum)[g]
	Postpubescent		Density = 1.1533 – 0.0643*log(sum)
Females	Prepubescent		Density = 1.2063 – 0.0999*log(sum)
	Postpubescent		Density = 1.1369 – 0.0598*log(sum)
Conversion to body fat (Siri 1961):			% body fat = ((4.95/density) – 4.5)*100
Population-specific equation			
3. Gurka[h] (Gurka et al. 2009), correction factors to Slaughter's equation:			
Overall			+12.2
Additional correction:			
	More severe GMFCS		+5.1
	Males		–5.0
	Black race		–3.1
	Pubescent		+2.0
	Postpubescent		–4.6
	Sum[a]>35 mm		–3.2

[a] Sum of triceps and subscapular skinfolds
[b] Applicable to children between eight and 18 years of age
[c] Prepubescent from the age of 8 years, Tanner stages 1 and 2
[d] Pubescent, Tanner stage 3
[e] Postpubescent, Tanner stages 4 and 5
[f] Applicable to children of all ages
[g] Sum of biceps, triceps, suprailiac, and subscapular skinfolds
[h] Applicable to children with CP between eight and 18 years of age, without genetic, metabolic, or neurodegenerative diseases

and adds correction factors for child-specific conditions. Gurka's equation has been developed for children aged 8–18 years with CP, excluding children with a history of metabolic, genetic, or neurodegenerative disorders. Agreement with the gold-standard method improved from 0.62 to 0.91 using Gurka's equation over Slaughter's equation. The development of this group-specific equation seems to be a promising improvement to the interpretation of skinfold measurements. Future research is needed, however, to cross-validate the developed equation, since it has been developed in a relatively small and narrow patient population, which may have affected its accuracy and limits its applicability to only part of the target population.

Table 177.5 Population-specific and generic equations for interpretation of outcome of BIA recordings in the target population

Equation for malnourished children	
1. Pencharz (Pencharz and Azcue 1996)	TBW = 2.99 + (0.649*H^2/R)
Population-specific equation	
2. Rieken (Rieken et al. 2009b)	TBW = 2.09 + (5.44*TL^2/R) + (0.19*weight)

TBW Total body water (kg), *H* Height (cm), *R* Resistance measured by BIA device, *TL* Tibia length, *W* Body weight in kilograms

177.2.2.2 BIA Recordings

Many medical disorders may affect aspects of body composition, as, for example, shifting of extra- to intracellular water or an altered electrolyte balance, and therewith may affect conductivity of the body and BIA outcome as well. The use of an interpretative equation that has been specifically developed for the target population is therefore an absolute requirement for a reliable BIA outcome. In 1996, a BIA equation was developed by Pencharz et al. for application in children with malnutrition (Pencharz and Azcue 1996) (Table 177.5), and since children with severe neurological impairment and ID are often undernourished, many researchers have applied this equation to the BIA outcome of the target population. Although malnutrition occurs frequently, clearly not all children are undernourished, and it is questionable whether such an equation may be applied to those children with normal nutritional status, since malnutrition largely affects body composition. Apart from that, detailed information on the population used for development of the equation, such as age range or medical conditions, is lacking. Standing height is a component of the equation; hence, the difficulty of an accurate height measurement in these children may be reflected by variable BIA outcome. Indeed, it was reported that the Pencharz equation largely overestimates fat-free mass in the target population, sometimes even resulting in values exceeding body weight and, thus, in negative values for fat mass (Liu et al. 2005; Veugelers et al. 2006). A few groups have validated the use of the Pencharz equation and found that fat-free mass values agreed reasonably well with those of a gold standard, while percentage body fat agreed poorly (Rieken et al. 2009a).

Recently, a population-specific equation was developed by Rieken et al. (Rieken et al. 2009b), in a population of 63 children of all ages and varying etiology (CP, syndromes, and unknown) with severe neurological impairment and ID (Table 177.5). Compared to the Pencharz equation, the new equation improved agreement with the outcome of the gold standard (DLW) from 0.94 to 0.96. However, the newly developed equation will be more applicable in clinical practice, since it includes measuring tibia length rather than standing height.

Both the newly developed population-specific skinfold (Gurka) and BIA equation (Rieken) may improve the reliability of nutritional assessment, although both equations should be cross-validated in a separate population prior to clinical use. Based on currently available information, it is not possible however to conclude which diagnostic method should be preferred, since the BIA and skinfold equation have comparable agreement with a gold standard. The major difference between both new equations is the population in which they have been developed, and one should keep in mind that the reliability of the skinfold equation when applied to children with etiologies other than CP is yet unknown. In clinical practice, the choice between both methods will depend on the clinician's preference and the availability of instruments.

177.2.3 Reference Values

After anthropometry or BIA, outcome is compared to reference or norm values in order to determine nutritional status and to estimate if the child is at risk for developing over- or undernutrition. Values for height for age, weight for age, and weight for height are compared to normative data from growth charts that are available for many nationalities and for specific patient populations. In addition, multiple reference charts are available for interpretation of body-composition outcomes, such as thickness of individual skinfolds for age and the sum of four skinfolds for age. It is questionable though whether these general pediatric reference values may apply to children with severe neurological impairment and ID as well, since they are generally shorter and lighter than the reference standards, indicating growth retardation. In addition, the shape of their bodies might be altered due to immobility and prolonged tube feeding, further limiting the use of general reference values.

In 1996, Krick et al. published population-specific growth charts (height and weight for age and weight for height) for boys and girls, based on measurements in 360 children with spastic quadriplegic CP (Krick et al. 1996). Although these reference values are based on a relatively large sample, they are only applicable until the age of 10 years. In addition, the reference curves were based on recordings in a clinical sample consisting of children visiting an orthopedic clinic, which increases the risk of selection bias. It could be suggested that these children have the most severe disabilities, which might have had additional effects on growth parameters. When obtaining a representative sample of children, as in the North American Growth in CP project (Stevenson et al. 2006), it may still remain unclear in how many of them growth is abnormal due to secondary disorders, such as growth-hormone deficiency and chronic or acute malnutrition, which limits the development of accurate predictive growth charts for clinical use.

In 2007, Day et al. published predictive growth charts for children with all subtypes of CP until the age of 20 years, including those with severe neurological impairment and ID, based on 141,961 measurements in 24,920 children (Day et al. 2007). Although the influence of secondary health problems on growth was not accounted for, the very large number of measurements may have eliminated some of this bias, although it still remains unknown if these charts represent how these children should grow rather than how they grew. The authors subdivided the children with CP into five subgroups, based on the level of motor disability, and children in groups 4 (do not walk, crawl, creep, or scoot; do not feed self; and are not fed by gastrostomy tube) and 5 (like group 4, but fed by gastrostomy tube) correspond with the target population. The authors compared their growth charts of group 4 and 5 children to those developed by Krick and found that centiles of weight for age of children in group 4 corresponded most to those of the Krick growth charts, while the children in group 5 had considerably higher centiles. Their gender-specific growth charts by subgroup (weight, height, and BMI for age) have been published online (http://www.lifeexpectancy.org/articles/GrowthCharts.shtml).

177.2.4 Results in Clinical Practice and Scientific Research

Due to the lack of clinical guidelines for performing and interpreting anthropometry in children with severe neurological impairment and ID, medical professionals are uncertain about their diagnosis. A recent investigation of currently applied nutritional assessment strategies by Dutch dietitians working in ID care, using a structured survey, showed that a variety of diagnostic measurements is applied, ranging from clinical judgment to anthropometry to blood nutrition panels. Only 2 of the 32

participating dietitians opined that the outcome of these methods is an accurate reflection of the child's nutritional status, while half of them said that current methods are indicative of their nutritional status only. Furthermore, several criteria for undernutrition were applied, for example, low body mass index (BMI), diminished food intake, stunted growth, or unwanted weight loss (Penning et al. 2010). During clinical follow-up by, for example, pediatricians, nutritional assessment is often incomplete or omitted, due to low feasibility of general nutritional-assessment methods and lack of group-specific norm values.

Apart from uncertainty in clinical practice, the lack of standardization of diagnostics has resulted in the use of a variety of nutritional assessment methods and equations in published research projects, which limits comparability of the outcome of different studies. When small sample sizes, the heterogeneity of the target population, and the lack of an internationally accepted definition for the disorder are added to that, it becomes clear that outcomes of many previously published reports on the epidemiology of nutritional problems should be interpreted with caution.

177.2.5 Future Research

In order to enhance the (international) generalizability of research outcomes, preferably consensus is attained first on the best terminology for these children. In the absence of consensus, it is essential that every research report clearly describes the characteristics of the population under study and provides detailed information on the severity of their disabilities.

In order to improve diagnostics and interpretation of nutritional assessment for clinical application in the target population, several additional research projects have to be performed: Newly developed equations for the interpretation of skinfold equations and BIA recordings have to be cross-validated in other groups within the target population. Due to the low incidence of the disorder, usually only small groups of children are available for participation in single-center research projects. When developing new predictive equations in small heterogeneous groups, the risk is high that the developed equations may only apply to the sample used for the developmental process and not to the entire target population. In order to reduce the error that is introduced this way, new equations should ideally be cross-validated. This means that the study population is subdivided into two subgroups: subgroup 1 is used for development of the equation, which is validated in subgroup 2. This process is repeated several times using different subgroups of the original study population, and the validation results of each round are averaged. However, proper cross-validation may be statistically impossible in small heterogeneous study populations, and development of valid predictive equations should ideally be done in an (international) multicenter setting, in order to include sufficient numbers of children.

Apart from the previously published population data for weight, height, and BMI for age, norm values for body composition, such as the thickness of individual skinfolds, the sum of four skinfolds, and body-fat percentage for age, should be developed for the target population in order to clinically monitor nutritional status of the child in more detail. For the development of norm values, data from a very large number of measurements, obtained in a large representative population, have to be gathered. The only viable method to achieve this will also be through (international) multicenter collaboration of expert clinical centers. The North American Growth in CP project is a good example of such collaboration, including six expert clinical centers in Canada and North America, and together these centers offer medical care to a large population of children with CP. Ideally, experts from several countries should collaborate in all applicable research projects that are done in this group of frail children, since performing research is complex in this group due to ethical and practical issues.

Studying relatively small patient groups hampers the extrapolation of results; hence, a long-term collaboration may enhance the clinical value of research outcomes in the target population.

After final development and reliability testing of group-specific interpretative equations and development of specific reference values for body composition, an evidence-based clinical guideline on nutritional assessment in children with severe neurological impairment and ID should be developed and implemented. This guideline should be targeted at pediatricians, intellectual disability physicians, and dietitians. The need for a guideline for nutritional assessment is high, and its implementation will be a step forward to improvement of care for the target population. In addition, standardization of anthropometric nutritional assessment in this population will enhance the comparability of international research outcomes.

177.3 Recommendations for Using Anthropometry and BIA Recordings in Clinical Practice Based on Current Knowledge

177.3.1 Linear Growth

- Instead of measuring standing height, measure upper-arm length or tibia length and predict the child's height using the equations by Stevenson (Stevenson 1995).
- Body weight should be measured with a wheelchair scales or by the electrical hoist used for patient transfers in the ID-care organization.
- Group-specific reference values for height, weight, and BMI for age are available (Day et al. 2007), although it remains unknown if these charts predict "healthy growth."

177.3.2 Body Composition – Skinfold Measurements

- It is recommended to measure triceps and subscapular skinfold thickness, to both include sites at the limbs and at the trunk. Percentage body fat can be estimated using a population-specific equation (Gurka et al. 2009).
- Specific reference values for triceps and subscapular skinfold thickness for age and for body-fat percentage are not available. Therefore, it is recommended not to use the outcome for diagnosing malnutrition or obesity, but for the child's clinical follow-up solely, for example, to monitor changes in body-fat percentage after PEG placement.

177.3.3 Body Composition – BIA Recording

- We recommend the use of a multifrequency hand-to-foot BIA device. Preferably, BIA recordings should be performed under standardized conditions (see Table 177.3).
- Percentage body fat can be calculated using a newly developed population-specific BIA equation that includes the measurement of tibia length rather than standing height, making it more applicable to clinical practice than previously published equations (Rieken et al. 2009b).
- In the absence of specific reference values, BIA outcome should not be used for diagnosis, but results are useful for individual follow-up.

177.4 Application to Other Areas of Health and Disease

This chapter describes the feasibility and interpretation of currently available anthropometric nutritional-assessment methods in children with severe neurological impairment and ID. It describes future research that is additionally needed for evidence-based guideline development, in order to improve the diagnostics of malnutrition or obesity and to identify children at risk. Summarizing, anthropometric methods that are commonly applied in the general pediatric population need to be adjusted for the target population to enhance feasibility and reliability. Therefore, the adapted methods described in this chapter cannot be applied to other pediatric patient groups. If nutritional assessment is currently inadequate in other patient groups as well, the following procedure should be used:

- Study feasibility and reliability of currently available instruments and methods.
- Adapt measurement procedures, if needed.
- Determine the predictive value of available (generic) equations for BIA and skinfold measurements, using outcome of a reference method that was applied at the same moment.
- If the predictive value is low, either develop a new population-specific equation or adapt an existing equation.
- Develop population-specific reference values using the adapted nutritional assessment methods, if generic reference values do not apply to the population.

Summary Points

- Children with severe neurological impairment and ID have a severe motor disability and a moderate-to-profound intellectual disability as a result of neurological damage. They are wheelchair bound and rely on specialized care for people with ID.
- These children may suffer from a variety of concomitant health problems, such as epilepsy and pulmonary or orthopedic problems. As a result, children are frequently admitted to the hospital and life expectancy is markedly reduced. In the past decade, medical care for this population has improved, resulting in lower mortality.
- Due to nutritional problems (dysphagia and gastro-esophageal reflux), daily caloric intake may be threatened and a large proportion of these children suffer from malnutrition. By contrast, others who receive tube feeding may develop obesity as a result of overfeeding. Therefore, regular nutritional assessment is essential in this frail population.
- In those children in whom measuring standing height accurately is not possible due to scoliosis or contractures, the use of segmental measures, such as upper-arm length or tibia length, is advocated.
- Skinfold measurements should include sites on the trunk and sites on the limbs, because of the proposed altered subcutaneous fat distribution. Previously, a generic equation (Slaughter) was applied to calculate percentage body fat using the outcome, but, recently, a population-specific equation has been developed (Gurka).
- Bioelectric impedance analysis is an alternative but feasible method for measuring body composition in the target population. It may be more reliable since it includes the measurement of internal fat mass. A population-specific equation has recently been developed by Rieken *et al.*, but needs to be cross-validated to establish its clinical value.
- Growth charts for the general pediatric population may not apply to the target population, because of growth retardation or an altered body shape due to immobility. Population values are available for weight, height, and BMI for age, but not for skinfold thickness or body-fat percentage.

- Due to the lack of evidence-based clinical guidelines for nutritional assessment in these children, medical professionals are uncertain about their diagnosis. In addition, a variety of anthropometric recordings has been applied in scientific research, which limits comparability of outcomes.
- Future research is needed to determine the predictive accuracy of the new skinfold and BIA equations and to develop specific reference values for body composition. With that information, a clinical guideline can be developed. Ideally, these studies should be performed in an international multicenter collaboration.
- In the absence of a clinical guideline, practical recommendations are given for anthropometric nutritional assessment in these children.

Key Points

See Table 177.6.

Table 177.6 Key points of anthropometric nutritional assessment in children with severe neurological impairment and intellectual disability

- As a result of nutritional problems, children with severe neurological impairment and ID are at risk of developing malnutrition. By contrast, the children who are tube-fed are at risk of developing obesity. Regular anthropometric nutritional assessment in this frail population is advocated
- Generic methods, equations, and reference methods for anthropometric nutritional assessment are not applicable to these children; either available methods should be adapted or new methods should be developed. In the absence of an evidence-based clinical guideline, clinicians should measure body weight and a segmental measure for predicting standing height
- Due to the low incidence of the disorder, development of applicable methods should preferably be done in an international multicenter setting

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Chapter 178
Eating Frequency and Anthropometry

Karine Duval and Éric Doucet

Abstract There is a belief that eating between meals, or snacking, leads to increases in weight and obesity. Public health advice for body weight control often suggests avoiding snacks between meals in order to not increase total energy intake. However, available results from research on the influence of eating frequency on body weight status are equivocal. Studies in both adults and children have either failed to find a significant relationship between eating frequency and adiposity, or have found an inverse relationship. Several methodological discrepancies have been proposed to explain some differences observed between studies or the lack of such a relationship: various definitions of eating occasions, under-reporting of food intake, especially among the obese, various methods of assessing food intake and body composition, and the fact that many studies did not take into account factors related to energy expenditure, especially physical activity. Despite the inconclusive results, eating frequency seems to be related with leanness in men. In women, many studies found no association or negative correlation between eating frequency and adiposity, despite a higher energy intake. It was suggested that a higher eating frequency could very well be a marker of a physically active lifestyle, at least in leaner individuals. The impact of eating frequency on weight loss during energy restriction and on energy expenditure is more conclusive. No difference in total energy expenditure has been documented as a function of daily eating occasions and weight loss does not seem to be facilitated by high meal frequency. There is a need to examine the relationship between eating frequency and adiposity using longer-term studies with sufficiently large sample sizes and using adequate and standardized methodologies.

Abbreviations

BMI	Body mass index
BMR	Basal metabolic rate
DLW	Doubly labeled water
EE	Energy expenditure
EF	Eating frequency
EI	Energy intake

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_178,

GIP	Glucose-dependent Insulinotropic Polypeptide
HMG-CoA	Hydroxymethylglutaryl-CoA
LDL	Low density lipoprotein
PAEE	Physical activity energy expenditure
PAL	Physical activity level
REE	Resting energy expenditure
RMR	Resting metabolic rate
TEE	Total energy expenditure
TEF	Thermic effect of food
VO_{2peak}	Peak oxygen uptake

178.1 Introduction

Over the last few decades, the prevalence of obesity has rapidly increased in many countries around the world and reached now epidemic proportions (Hedley et al. 2004). The dietary pattern has changed substantially over the years (Briefel and Johnson 2004). The environment we live in has become 'obesogenic' (obesity-promoting). Food is constantly available and in practically unlimited amounts, which can lead to excessive energy intake (EI) and therefore positive energy balance (WHO 2002). Changes in dietary habits and physical activity have also been implicated as potential causes of obesity (WHO 2002).

Total EI has increased over the past 20–30 years (Nielsen et al. 2002). Using a nationally representative data from adults, Kant and Graubard looked at the change in eating frequency (EF) of American men and women over a 30-year period using data collected in the National Health and Nutrition Examination Surveys (NHANES) I (1971–1975), II (1976–1980), III (1988–1994), 1999–2000, and 2001–2002 (Kant and Graubard 2006). Over the time period, the reported number of eating occasions increased slightly in women from 4.90 in 1971–1975 to 5.04 in 1999–2002 (see Fig. 178.1). Cutler et al. have also shown an increasing in EF for both men and women between 1970 and 1990 (see Fig. 178.2a) (Cutler et al. 2003). During this time period, the increase in EI seems to be related with the increased EF and the energy consumed during snacks (see Fig. 178.2b, c). This change in eating pattern is probably a result of the increased availability of snack foods.

Studies have suggested that several eating behaviors, such as EF, the temporal distribution of eating events across the day, breakfast skipping, portion size, and the frequency of meals eaten away from home, may have an influence on body-weight control (Seagle et al. 2009). Research on the possible body weight and health benefits of EF started from observational and interventional studies in the 1960s, suggesting an inverse relationship between EF and adiposity (Fabry et al. 1964; Fabry et al. 1966).

When to eat and how often? Is it preferable to eat multiple small meals daily? These questions are frequently posed by persons who would like to lose or maintain their weight, and most health professionals would like to be able to answer it. However, they are not easy questions to answer. As will be discussed throughout this chapter, the impact of EF on body weight is not simple and implies more than one aspect. A great deal research has investigated the relationship between eating pattern and body-weight status (Bellisle et al. 1997). However, no clear consensus on the optimal number of daily eating occasions to facilitate weight management has emerged. This book chapter reviews the literature on EF with respect to energy balance and body-weight control.

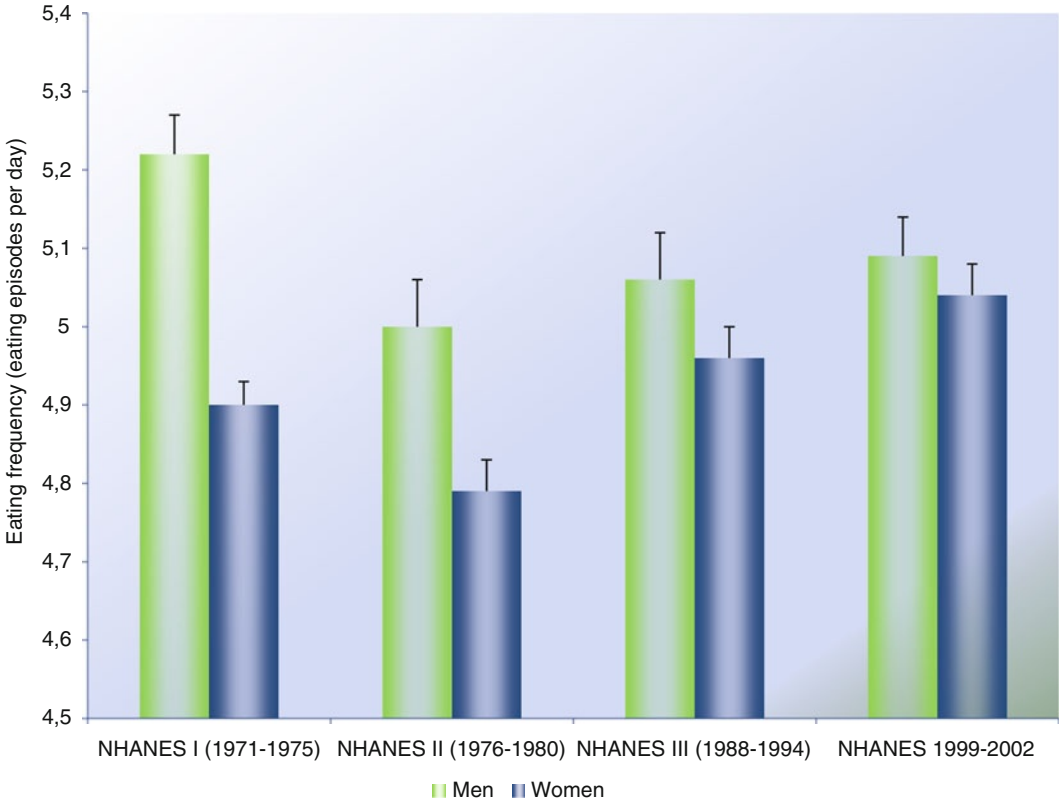


Fig. 178.1 Secular trends of eating frequency from National Health and Nutrition Examination Surveys (NHANES): NHANES 1971–1975 to NHANES 1999–2002. According to data collected in the National Health and Nutrition Examination Surveys from 1971–1975 to 1999–2002, this figure shows that EF of American adults, measured by 24-h recall, has increased significantly in women, but not in men during this time period. Results are presented as *mean* ± *SD*, *n* = NHANES I (men: 4,931; women: 5,060); NHANES II (men: 4,877; women: 5,241); NHANES III (men: 5,889; women 6,153); and NHANES 1999–2002 (men: 3,186; women: 3,211) (Data from Kant and Graubard 2006)

178.2 Part I: Methodological Aspects of Eating Frequency

178.2.1 Definitions of Key Eating-Frequency Terms

Part of the difficulty in identifying implications of eating more frequently is related to the lack of standardized definitions of key terms, such as eating occasions, meals and snacks (Drummond et al. 1996; Gatenby 1997; Gregori and Maffeis 2007). There have been several suggestions for these definitions, and each one was based on different cultural, biological, and empirical parameters of measurement (Drummond et al. 1996; Gibney and Wolever 1997). The type of definition used to describe key EF terms may significantly influence the outcomes and interpretation of results from different studies (Gatenby 1997; McBride et al. 1990). To date, no one definition has been universally accepted to categorize EF in the scientific literature. Comparisons among studies are even more difficult, as definitions of these terms were not always adequately reported in the literature.

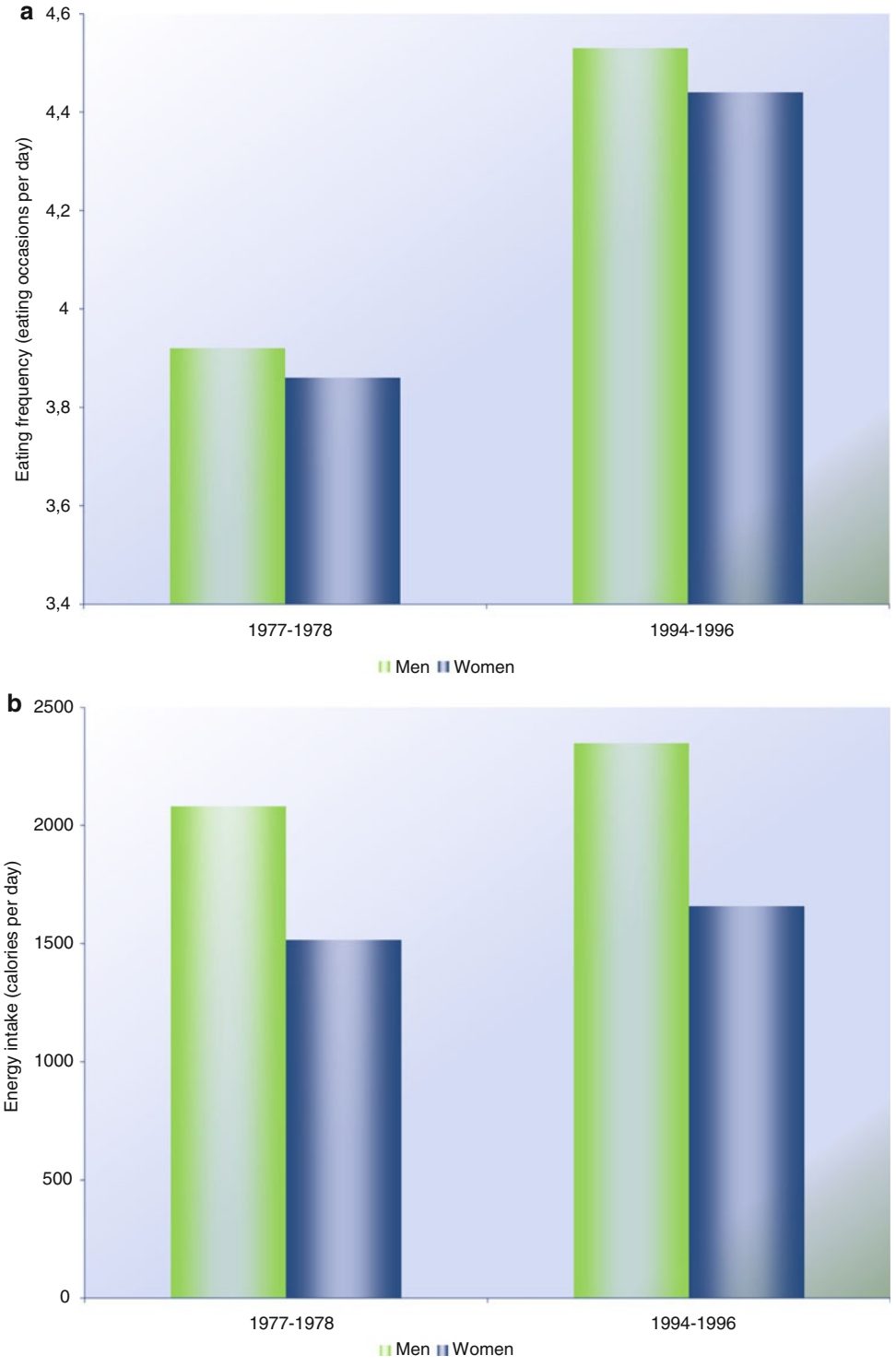


Fig. 178.2 (**a**) Secular trends of eating frequency among US adults from 1977–1978 and 1994–1996. According to cross-sectional data from the Continuing Surveys of Food Intake by Individuals (CSFII), this figure shows that EF has increased among American adults between 1977–1978 and 1994–1996 for both men and women. Results presented are means (Data from Cutler et al. 2003) (**b**) Secular trends of energy intake among US adults from 1977–1978 and 1994–1996. According to cross-sectional data from the Continuing Surveys of Food Intake by Individuals (CSFII), this figure shows that EI has increased among American adults between 1977–1978 and 1994–1996 for both men and women.

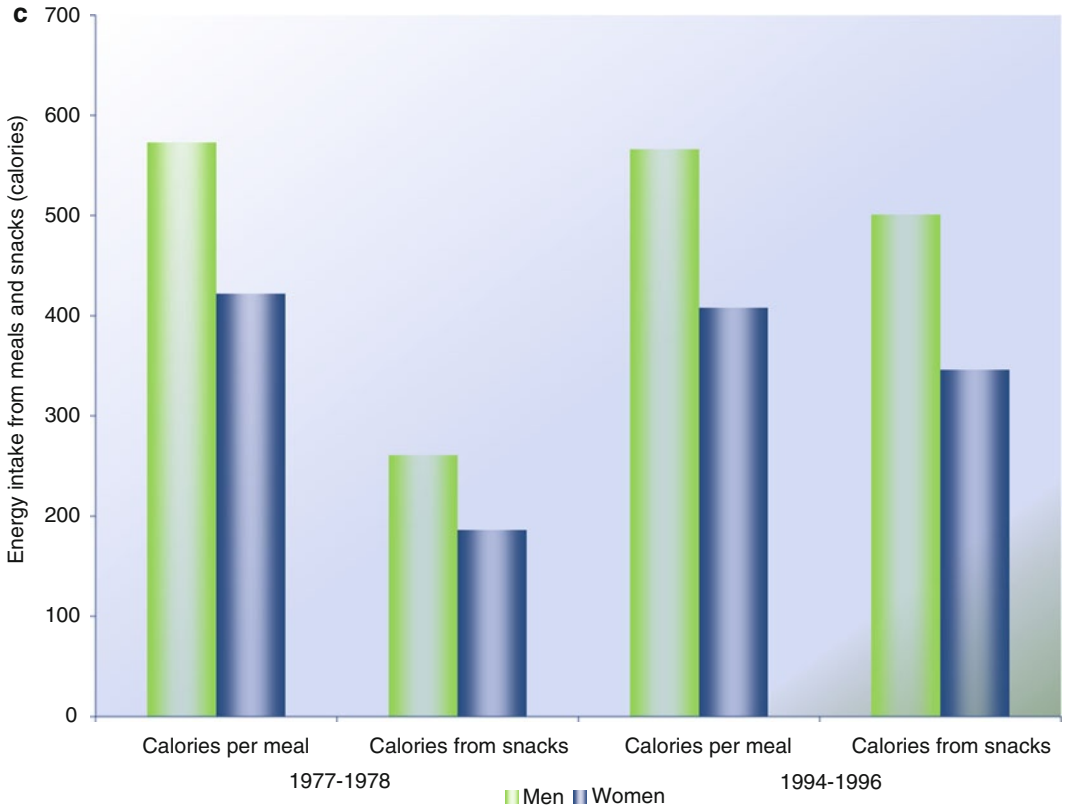


Fig. 178.2 (continued) Results presented are means (Data from Cutler et al. 2003) (**c**) Secular trends of energy intake from meals and snacks among U.S. adults from 1977–1978 and 1994–1996. According to cross-sectional data from the Continuing Surveys of Food Intake by Individuals (CSFII), this figure shows that most of the increase in EI is from calories consumed during snacks. Indeed, the energy consumed per meal has decreased (especially at dinnertime), while the energy consumed during snacks has increased by 90% among men and 112% among women between 1977–1978 and 1994–1996. Results presented are means (Data from Cutler et al. 2003)

178.2.1.1 Eating Frequency

Usually, low EF has been defined as "gorging" and high EF as "nibbling" (Berteus Forslund et al. 2002). However, there is no agreement about the number of meals required to be classified as frequent or non-frequent eater. In the literature, there is a wide range in the number of eating episodes used to describe "nibbling" (3–17 meals/snacks per day) and "gorging" (1–3 meals per day) (Berteus Forslund et al. 2002). Eating frequency is usually referred by a number of eating occasions, eating events or eating episodes per day. Two types of definition are normally reported to categorize EF: (1) predefined eating periods and (2) time interval between two eating occasions. Most studies that have been conducted until more recently used the predefined eating periods' definition to analyze EF (Summerbell et al. 1996; Dreon et al. 1988; Barba et al. 2006). In a study by Summerbell et al. (1996), daily food intake was divided into six eating periods (breakfast, mid-morning snacks, lunch, mid-afternoon snacks, evening meal, and evening snacks), which were defined as "meals" or "snacks." In this study, the maximum number of eating occasions was six. Such an approach may not permit an adequate analysis of EF due to inappropriate and insufficiently detailed information and may mask the actual EF (Gatenby 1997). The 'time interval' definition for calculating the total

number of eating occasions is now mostly used by the investigators (Drummond et al. 1998; Duval et al. 2008a; Yannakoulia et al. 2007; Ruidavets et al. 2002). The time interval between two eating occasions is normally ranged between 15 and 60 min. Drummond et al. (1998) defined an eating occasion as any occasion when food was consumed. If two eating occasions occurred in ≤15 min, both events were counted as a single occasion. Ruidavets et al. (2002) used a similar definition but with a longer time interval between two eating periods (60 min). Gibney and Wolever (1997) added energy content to this definition, which classifies an eating occasion as an event that provides at least 50 kcal (or 210 kJ) with a minimum time interval between occasions of at least 15 min. This type of definition allows to include all eating events in the calculation of EF and avoid the ambiguities of classifying eating events as either "meals" or "snacks," which, as mentioned earlier, can mask the number of actual eating occasions, especially when EF is high (Gatenby 1997).

178.2.1.2 Snack and Meal

The majority of investigators used quantitative definitions to describe what constitutes a "meal" and a "snack." These definitions were based mainly on the criteria of time of consumption and/or nutrient composition of the eating occasions (Gatenby 1997). Meals are generally described as one of the main eating occasions of the day, normally occurring in the morning (breakfast), mid-day (lunch), or evening (dinner) (Gatenby 1997; de Graaf 2006). Snacks refer to the other eating episodes consumed between meals, which are generally smaller and less structured than meals (de Graaf 2006; Gatenby 1997). However, it is difficult to obtain one specific universally accepted definition due to the problems inherent in individual perception of what constitutes a snack as opposed to a meal (Drummond et al. 1996).

Many criteria can be used to make a distinction between "meal" and "snack" (Gregori and Maffeis 2007; Vitapole 2003).

1. **Timing**
   Foods consumed at a specific period of time, for example, between 8:00 and 10:00 AM (breakfast), between 12:00 and 2:00 PM (lunch), and between 6:00 and 8:00 PM (dinner), are considered as meals. Anything else consumed between meals is thus considered as a snack (Gregori and Maffeis 2007). This criterion has to be used with caution because the time for a specific eating period may not always be the same for everyone depending on the work schedule, cultural aspects, or religious beliefs.
2. **Interval between adjacent eating episodes**
   It was observed that larger-size meals, as compared to snacks, are followed by longer periods of no eating (Bellisle et al. 2003).
3. **Social considerations**
   This criterion refers to the food consumed in the company of others or alone. Rotenberg used a social definition of eating occasions: the presence or absence of fellow diners (Rotenberg 1981). With this definition, a "meal" was defined as a planned social interaction centered on food, whereas a "snack" was identified as an eating event conducted individually.
4. **Nutrient composition**
   The nutrient-composition criterion of a meal or a snack includes the energy content and/or the type of food. Snacks are clearly different from meals. They differ in size (meals are about twice as large as snacks) and nutritional content (snack have a relatively high CHO content) (Drummond et al. 1996; Summerbell et al. 1996). Meals bring more energy and nutrient diversity than snacks.

Bernstein et al., studying the eating patterns of free-living subjects without time cues, defined "meal" as eating episodes of greater than 375 kJ (Bernstein et al. 1981).

5. **Hunger criterion**
   This criterion refers to the food consumed in either a hungry state or a non-hungry state. It was reported that a meal occurs usually when food is consumed in a state of hunger (Bellisle et al. 2003).

The definition of a meal or a snack should be based on more than one criterion in order to avoid ambiguities about what constitutes a meal and what constitutes a snack. As an example, a beverage with an apple consumed at 12:30 PM might be regarded as a snack or a meal depending on whether the definition refers to time of day or food type as a means of classification.

The problem with inconsistent definitions of eating occasion, meals, and snacks have been discussed earlier (Drummond et al. 1996; Gatenby 1997), and there is agreement on the need to clarify the terminology in order to be able to accurately investigate the role of EF on health (Gibney and Wolever 1997). A more consistent approach to the definition of eating occasions would facilitate appropriate interpretation of the available literature and future research. Even in the absence of a clear consensus, a clear description of what is considered to constitute an eating episode should always be provided in manuscripts investigating the topic of EF (Gregori and Maffeis 2007).

178.2.2 How to Measure Eating Frequency?

The methods used to assess food intake is worth taking into account when measuring EF. Various dietary-assessment methods have been developed for measuring food intake, and they have been extensively reviewed (Bingham 1987; Block 1982). Dietary methods most frequently used in research can be divided into three categories: (1) recall of actual food eaten, generally limited to the previous 24 h (24-h diet recall); (2) retrospective questionnaires or histories of the usual diet (food-frequency questionnaire or diet history); and (3) prospective diet records, usually for 3, 4, or 7 days, which are weighed or quantified by household measures, such as cups and spoons (Black et al. 1991; Barrett-Connor 1991; Block 1982; Livingstone 1995). Dietary recalls and food records are mostly used in EF studies. This can be explained by the fact that these two methods allow to determine more easily each eating occasion, as they provide information about the actual diet.

178.2.2.1 The 24-h Diet Recall

The 24-h diet-recall method is designed to quantitatively collect all foods consumed during the previous 24 h (Barrett-Connor 1991). This method typically involves face-to-face interview, although it may be conducted by telephone (Smith 1993; Block 1982). This technique demands high interviewing skills and can be affected by interaction between the interviewer and the interviewee and the subjective interpretation of questions and answers. Recall methods are prone to error of memory. However, the short-term memory required in the 24-h diet recall reduced the risk of errors. A 24-h diet recall obtained by a trained dietician takes normally around 30–60 min and can provide accurate quantitative information on recent intake. However, a single day of food intake may not be representative of habitual diet (Barrett-Connor 1991; Block 1982). Indeed, considering day-to-day variation in the food intake, multiple 24-h recalls are required to describe an individual's diet (Bingham 1987; Beaton et al. 1979; Basiotis et al. 1987).

178.2.2.2 Food Record or Diary

The food-record method provides a measure of current intake and involves a detailed record of all food consumed and measurements of portion size. Subjects have to record all food items consumed at the time of eating for a specified period, usually 3, 4, or 7 days. Subjects may estimate the portions eaten either by direct weighing (weighed food record) or by using household measures, such as cups or spoons (food diary). The accuracy of recording methods is based on the assumption that the usual dietary pattern is not changed because it is being recorded. Writing down everything they eat can be burdensome and time consuming for some subjects. Consequently, this method is often associated with poor compliance and an alteration of the diet and the dietary reporting during the recording period (Barrett-Connor 1991). In addition, recording intakes requires some literacy, which may limit the study to better-educated subjects. Nevertheless, the food record has often been considered the most accurate and precise method of dietary assessment (Barrett-Connor 1991). Whybrow et al. have shown that record of food intake for a period longer than 3 days and ideally 7 days is preferable (Whybrow et al. 2008). Seven-day food records are generally regarded as providing the best compromise between accurate data, investigator workload, and subject compliance (Black et al. 1991), although it is recognized that longer periods are needed to obtain precise measures of the habitual intakes of individuals (Basiotis et al. 1987; Beaton et al. 1979; Bingham 1987). However, for most studies in a free-living situation, it is unrealistic to collect dietary information for more than 3–7 days.

Data on the validity of recalls and records specifically for estimating EF are unavailable for the moment. Thus, the degree to which these methods accurately estimate the number of eating occasions is unclear. However, Longnecker et al. found that the day-to-day variation in a person's EF is larger than between-subject variation, which suggests that data from multiple days of a food diary are needed to measure a person's EF with precision (Longnecker et al. 1997). It has also been suggested that the use of a 7-day food diary provides a more accurate measurement of EI and is more representative of usual intake than is the use of food-frequency questionnaires or dietary recall (Block 1982).

The measurement of food intake is one of the hardest tasks in studies dealing with some forms of dietary assessments. None of the dietary-assessment methods is a priori better. The choice of the method will be based on the design and objectives of the study and the nature of the information required. Even when an appropriate method is selected, it remains difficult to acquire accurate data from food reporting (Livingstone 1995; Westerterp and Goris 2002).

178.2.2.3 Accuracy of Diet Reporting

During the past several years, there has been considerable discussion about the relevance of the dietary-survey methodologies, with much of this debate focused on their validity. A valid dietary report is one that measures the true intake, that is, all food consumed on specified days without exerting an influence on the choice of food and drinks consumed, during the period of study (Livingstone 1995). Accurate assessments of dietary intake are a prerequisite for assessing the relationship between diet and body-weight status (Gatenby 1997). Unfortunately, most of the methods for assessing dietary intakes have rarely been fully and independently validated because of the absence of accurate techniques to verify dietary-survey methodology.

Previous research in dietary assessment has indicated persistent errors in self-reported EI (Bailey et al. 2007; Livingstone 1995). The widespread occurrence of under-reporting of EI has been exposed by the introduction of the doubly labeled water (DLW) method for measuring total daily energy expenditure (TEE) (McCrory et al. 2002). The presence of error in self-reported dietary data may

attenuate or exaggerate associations between diet and weight status (Lissner et al. 1998). Most of the bias which appears when dietary intake is measured is mostly due to under-reporting (Livingstone 1995). When asked, people in general tend to underestimate the amount of food they eat. The only known method of gathering information on habitual diet intake is to ask subjects to supply this information themselves. Every self-report modality is prone to the problem of under-reporting. The problem of dietary under-reporting has been addressed in a number of articles as a major limitation in dietary assessments, and it is not easily overcome (Gatenby 1997; Garrow and Summerbell 1995; Bellisle et al. 1997). Under-reporting has been observed to vary from 10% to 50% (Livingstone 1995; Macdiarmid and Blundell 1997). Under-reporting of habitual intake can result from under-recording, under-eating, or a combination of both (McCrory et al. 2002; Bingham 1991). Under-recording refers to the failure to record all items and/or amounts of food consumed (McCrory et al. 2002). Under-eating corresponds rather to eating less than usual or than is required to maintain body weight (McCrory et al. 2002). A number of methodological and behavioral factors can generate these two biases. They include feeling embarrassed or guilty about recording specific foods or amounts, mostly foods perceived as "unhealthy," inability to estimate portion sizes accurately in non-weighed recording and recall methods, memory lapses, conscious or subconscious omissions to simplify the recording due to irritation and inconvenience in reporting, being more conscious of what they eat and, finally, using the study period as an opportunity to start dieting and to lose weight (Livingstone 1995). It has been documented that people admit that they would change their behavior when asked to complete dietary records (Mela and Aaron 1997)**.**

Reporting errors have been associated with a number of different subject characteristics, which was reviewed by Macdiarmid and Blundell (1997). Certain sub-populations are more likely to under-report their food intake than others, in particular the obese, the post-obese, the overweight, and the diet-restrained subjects (Livingstone and Black 2003; Heitmann and Lissner 1995). Westerterp and Goris (2002) have shown that percentage of under-reporting in normal-weight subjects varies from 0% to 25%, with an average of 16%. The range of under-reporting for obese subjects was twice as high as in normal-weight subjects, at 25–50%, with an average of 41% (Westerterp and Goris 2002). In a study conducted by Karelis et al., 57.5% of the overweight and obese postmenopausal women were identified as under-reporters (Karelis et al. 2010). In a context of EF measurement, it is also important to note that under-reporting affects not only EI, but also the daily number of eating occasions, and snacks are particularly prone to under-reporting (Bellisle 2004; Livingstone et al. 1990). Table 178.1 presents key features of under-reporting of EI.

To enhance the interpretation of studies examining food and nutrient intake in relation to EF, it is imperative that investigators validate EI data. Considerable caution needs to be employed when interpreting the self-reported energy intakes of weight-conscious subjects.

178.2.2.4 Evaluation of Under-Reporting in Dietary Surveys

There are a number of methods for validating reported EI. The reference methods include: (1) comparison between self-reported EI and the EI required to maintain body weight; (2) comparison between reported nitrogen (equal to protein intake) and 24-h urinary nitrogen excretion; (3) comparison between reported EI and TEE measured by the DLW; (4) comparison between reported EI and presumed energy requirements, both expressed as multiple of basal metabolic rate (BMR) (Goldberg cutoff) (Westerterp and Goris 2002; Livingstone and Black 2003); and (5) comparison of reported EI with predicted TEE using a combination of BMR and physical activity (Livingstone and Black 2003). In EF studies, the DLW technique, the Goldberg cutoff, and the predicted TEE are the most commonly used methods to evaluate dietary under-reporting.

Table 178.1 Key Features of under-reporting of energy intake (Source: Maurer et al. 2006; Livingstone 1995; Karelis et al. 2010; Macdiarmid and Blundell 1997)

1. Under-reporting of EI is a common problem. It can range from 10% to 50% depending on the population and the method and cut-point used to categorize under-reporters.
2. The use of invalid dietary data can biased the understanding of the association between diet and health or body weight.
3. Validity of dietary data can be verified by comparing self-reported EI with measured or estimated TEE.
4. Under-reporting of EI seems to be mainly a consequence of the omission of complete food items or meal/snack. Snacks are particularly prone to under-reporting.
5. Under-reporting of EI has been shown to be more prevalent in women, older adults, people with less education, overweight or obese subjects, and weight-conscious individuals.
6. Dietary patterns of under-reporters of EI include lower carbohydrate intake, lower fat intake, and eating on fewer occasions.
7. Behavioral characteristics of under-reporters of EI include frequent dieting attempts, lower level of physical activity, higher dietary restraint, and higher disinhibition.
8. Psychosocial characteristics of under-reporters of EI include higher social desirability, lower body image, depression, anxiety, and fear of negative evaluation.

This table presents key features of under-reporting food intake including the prevalence of under-reporting, the importance of using valid dietary data, methods to evaluate under-reporting in dietary survey, who under-report their food intake the most, what is most under-reported in general, the dietary patterns of under-reporters, and the psychosocial and behavioral characteristics of food intake under-reporters
EI energy intake, *TEE* total energy expenditure

Doubly Labeled Water

The DLW technique is the gold standard for measuring TEE (Livingstone and Black 2003). The comparison between reported EI and TEE measured by the DLW is also the most accurate method for the validation of reported EI by subjects under free-living situations (Bailey et al. 2007). However, for routine validation of EI data, this method is quite expensive and sophisticated (Bailey et al. 2007; McCrory et al. 2002; Livingstone and Black 2003).

Goldberg Cutoff

An alternative cost-effective technique for identifying inaccurate reports of EI was proposed by Goldberg et al. and Black et al. (Black et al. 1991; Goldberg et al. 1991). This method has been used by numerous investigators to identify under-reporters (Livingstone and Black 2003). In this method, the ratio of reported EI to BMR (EI:BMR) is used as a guide for the accuracy of food records. Reported EI is expressed as a multiple of the BMR estimated from equations and is compared with the presumed mean energy expenditure (EE) of the population, which is also expressed as a multiple of the BMR (EE:BMR). The ratio EE:BMR refers to the physical activity level (PAL). If there is no under-reporting, EE:BMR equals EI:BMR (Goris et al. 2001). A formula was elaborated by Goldberg et al. (1991) to calculate the lower 95% confidence limit of EI:BMR, assuming a given PAL requirement. Values of EI:BMR falling below the 95% confidence limit signify the presence of under-reporting. This formula considers errors associated with the number of subjects (n), the length of the dietary assessment (number of days), variation in both BMR and PAL, and daily variation in EI (Black 2000b).

The Goldberg cutoff has considerable limitations, which have been discussed (Black 2000a). It is best used for identifying the presence of bias in reported EI at the group level, but information on the habitual activity of the population is needed to choose an appropriate PAL for the calculation of

appropriate cutoffs. The ability of the Goldberg cutoff to identify under-reporting at the individual level is however limited (Black 2000a). At the individual level, the use of a single cutoff for EI:BMR applied to all subjects is inappropriate. Thus, for identifying under-reporters at the individual level, a short physical-activity questionnaire could be used to assign subjects to suitable PAL levels in large-scale studies. In small studies ($n < 100$), it would be desirable to obtain a measure of EE using detailed activities diaries, heart-rate monitors, or accelerometers. If these measurements are obtained, a comparison of reported EI and of a more objective measure of EE can be made, consequently reducing the limitations associated with the EI:BMR cutoff.

Predicted Total Energy Expenditure: Combination of Basal Metabolic Rate and Physical Activity Energy Expenditure

An easy and inexpensive method for validating reported EI of individuals is a combination of BMR (measured or calculated) and physical activity energy expenditure (PAEE), which can be assessed by physical-activity diaries, questionnaires, heart-rate monitors, or accelerometers. Accelerometers seem to be the most objective method that can be used to quantify PAEE at individual level in free-living situations (Goris et al. 2001). It was shown that the combination of measured resting metabolic rate (RMR) with PAEE was able to explain 85% of the variation in TEE measured with DLW (Westerterp and Goris 2002). Goris et al. (2001) found no significant difference between the percentages of under-reporting assessed with a tri-axial accelerometer as compared with DLW. The use of a combination of BMR (measured) and PAEE seems to be a good method for validating reported EI.

178.3 Part II: Eating Frequency and Body-Weight Status

Does snacking make you fat? There is a belief that eating between meals (snacking) leads to weight gain. Public-health advice for body weight control often suggests to avoid snacking between meals in order to not increase total EI (Kirk 2000). It has been suggested that snacking may be a cause of obesity, if, as assumed, the consumption of snack foods between meals increases total EI (Booth 1988; Basdevant et al. 1993). The work of Booth (1988) is frequently cited as evidence that snacking leads to over-consumption. Results reported by Booth suggest that snacks and/or high-energy drinks taken more than 1 h before meals fail to exert satiety and energy compensation (i.e., energy consumed at main meals is reduced) at subsequent meals, leading to overeating and ultimately to obesity. However, evidence supporting the implication of frequent eating in obesity is not that clear (Bellisle et al. 1997; Palmer et al. 2009).

178.3.1 Adult Studies

Many epidemiological and clinical studies have explored the association between EF and body weight in adults, but results have been inconsistent. Some studies observed an inverse relation between EF and body weight (Fabry et al. 1964; Metzner et al. 1977; Charzewska et al. 1981; Kant et al. 1995; Burley et al. 2002; Ruidavets et al. 2002; Drummond et al. 1998; Ma et al. 2003; Chapelot et al. 2006; Duval et al. 2008a), whereas others failed to detect any significant association (Dreon et al. 1988; Edelstein et al. 1992; Summerbell et al. 1996; Yannakoulia et al. 2007; Andersson and Rossner 1996) (see Table 178.2). One study observed a positive relationship between EF and

Table 178.2 Summary of studies investigating the relationship between eating frequency and adiposity in adults

Reference	Study population	EF measure			Control for under-reporting	Adiposity measures	Statistical significance
		Method	Definition	EF (daily)			
Fabry et al. (1964)	379 M; 60–64 years	Interview with a trained dietician	Data not provided	≤3, 3–4, ≥5	No	Overweight TSF SSF	Significant negative correlations[a]
Metzner et al. (1977)	2,028 M + F; 35–69 years	24-h diet recall interview	Time interval between two eating occasions	1 to ≥8	No	Adiposity index[b]	Significant negative correlations[a]
Charzewska et al. (1981)	886 M; 40–59 years	Data not provided	Data not provided	2, 3–4, 5–7	No	%BF[c] BMI	Significant negative correlations[a]
Dreon et al. (1988)	155 M; 30–59 years	7-day food diary	Predefined eating periods	1–7	No	%BF[c] BMI	$r = -0.07$, NS $r = -0.03$, NS
Edelstein et al. (1992)	2,034 M + F; 50–89 years	Diet-assessment questionnaire	Data not provided	1–2, 3, ≥4	No	BMI Waist: hip	NS[a] Significant negative correlation[a]
Kant et al. (1995)	7,147 M + F; 25–74 years (Baseline)	24-h dietary recall	Time interval between two eating occasions	≤2 to ≥7	No	Weight change Baseline BMI TSF[d] SSF	Significant negative correlations[a]
	7,101 M + F; 35–84 years (Follow-up)	Two questions on snack and meal frequency	Time interval between two eating occasions	≤2 to ≥7	No	Weight change Baseline BMI TSF[e] SSF[e]	NS[a] NS[a] NS[a] NS[a]
Summerbell et al. (1996)	220 M + F; *Elderly* (65–91 years) *Working age* (17–60 years) *Middle-aged* (39–59 years) *Adolescent* (13–14 years)	7-day weighed food record	Predefined eating periods	1–3, 4–6	Yes	*Elderly*: BMI *Working age*: BMI *Middle-aged*: BMI *Adolescents*: BMI	 NS[a] NS[a] NS[a] NS[a]

Andersson et al. (1996)	147 M; 20–60 years	24-h dietary recall	Predefined eating periods	3.8–9.5	Yes	BMI	NS[a]
Drummond et al. (1998)	95 M + F; 20–55 years	7-day food diary	Time interval between two eating occasions	2.4–9.0	Yes	*Men*:	
						Body weight	$r = -0.34$, S
						BMI	$r = -0.26$, NS
						%BF[f]	$r = -0.21$, NS
						Women:	
						Body weight	$r = -0.14$, NS
						BMI	$r = -0.15$, NS
						%BF[f]	$r = -0.01$, NS
Ruidavets et al. (2002)	330 M; 45–64 years	3-day food diary	Time interval between two eating occasions	1–2, 3, 4, >5	Yes	BMI Waist: hip	Significant negative correlations[a]
Burley et al. (2002)	1,214 F; 35–69 years	4-day food diary	Time interval between two eating occasions	Low 5.6, Medium 7.7 High 10.4	No	Body weight[g] BMI HC[g]	Significant negative correlations[a]
						WC[g]	NS[a]
						Waist: hip	NS[a]
Ma et al. (2003)	499 M + F; 20–70 years	24-h dietary recall	Time interval between two eating occasions	≤3, ≥4	No	Obesity	Significant negative correlation[a]
Chapelot et al. (2006)	24 M; 19–25 years	3 weekdays' food diary	Data not provided	3–4 or 4–3	No	Body weight	NS[a]
						BMI	NS[a]
						FM[h]	Significant negative correlation[a,i]
Howartz et al. (2007)	2,685 M + F; *Younger* (20–59 years) *Older* (60–90 years)	24-h dietary recalls	Time interval between two eating occasions	≤3, 3.5–6, >6	Yes	BMI	Significant positive correlation[a]

(continued)

Table 178.2 (continued)

Reference	Study population	EF measure			Control for under-reporting	Adiposity measures	Statistical significance
		Method	Definition	EF (daily)			
Yannakoulia et al. (2007)	220 F; 24–74 years	3-day food diary	Time interval between two eating occasions	2.7–10.0	Yes	*Premenopausal women*:	
						BMI	$r = 0.16$, NS
						%BF[h]	$r = 0.17$, NS
						WC	$r = 0.11$, NS
						Waist: hip	$r = 0.15$, NS
						Postmenopausal women:	
						BMI	$r = 0.16$, NS
						%BF[h]	$r = 0.30$, S
						WC	$r = 0.08$, NS
						Waist: hip	$r = -0.16$,NS
Duval et al. (2008a)	85 F; 47–56 years	7-day food diary	Time interval between two eating occasions	3.0–7.1	Yes	Body weight	$r = -0.19$, NS
						BMI	$r = -0.25$, S[j]
						WC	$r = -0.32$, S
						%BF[h]	$r = -0.26$, S[j]
						FM[h]	$r = -0.27$, S[j]
						FFM[h]	$r = -0.04$, NS

This table presents a summary of studies that have investigated the relationship between EF and adiposity in adults. It gives some information about the study population, methods used to assess EF, definition choose to describe EF, categories of EF used to compare the results, information about the control of under-reporting, adiposity measures used to assess the relationship between EF and adiposity, and statistical significance of the results

EF eating frequency, *TSF* triceps skinfold, *SSF* subscapular skinfold, *BMI* body mass index, *WC* waist circumference, *%BF* percentage of body fat, *FM* fat mass, *FFM* fat-free mass, *NS* Not significant, *S* significant, *M* male, *F* female

[a]The correlation coefficients are not provided

[b]Adiposity index combines two skinfold measurements, height, and weight

[c]Measured from underwater weighing

[d]Significant negative correlation for women only

[e]Significant negative correlation for men only

[f]Estimated using the method of Durnin and Womersley

[g]Self-reported measures

[h]Measured from dual-energy X-ray absorptiometry

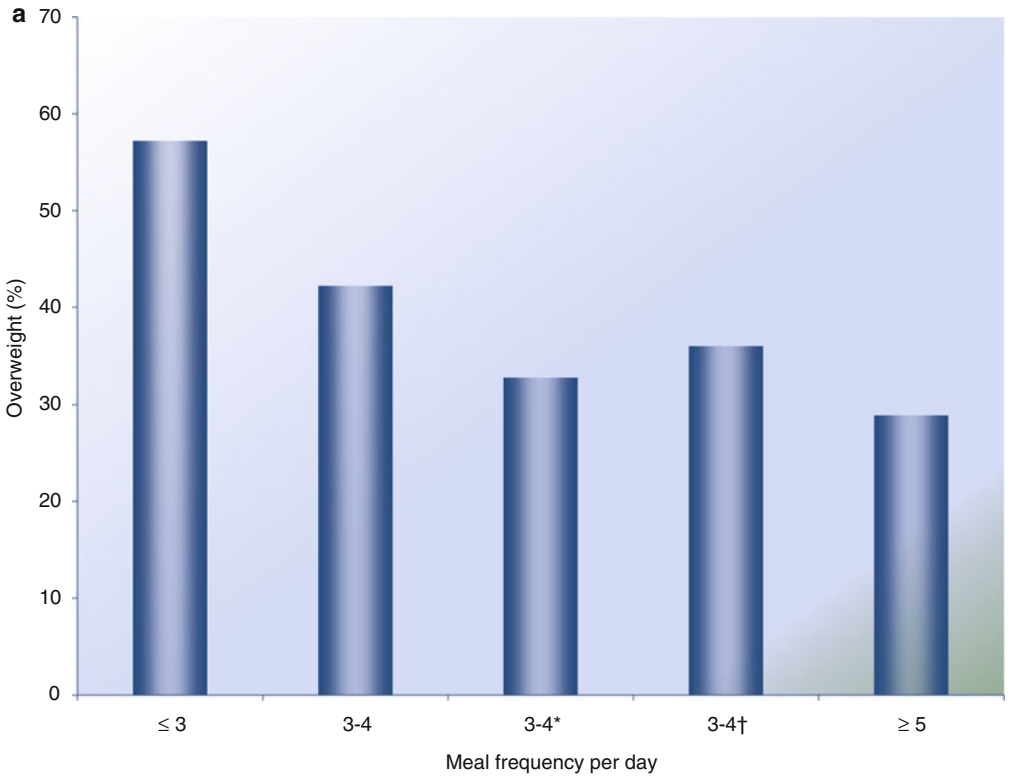
[i]Significant only for the group who switch from a four- to a three-meal pattern by removing their usual afternoon meal

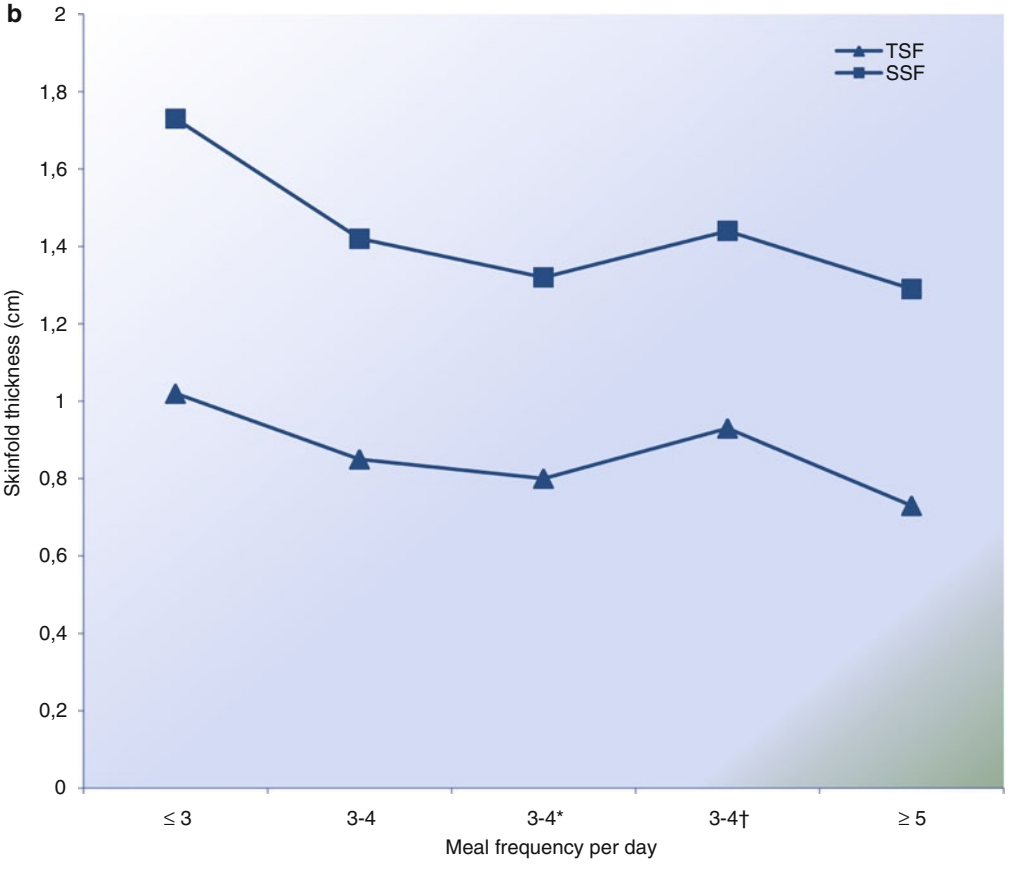
[j]The associations between adiposity and EF disappeared after correction for PAEE and VO_{2peak}

obesity (Howarth et al. 2007). Howarth et al. (2007) observed that eating more than three times a day was associated with being overweight or obese in both younger (20–59 years) and older (60–90 years) groups. Fabry et al. (1964) were the first investigators to show an inverse association between EF and body weight, suggesting that a "nibbling" pattern could help to prevent obesity. They found that, in a sample of 379 men aged 60–64 years, skinfold thickness and incidence of overweight were significantly greater in those who consumed three or less meals a day compared to those who ate five or more meals a day (see Fig. 178.3a, b). Metzner et al. (1977) also studied the relationship between EF and adiposity in 2,028 men and women aged 35–69 years. They found that subjects who ate six meals a day had a significantly lower adiposity index than those who ate two meals a day. In a cross-sectional study, EF and body mass index (BMI) were assessed in 220 free-living people in four age groups (adolescent, working age, middle-aged, and elderly) (Summerbell et al. 1996). Summerbell et al. (1996) found no significant relationship between eating pattern and BMI for each group after exclusion of under-reporters (see Fig. 178.4). More recently, Drummond et al. (1998) showed that eating more frequently was related to leanness in men but not in women. In women, although a positive correlation between EF and EI was observed, no relation was found between body weight and EF. A positive association between EF and PAEE at leisure time was found in women, suggesting that the higher EI associated with a high EF appears to have been balanced by greater EE from physical activity, sufficient to prevent an increase in body weight. Yannakoulia et al. (2007) found similar results in a cross-sectional study of 220 women. Indeed, they demonstrated that, in premenopausal women, frequent eating was not related to adiposity, but it was associated with high EI and high EE, especially PAEE spent at home. They also observed that EF was positively correlated with adiposity and EI in postmenopausal women. Possible explanations could be that frequent eating is not associated with a physically active lifestyle in postmenopausal women. In middle-aged women, decrease in RMR and physical activity could be accentuated (Evenson et al. 2002). This decline in EE, without a proportional reduction in EI, may explain a higher adiposity level in postmenopausal women who also display frequent eating patterns. Another study reinforces the findings of Drummond et al. (1998) and Yannakoulia et al. (2007). In a sample of 85 premenopausal women, Duval et al. (2008a) found that women who ate more frequently tended to have higher EI, but they were also leaner (see Fig. 178.5). Interestingly, they noted that the association between adiposity and EF disappeared after correction for PAEE and VO_{2peak}. These results indicated that a physically active lifestyle may be an important confounder of the relationship between adiposity and eating frequency. In a cross-sectional study where EF was collected at five equally spaced time points over a 1-year period in 499 participants, Ma et al. (2003) found that subjects who reported four or more eating episodes per day had a lower obesity risk, which is decreased by 45%.

178.3.2 Children Studies

Similar to results in adults, in children and adolescents, the association between EF and body weight is also inconclusive (see Table 178.3). Fabry et al. were again among the first investigators to show an inverse association between EF and body weight in children (Fabry et al. 1966). They performed a 1-year intervention study in which 226 children aged 6–16 years in three schools were selected for comparison. Children in one school were allowed to continue their habitual eating pattern of five meals a day. Children in the second school were switched to three meals a day and children in the third school to seven meals daily. After 1 year, the children who ate seven meals a day were charac-


a
70
60
50
40
30
20
10
0
Overweight (%)
≤ 3
3-4
3-4*
3-4†
≥ 5
Meal frequency per day


b
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
Skinfold thickness (cm)
TSF
SSF
≤ 3
3-4
3-4*
3-4†
≥ 5
Meal frequency per day

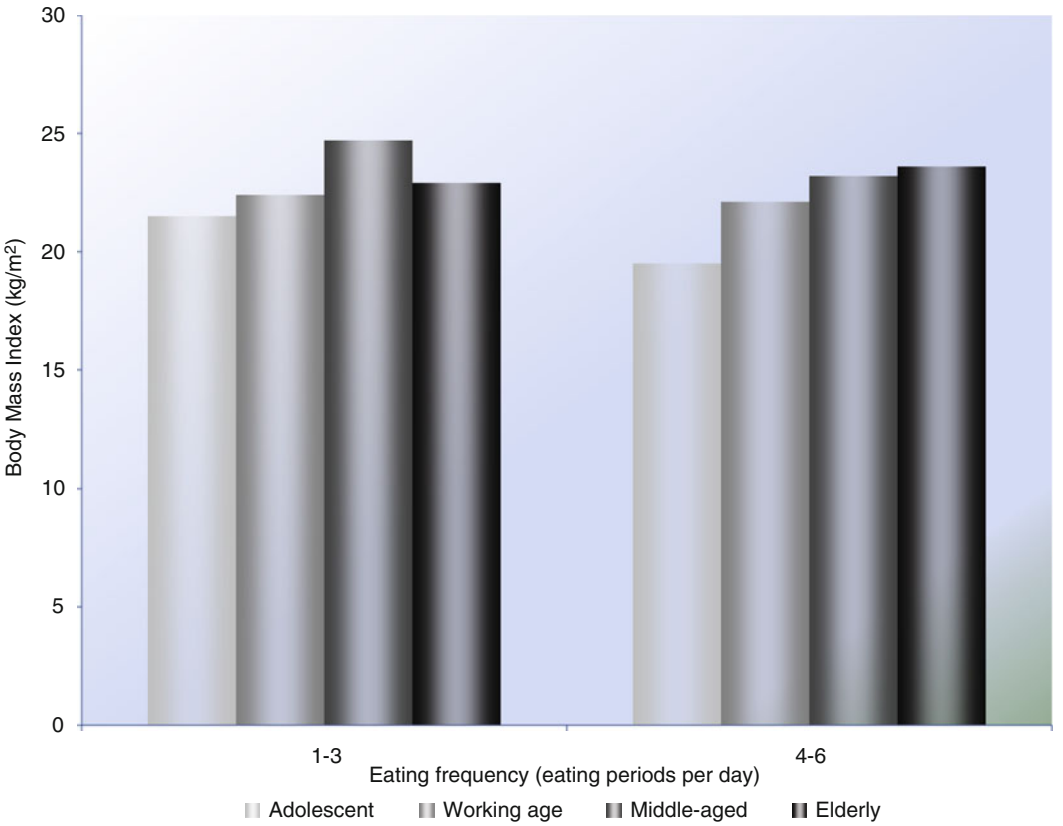


Fig. 178.4 Relationship between eating frequency and body mass index in 220 free-living people in four age groups. This figure shows that there was no relationship between BMI and EF for the four age groups after exclusion of invalid food records. Results presented are means, *n* = adolescent (33); working age (59); middle-aged (40); and elderly (88) (Data from Summerbell et al. 1996)

terized by significantly lower body weight and skinfold thickness. In another study conducted by Toschke et al., the prevalence of overweight and obesity decreased along with the number of meals per day in a sample of 4,370 German children aged 5–6 years (Toschke et al. 2005). The prevalence of obesity in children who ate three or fewer meals was 4.2%; four meals, 2.8%; and five or more meals, 1.7%. In this cohort, a higher EF was inversely related to the prevalence of childhood overweight and obesity, suggesting that a frequent eating pattern might exert protective effects against excess adiposity. In a large sample of schoolchildren aged 6–11 years participating in a cross-sectional survey of childhood obesity, Barba et al. (2006) found that daily EF was inversely associated with adiposity and central fat deposition (see Fig. 178.6 a, b). Also, in a 10-year longitudinal study, Franko et al. also found that girls who ate more than three meals per day had lower BMI *z*-scores for

Fig. 178.3 (**a**) Relationship between meal frequency and incidence of overweight in 379 men aged 60–64 years. This figure shows that the incidence of overweight tended to increase as the frequency of meals decreases in men aged 60–64 years. *Additional snacks between meals; †Additional snack at bedtime. Results presented are means (Data from Fabry et al. 1964) (**b**) Relationship between meal frequency and adiposity in 379 men aged 60–64 years. This figure shows that adiposity, measured by skinfold thickness, tended to decrease as the frequency of meals increases in men aged 60–64 years. TSF: Triceps skinfold thickness; SSF: Subscapular skinfold thickness; *Additional snacks between meals; †Additional snack at bedtime. Results presented are means (Data from Fabry et al. 1964)

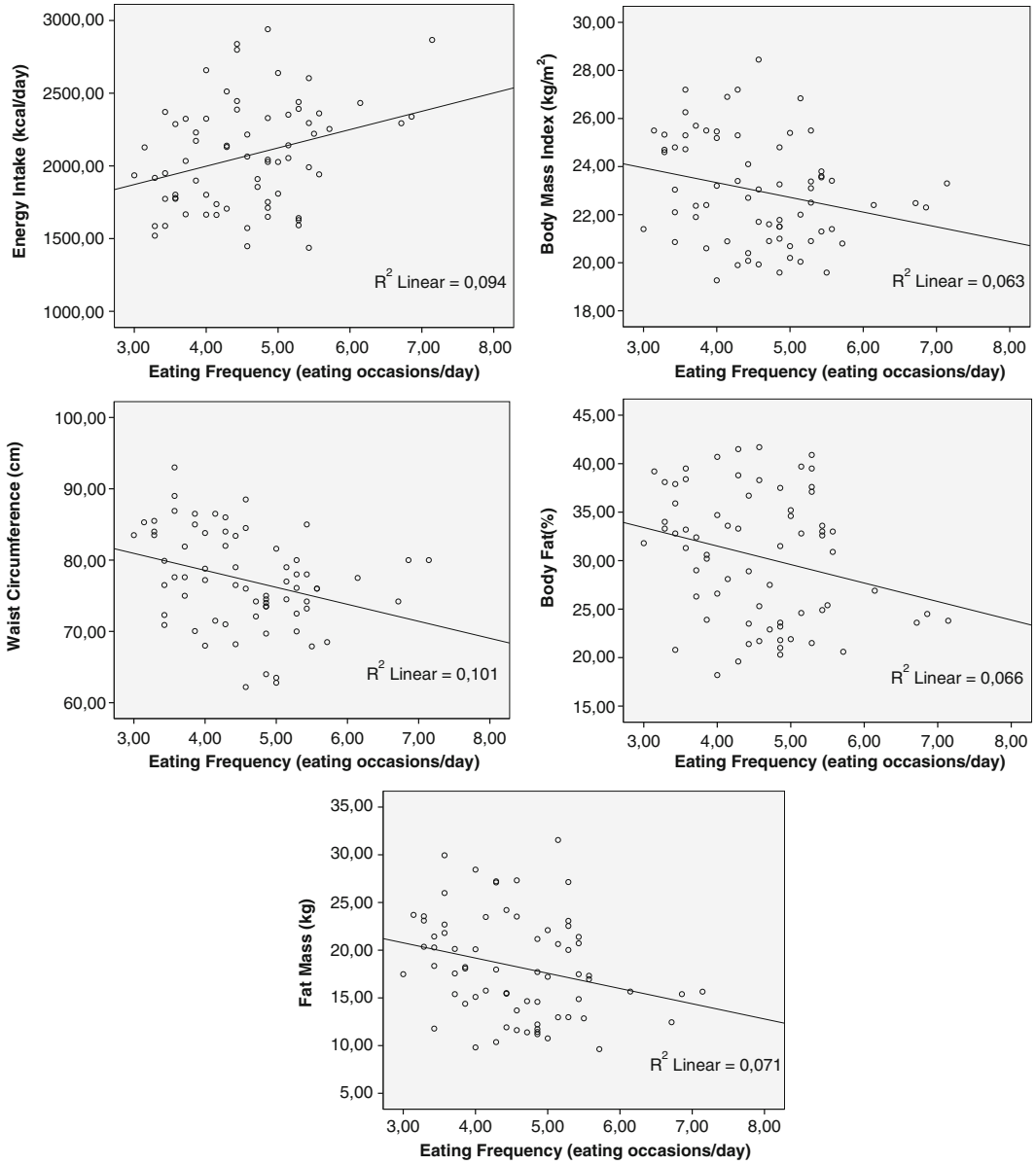


Fig. 178.5 Effects of eating frequency on energy intake and body composition in 85 premenopausal women. This figure illustrates correlations of EF with EI and body composition in a sample of 85 premenopausal women. These correlations show that EF was positively associated with EI and negatively associated with adiposity, measured by dual-energy X-ray absorptiometry. Women who ate more frequently tended to have higher EI, but they had also lower adiposity. However, these associations disappeared after correction for PAEE and VO_{2peak}. Values were obtained with the use of Pearson's correlation coefficient (Data from Duval et al. 2008a)

age (Franko et al. 2008). Zerva et al. conducted a study in a sample of 151 children aged 9–11 years (Zerva et al. 2007). Children were categorized in tertiles based on the daily number of eating occasions (≤4.1, 4.2–5.4, and ≥5.5). Physical activity was also assessed with 4-day accelerometry. The results of this study have shown that a higher EF was associated with a better body composition. This association occurred despite the higher EI of the frequent eaters compared with the non-frequent

Table 178.3 Summary of studies investigating the relationship between eating frequency and adiposity in children

Reference	Study population	EF measure			Control for under-reporting	Adiposity measures	Statistical significance
		Method	Definition	EF (daily)			
Fabry et al. (1966)	226 M + F; 6–16 years	Dietician	Data not provided	3, 5, and 7	No	Body weight SFT	Significant negative correlations[a]
Morgan et al. (1983)	972 M + F; 5–18 years	7-day food diary	Predefined eating periods	1–5	No	BMI[b]	NS[a]
Ruxton et al. (1996)	136 M + F; 7–8 years	7-day weighed food record	Predefined eating periods	Low and high snackers	No	Body weight BMI SFT	NS[a] NS[a] NS[a]
Crawley and Summerbell (1997)	731 M + F; 16–17 years	4-day food diary	Time interval between two eating occasions	Data not provided	Yes	BMI	NS[a]
Nicklas et al. (2003)	1,562 M + F; 10 years	24-h dietary recall	Time interval between two eating occasions	Data not provided	No	Overweight status	NS[a]
Nicklas et al. (2004)	1,584 M + F; 10 years	24-h dietary recall	Time interval between two eating occasions	2–11	No	Overweight status	NS[a]
Toschke et al. (2005)	4,370 M + F; 5–6 years	Self-administered questionnaire	Predefined eating periods	≤3, 4 and ≥5	Yes	Overweight Obesity	Significant negative correlations[a]
Barba et al. (2006)	3,668 M + F; 6–11 years	"Yes" or "No" questions referring to the EF of the last 12 months	Predefined eating periods	≤3, 4, and ≥5	No	BMI WC	Significant negative correlations[a]
Zerva et al. (2007)	131 M + F; 9–11 years	3-day food diary	Time interval between two eating occasions	≤4.1, 4.2–5.4, and ≥5.5	Yes	SFT %BF[c] TER[d]	$r = -0.17$, S $r = -0.18$, S Significant negative correlation[a]
Franko et al. (2008)	2,375 F; 9–19 years	3-day food diary	Time interval between two eating occasions	≤3 and >3	No	BMI	Significant negative correlation[a]

This table presents a summary of studies that have investigated the relationship between EF and adiposity in children. This table gives some information about the study population, methods used to assess EF, definition choose to describe EF, categories of EF used to compare the results, information about the control of under-reporting, adiposity measures used to assess the relationship between EF and adiposity, and statistical significance of the results

EF eating frequency, *SFT* skinfold thickness, *BMI* body mass index, *WC* waist circumference, *%BF* percentage of body fat, *TER* trunk-to-extremity ratio, *NS* not significant, *S* significant, *M* male, *F* female

[a]The correlation coefficients are not provided

[b]Self-reported measures

[c]Percent of body fat was estimated from triceps and subscapular skinfolds from which fat mass and fat-free mass were calculated

[d]The trunk-to-extremity ratio (TER) is an index of body-fat distribution. It was calculated by dividing the sum of central (subscapular and suprailiac) by the sum of peripheral skinfolds (triceps and biceps)

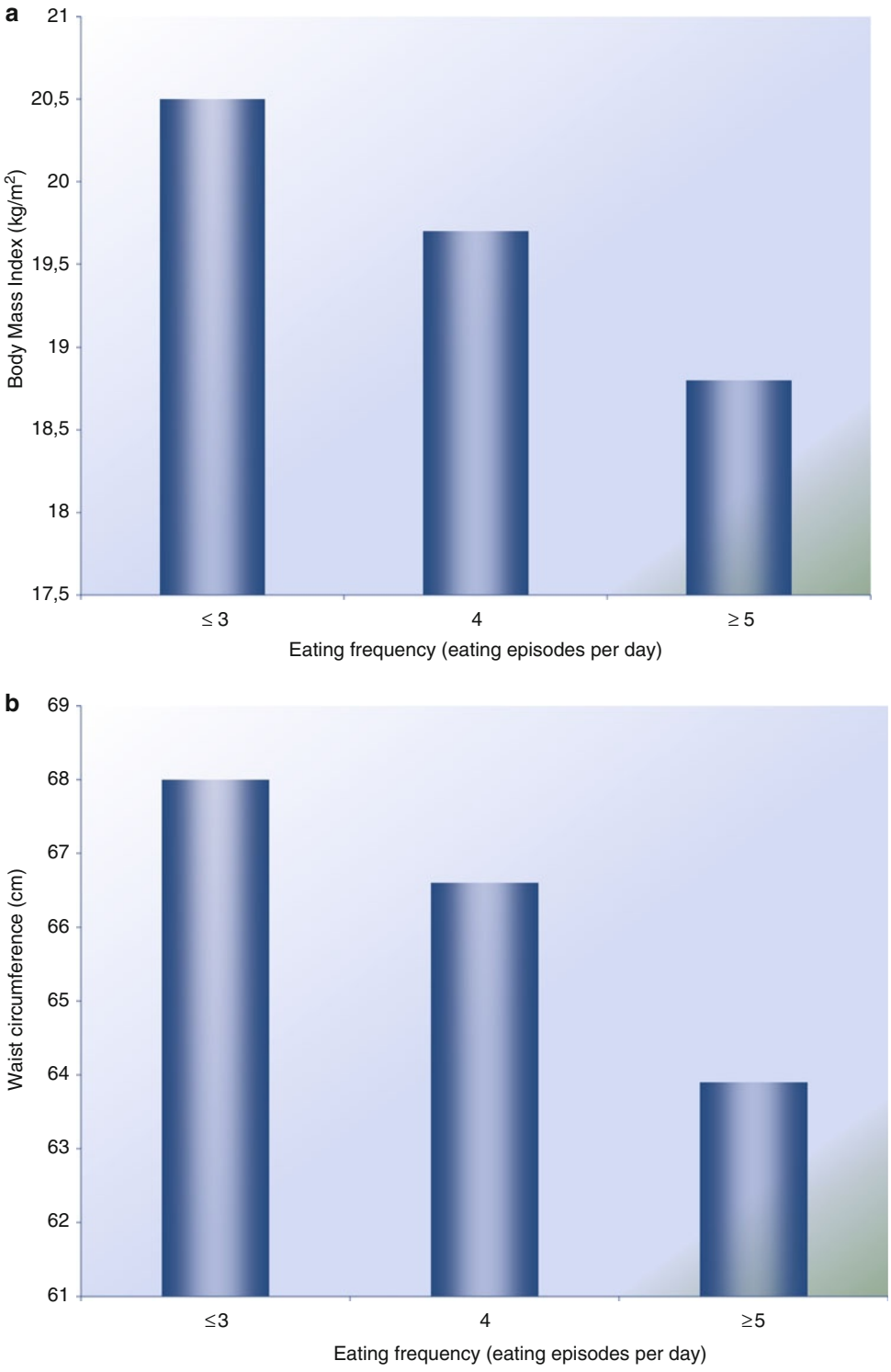


Fig. 178.6 (**a**) Relationship between eating frequency and body mass index in 3,668 school-children aged 6–11 years in the ARCA project. This figure shows that BMI was negatively associated with EF in schoolchildren aged 6–11 years. Results presented are means, $n = \leq 3$ (332); 4 (1334); and ≥5 (2002) (Data from Barba et al. 2006) (**b**) Relationship between eating frequency and waist circumference in 3,668 schoolchildren aged 6–11 years in the ARCA project. This figure shows that waist circumference was negatively associated with EF in schoolchildren aged 6–11 years. Results presented are means, $n = \leq 3$ (332); 4 (1334); and ≥5 (2002) (Data from Barba et al. 2006)

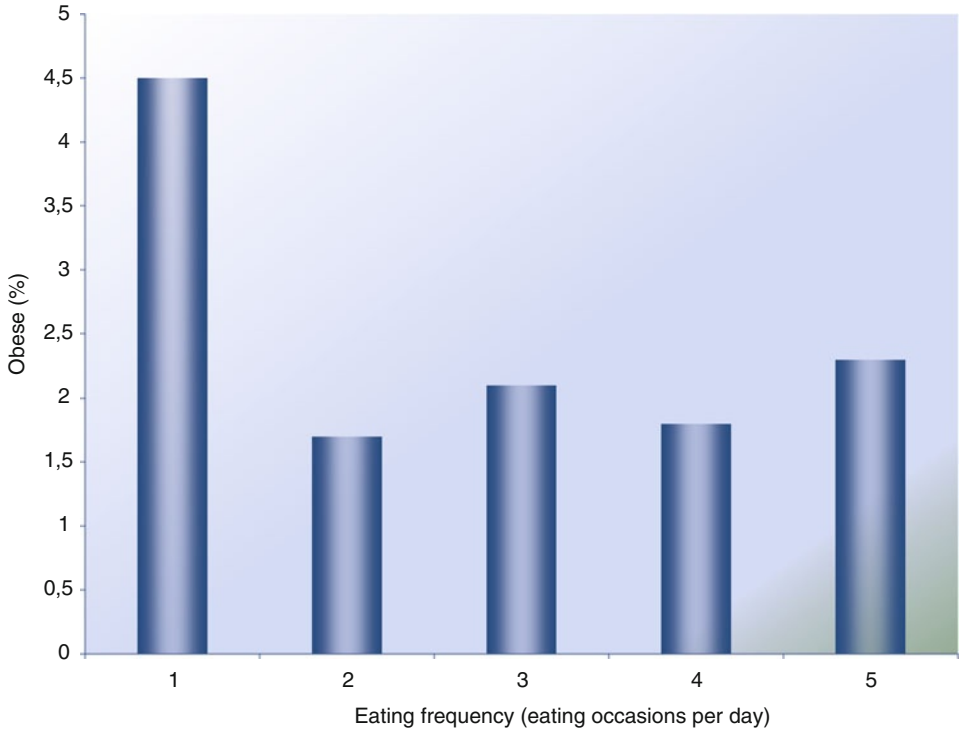


Fig. 178.7 Relationship between eating frequency and obesity in 972 children aged 5–18 years. This figure shows that there was no significant relationship between EF and occurrence of obesity in children aged 5–18 years. Results presented are means, n = 1 (267); 2 (129); 3 (129); 4 (162); and 5 (281) (Data from Morgan et al. 1983)

eaters. Higher physical activity was found in the frequent-eaters group, and it was suggested that this result may, at least partially, explain the findings of this study.

By contrast, findings from others' studies in children failed to identify a significant association between EF and childhood obesity (Morgan et al. 1983; Ruxton et al. 1996; Nicklas et al. 2003, 2004; Crawley and Summerbell 1997). In a group of schoolchildren, Ruxton et al. (1996) found no significant association between snacking frequency and weight, BMI, or skinfold thickness. These results confirm the findings of Morgan et al. (1983) reported 10 years earlier in a group of children aged 5–18 years. In this study, no relationship between eating patterns and obesity was observed (see Fig. 178.7). As well, they found no differences in snacking frequency between obese, heavy, average, and normal weight children. Similarly, results from Crawley et al. (1997) failed to produce results supporting a significant association between BMI and EF in a free-living sample of teenagers aged 16–17 years. Finally, in two different studies based on data from the Bogalusa Heart Study, Nicklas et al. (2003, 2004) found no significant relationship between overweight status and the number of eating episodes.

178.3.3 Weight-Loss Studies

The potential benefits of a nibbling versus a gorging meal pattern for body-weight loss were investigated in obese patients. With the exception of only one study, there is no evidence that EF can have a significant impact on weight loss in energy-restricted diets (see Table 178.4) (Bellisle et al. 1997;

Palmer et al. 2009). Indeed, most of the interventional studies failed to show any influence of EF on weight loss (Bortz et al. 1966; Young et al. 1971; Garrow et al. 1981; Finkelstein and Fryer 1971; Antoine et al. 1984; Schlundt et al. 1992; Verboeket-van de Venne and Westerterp 1993; Poston et al. 2005; Vander Wal et al. 2006; Berteus Forslund et al. 2008; Cyr et al. 2007; Duval et al. 2008b). In 1973, Debry et al. have shown a greater weight loss in dieting overweight subjects who were eating seven meals a day than in those who were eating only three meals a day (142 vs 78 g/day) (Debry et al. 1973). However, as shown in Table 178.4, other studies which have addressed the same issue found no significant effect of EF on weight loss. In a crossover study, Bortz et al. (1966) saw no difference in weight loss in a group of six obese women on an isoenergetic diet of 600 kcal daily in either one, three, or nine meals per day. Finkelstein and Fryer (1971) and Young et al. (1971) conducted weight-loss studies in students. The effects of different meal patterns (one, three, or six meals/day – Young et al.; three or six meals/day – Finkelstein and Fryer) were studied. Both studies failed to show any significant relationship between meal frequency and weight change. In a study conducted by Garrow et al. (1981), obese subjects were on an 800 kcal/d diet over 3 weeks. Weight loss was lower when subjects ate five times per day (0.22 kg/day) compared with one meal per day (0.26 kg/day), but this difference was not statistically significant. Verboeket-van de Venne et al. (1993) found that the intake of two or three to five meals per day has no significant effect on the rate and composition of weight loss in obese women on a 1,000 kcal/day diet. More recently, Duval et al. (2008b) found that eating more frequently does not seem to be related with a better body-weight status during weight loss in a sample of 79 obese postmenopausal women who participated in a 6-month weight-reduction program consisting of an 500–800 kcal daily energy deficit. In an 8-week study where subjects were prescribed a dietary energy restriction of 700 kcal/day, Cyr et al. (2007) shown that eating six versus three times per day does not promote greater weight loss. Also, in a ten-y prospective study, Burley et al. found that more-frequent eating and drinking was not associated with greater weight gain in middle-aged women (Burley et al. 2008). Finally, Berteus et al. (2008) observed that recommending snacks or not between meals does not influence 1-year weight loss. In summary, weight loss is not facilitated by high EF.

178.3.4 How Could High Eating Frequency Help Weight Management?

Kirk (2000) highlighted some of the possible advantages associated with a high EF that may help in the control of body weight. First, several studies have shown that snack foods are often higher in carbohydrates and lower in fat than meals (Basdevant et al. 1993; Summerbell et al. 1995; Drummond et al. 1996; Kirk 2000). Thus, a higher EF may be associated with an increased carbohydrate: fat ratio, which may be beneficial in body-weight control. Studies show that high-fat diets are positively associated with overweight and obesity, whereas high-carbohydrate diets are associated with leanness (Gazzaniga and Burns 1993; Miller et al. 1990; Tucker and Kano 1992). Second, eating more frequently may help to spread the EI over the day. It was suggested that obese individuals tend to eat little in the morning (skip breakfast) and much in the afternoon and the evening (Bellisle 2004; Fricker et al. 1990). Furthermore, it was shown that an individual who consumed fewer meals per day and who consumes more food in the evening may be more prone to weight gain (Fricker et al. 1990). Third, another argument for the potential beneficial effects of frequent eating on body-weight control relates to the reduction in hunger that has been postulated to occur with higher EF (Drummond et al. 1996). Burley et al. have shown that eating five times per day (three meals and two snacks) rather than three meals resulted in a flatter profile of hunger throughout the day (Burley et al. 1993). Eating more frequently may also have a beneficial effect in preventing subsequent overcompensation (Westerterp-Plantenga et al. 1994). In addition, spreading the energy load over the day by including

Table 178.4 Summary of weight-loss studies comparing different eating frequency patterns

Reference	Study population	Weight-loss duration	EF pattern	Weight and adiposity changes	Statistical significance
Bortz et al. (1966)	6 F; 19–56 years; Obese	60 days (20 days on each EF pattern)	3 1 9	No data provided −0.23 kg/day −0.24 kg/day	NS[a]
Finkelstein and Fryer (1971)	8 F[b]; 20–22 years; BMI 27–33 kg/m²	60 days	3 6	−6.1 kg −5.5 kg	NS[a]
Young et al. (1971)	11 M; 20–25 years; Mean BMI 34 kg/m²	5 weeks' crossover (14 weeks in total)	1 3 6	−6.08 ± 1.03 kg −4.88 ± 1.31 kg −6.10 ± 1.75 kg Greater versus lesser EF −0.12 ± 0.84 kg FM[c]	NS[a] NS[a]
Debry et al. (1973)	32 M + F; 16–65 years; 120–220% IBW	1-month crossover	3 and 7	−78 g/day	Significant positive correlation[a] N > G
Garrow et al. (1981)	14 F; 18–56 years; Mean BMI 37.7 kg/m²	3 weeks[d]	1 5	−0.26 kg/day −0.22 kg/day	NS[a]
Antoine et al. (1984)	10 F; Mean age 41 years; Mean BMI 31.8 kg/m²	2 weeks' crossover	3 6	−0.15 ± 0.05 kg/day −0.18 ± 0.05 kg/day	NS[a]
Schlundt et al. (1992)	52 F; 18–55 years; Mean BMI 30.6 kg/m²	12 weeks	2 meals (breakfast eater who now has no breakfast) 2 meals (breakfast skipper who now has no breakfast) 3 meals (breakfast eater who now has no breakfast) 3 meals (breakfast skipper who now eats breakfast)	−8.9 ± 4.2 kg −6.0 ± 3.9 kg −6.2 ± 3.3 kg −7.7 ± 3.3 kg	NS[a]
Verboeket-van de Venne and Westerterp (1993)	14 F; 20–58 years; Mean BMI 30.2 kg/m²	4 weeks[e]	2 3–5	−4.1 ± 0.5 kg BW −2.3 ± 0.6 kg FM −1.8 ± 0.5 kg FFM −4.7 ± 0.4 kg BW −2.7 ± 0.5 kg FM −2.0 ± 0.4 kg FFM	NS[a] for BW, FM and FFM

(continued)

Table 178.4 (continued)

Reference	Study population	Weight-loss duration	EF pattern	Weight and adiposity changes	Statistical significance
Poston et al. (2005)	100 M + F; 40–42 years; BMI 31–33 kg/m²	24 weeks	3 meals (snacker) 3 meals + 3 snacks (non-snacker) 3 meals + 3 snacks (snacker) 3 meals (non-snacker)	−2.9 ± 3.2 kg −3.5 ± 5.5 kg −2.4 ± 3.2 kg −2.1 ± 3.4 kg	NS[a]
Vander Wal et al. (2006)	80 M + F; 45–48 years; Mean BMI 38 kg/m²	8 weeks	3 meals + 2 snacks (post-dinner snack) 3 meals + 1 snack (no post-dinner snack)	−3.7 ± 3.3 kg BW −5.6 ± 6.0 kg WC −1.5 ± 1.7 kg %BF −4.7 ± 3.8 kg BW −7.3 ± 5.9 kg WC −1.3 ± 2.6 kg %BF	NS[a] for BW, WC and %BF
Berteus Forslund et al. (2008)	140 M + F; Mean age 39–40 years; Mean BMI 38 kg/m²	52 weeks	3 6 (3 meals + 3 snacks)	−4.1 ± 6.1 kg −5.9 ± 9.4 kg	NS[a]
Cyr et al. (2007)	16 M + F; Mean age 35 years; Mean BMI 37.1 kg/m²	8 weeks	3 6 (3 meals + 3 snacks)	−4.7% BW −3.1 ± 2.9 kg FM −2.0 ± 3.1 kg FFM −1.7 ± 0.8 kg/m² BMI	NS[a] NS[a] NS[a] NS[a]
Duval et al. (2008b)	79 F; 50–69 years; Mean BMI 32.6 kg/m²	6 months	No specific EF pattern	−6.9% BW	NS[a,f]

This table presents a summary of weight-loss studies that have compared the effect of different EF patterns on weight loss. This table gives some information about the study population, weight-loss duration, EF patterns used to compare the results, weight and adiposity changes, and statistical significance of the results (Adapted from Bellisle et al. 1997)

EF eating frequency, *IBW* ideal body weight, *FM* fat mass, *FFM* fat-free mass, *BW* body weight, *BMI* body mass index, *%BF* percentage of body fat, *WC* waist circumference, *N* nibbling, *G* gorging, *NS* not significant, *M* male, *F* female

[a]The correlation coefficients are not provided

[b]Four subjects followed each EF pattern

[c]Measured from underwater weighing

[d]Participants were on a three-meal EF regimen for the first week. Eating-frequency effect was tested for 1 week during weeks 2 and 3 in randomized order

[e]Seven subjects followed each EF pattern

[f]Analyses were repeated controlling for PAEE with no change in the results

Table 178.5 Summary of studies that have investigated the effect of eating frequency on total energy expenditure

Reference	Study population	Measure	EF pattern	TEE	Statistical significance
Dallosso et al. (1982)	8 M; 18–23 years; Mean BMI 22 kg/m²	24-h EE 7–14 days' adaptation	2 6	9,759 ± 408 kJ/day 9,639 ± 314 kJ/day	NS[a]
Wolfram et al. (1987)	8 M + F; 20–23 years; Mean BMI 23 kg/m²	48-h EE 14 days' adaptation	1 5	8.42 ± 1.15 MJ/day 8.37 ± 1.32 MJ/day	NS[a]
Verboeket-van de Venne and Westerterp (1991)	13 M + F; 18–23 years; Mean BMI 21 kg/m²	24-h EE No adaptation	2 7	7,282 ± 230 kJ/day 7,834 ± 259 kJ/day	NS[a]
Verboeket-van de Venne and Westerterp (1993)	14 F; 20–58 years; Mean BMI 30 kg/m²	24-h EE 4 weeks	2 3–5	7,838 ± 416 kJ/day 7,867 ± 202 kJ/day	NS[a]
Verboeket-van de Venne et al. (1993)	10 M; 25–61 years; Mean BMI 25 kg/m²	24-h EE 6 days' adaptation	2 7	9.4 ± 0.2 MJ/day 9.4 ± 0.2 MJ/day	NS[a]
Taylor et al. (2001)	26 F; 36–51 years; BMI 38–42 kg/m²	24-h EE No adaptation	6 versus 2[b] 6 versus 2[c] 6 versus 4[d]	9.99 versus 9.95 MJ/day 9.27 versus 8.97 MJ/day 9.03 versus 9.13 MJ/day	NS[a] NS[a] NS[a]
Smeets et al. (2008)	14 F; Mean age 24.4 years; Mean BMI 23.2 kg/m²	24-h EE 3 days' adaptation	2[e] 3	8.2 ± 0.8 MJ/day 8.5 ± 0.6 MJ/day	NS[a]

This table presents a summary of studies that have investigated the effect of EF on TEE. This table gives some information about the study population, how TEE was measured, EF patterns used to compare the results, TEE results, and statistical significance of the results (Adapted from Bellisle et al. 1997)

EF eating frequency, *EE* energy expenditure, *TEE* total energy expenditure, *BMI* body mass index, *NS* not significant, *M* male, *F* female

[a]The correlation coefficients are not provided

[b]Without access to additional foods

[c]With access to additional foods

[d]The first two meals of the day were omitted to create a morning fast

[e]Lunch was omitted

several snacks may reduce appetite and as a consequence, decrease EI and body weight (Speechly et al. 1999). However, Cyr et al. (2007) shown that eating more frequently (three vs six times per day) does not have an impact on appetite. Fourth, higher levels of physical activity may promote a higher EF to meet increased energy requirements. As mentioned earlier, some studies on EF and body weight found that a higher EF could very well be a marker of a physically active lifestyle and may help in weight management (Duval et al. 2008a). However, as few EF studies have included a measure of physical activity, more studies are needed to confirm this finding.

178.3.5 Eating Frequency and Energy Expenditure

In the investigation of the association between EF and body weight and adiposity, both sides of the energy balance equation should be taken into account. TEE can be divided into three major components: thermic effect of food (TEF) (i.e., the increase in EE after ingestion of food), resting energy expenditure (REE), and PAEE. Most studies of EF and energy metabolism have failed to show any influence of EF on EE. Seven studies have investigated the effect of EF on TEE (see Table 178.5)

Table 178.6 Summary of studies that have investigated the effect of eating frequency on the thermic effect of food

Reference	Study population	Measure	EF pattern	TEF	Statistical significance
Belko and Barbieri (1987)	12 M; 18–34 years; Mean BMI 22 kg/m²	TEF for 10 h	2 4	43.3 ± 4.7 LO_2 43.4 ± 5.0 LO_2	NS[a]
Kinabo and Durnin (1990)	18 F; 18–34 years; Mean BMI 21 kg/m²	TEF for 6 h	High fat 1 2 Low fat 1 2	 356 ± 23 kJ 340 ±16 kJ 377 ± 30 kJ 381 ± 27 kJ	 NS[a] NS[a]
Tai et al. (1991)	7 F; 23–30 years; Mean BMI 20.8 kg/m²	TEF for 5 h	1 6	241 ± 34 kJ 174 ± 25 kJ	Significant negative correlation[a] G > N
Molnar (1992)	11 M + F; Mean age 12 y; obese	TEF for 6 h	1 3	11.9 ± 1.3%[b] 8.5 ± 0.7%[b]	Significant negative correlation[a] G > N
Verboeket-van de Venne et al. (1993)	10 M; 25–61 years; Mean BMI 25 kg/m²	TEF was calculated from 24-h EE measurement[c]	2 7	0.9 ± 0.1 MJ/d 0.9 ± 0.1 MJ/d	NS[a]
Leblanc et al. (1993)	6 M + F; 21–28 years; Mean BMI 23 kg/m²	TEF for 4 h	1 4	180 ± 16 kJ 259 ± 29 kJ	Significant positive correlation[a] N > G
Smeets et al. (2008)	14 F; Mean age 24.4 years; Mean BMI 23.2 kg/m²	TEF was calculated from 24-h EE measurement[c]	2[d] 3	0.86 ± 0.23 MJ/d 0.90 ± 0.30 MJ/d	NS[a]

This table presents a summary of studies that have investigated the effect of EF on TEF. This table gives some information about the study population, how TEF was measured, EF patterns used to compare the results, TEF results, and statistical significance of the results (Adapted from Bellisle et al. 1997)

EF eating frequency, *TEF* thermic effect of food, *EE* energy expenditure, *BMI* body mass index, *N* nibbling, *G* gorging, *NS* not significant, *M* male, *F* female

[a]The correlation coefficients are not provided

[b]Percent energy in meals

[c]Thermic effect of food was determined by subtracting sleeping metabolic rate from resting metabolic rate

[d]Lunch was omitted

(Taylor and Garrow 2001; Smeets and Westerterp-Plantenga 2008; Wolfram et al. 1987; Dallosso et al. 1982; Verboeket-van de Venne and Westerterp 1991, 1993; Verboeket-van de Venne et al. 1993). In these studies, rigorous measurements were made to compare subjects between a gorging (1–2 meals/day) or a nibbling (5–7 meals/day) eating pattern, including one study in which the 24-h whole-body calorimetry results were confirmed with DLW measurement of free-living EE (Verboeket-van de Venne et al. 1993). None of these studies reported any significant effect of EF on TEE. These studies provide evidence that there is no effect of meal pattern on TEE.

The results of the studies which specifically assessed TEF, as opposed to TEE, are inconsistent (see Table 178.6). While half of the studies found no significant differences between a gorging or a nibbling eating pattern (Belko and Barbieri 1987; Kinabo and Durnin 1990; Smeets and

Westerterp-Plantenga 2008; Verboeket-van de Venne et al. 1993), others reported either a higher TEF of food with lower EF (Tai et al. 1991; Molnar 1992) or the opposite (LeBlanc et al. 1993). Tai et al. (1991) found that the TEF of food was significantly higher in the low-EF group (one meal) than in the high-EF group (six meals) (7.68% vs 5.56%, respectively). Molnar et al. (1992) also found that the TEF (expressed as a percent of the energy ingested) was significantly higher with the single meal (11.9% ± 1.3%) than with the three small meals (8.5% ± 0.7%) in children. Inversely, LeBlanc et al. (1993) found an 8% lower TEF with one versus four meals a day. In light of the absence of effect of EF on TEE and the inconclusive evidence to support differences in TEF according to eating patterns, there is currently no reason to believe that changing EF would alter EE.

Concerning REE, it was found that higher EF has no effect on REE (Verboeket-van de Venne et al. 1993; Smeets and Westerterp-Plantenga 2008). Few of the published studies of EF and body weight have included a measure of the subjects' daily physical activity (Drummond et al. 1998; Duval et al. 2008a; Yannakoulia et al. 2007). As mentioned earlier in this chapter, it has been suggested that the inconsistent associations reported between EF, adiposity, and EI, especially in women, are due to differences in physical activity (Drummond et al. 1998; Duval et al. 2008a). Drummond et al. (1998) hypothesized that the absence of a relationship between EF and adiposity may be explained by the fact that frequent eaters may have higher EI due to higher physical activity levels. Duval et al. (2008a) found a positive correlation between EF and PAEE. Moreover, the results of this study showed that, after correction for PAEE and VO_{2peak}, the associations between adiposity and EF were no longer significant, which suggests that the relation between EF and body composition may be an artifact of higher PAEE and greater physical fitness. Therefore, higher EF resulting from higher physical activity and greater physical fitness could very well be a marker of a physically active lifestyle, at least in leaner persons. More studies will however be needed to confirm this finding.

178.3.6 Results' Discrepancies' Explanation

Methodological discrepancies have been proposed in order to explain some of the differences between studies in terms of the relationship between adiposity and EF: various definitions of eating occasions; under-reporting of food intake, especially among the obese; various methods of assessing food intake and body composition; and the fact that many studies did not take into account factors related to EE, especially physical activity. These methodological issues have been reviewed by Gatenby (1997).

As mentioned earlier in this chapter, the type of definition used to describe eating occasions may significantly influence the outcomes and interpretation of the studies. Inconsistencies in the definitions of EF used across studies, that is, time interval between two eating occasions versus predefined meal periods, make comparisons between studies hard to interpret and might have contributed to the heterogeneity of the findings.

Previous observations regarding eating patterns may also be affected by under-reporting of food intake. Since the Fabry et al. (1964) study, many studies have reported an inverse relationship between EF and body weight, suggesting that a "nibbling" pattern could help to prevent obesity. This notion has been put into question by the recognition of a high level of dietary under-reporting. In support of the latter idea, data from Summerbell et al. (1996) showed an inverse relationship between meal frequency and BMI in adolescents, which disappeared when dietary

Table 178.7 The associations between eating frequency and the variables related to energy balance

	EF correlates with…					
Population	Adiposity	TEE	REE	TEF	PAEE	Weight loss
Men	0 or –	0	0	0 or +	+	0
Women	0 or – (+ in postmenopausal women)	0	0	0 or – or +	+	0
Children	0 or –	No data	0	–	+	No data

This table presents a summary of the associations between EF and the variables related to energy balance. The associations are presented for three different populations (men, women, and children)
Plus (+) indicates significant relationship; negative (–) indicates significant inverse relationship; and zero (0) indicates non-significant relationship between EF and adiposity and EE and weight loss
EF eating frequency, *TEE* total energy expenditure, *REE* resting energy expenditure, *TEF* thermic effect of food, *PAEE* physical activity energy expenditure

records from under-reporters were excluded. Summerbell et al. (1996) has proposed that these findings may have repercussions for the interpretation of earlier studies, which did not screen for invalid dietary records. Research evidence indicates that under-reporting is particularly more frequent in overweight and obese persons (Livingstone and Black 2003; Heitmann and Lissner 1995), giving the impression that a low EF is positively related to adiposity. Even when under-reporters have been excluded, it was suggested that other factors, such as dietary restraint, have to be assessed. Indeed, in a study of a sample of 731 free-living teenagers, Crawley and Summerbell (1997) found an inverse relationship between meal and BMI, which was significant after exclusion of under-reporters. However, this relationship disappeared when dieting behavior and dietary restraint were taken into account. Under-reporting affects not only EI, but also the daily number of eating occasions, and snacks are particularly prone to under-reporting (Livingstone et al. 1990; Bellisle 2004).

The method used to assess food intake is another methodological issue which has been proposed to explain the contradictory results. However, while various methods have been used in EF studies, results do not differ consistently according to the method of assessment. Indeed, Metzner et al. (1977) (24-h diet recall) and Burley et al. (2002) (4-day food diary) found an inverse relation between EF and adiposity, whereas Drummond et al. (1998) (7-day food diary) and Yannakoulia et al. (2007) (3-day food diary) found no such relation in women. Most existing dietary-assessment methods are developed to analyze energy and nutrient intake but rarely eating patterns.

The techniques used to measure body fatness can have an effect on the relation between EF and body composition. Most studies of EF used BMI or included a measure of body composition using either skinfold-thickness measurements taken with calipers or underwater weighing to assess body fatness. Only two studies have used dual-energy X-ray absorptiometry for the measurement of body composition (Duval et al. 2008a; Yannakoulia et al. 2007). Duval et al. (2008a) found a negative relation between EF and adiposity, while Yannakoulia et al. (2007) did not find any relationship between EF and adiposity; conversely, Duval et al. (2008a) found a negative relation between EF, which was no longer significant after correction for PAEE and VO_{2peak}.

To obtain more accurate data, future studies need to identify under-reporters and individuals characterized by high levels of dietary restraint and exclude these from the analysis. They also need to use standardized criteria for defining EF in order to be able to compare results from different studies, and they should include an objective and valid measure of PAEE. The associations between EF and the variables related to energy balance are presented in Table 178.7.

178.4 Conclusion

Despite more than 40 years of research in this field, the influence of EF on body weight and adiposity is still not clear. The majority of the studies on EF and body weight status does not support the view that eating between meals, or snacking, leads to increases in weight and obesity. Indeed, some studies have reported a negative relation between EF and adiposity, whereas other studies found no association. The impact of EF on weight loss during energy restriction and on EE is more conclusive. Increasing EF does not promote greater weight loss. No difference in TEE has been documented as a function of daily eating occasions and weight loss is not facilitated by high EF. Several methodological discrepancies have been proposed to explain the differences observed between studies, especially the under-reporting of food intake and the lack of a standardized definition of key terms for EF.

Despite the inconclusive results, EF seems to be related with leanness in men (Drummond et al. 1998; Chapelot et al. 2006; Ruidavets et al. 2002). In women, many studies found no association or negative correlation between EF and adiposity, despite a higher EI (Burley et al. 2002; Drummond et al. 1998; Duval et al. 2008a; Yannakoulia et al. 2007). It was suggested that a higher EF could very well be a marker of a physically active lifestyle, at least in leaner persons. The combination of a high EF and increased physical activity may be an effective strategy for the control of body weight. In children, while some studies found no relationship between EF and body-weight status, the negative association between an increased EF and childhood overweight/obesity found by other investigators highlights the importance to assess eating pattern in childhood. Skipping meals might not be an appropriate approach for reducing the risk of obesity in children.

There is clearly a need to examine the relationship between EF and adiposity using both cross-sectional and longitudinal approaches. More long-term studies with sufficiently large sample sizes and using adequate and standardized methodologies are needed in order to provide accurate information on the association between eating occasions and body-weight control, which will be relevant for health-promotion strategies.

While the effects of EF on body-weight control are controversial, there is no evidence that dividing food intake in several daily eating episodes adversely affect body weight status. It was suggest that as long as EI is not greater than EE and that individuals eat only when they are hungry, splitting energy intake in several eating occasions over the day may be useful (Louis-Sylvestre et al. 2003). Louis-Sylvestre et al. (2003) also proposes that the EF pattern cannot be completely separated from the macronutrient composition of foods consumed. The composition of the food intake has also to be taken into account to be sure that low-energy, dense, high-carbohydrate foods are consumed. By itself, the currently available evidence does not support that increasing EF is associated to lesser adiposity, greater weight loss, or even the prevention of weight gain.

178.4.1 Applications to Other Areas of Health and Disease

There is some evidence that EF may be implicated in certain health parameters, notably diabetes, hypercholesterolemia, and colon cancer (Palmer et al. 2009). Studies investigating the metabolic effects of eating patterns have shown that, for a given EI, eating more frequently may lead to an improvement in blood lipid profile (decrease total and low-density lipoprotein (LDL) cholesterol), a better glucose tolerance, an improvement in insulin resistance, and a reduction of insulin concentration (Edelstein et al. 1992; Arnold et al. 1993; Jenkins et al. 1989, 1992, 1995; Gwinup et al. 1963a, b;

Carlson et al. 2007; Fabry et al. 1964). The lower levels of total and LDL cholesterol observed in more frequent eaters may help to reduce the risk of myocardial infarction (Fabry et al. 1968). However, more long-terms studies are needed to confirm these results. It should nonetheless be noted that results from at least one study suggest that the risk of colorectal cancer is proportional to EF (Gerhardsson de Verdier and Longnecker 1992).

Several physiological reasons have been proposed to explain the association between EF and diabetes risk indicators. It have been suggested that higher EF may lower insulin requirements and blood-glucose concentrations over the day (Jenkins et al. 1992). Indeed, Jenkins et al. (1992) have shown that spreading the nutrient intake throughout the day may promote glucose disposal resulting from a reduction of free-fatty acids' concentration. Another possible explanation is that more frequent eaters tend to produce less glucose-dependent insulinotropic polypeptide (GIP), which is an insulin stimulant and inhibits gastric emptying (Jenkins et al. 1990; Vitapole 2003). Thus, this decreased GIP production results in a decreased insulin secretion and a slowed rate of stomach emptying with consumption of smaller meals, which results in a slower rate of energy delivery to the intestine and less insulin required to control blood-glucose levels (Macdonald 1996; Doran et al. 1998).

Concerning the physiological mechanisms to explain the inverse associations between EF and total and LDL cholesterol, it was suggested that the reduction in insulin concentration observed in more frequent eaters may have an impact on the reduction of the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase, responsible for hepatic cholesterol synthesis (Jenkins et al. 1989). A decrease in cholesterol synthesis increases LDL receptors, resulting in lower concentrations of total and LDL cholesterol (Jenkins et al. 1989). A nibbling eating pattern may also give more opportunities to remove cholesterol, which is normally removed in the postprandial phase (Mann 1997).

Summary Points

- There is a lack of standardized definition of eating frequency. Two types of definition are normally reported to categorize eating frequency in the literature: predefined eating periods and time interval between two eating occasions.
- The 24-h dietary recall and the food record/diary are mostly used to assess eating frequency.
- Under-reporting has been recognized as an important methodological issue in the relation between eating frequency and body weight. Overweight, obese, and diet-restrained subjects are more likely to under-report their food intake.
- The association between eating frequency and body-weight status is not clear. Studies in both adults and children have either failed to find a significant relationship between eating frequency and adiposity or have found an inverse relationship.
- A high eating frequency may be associated with an increased carbohydrate: fat ratio and a reduction in hunger, which may help for body-weight control. A high eating frequency may also help to spread the energy intake over the day.
- The impact of eating frequency on weight loss during energy restriction and on energy expenditure is more conclusive. No difference in total energy expenditure has been documented as a function of daily eating occasions, and weight loss is not facilitated by high eating frequency.
- Physical activity seems to be related with a higher eating-frequency pattern. Subjects who eat more frequently tend to have a physically active lifestyle.
- Several methodological discrepancies have been proposed to explain some differences observed between studies: various definitions of eating occasions, under-reporting of food intake, various methods of assessing food intake and body composition, and the lack of physical-activity measurement.

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Part XXV
Anthropometry and Nutrition: Micro- and Macro-Nutrients

Chapter 179
Relationship Between Calcium Intake and Anthropometric Indices

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Abstract An emerging body of literature suggests that dietary calcium may play a role in the regulation of body weight and body fat. Literature has shown inverse relationships between calcium intake and body fat percentage and body mass index (BMI) of children and adults of different ethnic groups. In some studies, however, no association between dietary calcium intakes and body weight, BMI or fat mass was found. The aim of this study was to assess the association between dietary calcium intakes and anthropometric indices in different age groups and people from different ethnic groups worldwide. Results of cross-sectional studies of the relationship between calcium intake and anthropometric indices indicate inverse associations between calcium intakes and BMI among adolescents and adults. These associations were not found consistently, especially not in groups with a relatively low calcium intake. In most studies adjustment was made in statistical analyses for age, gender, total energy intake and smoking, but adjustment was seldom made for physical activity, which could have an important effect on the body mass index and skinfold thickness of the study participants and could be a confounder in the association between dietary calcium intakes and body composition. Longitudinal studies in children and young adults indicate an inverse association between dietary calcium intake over time and body fat or sum of skinfolds. Randomised controlled intervention trials showed inconsistent results and a meta-analysis of 13 randomised controlled trials showed no association between dietary calcium intake and body fat. In a cross-over clinical trial where the effects of low and high calcium diets were compared fecal fat excretion increased 2.5-fold when the participants took the 1,800 mg calcium diet with 15% of energy from protein compared to a 500 mg calcium diet. The authors proposed that increased fat and energy excretion over time may contribute to a decreased gain in fat mass, or a loss of body fat. Other plausible mechanisms include higher fat oxidation or protection against fat gain by creating a balance of lipolysis over lipogenesis in adipocytes. High calcium intake depresses 1,25-dihydroxy vitamin D leading to decreases in intracellular calcium, thereby inhibiting lipogenesis and stimulating lipolysis. Available data do not unequivocally support the hypothesis that a causal relationship exists between high dairy food intake and/or high dietary calcium intake and lower fat mass deposition. Daily calcium intake should, however, be encouraged to achieve optimal health.

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_179,

Abbreviations

24h	24 hour
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BMI	Body mass index
Ca	Calcium
d	Day
EE	Energy expenditure
g	Gram
HOMA	Homeostasis model assessment
HOMA-IR	Homeostasis model assessment of insulin resistance
kg	Kilogram
kg/m^2	kilogram per square meter
mg	Milligram
NHANES	National Health and Nutrition Examination Survey
SE	Standard error
y	Year

179.1 Introduction

The prevalence of obesity is increasing in developed, as well as developing countries, and with that, the burden of chronic diseases associated with obesity, namely diabetes mellitus, coronary heart disease, and hypertension. Results from studies of coronary artery risk development have shown that people from different ethnic groups should avoid excess adiposity to improve their health (James 1998). There is little understanding of the optimal dietary composition necessary to promote weight loss and prevent weight gain, whereas it is of major importance to interpret dietary influences on body composition in order to develop practical guidelines for obesity treatment and prevention (Astrup et al. 2000). While much attention has been focused on macronutrient intake and body-weight regulation, particularly dietary fat, an emerging body of literature suggests that dietary calcium may play a role in the regulation of body weight and body fat (Barba and Russo 2006; Heaney et al. 2002; Heaney 2003; Zemel et al. 2000). Literature has shown inverse relationships between calcium intake and body fat percentage and body mass index (BMI) of children (Carruth and Skinner 2001; Skinner et al. 2003; Palacios et al. 2007) and adults in Western communities (Loos et al. 2004; Marques-Vidal et al. 2006), as well as in American Indians (Eilat-Adar et al. 2007) and African-Americans (Loos et al. 2004). Epidemiologic and limited experimental data from some studies suggest that differences in calcium intake may be associated with changes in body weight of 0.42 kg year (Heaney et al. 2002; Heaney 2003). In some studies, however, no association between dietary calcium intakes and body weight, BMI or fat mass were found (Brooks et al. 2006; Eilat-Adar et al. 2007) and, also, no difference in increase in body weight and BMI of fat mass between calcium supplemented and control groups (Lappe et al. 2004; Trowman et al. 2006; Yanovski et al. 2009).

Dietary calcium intakes vary, but generally African populations (Kruger et al. 2007) and American-Indians (Eilat-Adar et al. 2007) have usual calcium intakes much lower than the recommendations for health. In some studies, lower usual calcium intakes were reported for obese groups (dos Santos et al. 2008; Eilat-Adar et al. 2007; Marques-Vidal et al. 2006), and concern was expressed about the low calcium intakes of children and young adolescents (Barba and Russo 2006; Poddar et al. 2009). The aim of this study was to assess the association between dietary calcium intakes and anthropometric

indices in different age groups and in people from different ethnic groups worldwide. A large number of studies have been done in this field, and the author will include studies from a range of age groups, ethnic groups and countries in this review within the limits set for this textbook.

179.2 Cross-Sectional Studies

Results of cross-sectional studies of the relationship between calcium intake and anthropometric indices are summarized in Table 179.1. These results indicate inverse associations between calcium intakes and measures of adiposity among adolescent groups (Palacios et al. 2007; dos Santos et al. 2008). The association was clear in boys 13–15 years old, with a wide range of BMI values. In boys 16–18 years old and girls 13–18 years old, most children had BMI values within the normal range as well as high calcium intakes, and no significant association between calcium intakes and BMI was found (Palacios et al. 2007). A study, in adolescents, with more than 50% obese participants and a wide range of calcium intakes also indicated an inverse association between calcium intakes and body fat. Moreover, body trunk fat, fasting insulin, and homeostasis model assessment (HOMA) of insulin resistance were all inversely associated with calcium intakes, indicating increased risk of non-communicable diseases in the girls with low calcium intakes (dos Santos et al. 2008).

Table 179.1 also shows inverse associations between calcium intake and BMI, as well as body-fat percentage and skinfold thickness (Loos et al. 2004; Eilat-Adar et al. 2007; Garcia-Lorda et al. 2007; Kruger et al. 2007). These associations were not found in all groups studied. Two studies found no association between calcium intakes and BMI of black women (Loos et al. 2004; Kruger et al. 2007). In both studies, calcium intakes were adjusted for total energy intake, but black women had lower calcium intakes than white women. Kruger et al. (2007) suggested that a minimum calcium intake, combined with a relatively high fat intake, is necessary before calcium intake can have an effect on adiposity. No association was also found between the calcium intakes and BMI of whites in USA in the NHANES III Study (Eilat-Adar et al. 2007), young adults in USA (Brooks et al. 2006), and adults older than 55 years in Portugal (Marques-Vidal et al. 2006). For all these groups, relatively low calcium intakes ranging from around 300 to 800 mg per day were reported. The range between the lowest and the highest calcium intake quintiles in the study of American Indians was potentially large enough to produce an association, whereas this range in the NHANES III Study was not as large (Eilat-Adar et al. 2007). In most studies, adjustment was made in statistical analyses for age, total energy intake, and smoking, but adjustment was seldom made for physical activity, which could have an important effect on the body mass index and skinfold thickness of the study participants (Marques-Vidal et al. 2006; Varenna et al. 2007). The differing results across analyses may also have resulted from differences in age and gender distributions, as well as fewer adjustments for confounders in the NHANES III analysis (Eilat-Adar et al. 2007). A possible reason for a lack of association between number of dairy portions per day and BMI or percentage body fat could be that most of the dairy portions, for example, cheese, were also high in fat. The effect of fat intake on body composition was probably stronger than the effect of calcium intake (Kruger et al. 2007).

179.3 Longitudinal Studies

Generally, it is difficult to prove causality in cross-sectional studies, and many confounding variables may not be measured and adjusted for in statistical analyses. In longitudinal studies, a cohort of participants can be followed over time and outcomes of an exposure can be assessed. Table 179.2 summarizes

Table 179.1 Cross-sectional studies of the relationship between calcium intake and anthropometric indices

Author (year)	Study subjects	Method of measuring calcium intake	Statistical method and factors controlled for in analyses	Results
Adolescents				
Palacios et al. (2007)	100 adolescents, aged 13–18 y	Food-frequency questionnaire 1,076 mg/d	Correlation analysis	Significant negative correlation found between calcium intake and BMI in boys 13–15 y ($r = –0.39$, $p < 0.05$). This subgroup exhibited the widest range of BMI values among all groups evaluated. No correlation was seen in boys aged 16–18 y or girls, in whom BMI was in the normal range and with relatively high calcium intake
dos Santos et al. (2008)	96 postpubertal adolescents: 47 normal weight and 49 obese, mean age 16.6 +/– 1.3 y	3-day dietary record; Obese children: 585 mg/d Normal weight: 692 mg/d	Quartile analysis; Adjusted for energy intake	Calcium intake was inversely associated with body trunk fat, insulin, and HOMA-IR in the obese group. Girls in the highest quartile of Ca intake had decreased adiposity
Adults				
Brooks et al. (2006)	1,306 young adults 19–38 y	Semi-quantitative food frequency questionnaire; 799 ± 417 mg/d	Analysis of covariance; separately for gender and ethnic groups	No significant association was found between dairy product consumption, calcium intake, and body mass index or waist circumference. A significant inverse association was seen between calcium intake, low-fat dairy-product consumption, and waist-to-hip ratio in white males
Marques-Vidal et al. (2006)	17,771 men and 19,742 women aged > /= 18 y	Milk-intake frequency questionnaires Men: 187 ± 5–252 ± 3 ml milk/d Women: 222 ± 5–243 ± 3 ml milk/d	Correlation analysis adjusted for age, region, physical activity, smoking, number of meals, and educational level. Chi-square test, *t*-tests, and general linear model with post hoc Scheffe's test	In men, milk intake was inversely related to BMI (r = –0.10, $p < 0.001$); the relationship in women was weaker ($r = –0.06$, $p < 0.001$). In men, prevalence of milk consumers was lower in obese (62%) and in overweight (68%) than in normal-weight subjects (71%, $p < 0.001$). In women younger than 55 y, milk intake decreased with increased BMI categories (291 ± 9, 271 ± 10, and 269 ± 11 ml/d for normal, overweight, and obese subjects, respectively, $p < 0.001$); no relationship was found in the older group

Garcia-Lorda et al. (2007)	261 men and 313 women, 18–70 y	24-h dietary recall	Odds ratio analysis within quartiles of calcium intake adjusted for age, energy, total fat, and fiber intake	Odds ratio of being in the highest quartile of BMI was significantly reduced in the highest quartile of calcium intake [men: 0.63 (0.30–1.29); women: 0.36 (0.17–0.79)], compared to the lowest quartile.
Multiethnic groups				
Loos et al. (2004)	109 black and 253 white men, 201 black and 261 white women of the HERITAGE Family Study	Food-frequency questionnaires Black men: 766 ± 49 mg/d Black women: 825 ± 42 mg/d White men: 1,098 ± 38 mg/d White women: 1,060 ± 34 mg/d	ANOVA and regression against the energy-adjusted calcium intake to test for a linear trend	No significant associations were found in black women. Low Ca intake may be associated with higher adiposity, particularly in men and white women The percentage of fat of white men in the highest Ca-intake group was significantly lower than in the lowest calcium group ($p = 0.04$). The strongest inverse associations appeared in black men and white women. Black men in the high-Ca-intake group were leaner than those in the low-Ca-intake group: BMI 23.4 ± 0.9 versus 26.7 ± 1.1 kg/m^2 ($p = 0.01$); for all other adiposity measures, $p < 0.05$. In white women, regression analyses showed significant inverse associations between Ca intake and BMI ($p = 0.02$) and skinfold thicknesses ($p = 0.01$–0.006).
Eilat-Adar et al. (2007)	2,975 American Indians and 2,755 US whites aged 47–79 y	24-h dietary recall. Indian men: 680 ± 14 mg/d Women: 610 ± 10 mg/d White men 852 ± 20 mg/d White women 673 ± 13 mg/d	Generalized logit model for quintile analysis by gender, age, study center, years of education, income, alcohol consumption, smoking, diabetes status, diabetes duration in participants with diabetes, and energy intake	In American Indians, %body fat and BMI (as adjusted mean differences in higher calcium quintiles compared with the lowest quintile) decreased as calcium intake increased after controlling for other confounders. In NHANES III US whites, no trend was observed in either BMI or %body fat across calcium-intake categories
Kruger et al. (2007)	102 black women, 106 white women	Food-frequency questionnaires Black women: 523 ± 63 mg/d White women: 1,054 ± 10 mg/d	Partial correlation adjusted for age, energy intake, and smoking	Significant negative correlation seen between dietary calcium:fat ratio and BMI in white women only No association observed between calcium intake and anthropometric indices in black women

(continued)

Table 179.1 (continued)

Author (year)	Study subjects	Method of measuring calcium intake	Statistical method and factors controlled for in analyses	Results
Women only				
Varenna et al. (2007)	1,771 healthy early postmenopausal women	Frequency of dairy-food consumption questionnaire of number of servings with 300 mg Ca. Calculated calcium intakes ranged between <300 and 685+ mg/d	ANOVA and chi-square test, stepwise multiple logistic regression adjusted for age, age at menopause, physical activity, and smoking	BMI and prevalence of overweight showed significant inverse trends with increasing dairy intake
Azadbakht et al. (2008)	926 women aged 40–60 y	Quantitative food-frequency questionnaire	Logistic regression analysis adjusted for age, medications, and BMI. Pearson correlation between dietary components and WHR. Analysis of covariance to compare the mean values of WHR in different lifestyle groups, with adjustment for BMI and age	Dairy consumption was inversely correlated with central fat accumulation (r = -0.2, $p < 0.05$) Low calcium intake (1.30; 1.07–3.78) was associated with central fat accumulation

This table summarizes cross-sectional studies of the relationship between calcium intake and anthropometric indices according to authors, study subjects, method of measuring calcium intake, statistical methods, factors controlled for in analyses, and key results

ANOVA analysis of variance, *BMI* body mass index, *Ca* calcium, *d* day, *HOMA-IR* homeostasis model assessment of insulin resistance, *kg/m²* kilogram per square meter, *mg* milligram, *NHANES* National Health and Nutrition Examination Survey, *y* year

Table 179.2 Longitudinal studies of the relationship between calcium intake and anthropometric indices

Author (year)	Study subjects and duration of follow-up	Method of intake assessment and mean intakes	Statistical method and factors controlled for in analyses	Results
Children				
Carruth and Skinner (2001)	53 children 70 ± 2 months (6 y) 4 years of follow-up	24-h recall +2-day diet records by personal interview; Boys: 791–949 mg/d Girls: 698–808 mg/d	General linear models; gender, dietary fat, protein, and monoun-saturated fat	Both dietary calcium intake and dairy product intake were significantly negatively associated with body fat
Skinner et al. (2003)	52 children, 8 years old; 6 years of follow-up	24-h recall +2 d diet records by interview Boys 912 mg/d Girls 805 mg/d	Multiple regression; total dietary fat, saturated fat, gender, sedentary activity, father's BMI, and mothers' percent body fat	Dietary calcium and polyunsaturated fat intake were negatively related to body fat in three statistical models, which predicted 28–34% of the variability in body fat among children
Adolescent to adult				
Boon et al. (2005)	391 subjects from age 13 years in 1977 to age 36 years; 23 years of follow-up	Cross-check diet history interview; Men 1,122–1,435 mg/d Women 921–1,264 mg/d	Linear regression analysis adjustment for age only, then with additional adjustment for total dietary energy intake, fiber intake, and level of habitual physical activity	For men in the age-adjusted model, a 1,000 mg/d higher dietary calcium intake was related to a 0.2 cm lower sum of four skinfolds ($p = 0.004$). For women in the age-adjusted model, the highest dietary calcium intake group (>1,200 mg/d) had a significantly lower sum of four skinfolds than those consuming <800 mg/d of calcium ($p = 0.04$). A comparable, not statistically significant trend was found for BMI. The significant associations disappeared after adjustment for putative confounders. No differences were observed between the middle (800–1,200 mg/d) and high (>1,200 mg/d) groups of calcium intake
Poddar et al. (2009)	65 women and 11 men; mean age 19.2 ± 0.2 y; 7 months of follow-up	7-day food records Dairy: 1.4 ± 0.1 servings/d; low-fat dairy: 0.5 ± 0.1 servings/d; calcium: 815 ± 41 mg/d	One-way multivariate analysis of covariance race, sex, and percent intake of estimated energy requirement were included as covariates	Higher low-fat dairy intakes (0.8 servings/d): gained less body weight and had reductions in waist circumference, percentage truncal fat, and percentage total body fat compared to those with lower intake (0.1 serving/d) Subjects who consumed a higher amount of low-fat dairy products (mean ± SE = 0.8 ± 0.1 servings/day) had better diet quality

This table summarizes longitudinal studies of the relationship between calcium intake and anthropometric indices according to authors, study subjects, duration of follow-up, method of measuring calcium intake, statistical methods, factors controlled for in analyses, and key results
BMI body mass index; *mg/d* milligram per day; *SE* standard error; *y* year

the methods and results of longitudinal studies done in children and young adults. The two studies in children show results of the same cohort (Carruth and Skinner 2001; Skinner et al. 2003) but with additional analyses done over 2 years in the second study (Skinner et al. 2003). All studies indicate an inverse association between dietary calcium intake over time and body fat or sum of skinfolds (Carruth and Skinner 2001; Skinner et al. 2003; Boon et al. 2005; Poddar et al. 2009).

No differences were observed between body composition of the middle (800–1,200 mg/d) and high (>1,200 mg/d) groups of calcium intake in Dutch subjects, suggesting a threshold of approximately 800 mg/d, above which calcium intake has no additional beneficial effect on adiposity (Boon et al. 2005). If it is considered that a minimum calcium intake of about 600 mg/d for an effect on adiposity has been proposed (Kruger et al. 2007), then a small range of calcium intakes of 600–1,000 mg/d is proposed for an effect on adiposity.

179.4 Randomized Controlled Trials

Randomized controlled trials provide the most powerful tool to assess a relationship between an exposure, such as calcium intake, and an outcome, in this case, anthropometrical indices indicating obesity. Components of the methods and results of randomized controlled trials of calcium intake and anthropometric indices are summarized in Table 179.3. In a relatively small study of 59 prepubertal girls, randomized to either a calcium-rich diet or their usual diet, no difference in increase in BMI, fat, or lean mass over 2 years was found, although the intervention group consumed nearly twice as much dietary calcium as the control group (Lappe et al. 2004). Similarly, Yanovski et al. (2009) found no difference between body weight or BMI of a calcium supplemented group and a placebo group of overweight adults after 2 years of intervention. However, in a study of only 51 young women, mean calcium intake over 18 months predicted changes in fat mass, suggesting that women on low calcium intakes will gain fat mass and those on high calcium intakes will reduce fat mass. Adjustment for total energy intake and physical activity did not alter the predicted changes (Eagan et al. 2006). Zemel et al. (2004) also found increased fat loss in the intervention groups with higher calcium intakes, with the highest fat loss in the group with the highest dairy food intake. Moreover, fat loss from the trunk region represented 19 ± 7.9% of total fat loss on the low-calcium diet, and 50 ± 6.4% and 66 ± 3% on the high-calcium and high-dairy diets, respectively.

Jacobsen et al. (2005) carried out a randomized cross-over study to assess the effects of calcium intake on energy expenditure, fat oxidation, and fat excretion, in an attempt to explain the mechanism underlying the inverse association between calcium intake and body fat. Calcium intake had no effect either on energy expenditure, measured in open-circuit respiratory chambers, or on fat oxidation, calculated from gas exchange in the chamber. Fecal fat excretion did, however, increase 2.5-fold when the participants took the 1,800 mg calcium diet with 15% of energy from protein, compared to the 500 mg calcium diet and the 1,800 mg calcium diet with 23% of energy from protein. The authors proposed that increased fat and energy excretion over time may contribute either to a decreased gain in fat mass, or to a loss of body fat.

179.5 Reviews and Meta-Analysis

Table 179.4 shows the results of a narrative review, reanalyses of several studies, and a meta-analysis of randomized controlled trials. Reanalyses of studies (Heaney et al. 2002; Heaney 2003; Zemel et al. 2000) showed a consistent association between higher calcium intakes and lower body fat and/or body

Table 179.3 Randomized controlled trials of the relationship between calcium intake and anthropometric indices

Author (year)	Study subjects and duration of the intervention	Mean calcium or dairy-food intakes of intervention and control groups	Statistical method and factors controlled for in analyses	Results
Lappe et al. (2004)	59 girls, 9 y; 2 years	Calcium-rich diet supplying at least 1,500 mg calcium per day or their usual diet (731 ± 105 mg calcium/day); 3-day food diaries	Analysis of covariance to model the effect of tertile (lowest vs. highest) of calcium on weight gain while adjusting for baseline weight, energy, and protein intake averaged over the 2 years of study as covariates/predictors. Mann–Whitney *U* test was used to test the differences in percentile ranking of BMI	Participants in the treatment group consumed nearly twice as much dietary calcium as the control group, primarily from dairy foods, but they did not have greater increases in body weight, body mass index, or fat or lean mass than the control group. Calcium-rich diets do not cause excessive weight gain in pubertal girls but do contribute positively to overall nutrition
Eagan et al. (2006)	51 normal-weight young women; 1-year dairy intervention 6 months after completion of the intervention	Control group (<800 mg Ca/d), medium dairy (1,000–1,100 mg Ca/d), and high dairy (1,300–1,400 mg Ca/d)	ANOVA, Pearson correlation, and general linear model were used as described in the results. Dependent variables include absolute values and changes in fat mass, lean mass, weight, and BMI. Predictive variables include dietary group assignment, calcium intake, and change in calcium intake. Covariates were absolute values and changes in BMI, energy intake, and 25-hydroxy-vitamin D	Mean calcium intake over the 18 months predicted a negative change in fat mass ($p = 0.04$). There was a trend for 18-month dietary calcium intake to correlate with change in fat mass when uncontrolled ($r = 0.25$; $p = 0.08$), and when controlled for baseline BMI ($r = 0.27$, $p = 0.06$). This trend was significant($r = 0.28$; $p = 0.05$) when analyses were controlled for group and baseline BMI. Physical activity or mean energy intake in the model did not alter the results. Mean calcium intake of 6-, 12-, and 18-month dietary records predicted the 18-month change in fat mass when controlled for baseline BMI in regression ($R^2 = 0.11$). Substituting calcium intakes into the regression equation yields for 500 mg/d, a fat mass gain of 1.26 kg over 18 months, and for 1,200 mg/d, a fat mass loss of 0.631 kg over 18 months. The difference in fat mass is 1.89 kg between dietary calcium intake exposures over 18 months in normal-weight young women

(continued)

Table 179.3 (continued)

Author (year)	Study subjects and duration of the intervention	Mean calcium or dairy-food intakes of intervention and control groups	Statistical method and factors controlled for in analyses	Results
Jacobsen et al. (2005)	Eight women, two men, 18–50 y; cross-over study of three isocaloric 1-week diets (3× 1-weeks)	Low calcium and normal protein: 500 mg calcium, 15% of energy (E%) from protein (LC/NP); high calcium and normal protein: 1,800 mg calcium, 15E% protein (HC/NP); and high calcium and high protein: 1,800 mg calcium, 23E% protein, (HC/HP)	Differences between the three diets were analyzed by a mixed model for analysis of covariance with values from after the diet period as the dependent variable and subjects as a random variable. Adjustments were made for various covariables. Baseline values were not included in the analyses. Differences in the fecal parameters were analyzed by analyses of variance, with subjects included as a random effect and Tukey correction for post hoc comparisons. Differences between values measured before and after the diet period were analyzed by a paired *t*-test. Correlation between calcium intake and fat excretion was calculated using Pearson's correlation. Linear regression was used to relate calcium intake to fat excretion	The calcium intake had no effect on 24-h energy expenditure or fat oxidation, but fecal fat excretion increased approximately 2.5-fold during the HC/NP diet compared with the LC/NP and the HC/HP diets (14.2 vs. 6.0 and 5.9 g/d; $p < 0.05$). The HC/NP diet also increased fecal energy excretion as compared with the LC/NP and the HC/HP diets (1,045 vs. 684 and 668 kJ/d; $p < 0.05$)
Yanovski et al. (2009)	340 overweight (BMI >/= 25–30 kg/m^2) adults, mean age 38.8 y, 2 years	Elemental calcium, 1,500 mg/d or placebo	Intention-to-treat sample of all randomly assigned participants Multiple imputation model for missing data under a missing-at-random assumption. All baseline, one y and two y outcome measures were used in an imputation model along with age, sex, race, baseline serum 25-hydroxy-vitamin D concentration, baseline calcium intake, and study group. The coefficients from analyses of 20 imputed data sets were combined into a single set of estimates. Multiple imputations were done to impute the missing 2-year weight measurements by using the same imputation model used for the main analysis. Fixed amounts were added to imputed values, and results were reanalyzed by using analysis of covariance	No statistically or clinically significant differences between the calcium and placebo groups regarding change in body weight (difference, 0.02 kg [95% CI:1.64–1.69 kg]; $p = 0.98$), BMI (difference, 0.32 kg/m^2 [CI:0.41–1.02 kg/m^2 $p = 0.39$), or body fat mass

Author (year)	Study subjects and duration of the intervention	Mean calcium or dairy-food intakes of intervention and control groups	Statistical method and factors controlled for in analyses	Results
Zemel et al. (2004)	32 obese adults, 24 weeks	Balanced 500 kcal/d deficit diets and 400–500 mg dietary calcium/d supplemented with placebo, a high-calcium diet supplemented with 800 mg calcium/d, or a high-dairy diet (1,200–1,300 mg of calcium/d)	Multivariate ANOVA to facilitate evaluation of both the repeated measures and independent group comparisons inherent to this study design	Adults on a standard diet lost 6.4 ± 2.5% of their body weight, those on a high-calcium diet lost 8.6 ± 1.1%, and those on the high-dairy diet lost 10.9 ± 1.6% of body weight Fat loss from the trunk region represented 19.0 ± 7.9% of total fat loss on the low-calcium diet, and 50.1 ± 6.4% and 66.2 ± 3.0%, respectively on the high-calcium and high-dairy diets

This table summarizes randomized controlled trials of the relationship between calcium intake and anthropometric indices according to authors, study subjects, duration of the intervention, mean calcium or dairy food intakes of intervention and control groups, statistical methods, factors controlled for in analyses, and key results
ANOVA analysis of variance; *BMI* body mass index; *kg/m²* kilogram per square meter; *mg/d* milligram per day; *y* year

Table 179.4 Reviews of the relationship between calcium intake and anthropometric indices

Author (year)	Study subjects	Mean calcium or dairy-food intakes of groups	Statistical method and factors controlled for in analyses	Results
Heaney et al. (2002)	564 women; reanalysis of published data from nine studies	In both groups of women, calcium intake was obtained from seven-d diet The calcium contents of the three regimens were not described, but can be estimated to be below 500 mg for the conventional regimen and from 1,500–2,100 mg for the milk-based diets	Comparison of prevalence of overweight by percentile of calcium intakes by odds ratio analysis. Estimates of calcium effect size calculated for a 1,200 mg difference between top and bottom quartiles of calcium intake	A reduction in overweight prevalence in the upper tail area from 25% to 4.2% and an estimated population standard deviation for weight at 18% of the mean. At the 25th percentile of calcium intakes, 15% of young women were overweight, compared to only 4% at calcium intakes at current recommendations. At midlife, women at the 25th percentile of intakes gained weight at an average rate of 0.42 kg/y. This change dropped to a weight loss of 0.011 kg/y at currently recommended calcium intakes
Heaney (2003)	564 women; reanalysis of six observational studies and three controlled trials	Data were reevaluated, focusing on the distribution of values around the regression lines relating calcium intake to BMI in young women and to weight gain at midlife. The calcium contents of the three regimens were not described but can be estimated to be below 500 mg for the conventional regimen and from 1,500–2,100 mg for the milk-based diets	The fraction of the population above any specified value was calculated from the integral of the normal distribution for the respective means and standard deviations. Error terms for these fractions were calculated from the confidence intervals of the slope of the relationship of the dependent variable on calcium intake, at the specifically tested calcium intakes. Regression was done relating dietary calcium:protein ratio to weight gain. Superimposed on this regression line are plots of the normal distribution with means at predicted weight gain for calcium:protein ratios of 9 and 20 mg Ca:g protein, set to the standard error of the estimate for the regression	Consistent effect of higher calcium intakes, expressed as lower body fat and/or body weight, and reduced weight gain at midlife. Predicted BMI at 10 mg Ca:g protein was 22.5, and the probability of having a BMI> 26 was 0.146. This probability drops to 0.04 at 20 mg Ca:g protein, and the relative risk of being overweight at the 25th percentile of calcium intakes, relative to the recommended intake, is thus 3.6. Similarly, the probabilities of being obese are 0.014 and 0.002 for the two calcium intakes, with a relative risk of 6.9 at the 25th percentile of calcium intakes, relative to the recommended intake

Author (year)	Study subjects	Mean calcium or dairy-food intakes of groups	Statistical method and factors controlled for in analyses	Results
Zemel et al. (2000)	NHANES III data set; secondary analysis	A large cross-sectional survey conducted between 1988 and 1994 Calcium intakes not reported per group	Relative risk analysis by quartile group, controlling for energy intake, ethnicity, and activity level. Odds ratios for percent body fat and 95% confidence intervals were estimated by multiple logistic regression analysis with a robust variance estimation method. Point estimates for all parameters were weighted to reflect the population distribution of each; variances were calculated to take the complex sampling design into account. Analyses were done separately for men and women; odds ratios were adjusted for age	After controlling for energy intake and physical activity, relative risk of being in the highest quartile of body fat was set to 1.00 for the lowest quartile of Ca intake and was reduced to 0.75, 0.40, and 0.16 for the second, third, and fourth quartiles of calcium intake for women ($n = 380$; $p < 0.0009$); there was a similar inverse relationship in men ($n = 7{,}114$; $p < 0.0006$)
Barba and Russo (2006)	Prospective studies on adults/ children and randomized controlled trials	Narrative review; calcium intakes not reported per group	Narrative review	A dairy-food-rich diet was associated with lower fat accumulation in most cross-sectional studies. Prospective studies and randomized controlled intervention trials have yielded inconsistent results
Trowman et al. (2006)	Persons >/= 18 y from 13 randomized controlled trials in a meta-analysis	Systematic review and subsequent meta-analysis of randomized controlled trials that used calcium supplementation as an intervention	ANCOVA to provide an estimated treatment effect when differences between the treatment groups at baseline were accounted for. Regression of final mean weights (dependent variable) versus treatment group (independent variable), adjusting for mean baseline weights (covariate), weighted by the sample size of each treatment group	No association between the increased consumption of either calcium supplements or dairy products and weight loss after adjusting for differences in baseline weights between the control and intervention groups ($p = 0.19$ and 0.85, respectively). Calcium supplementation had no statistically significant association with a reduction in body weight

This table summarizes reviews of the relationship between calcium intake and anthropometric indices
ANCOVA analysis of covariance; *Ca* calcium; *d* day; *kg* kilogram; *mg* milligram; *NHANES* National Health and Nutrition Examination Survey; *y* year

weight and reduced weight gain at midlife. Although calcium intake explains only a small fraction of the variability in weight or weight gain, shifting the mean of the distributions downward by increasing calcium intake can be estimated to reduce the prevalence of overweight and obesity by perhaps as much as 60–80% (Heaney 2003), with each 300 mg increment in regular calcium intake associated with approximately 1 kg less body fat in children and 2.5–3.0 kg lower body weight in adults. Taken together, these data suggest that increasing calcium intake by the equivalent of two dairy servings per day could reduce the risk of overweight substantially, perhaps by as much as 70% (Heaney 2003).

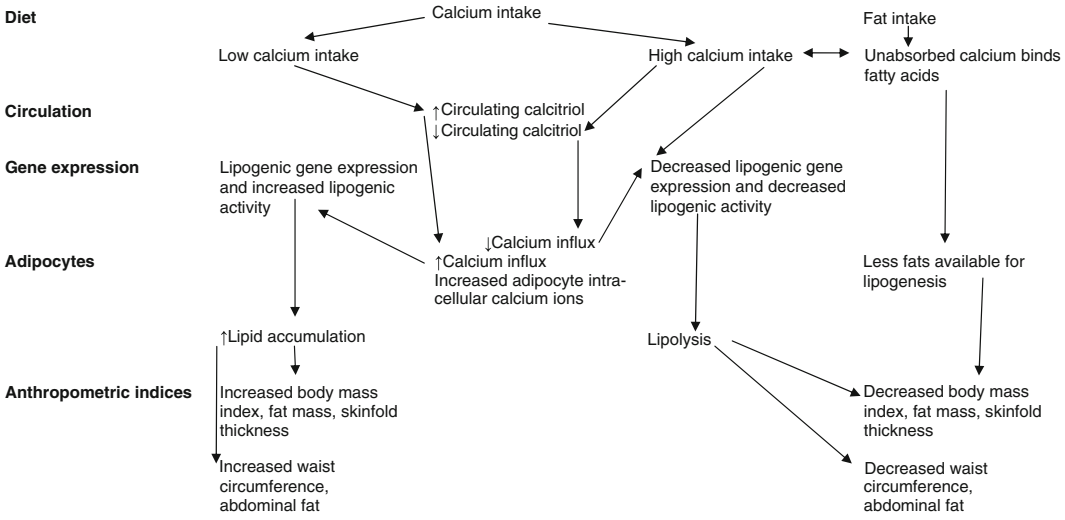
The narrative review states that available data do not unequivocally support the hypothesis of a causal relationship between high-calcium or high-dairy-food intake and lower gain in fat mass (Barba and Russo 2006). A systematic review and subsequent meta-analysis of 13 randomized controlled trials that used calcium supplementation as an intervention in persons older than 18 years found no association between the increased consumption of either calcium supplements or dairy products and weight loss after adjusting for differences in baseline weights between the control and intervention groups ($p = 0.19$ and 0.85, respectively). The authors concluded that calcium supplementation and/or increase intake of dairy foods had no statistically significant association with a reduction in body weight (Trowman et al. 2006).

179.6 Possible Reasons for Inconsistent Results of Studies of the Relationship Between Calcium Intake and Anthropometric Indices

Although many studies indicate an association between calcium intake and anthropometric indices of adiposity, inconsistent results could have been due to methodological problems in the assessment of dietary intake of either calcium or dairy foods. Moreover, multiple factors are involved in the regulation of body weight and skinfold thickness, and it is possible that confounders have not been sufficiently controlled for in the design and analyses of studies reporting either an effect or no effect (Barba and Russo 2006). The lack of relationship between calcium intake and BMI in older women may, for example, be due to differences in hormonal status (Marques-Vidal et al. 2006). Another possibility is that a low calcium intake tends to be a marker for a poor diet and that a poor diet is a good predictor of obesity. There are also indications that a high calcium intake and, especially a high intake of low-fat dairy foods, serve as a marker for a healthy lifestyle, which is associated with lower BMI and fat mass (Barba and Russo 2006).

179.7 Proposed Mechanisms for the Effect of Dietary Calcium Intake on Body Fat

Studies provided plausible explanations for an association between calcium intake as well as dairy foods and body fat, and there are also signs of a dose–response effect. Possible mechanisms for this effect include an inhibiting effect of calcium on fat absorption (Jacobsen et al. 2005). The mechanism by which calcium increases fat excretion is probably an interaction between calcium and fatty acids, resulting in the formation of insoluble calcium fatty acid soaps, and hence in reduced fat absorption. The mechanism for the interaction between fat and calcium is shown in Fig. 179.1. There was a difference between the low-calcium and the high-calcium diet of 1,190 mg/d in fecal calcium excreted. The maximum amount of fat that can be bound to this amount of calcium is about 60 mmol



(Zemel and Miller, 2004; Jacobsen et al 2005)

Fig. 179.1 Possible mechanisms to explain the relationship between calcium intake and anthropometric indices. This figure outlines possible mechanisms to explain the relationship between calcium intake and anthropometric indices. ↑ increase, ↓ decrease (Zemel and Miller 2004; Jacobsen et al. 2005)

Table 179.5 Key features of dietary calcium

Food sources of calcium	Milk, yogurt, cheese, sardines with bones, and tofu
Key roles of calcium in the body	Forms an integral part of bone structure; helps to maintain normal blood pressure and blood clotting
Recommended intakes of calcium (adequate intake, AI) (mg/day)	Infants 0–6 months old: 210, 6–12 months old: 270
	Children 1–3 y: 500, 4–8 y: 800, 9–18 y: 1,300
	Adults 19–50 y and pregnant women: 1,000, 51 + y: 1,200
	Pregnant and lactating girls </= 18 y: 1,300
Factors affecting bioavailability of calcium	Vitamin D and lactose enhance calcium absorption
	Phytates in grains and oxalates in greens inhibit calcium absorption

(Whitney and Rolfes 2008)

This table lists key features of dietary calcium, including food sources of calcium, recommended intakes, and factors affecting bioavailability of calcium
mg milligram; *y* year

fatty acids. Assuming a molecular mass of about 270 g/mol for fatty acids, this corresponds to a maximum increased fat excretion of 16 g/d. Not all calcium would, however, be available for binding fatty acids. The increase in excreted fat of 8.2 g/d found in the study of Jacobsen et al. (2005) could be a realistic loss of fat as calcium fatty acid soaps (Jacobsen et al. 2005).

This difference between effects of calcium intake on body fat and BMI of white women and black South African women could be attributed to the difference in dietary composition between the two groups. In this study, mean total dietary calcium intake was significantly higher in the white women (mean 1,054 mg/d, 95%CI 952, 1,156) than in black women (mean 523, 95%CI 437, 562 mg/d). Mean fat intake in the black women was 69 g/d, compared to 103 g/d in the white women. Thus, the calcium:fat-intake ratio in white women was higher than in black women (11 and 7.7 mg/g, respectively). For a sufficient amount of 8–10 g/d fat to be bound by calcium and excreted, a dietary calcium:fat ratio of 11 mg/g or more may be necessary (Kruger et al. 2007) (Table 179.5).

It has also been hypothesized that high-calcium diets protect against fat gain by creating a balance of lipolysis over lipogenesis in adipocytes. High calcium intake depresses 1,25-dihydroxy vitamin D, leading to decreases in intracellular calcium, thereby inhibiting lipogenesis and stimulating lipolysis (Zemel and Miller 2004). The mechanism for this interaction is shown in Fig. 179.1. The possibility that high-calcium diets promote greater rates of whole-body fat oxidation has also been studied (Jacobsen et al. 2005). In the study of Jacobsen et al. (2005), calcium intake had no effect on 24-h EE. The results of one study suggested that calcium and vitamin D intakes may have opposing effects on body weight, which is difficult to explain, given current knowledge of calcium metabolism (Kamycheva et al. 2003).

179.8 Applications to Other Areas of Health and Disease

A significant negative correlation was found between calcium intake and insulin resistance assessed by HOMA, as well as fasting insulin and insulin area under the curve, which all indicate that lower calcium intakes were associated with higher insulin resistance in white South-African women. Insulin resistance could favor fatty-acid synthesis and, with that, increased percentage body fat. After adjustment for body mass index, dietary calcium intake still correlated significantly negatively with HOMA insulin resistance ($r = -0.3$, $p = 0.02$) and fasting plasma insulin concentration ($r = -0.31$, $p = 0.02$). The association between calcium intake and plasma-insulin concentration seems to be independent of the association between calcium intake and body composition (Kruger et al. 2007). Calcium intake was not only inversely associated with body trunk fat, but also with insulin and HOMA-IR in Brazilian girls. The negative relationship between calcium intake and body fat and insulin resistance, mainly in obese girls, demonstrates the importance of an increased dietary calcium intake (dos Santos et al. 2008).

A negative correlation was found in South-African black women between dietary calcium intake and systolic blood pressure and diastolic blood pressure, respectively (Kruger et al. 2007). High-calcium diets in a study in Denmark also showed a trend to a minor but still important decrease in blood pressure in adults (Jacobsen et al. 2005).

Although there is no absolute proof that calcium-rich diets contribute to lower weight gain, such diets do contribute positively to overall nutrition. Low-fat dairy intake is generally associated with overall better diet quality (Poddar et al. 2009). These findings provide support for programs to promote calcium-rich diets, which are critical for attaining peak bone mass during childhood and adolescence (Lappe et al. 2004; Palacios et al. 2007).

179.9 Practical Guidelines

Low-fat dairy-food supplementation could be a simple public-health approach to prevent excessive weight gain and obesity. Primary-care providers should include recommendations about adequate calcium intake in standard dietary counseling not only for weight management but also for bone health and general optimal health. Calcium from dairy foods should be recommended, rather than calcium supplements, but for those allergic to milk proteins, calcium supplements could be an alternative.

179.10 Applications

Attention should be given to the calcium content of diets of people of all ages, to ensure intakes of at least close to the adequate intake of 1,000 mg/d. Parents should be encouraged to help children develop health-promoting habits that include regular intake of calcium-rich foods, such as skim, 1%, or 2% fat milk, and other low-fat dairy products. Intake of carbonated beverages and other low-nutrient beverages, such as fruit drinks, fruit 'ades', and tea, which could replace milk in the diet, should be restricted.

Summary Points

- Given the high prevalence of obesity globally, along with its significant medical consequences and the relative cost-effectiveness and safety profile of calcium and dairy supplementation, more research may be warranted to determine whether the body weight of overweight adults can be altered by either calcium or low-fat dairy food supplementation.
- Different reasons could explain these findings that consider the evaluation of either the exposure, for example, methodological problems in the assessment of dietary intake of calcium, or the outcome due to multiple factors involved in the regulation of body weight.
- Calcium supplementation seems unlikely to have clinically significant efficacy as a preventive measure against weight gain.
- Available data do not unequivocally support the hypothesis that a causal relationship exists between high-dairy-food intake and/or high-dietary-calcium intake and lower-fat-mass deposition.
- Daily calcium intake and dairy foods for those not allergic to milk proteins should be encouraged to achieve optimal bone strength and general health.

Acknowledgments All work for this review was undertaken as part of the academic work of the author at the North-West University, Potchefstroom campus, South Africa.

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Chapter 180
Dietary Protein Intake and Anthropometric Indices of Muscle Mass in Elderly

Karine Perreault and Isabelle J. Dionne

Abstract The etiology of the loss of muscle mass with aging is not yet fully understood but compelling evidence supports the important contribution of lifestyle in its process. Physical activity and dietary protein intake were identified as efficient means of promoting muscle hypertrophy. One of the most important prerequisite for the accretion of muscle mass is the availability of amino acids, which are ingested through diet under the form of protein. It has been demonstrated that the anabolic response to a mixed-nutrient meal is blunted with aging. However, some interventions can overact this blunted response and allow muscle accumulation. The most important parameters identified to date are the sources of protein ingested and its content in essential amino acids, especially leucine, the amount and distribution of protein intake throughout the day, physical activity as co-intervention, especially resistance training, and the timing of ingestion with resistance training. According to the current knowledge, animal sources of protein are more likely to enhance muscle mass accretion than vegetable source of protein. Among essential amino acids, leucine is a key regulator of protein synthesis. The distribution of a sufficient amount of protein throughout three meals during the day (30 g/meal), as opposed to a large amount in one meal, is preferred. When resistance training and protein intake are combined, the most efficient timing for the ingestion is immediately (or within 2 h) after training. The stimulus of protein intake and physical activity promote protein synthesis and inhibit protein breakdown. In the long term, a positive balance between protein synthesis and breakdown would have significant impact on muscle mass, strength, physical capacity and quality of life.

Abbreviations

EAA	Essential amino acids
NEAA	Non-essential amino acids
RDA	Recommended dietary allowance

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_180,

180.1 Introduction

Skeletal-muscle-fiber atrophy, regardless of the underlying mechanisms, results from the imbalance between muscle-protein synthesis and breakdown. Over time, the age-associated bias toward skeletal muscle catabolism leads to a net loss of muscle proteins and to the associated decline in muscle mass and force production. Conversely, protein synthesis, which is dependent upon amino-acid availability, is the process that needs to be stimulated in order to promote muscle-mass gains. Therefore, the study of skeletal-muscle-protein metabolism is a very useful tool to assess the mechanism(s) that are involved in the loss of muscle mass with aging. For the past two decades, research pertaining to mechanisms and strategies aiming at the prevention and treatment of sarcopenia has received increasing attention. This chapter focuses on the potential role of nutrition, especially protein intake, in muscle size in the elderly.

180.2 Changes in Muscle Size with Aging

Cross-sectional area measures taken directly from whole muscles obtained post mortem showed an average reduction of 40% between 20 and 80 years of age. The average loss of muscle mass has been estimated to range between 3% and 8% per decade after the age of 30, and this rate of decline is even higher after the age of 60. Lean-muscle mass generally contributes up to ~50% of total body weight in young adults but declines with aging to 25% by the age of 75–80 years. The loss of muscle mass is typically concurrent with gains in fat mass (Fig. 180.1).

Several conditions are known to influence muscle size in older adults. Among those, cachexia represents the loss of muscle mass that is the result of a chronic inflammation state. Sarcopenia, however, is the loss of muscle mass and strength that occurs with aging and does not require the presence of an underlying illness. Finally, anorexia is also observed in older adults and leads to significant losses in muscle mass as well as in fat mass, resulting in an overall decrease in body weight. The prevalence of sarcopenia is approximately 13–24% for individuals younger than 70 years and up to 60% in individuals over 80 years of age. The number of individuals who fulfilled the definition of cachexia is about 20% of the total population (Tan et al. 2008), while anorexia is prevalent in about one-third of the population of older men and women (Thomas 2009). Most of the time, however, it is difficult to determine what condition exactly prevails, and it is possible that one individuals falls within more than one category. Regardless of the underlying condition, treatment will likely be to increase energy and protein intakes and to perform regular resistance training.

While cachexia may not be associated with changes in dietary intakes, sarcopenia is largely believed to occur following an inadequate protein intake. Anorexia is defined as an exaggerated restriction in energy intake, including proteins. Inadequate protein intakes fail to stimulate protein synthesis. Since sufficient amino acids need to be available at rest and following resistance exercise, a low intake would thus fail to provide the essential material needed to synthesize proteins and, in turn, muscle tissue. Because muscle mass is a dynamic tissue, synthesis needs to equal breakdown for muscle size to remain constant. If the proper amount of ‘building blocks’ is not provided, breakdown will surpass synthesis and, if protracted over time, muscle will decrease in size.

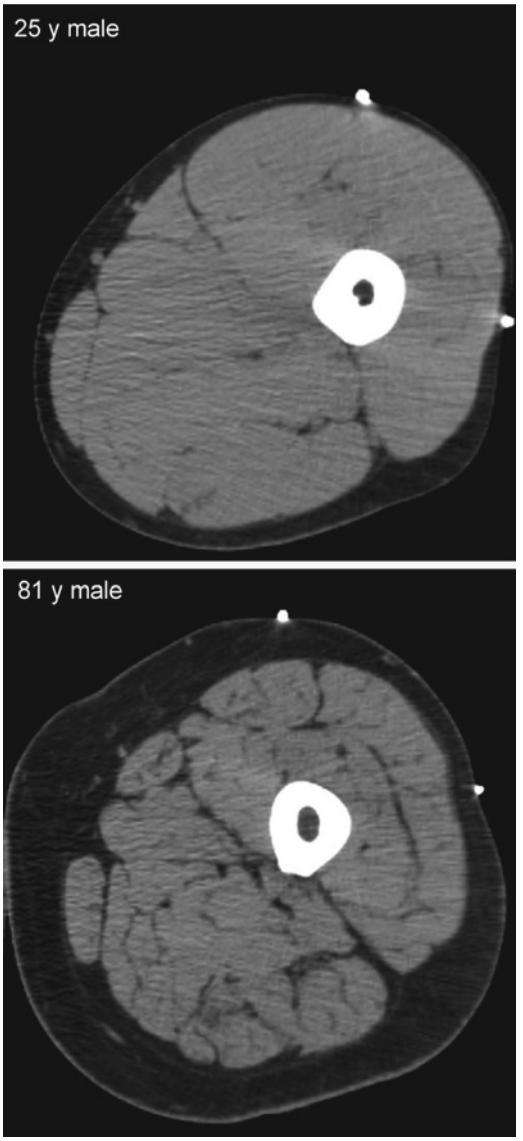

Fig. 180.1 Computed tomography (CT) scan of the upper leg (mid-thigh level) in a young and an old subject, matched for body mass and height. Computed tomography (CT) scan of the upper leg (mid-thigh level) in a young and an old subject, matched for body mass and height. Note the reduced muscle area, increased subcutaneous fat, and increased fat and connective-tissue infiltration into the muscle in the elderly subject (Source: Koopman and van Loon 2009)

180.3 Dietary Proteins

180.3.1 Protein Requirements in Aging

The adequacy of the recommended dietary allowance (RDA) for protein has been the subject of renewed debate in recent years. The current recommendation for protein intake for all men and women aged 19 years and older is 0.8 g/kg/day. It was established by the Institute of Medicine and based on short-duration nitrogen-balance studies in young adults. Much of the recent commentary has argued that the current RDA for protein, while fulfilling the criteria as the "minimal daily average dietary intake level that meets the nutritional requirements of nearly all healthy individuals," does not promote optimal health or protect elders from sarcopenic muscle loss. Although there is no

consensus on the degree to which dietary protein needs change with advancing age, there is general agreement that additional longer-term trials with defined health outcomes are needed to firmly establish the optimal protein intake range for various population groups. Nevertheless, experts agree that nitrogen balance may not be the best indicator of protein requirements in older adults and, for this reason, many studies suggest to increase the RDA to 1.0–1.3 g of protein/kg/day, especially in terms of maintaining muscle mass, strength, and metabolic function in aging populations or of 0.9 g/kg/day when combined with resistance training. That being said, there is actually no specific nutritional recommendations for protein intake in elderly individuals.

180.3.2 Essential and Non-essential Amino Acids

Each protein has its own specific number and sequence of amino acids. Amino acids can be classified as either essential or non-essential. Non-essential amino acids can be produced in the body from other proteins or carbohydrates. Essential amino acids, however, cannot be produced during metabolism by the body and therefore must be provided by the diet. Eight amino acids (leucine, isoleucine, valine, threonine, methionine, phenylalanine, tryptophan, and lysine) are considered essential for adults, while nine (those mentioned above plus histidine) are considered essential in specific conditions, including for children. Others (cystine, tyrosine, valine, arginine, alanine, aspartic acid, glutamic acid, glycine, proline, and serine) are considered non-essential.

Essential amino acids (EAAs), in particular, are able to stimulate muscle-protein synthesis in the elderly, whereas non-EAAs do not appear to provide such an effect. Among the EAAs, leucine has been shown to be a key regulator of muscle-protein synthesis in both humans and rats.

180.3.3 Biological Value

When a protein contains the essential amino acids in a proportion similar to that required by humans, it is considered to have a high biological value. When one or more essential amino acids are scarce, the protein is said to have low biological value. The amino acid that is in shortest supply in relation to need is termed the ‘limiting amino acid’. The limiting amino acid tends to be different in different proteins hence, when two foods providing vegetable protein are eaten at a meal, such as a cereal (e.g., bread) and a pulse (e.g., baked beans), the amino acids of one protein may compensate for the limitations of the other, resulting in a combination of higher biological value. High-biological-value proteins are provided by animal sources of protein, such as meat, poultry, fish, eggs, milk, cheese, and yogurt. Low-biological-value proteins are found in plants, legumes, grains, nuts, seeds, and vegetables.

180.3.4 Leucine

Leucine is an insulin secretagog with well-described effects on translation initiation and muscle-protein synthesis. With increasing age, muscle may become resistant to the stimulatory effects of normal postprandial concentrations of leucine. Although such a deficit could contribute to reduced muscle-protein anabolism and a loss of muscle mass, recent acute studies in both animals and humans suggest that the addition of supplemental leucine to normal mixed-nutrient meals may improve or normalize muscle-protein synthesis in aging muscle. In a follow-up study in older humans, the addition of leucine to a mixed-nutrient meal also resulted in a significant increase in muscle-protein synthesis.

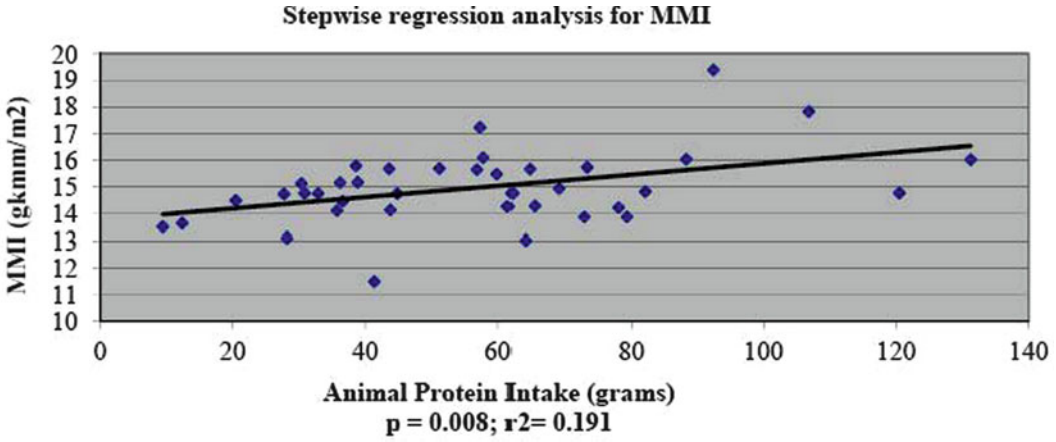

Fig. 180.2 Linear regression analysis between animal protein and muscle mass index (MMI). Individuals who consume more animal protein have a greater muscle mass index (MMI) than individuals displaying a lower animal-protein intake (Source: Lord et al. 2007)

180.3.5 Animal Versus Vegetable Proteins

Animal proteins contain all of the EAAs in appropriate ratios. Beef is a common source of dietary protein and contains all EAAs in a proportion similar to that found in human skeletal muscle. A standard serving of 113.4 g (4 oz) lean beef contains sufficient amino acids (~10 g EAAs) to increase mixed-muscle-protein synthesis by ~50% in both young and elderly men and women. Other foods, such as tuna fish, cheddar and cottage cheese, low-fat milk, and soy products, also contain significant amounts of EAAs (2–10 g of EAAs per portion; Canadian Nutrient File).

In addition to consuming inadequate amounts of total dietary protein, older adults may be at risk of consuming inadequate amounts of animal protein, a source of high-biological-value protein, because of age-associated factors including costs, difficulty in chewing, fear of consuming too much fat or cholesterol, and perceived intolerance of certain foods. Over a 3-year follow-up among older, community-dwelling adults, it was found that dietary-protein intake was associated with changes in lean mass and appendicular lean mass. Participants in the highest quintile of energy-adjusted protein intake lost ~40% less lean mass and appendicular lean mass than did those in the lowest quintile. Further, within a cohort of 2,732 participants, significant associations between animal-protein intake and changes in lean mass were found, but no such association was highlighted with vegetable protein. In a cohort of 12 elderly women, protein breakdown in the absorptive state was inhibited to a lesser extent in the high-vegetable-protein diet versus the high-animal-protein diet, resulting in less net protein synthesis during the high-vegetable-protein diet than during the high-animal-protein diet. In the same line, we observed that animal-protein intake was the only independent predictor of muscle mass in a group of 38 elderly women (Fig. 180.2). Hence, we and others showed a close relationship between animal-protein intake and lean mass but no such association with vegetable proteins. We also found that individuals with a high animal-protein diet displayed greater increases in muscle mass than those on a low animal-protein diet during resistance training (preliminary findings, to be published). The source of protein ingested thus seems to have an important role to play in the maintenance of muscle mass in older adults.

As far as we acknowledge, few studies have compared the effect of protein sources on muscle size of older adults. Further, no recent initiative has combined both nutritional and exercise intervention, despite the fact that these approaches benefit from a growing scientific support.

180.3.6 Mistaken Beliefs About Protein-Rich Food and CVD

The greatest obstacle to adequate consumption of dietary protein is the common belief that eating foods that contain cholesterol is a major factor in coronary heart disease; in fact, dietary risk factors for heart disease change with advancing age. Dietary cholesterol and other dietary fats become less of a factor in heart-disease risk than in young and middle ages, with cholesterol levels diminishing as people get older. Other risk factors become more highly correlated to coronary heart disease in later years, with systolic hypertension becoming a more reliable indicator of potential future coronary events. Diabetes tends to be a factor that contributes to the risk of a future heart attack. The combination of diabetes and systolic hypertension increases the likelihood that heart disease may contribute to premature death. The importance of dietary protein cannot be underestimated in the diets of older adults; inadequate protein intake contributes to a decrease in reserve capacity, increased skin fragility, decreased immune function, poor healing, and longer time to recuperation from illness.

180.3.7 Digestion Impairments

The presence of impairments in dietary protein digestion and/or amino-acid absorption might also be (partly) responsible for a blunted muscle-protein synthetic response to amino-acid/protein ingestion in the elderly. It has been proposed that the digestion rate of protein is an independent regulating factor of postprandial protein anabolism. Impaired protein digestion and/or absorption might attenuate and/or reduce the appearance rate of dietary amino acids in the circulation, thereby lowering the postprandial muscle-protein synthetic rate. Furthermore, amino-acid uptake in the splanchnic area has been shown to be elevated in the elderly, which implies that less of the ingested amino acids are available for muscle-protein synthesis.

Several recent studies showed that ingestion of a slowly digested protein (casein) leads to a more positive protein balance compared with the ingestion of a quickly digestible protein (whey) or a mixture of free amino acids in healthy, young subjects. However, in the elderly, the postprandial protein-anabolic response was observed to be the opposite. Ingestion of a fast protein (whey) was shown to result in greater net protein retention compared with a slow protein (casein), when provided in healthy, elderly men. The latter might be attributed to the proposed anabolic resistance of the muscle-protein synthetic machinery to become activated in elderly muscle (Table 180.1).

180.4 Nutritional Interventions Using Proteins and Muscle Mass

Several studies demonstrated that increased amino-acid- or protein availability can enhance muscle-protein synthesis and anabolism in young and older subjects. Based on these, it has been widely suggested that older adults should consume more proteins. Nevertheless, the use of high-protein diets alone (without exercise) to increase muscle mass and strength in the elderly has been mostly ineffective.

In agreement, studies utilizing a balanced meal consisting of protein, fat, and carbohydrate demonstrated no or few benefits from mixed nutritional supplements in older adults. Thus, when proteins are mixed with other nutrients, such as glucose and fat, it does not seem to lead to increases in muscle size. Consequently, the hypothesis that the muscle's ability to adapt to feeding may be impaired in aging under certain circumstances was raised. This blunted anabolic response is now believed to represent one of the key factors responsible for the age-related decline in skeletal muscle mass.

Table 180.1 Key facts about dietary proteins

The assembly of new proteins requires a source of amino acids. These 'building blocks' are generated by the digestion of proteins and their degradation within the cell.
Many cellular proteins are constantly degraded and resynthesized.
The main amino-acid reservoir in the body is skeletal muscle, which contains 50–75% of all proteins in the human body.
When muscle-protein synthesis is greater than muscle-protein degradation, the positive balance generates muscle gain. Inversely, a negative balance generates muscle loss.
The current recommended dietary allowance (RDA) for protein (0.8 g/kg/day) may not be sufficient in terms of preventing the loss of muscle mass with aging.
The non-essential amino acids (NEAA) represent the category of amino acids that can be synthesized in the body.
The essential amino acids (EAAs) are the amino acids that cannot be synthesized in the body and therefore must be provided by the diet.
The essential amino acids (EAAs) have been associated with a greater accretion of muscle mass in older adults.
Among the EAAs, leucine has been shown to be a key regulator of muscle tissue.
High-biological-value proteins are provided by animal sources of protein (meat, milk products, etc.), while low-biological-value proteins are provided by vegetable sources of protein (beans, soy products, etc.).
Animal sources of proteins represent a stronger predictor of muscle-mass gains than vegetable sources of proteins.
The importance of dietary protein cannot be underestimated in the diets of older adults, and it is important to promote proper information about protein-rich foods, cholesterol, and coronary heart diseases.
The digestion impairments often observed in older adults may cause a reduced rate of amino acids in the circulation and therefore may lower the amount of 'building blocks' available for muscle accretion.

This table lists the basic facts about dietary proteins related to amino acids, recommended dietary allowance, animal and vegetable sources of proteins, and the impact of digestion impairments

180.4.1 Meal Replacement

There are a number of reasons why these nutritional interventions may have failed to produce positive results. First, energy-dense supplements may act as a meal replacement, especially in elders, resulting in little or no change in daily protein intake and thus negate any anabolic effects associated with protein supplementation.

180.5 Nature and Amount of Protein Intake

Acknowledging that advancing in age is likely to induce a blunted anabolic response to the stimulus of protein ingestion, the optimal nature and amount of protein ingested both become of great interest.

180.5.1 Dose

Muscle-protein synthesis appears to respond in a dose-dependent manner to essential-amino-acid consumption. It was demonstrated that a dose of essential amino acids of approximately 10 g maximally stimulates rates of both myofibrillar and sarcoplasmic protein synthesis at rest. It was also found that 20 g of proteins (or approximately 8.5 g of essential amino acids) also maximally stimulates myofibrillar protein synthesis after resistance exercise, with minimal increases in amino-acid oxidation.

180.5.2 Potential Adverse Effects of High Protein Intake

Recommendations of protein intakes greater than the current RDAs, however, should be weighed against any potential increase in the risk of toxicity or impaired renal function. Although there is no official definition of what should be considered a *high-protein diet* (over 2.0 g of protein/kg/day has been suggested), a number of negative consequences have been associated with increased protein intake, most notably bone loss and renal impairment.

Because excess amino acids are deaminated and excreted by the kidney as urea, some view high-protein diets as "stressful" to the kidneys. In a recent review, it was concluded that there are no clear renal-related contraindications to high-protein diets in those with healthy renal function, but high-protein diets are contraindicated in those with renal impairment. It might be prudent to screen for proteinuria to rule out renal impairment in older individuals before they embark on diets more than double the RDA.

Still, the aging kidney appears to have a reduced capacity to excrete acid. Because bone acts as a buffer via bone resorption, the possible adverse consequences of the acid load from dietary protein is of particular concern in terms of bone health in older individuals. Recent studies have examined the association between dietary protein and skeletal health in elderly men and women. Some found a positive correlation between protein and bone mass density, while others found that higher protein intake was associated with increased fracture rates in the elderly.

Hence, proteins also interact with other nutrients to influence bone health. Adequate calcium is necessary to promote bone health with increased protein. When phosphorus intake increases with protein intake, calcium balance is preserved. Phosphorus intake generally increases with protein intake because many high-protein foods are also good sources of phosphorus. In addition, increased calcium excretion that might occur with high protein intakes might be attenuated with the consumption of alkali buffers, such as fruits and vegetables. It appears that, when taken in the context of a healthy diet (i.e., adequate in calcium and rich in fruits and vegetables), moderately high protein intake from commonly consumed foods is not harmful.

180.5.3 Is Supplementation Needed for Optimal Gain in Muscle Mass in the Elderly Population?

The rationale for the use of a nutritional supplement to slow or prevent sarcopenic muscle loss is based on the assumption that it will improve net muscle-protein synthesis above that afforded by regular meals alone. In some cases, protein–energy supplementation has been shown to be effective. Other trials, particularly those involving acutely ill or frail patients, have been unsuccessful. In some instances, protein supplementation increases satiety and simply replaces voluntary ingestion of regular menu items. For others, cost, availability, or medical complications, such as dysphagia or impaired kidney function, may limit the applicability or efficacy of protein-supplementation regimens. In such cases, maximizing protein anabolism while minimizing the amount or volume of supplementation ingested would be desirable.

180.5.4 A More Practical Approach: Protein-Rich Foods at Each Meal

It may not be appropriate to recommend the use of amino-acid supplements in older adults, and it is thus believed that the use of protein-rich food has several advantages over supplementation for

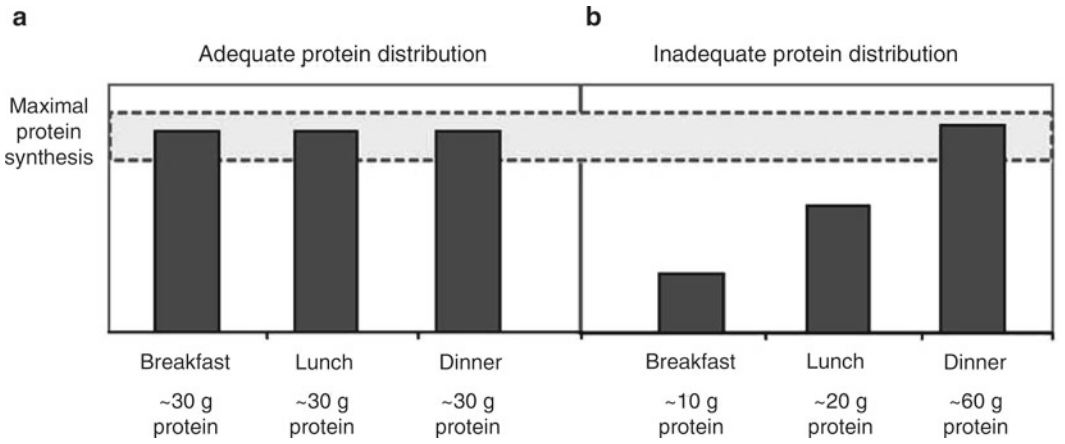

Fig. 180.3 A pictorial example of the proposed relationship between the amount of protein ingested per meal and the resultant anabolic response. (**a**) Ingestion of 90 g of protein, distributed evenly over three meals. (**b**) Ingestion of 90 g of protein unevenly distributed throughout the day. Stimulating muscle-protein synthesis to a maximal extent during the meals shown in Fig. 180.1a is more likely to provide a greater 24-h protein anabolic response than an unequal protein distribution (Source: Paddon-Jones and Rasmussen 2009)

several reasons: they are readily accessible, relatively inexpensive, palatable, and are not susceptible to engender secondary effects, such as an alteration in blood lipids and kidney problems, as supplements do.

As mentioned, numerous studies support the notion that ingestion of a sufficient amount of amino acids or protein results in similar benefits for muscle mass in young and elderly. However, several recent studies have adopted a more practical approach and have sought to examine the ability of protein-rich foods (e.g., milk) to stimulate muscle mass.

In the following sections, we argue that, whereas a modest increase in protein intake beyond 0.8 g/kg/day may indeed be beneficial for some elders, there is a greater need to specifically examine the dose and distribution of protein across each meal.

Although specialized supplementation with amino-acid products may be beneficial or necessary in specific elderly or clinical populations, the most practical means to favor muscle hypertrophy for the majority of older adults is to include a moderate serving of protein of high biological value during each meal. In fact, the distribution of proteins across three or more daily meals is highly important. For a 75-kg individual, the RDA represents 60 g of proteins/day, or if distributed evenly across three meals, 20 g of proteins/meal. A 20-g serving of most animal- or plant-based proteins contains 5–8 g of essential amino acids, which are the building material of muscles.

On the other hand, it was recently demonstrated that ingestion of a large, single 340-g serving of lean beef (90 g protein) in a cohort of healthy young and elderly individuals does not elicit a greater response than a serving one-third the size. Although this response may be influenced by physical activity (habitual and acute) and body size (it may be easier to increase muscle mass when it is initially low), the data suggest that, despite the additional protein and energy content, ingestion of more than 30 g of protein in a single meal may be useless. If we accept that 25–30 g of high-quality protein (~10 g EAA) is necessary to maximally stimulate skeletal-muscle protein synthesis, then it seems reasonable to suggest that ingesting this amount of high-quality protein at each meal could be a useful strategy to maintain muscle mass in the elderly (Fig. 180.3).

180.6 Exercise and Muscle-Protein Synthesis

Resistance-exercise- or strength training involves a relatively small number of muscle contractions against a heavy load. It has been shown that this type of exercise acutely increases whole-body insulin sensitivity, which can partly be attributed to a reduction in muscle-glycogen stores. However, the most apparent adaptation to resistance training is the increase in muscle mass and strength, or muscle hypertrophy.

The primary determinant of skeletal-muscle hypertrophy following resistance training is the external load that is applied. Several animal models have shown that loading results in an increased muscle mass and protein content per muscle. Increased loading amplifies muscle-protein synthesis and breakdown (protein synthesis is amplified by a greater extent than protein breakdown) and this training-induced elevation in muscle-protein turnover leads to a more rapid protein remodeling and, therefore, allows a faster adaptive response.

It generally takes weeks to months before these physical changes become apparent. The prolonged time course for hypertrophy is a reflection of a slow turnover rate of muscle protein – about 1% per day for contractile proteins. Muscle hypertrophy can only occur when muscle-protein synthesis is exceeding protein breakdown for a prolonged period of time.

Similar to feeding, the primary variable affected by resistance exercise is muscle-protein synthesis, which is stimulated 40–100% over and above resting levels with exercise. Although muscle-protein breakdown also rises with resistance exercise in the fasted state, the provision of amino acids or carbohydrate completely inhibits this response. A single session of resistance training accelerates the muscle-protein synthesis rate within 2–4 h. Accelerated protein-synthesis rates have been reported to last for 24–48 h. It could then be suggested that an appropriate frequency of exercise sessions would allow 1 day of rest between two training sessions.

180.7 Synergetic Use of Dietary Protein and Resistance Exercise

The synergetic effects of protein supplementation and resistance exercise on muscle mass and function in aging populations is unclear. Some authors showed that total daily protein intake does not influence muscle-mass gains when combined with resistance exercise. Despite numerous studies addressing the need for protein and/or carbohydrate ingestion before, during, and/or after exercise to allow net muscle-protein accretion, there is remarkably little evidence that dietary combined interventions can further augment the adaptive response to prolonged exercise training in the elderly. For example, dietary intervention using supplementation with carbohydrate, protein and fat, protein or branched chain amino acids (BCAAs), or by including changes in meal protein content have failed to promote muscle hypertrophy in response to exercise training.

When habitual dietary protein intake is standardized at 0.9 g/kg/day, exercise-induced increases in muscle mass become apparent, and a further increase in protein intake does not seem to have any additional effect. The latter might explain why most studies fail to observe any additional benefit of nutritional combined intervention on the skeletal-muscle adaptive response to prolonged resistance-type exercise training in the elderly.

However, both exercise and nutrition are required to obtain a positive protein balance and, as such, allow muscle hypertrophy. Although a single bout of resistance-type exercise stimulates muscle-protein synthesis to a greater extent than protein degradation, net muscle-protein balance remains negative in the absence of nutrient intake. Likewise, it appears that diet-derived amino acids

act as a prerequisite for muscle-protein synthesis. As mentioned in a recent review, the most important anabolic stimulus for muscle proteins is nutrient intake because it allows for replacement of the essential amino acids (EAAs) lost through oxidation. Carbohydrate and/or protein/amino-acid ingestion during recovery from exercise forms an effective strategy to stimulate muscle-protein synthesis, inhibit protein degradation, and, as such, to enable net muscle-protein accretion. Such an effect has been demonstrated both with the consumption of crystalline amino acids as well as whole proteins.

The absence of any benefits of nutritional combined intervention may also be attributed to a less-than-optimal timing of amino acid and/or protein supplementation that was applied (which should be immediately after each bout of resistance-type exercise, as opposed to before, during, or 2 h later).

180.7.1 The Timing of Protein Intake and Resistance Exercise

We know that, for resistance exercise to result in a positive net balance, feeding needs to occur sometime within the few hours following exercise. In fact, several studies suggest that provision of protein within the acute period following exercise may be quite important for hypertrophy. Most evidence indicates that the period immediately post exercise (or at least within approximately 2 h) produces a muscle environment that favors augmented protein synthesis over and above that provided by amino acids/protein alone. Although some controversy remains, chronic studies support this notion showing that individuals receiving protein in the post-exercise period gain greater lean mass compared with those receiving nothing or simply energy as carbohydrate, even in older adults. Recent evidence suggests that the type (i.e., source) of protein consumed may as well affect the anabolic response to resistance exercise.

180.7.2 Sources of Protein and Resistance Exercise

Differences in lean-mass gains with resistance training have also been observed when comparing other apparently complete and high-quality protein sources, such as whey and soy. Ingestion of milk, whey, casein, and soy following resistance exercise has been reported to stimulate muscle-protein synthesis when consumed either in isolation or in liquid supplements. It appears from a series of studies that not all 'high-quality' proteins are equal in how they are digested and how this variable affects protein retention. On examining the findings of these studies collectively, the results appear to indicate that milk proteins are superior to soy in supporting muscle-mass accretion with resistance training and that both are superior to carbohydrate (i.e., energy) alone (Fig. 180.4). It was hypothesized that these findings resulted because of minor differences in amino-acid composition and possibly protein-digestion rate. Such an effect could be because of the difference in energy content or how whole milk might be digested differently as versus fat-free milk. Data demonstrating how milk and soy proteins are partitioned for use between splanchnic and peripheral (i.e., muscle) tissues have shown that soy proteins are preferentially directed toward splanchnic-protein synthesis and are converted to urea to a greater extent than milk proteins.

Resistance exercise appears to augment the effect of whey protein in supporting lean-mass gains when compared to either casein or milk. In addition to digestion rate, the mechanism by which whey more effectively promotes protein gain than casein in the elderly may also be related to the slightly higher leucine content of whey, especially if the 'leucine trigger' has a higher set-point for older individuals. It was also speculated that the ability of whey to stimulate protein synthesis by either suppressing inflammation or possibly activation of satellite cells in aged muscle may also be important (Table 180.2).

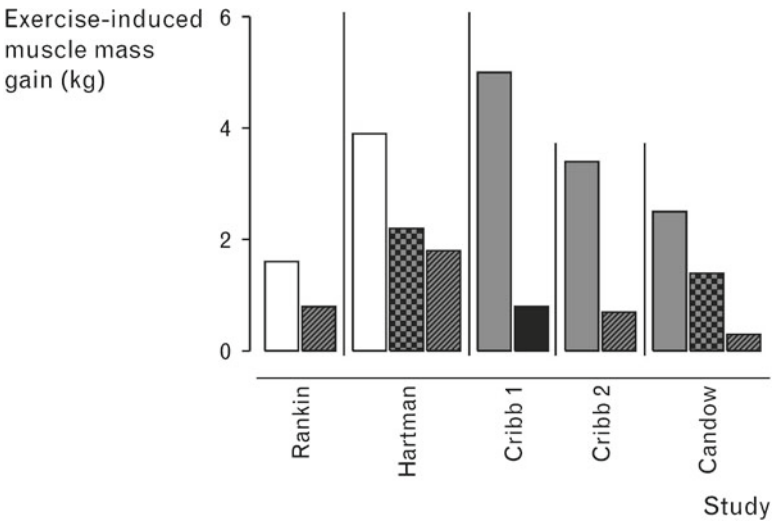

Fig. 180.4 Resistance training-induced changes in lean mass in studies of patients receiving supplemental protein sources – soy, whey, or casein, or an energy-matched carbohydrate drink. Values are presented as the absolute exercise-induced mean gain (±SD) in lean mass. The studies included are those of Rankin et al. (2004), Hartman et al. (2007), Cribb et al. (2006, 2007), and Candow et al. (2006) (Source: Tang and Phillips 2009)

Table 180.2 Key points of dietary protein with and without exercise to promote muscle hypertrophy in older adults

The muscle-protein synthetic response to the ingestion of a mixed-nutrient meal is attenuated in the elderly, and this represents one of the key factors responsible for the age-related decline in skeletal-muscle mass.
Protein supplementation may act as meal replacement, resulting in little or no change in daily protein intake.
Some potential adverse effects have been identified with high protein intake (over 2.0 g of protein/kg/day), most notably bone loss and renal impairment.
A novel dietary approach to prevent or slow down muscle loss suggests ingesting a sufficient amount of protein divided over a maximum of three meals per day. That represents ~25–30 g of high quality proteins (~10 g EAA) per meal.
Physical activity, in particular resistance-type exercise, is a powerful stimulus to promote net muscle-protein anabolism, resulting in specific metabolic and morphological adaptations in skeletal-muscle tissue.
Resistance-type exercise training can effectively increase muscle strength, muscle mass, and, as such, improve physical performance and functional capacity in the elderly.
Resistance training can promote muscle hypertrophy in older adults but amino acids/protein ingestion is still required to produce an anabolic effect.
The available data suggest that certain amount of amino acids/proteins should be ingested (0.9 g/kg/day) when combined with resistance training and that any additional intake would not produce further improvements.
Ingesting proteins within 2 h after resistance exercise has been identified as the best timing to maximizing post-exercise anabolism.
Several studies have indicated that high-quality proteins, such as milk, whey, casein, and soy, can support muscle-protein synthesis.
Differences in the rate of digestion of these high-quality proteins can modulate the muscle-protein synthesis response both after an acute bout of resistance exercise and following long-term training.

This table summarizes the main elements related to dietary protein intake and exercise to promote muscle hypertrophy in older adults

180.8 Conclusion

Aging is associated with a reduced ability to muscle hypertrophy in response to feeding. Among the conditions to this response, sources and amounts of proteins are particularly important. To promote optimal health or protect elders from muscle loss, it might be necessary to increase the current RDA up to 1.0 g/kg/day. A novel dietary approach to favor muscle mass is to ingest a sufficient amount of protein divided over a maximum of three meals per day. Resistance-type exercise is also a powerful stimulus to promote morphological adaptations in skeletal-muscle tissue. Such exercise training can effectively increase muscle strength and muscle mass, and, as such, improve physical performance and functional capacity. Altogether, the available data suggest that a certain amount of amino acids/proteins should be ingested (0.9 g/kg/day was suggested) when combined with resistance training and that any additional intake would not produce further improvements. Sufficient habitual protein intake combined with a normal meal pattern (i.e., providing ample protein three times per day) will allow substantial gains in muscle mass and strength following resistance-type exercise training in the elderly.

180.9 Applications to Other Areas of Health and Disease

180.9.1 Physical Capacity

Because muscle mass and strength are major predictors of physical capacity in older individuals, their evolution will greatly determine the trajectory of physical independence. In that sense, lifelong adequate consumption of proteins is an important component of physical dependency and quality of life.

180.9.2 Insulin Sensitivity

Although adding carbohydrate to an amino-acid meal (as in a normal mixed-nutrient meal) enhances muscle-protein synthesis in young subjects, no such results were found in older subjects. This is potentially due to insulin resistance of muscle-protein metabolism in aging, independent of glucose tolerance. This occurs possibly through an exercise-reversible reduced vasodilatory response of older human muscle to insulin, thus decreasing nutrient flow and availability. On the other hand, resistance exercise increases insulin sensitivity and improving this physiological function has been associated with an improved anabolic response of muscle proteins to insulin in older subjects. Therefore, it is possible that combining exercise with EAA would maximize its anabolic effect and then create substantial gains in muscle mass compared with exercise alone.

180.9.3 Frailty

Frailty is the sum of several conditions, including muscle weakness and/or sarcopenia. The functional benefits of resistance exercise training in a large-scale trial of 72–98-year-old physically frail nursing-home residents showed that lower-extremity resistance exercise training increased muscle

strength (113%), gait velocity (12%), stair-climbing power (28%), level of spontaneous physical activity, and thigh-muscle cross-sectional area (2.7%). In addition to physical dependence, frailty unfortunately leads to institutionalization. Again, adequate consumption of proteins over life can significantly retard institutionalization.

Summary Points

- The loss of muscle mass is typically observed with aging and is concurrent with gains in fat mass.
- Essential amino acids (EAAs), in particular, are able to stimulate muscle-protein synthesis in the elderly, whereas non-EAAs do not appear to provide such effects.
- Among the EAAs, leucine has been shown to be a key regulator of muscle-protein synthesis.
- Some studies have reported protein supplementation as an ineffective method of enhancing muscle-protein synthesis. The most reported reasons to explain that are the meal replacement theory, the blunted anabolic response to a mixed-nutrient meal, and the mistaken beliefs about protein-rich food and CVD.
- A dose of EAAs of approximately 10 g maximally stimulates rates of protein synthesis at rest.
- The current RDA for protein (0.8 g/kg/day) might not be sufficient in terms of promoting optimal health or protecting elders from sarcopenic muscle loss. Some authors have proposed that protein requirements for older individuals may be either greater than 1.0 g/kg/day or of 0.9 g/kg/day when combined with resistance training.
- A novel dietary approach to prevent or slow down muscle loss suggested ingesting a sufficient amount of protein with each meal (as opposed to a large amount of protein in one meal or in supplementation).
- There are compelling evidences supporting the efficacy of physical activity, especially resistance training, to counter the loss of muscle mass with aging.
- Resistance exercise performed in the absence of an increase in amino-acid availability improves net muscle-protein balance, but there remains a net loss of muscle protein.
- When resistance exercise is accompanied by an increased availability of amino acids, the result is a synergistic stimulation of protein synthesis and muscle accretion occurs.

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Chapter 181
Anthropometry and the Prevalence of Child Protein–Energy Malnutrition in China and Japan

Liubai Li, Hui Li, and Hiroshi Ushijima

Abstract Protein–energy malnutrition (PEM) remains the top leading cause of death in children in the world. Stunting, underweight, and wasting are common indicators for estimating the prevalence of PEM. Anthropometrical indices (length/height-for-age, weight-for-age and weight-for-length/height) and BMI (body mass index)-for-age of children (0–18) are prerequisites for malnutrition screening. This chapter presents PEM relating anthropometrical indices (in *Z*-scores and percentiles) and cut-offs for PEM in Chinese and Japanese children. Most data were based on national data sets, and the cut-offs for PEM were recommended by the academic associations in the two countries.

Prevalence of stunting, wasting, and underweight in 2002 was 14.3%, 2.5%, and 7.8%, respectively, in Chinese children under 5 years old as estimated by the *Z*-score criterion recommended by the World Health Organization (WHO) in 1978. For children and adolescents aged 7–17 years, the prevalence of stunting and wasting was estimated as 2.7% and 10.5% in urban boys and 3.0% and 9.7% in urban girls in rural areas, the prevalence was 7.4% and 14.6% in boys, and 7.7% and 11.5% in girls, as estimated by the new WHO criterion (2006). Although the nutritional status in Chinese children has improved remarkably in the past two decades, it still remains a problem – especially in the rural areas of Western China. In Japan, the prevalence of thinness in boys and girls has been very low (under 4%) in the past three decades as estimated by the percentage of standard weight-for-height (POW).

Abbreviations

2002 CHNS	The 2002 China National Health and Nutrition Survey
BMI	Body mass index
PEM	Protein–energy malnutrition
POW	Percentage of standard weight-for-height
SD	Standard deviation
WHO	World Health Organization

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_181,

181.1 Introduction

Protein–energy malnutrition (PEM) in children is a serious public-health problem that has been linked to a substantial increase in the risk of mortality and morbidity. It remains the leading cause of death in children in the world (WHO 2008) and was associated with 54% of child deaths (10.8 million children) in developing countries in 2001. (WHO 2004) In 2004, an estimated 32% of children aged less than 5 years were stunted and 20% were wasted (WHO 2008).

Stunting, underweight, and wasting are common indicators for estimating the prevalence of PEM. To assess the level of malnutrition, a child's height (or length) and weight anthropometric parameters are measured and compared with an internationally accepted reference standard (WHO 2006) or a national standard.

In this article, we report the prevalence of PEM in Chinese and Japanese children and present the anthropometric indicators and the relating cutoffs for malnutrition identification.

181.2 International Definition of Child PEM

Box 181.1 shows the internationally accepted definitions and the meaning of the indices for child PEM.

Box 181.1 Child PEM Screening Criterion

There are three primary anthropometric indices for child PEM screening: stunting, wasting, and underweight.
Stunting: Height-for-age below -2 standard deviation (SD) or -2 *Z*-score of the reference;
Underweight: Weight-for-age below -2 SD of the reference; and
Wasting: Weight-for-height below -2 SD of the reference.

Each indicator signals distinct biological processes.

Stunting reflects a failure to reach linear growth potential as a result of suboptimal health and/or nutritional conditions; *wasting* describes recent and significant weight loss, usually as a consequence of famine or severe disease; and *underweight*, or low weight-for-age, reflects both wasting and stunting and is thus a synthesis of the current status of body proportion and linear growth (De Onis et al. 1993; WHO 1995).

Body Mass Index (BMI), expressed as body weight (kg) divided by the square of height (m) (weight (kg)/height $[m]^2$), is also used in malnutrition definition for children in some age groups (WHO 2006). For adolescents, the WHO recommends using BMI-for-age as the criterion in defining PEM. The diagnostic criterion for defining *stunting in adolescents* is either a height-for-age less than the third percentile of the WHO reference data or less than -2 *Z*-score.

Undernutrition or thinness in adolescence is indicated by a BMI less than the fifth percentile of the reference data (WHO 1995).

181.3 Protein–Energy Malnutrition in China

181.3.1 Prevalence of Child PEM in China

The 2002 China National Health and Nutrition Survey (2002 CHNS) report analyzed the prevalence of PEM in Chinese children aged under 5 years using the WHO-recommended *Z*-score criteria (De Onis 1996). A data set of 15,851 urban and rural children aged less than 5 years was used. Figure 181.1 displays the rate of PEM in 2002 and 1992 (Wang 2005). Dramatic improvements occurred between 1992 and 2002. In 2005, nutrition-tracking survey data sets for 15,987 children aged under 5 years (50.4% were boys, 10,468 were rural children) were analyzed using the 2006 WHO child-growth standards (WHO 2006). Prevalence of stunting and underweight were 16.3% and 6.1%, respectively (Yuying 2007).

In China, there were significant differences in malnutrition prevalences between the urban and rural areas, with the rural area having higher malnutrition rates. In 2002, the prevalence of malnutrition among children under 5 years in the six-class economic areas was estimated by using the 2002 CHNS data sets and the reference recommended by WHO (De Onis 1996) (Fig. 181.2). Prevalence of malnutrition was different in the six areas, with big cities demonstrating the lowest (stunting was

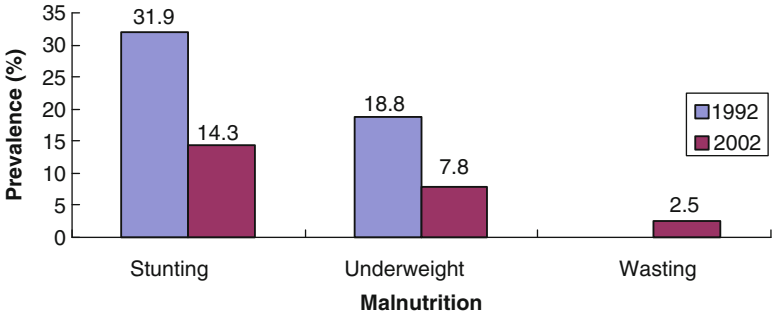

Fig. 181.1 Prevalence of malnutrition in Chinese children aged less than 5 years between 1992 and 2002. Prevalence of stunting and underweight in children aged less than 5 years decreased remarkably between 1992 and 2002 (Wang 2005)

Fig. 181.2 Prevalence of malnutrition in Chinese children aged less than 5 years in the six-class areas in 2002. The prevalence of malnutrition was higher in rural areas than that in urban areas, with the poorest area having the highest rate of malnutrition. Sample sizes were 3,279 in big cities, 3,747 in middle and small cities, 2,001 in Rural I, 2,177 in Rural II, 2,119 in Rural III, and 2,528 in Rural IV (Data source: Zhihong 2007)

Fig. 181.3 Prevalence of malnutrition in urban Chinese children aged 7–17 years between 1985 and 2005. The prevalence of malnutrition decreased remarkably from 1985 to 2005, but wasting still remained very high in 2005. The sample sizes were 204,727 in 1985 and 116,720 in 2005 (Cheng-ye 2008)

Fig. 181.4 Prevalence of malnutrition in rural Chinese children aged 7–17 years between 1985 and 2005. The prevalence of malnutrition decreased remarkably from 1985 but wasting still remained very high in 2005. The sample sizes were 205,219 in 1985 and 116,423 in 2005 (Cheng-ye 2009)

1.6%) and the rural IV (29.3%) the highest (Zhihong 2007). The stunting status of children under 5 years in 50 counties of Midwestern China (poorer areas) was 30.2% in 2005, as evaluated using the 2006 WHO Child Growth Standards (Wen-yuan 2008).

For schoolchildren, the prevalence of PEM in urban and rural areas was also evaluated using national data sets on student health survey and the new WHO criterion (WHO 2006). Stunting and wasting were screened by using height-for-age and BMI-for-age cutoffs, respectively. The results are shown in Figs. 181.3 and 181.4. Despite significant improvements in nutrition status during the recent 20 years, wasting was still a health problem in Chinese urban and rural students, with that in boys being relatively higher than in girls and in adolescents than in children (Cheng-ye 2008, 2009).

Socioeconomic developments in the recent two to three decades in China have improved the nutritional status in Chinese children. The overall prevalence of PEM decreased remarkably. However, nutrition and health inequity remain due to differences in natural conditions, economic developments, and family socioeconomic status. Rural children have a far higher rate of malnutrition than urban children, with the highest rate in Western China.

181.3.2 Anthropometry of Chinese Children and the Criterion for Undernutrition Identification

There are two ways to express how far an individual's nutritional status deviates from the reference population. It is expressed either as a percentage of the reference value, or as a *Z*-score. Tables 181.1–181.4 display *Z*-scores and percentiles of some anthropometric index (length/height-for-age, weight-for-age, and weight-for-length/height) references in Chinese children aged under 7 years. The data sets were constructed from well-nourished, healthy, urban children (healthy reference

Table 181.1 Length/height-for-age (cm) for Chinese children aged under 7 years (Data source: Ministry of Health of China et al. (2009). With permission)

	Length/height (cm)								
	Z-scores				Percentiles (cm)				
Age(years/months)	-3 SD	-2 SD	-1 SD	Median	3rd	5th	25th	50th	75th
Boys									
0 month	45.2	46.9	48.6	50.4	47.1	47.5	49.2	50.4	51.6
3 months	55.3	57.5	59.7	62.0	57.7	58.3	60.4	62.0	63.5
6 months	61.4	63.7	66.0	68.4	64.0	64.5	66.8	68.4	70.0
9 months	65.2	67.6	70.1	72.6	67.9	68.5	70.9	72.6	74.4
12 months	68.6	71.2	73.8	76.5	71.5	72.1	74.7	76.5	78.4
15 months	71.2	74.0	76.9	79.8	74.4	75.1	77.8	79.8	81.8
18 months	73.6	76.6	79.6	82.7	76.9	77.6	80.6	82.7	84.8
21 months	76.0	79.1	82.3	85.6	79.5	80.3	83.4	85.6	87.9
2.0 years	78.3	81.6	85.1	88.5	82.1	82.9	86.2	88.5	90.9
2.5 years	82.4	85.9	89.6	93.3	86.4	87.2	90.8	93.3	95.9
3.0 years	85.6	89.3	93.0	96.8	89.7	90.6	94.2	96.8	99.4
3.5 years	89.3	93.0	96.7	100.6	93.4	94.3	98.0	100.6	103.2
4.0 years	92.5	96.3	100.2	104.1	96.7	97.6	101.4	104.1	106.9
4.5 years	95.6	99.5	103.6	107.7	100.0	100.9	104.9	107.7	110.5
5.0 years	98.7	102.8	107.0	111.3	103.3	104.3	108.4	111.3	111.3
5.5 years	101.6	105.9	110.2	114.7	106.4	107.4	111.7	114.7	117.7
6.0 years	104.1	108.6	113.1	117.7	109.1	110.2	114.6	117.7	120.9
6.5 years	106.5	111.1	115.8	120.7	111.7	112.8	117.4	120.7	123.9
Girls									
0 month	44.7	46.4	48.0	49.7	46.6	46.9	48.6	49.7	50.9
3 months	54.2	56.3	58.4	60.6	56.5	57.0	59.1	60.6	62.1
6 months	60.1	62.3	64.5	66.8	62.5	63.1	65.2	66.8	68.4
9 months	63.7	66.1	68.5	71.0	66.4	67.0	69.3	71.0	72.8
12 months	67.2	69.7	72.3	75.0	70.0	70.6	73.2	75.0	76.8
15 months	70.2	72.9	75.6	78.5	73.2	73.9	76.6	78.5	80.4
18 months	72.8	75.6	78.5	81.5	76.0	76.7	79.5	81.5	81.5
21 months	75.1	78.1	81.2	84.4	78.5	79.2	82.3	84.4	86.6
2.0 years	77.3	80.5	83.8	87.2	80.9	81.7	84.9	87.2	89.6
2.5 years	81.4	84.8	88.4	92.1	85.2	86.1	89.6	92.1	94.6
3.0 years	84.7	88.2	91.8	95.6	88.6	89.5	93.1	95.6	98.2
3.5 years	88.4	91.9	95.6	99.4	92.4	93.2	96.8	99.4	102.0
4.0 years	91.7	95.4	99.2	103.1	95.8	96.7	100.4	103.1	105.7
4.5 years	94.8	98.7	102.7	106.7	99.2	100.1	104.0	106.7	109.5
5.0 years	97.8	101.8	106.0	110.2	102.3	103.3	107.3	110.2	113.1
5.5 years	100.7	104.9	109.2	113.5	105.4	106.4	110.6	113.5	116.5
6.0 years	103.2	107.6	112.0	116.6	108.1	109.1	113.5	116.6	119.7
6.5 years	105.5	110.1	114.7	119.4	110.6	111.7	116.2	119.4	122.7

Note: Length in children aged under 3 years and height in children aged over 3 years

Table 181.2 Weight-for-age (kg) for Chinese children aged under 7 years (Data source: Ministry of Health of China et al. (2009). With permission)

	Weight (kg)								
	Z-scores				Percentiles (%)				
Age (years/months)	-3 SD	-2 SD	-1 SD	Median	3rd	5th	25th	50th	75th
Boys									
0 month	2.26	2.58	2.93	3.32	2.62	2.70	3.06	3.32	3.59
3 months	4.69	5.29	5.97	6.70	5.37	5.53	6.20	6.70	7.24
6 months	5.97	6.70	7.51	8.41	6.80	6.98	7.80	8.41	9.07
9 months	6.67	7.46	8.35	9.33	7.56	7.77	8.66	9.33	10.06
12 months	7.21	8.06	9.00	10.05	8.16	8.38	9.33	10.05	10.83
15 months	7.68	8.57	9.57	10.68	8.68	8.91	9.91	10.68	11.51
18 months	8.13	9.07	10.12	11.29	9.19	9.43	10.48	11.29	12.16
21 months	8.61	9.59	10.69	11.93	9.71	9.97	11.08	11.93	12.86
2.0 years	9.06	10.09	11.24	12.54	10.22	10.48	11.65	12.54	13.51
2.5 years	9.86	10.97	12.22	13.64	11.11	11.40	12.66	13.64	14.70
3.0 years	10.61	11.79	13.13	14.65	11.94	12.25	13.61	14.65	15.80
3.5 years	11.31	12.57	14.00	15.63	12.73	13.05	14.51	15.63	16.86
4.0 years	12.01	13.35	14.88	16.64	13.52	13.87	15.43	16.64	17.98
4.5 years	12.74	14.18	15.84	17.75	14.37	14.75	16.43	17.75	19.22
5.0 years	13.50	15.06	16.87	18.98	15.26	15.67	17.52	18.98	20.61
5.5 years	14.18	15.87	17.85	20.18	16.09	16.54	18.56	20.18	21.98
6.0 years	14.74	16.56	18.71	21.26	16.80	17.28	19.49	21.26	23.26
6.5 years	15.30	17.27	19.62	22.45	17.53	18.06	20.49	22.45	24.70
Girls									
0 month	2.26	2.54	2.85	3.21	2.57	2.64	2.96	3.21	3.49
3 months	4.40	4.90	5.47	6.13	4.96	5.09	5.68	6.13	6.62
6 months	5.64	6.26	6.96	7.77	6.34	6.50	7.21	7.77	8.37
9 months	6.34	7.03	7.81	8.69	7.11	7.29	8.08	8.69	9.36
12 months	6.87	7.61	8.45	9.40	7.70	7.90	8.74	9.40	10.12
15 months	7.34	8.12	9.01	10.02	8.22	8.42	9.33	10.02	10.79
18 months	7.79	8.63	9.57	10.65	8.73	8.95	9.91	10.65	11.46
21 months	8.26	9.15	10.15	11.30	9.26	9.49	10.51	11.30	12.17
2.0 years	8.70	9.64	10.70	11.92	9.76	10.00	11.08	11.92	12.84
2.5 years	9.48	10.52	11.70	13.05	10.65	10.92	12.12	13.05	14.07
3.0 years	10.23	11.36	12.65	14.13	11.50	11.80	13.11	14.13	15.25
3.5 years	10.95	12.16	13.55	15.16	12.32	12.63	14.05	15.16	16.38
4.0 years	11.62	12.93	14.44	16.17	13.10	13.44	14.97	16.17	17.50
4.5 years	12.30	13.71	15.33	17.22	13.89	14.26	15.92	17.22	18.66
5.0 years	12.93	14.44	16.20	18.26	14.64	15.04	16.84	18.26	19.83
5.5 years	13.54	15.18	17.09	19.33	15.39	15.82	17.78	19.33	21.06
6.0 years	14.11	15.87	17.94	20.37	16.10	16.57	18.68	20.37	22.27
6.5 years	14.66	16.55	18.78	21.44	16.80	17.30	19.60	21.44	23.51

population with both of the prevalence of malnutrition and overweight less than 5%) in nine Chinese cities in 2005 (Ministry of Health of China 2009).

Tables 181.5–181.7 display the mean (SD) and percentiles of height-for-age, weight-for-age, and BMI-for-age in Chinese children and adolescents aged over 6 years. The data sets were based on the anthropometric measurements in Han ethnic students of Beijing in The National Physical Fitness and Health Status Survey of Chinese Students in 2000. A weight-for-height criterion has long been used in PEM identification for Chinese schoolchildren aged over 6 years in China. However, it is

Table 181.3 Weight-for-length for Chinese children aged under 7 years (45–105 cm) (kg) (used in 0–3 year-old children) (Data source: Ministry of Health of China et al. (2009). With permission)

Length (cm)	Weight (kg)								
	Z-scores				Percentiles				
	-3 SD	-2 SD	-1 SD	Median	3rd	5th	25th	50th	75th
Boys									
45	1.64	1.81	2.00	2.20	1.83	1.88	2.06	2.20	2.53
48	2.11	2.34	2.58	2.84	2.36	2.42	2.66	2.84	3.02
51	2.59	2.86	3.15	3.47	2.89	2.96	3.25	3.47	3.70
54	3.19	3.51	3.87	4.25	3.55	3.64	3.99	4.25	4.53
57	3.89	4.27	4.69	5.15	4.32	4.42	4.84	5.15	5.49
60	4.61	5.05	5.53	6.06	5.10	5.22	5.70	6.06	6.45
63	5.32	5.81	6.35	6.94	5.87	5.99	6.53	6.94	7.38
66	5.97	6.50	7.09	7.74	6.57	6.71	7.30	7.74	8.23
69	6.57	7.14	7.76	8.46	7.21	7.35	7.98	8.46	8.98
72	7.12	7.72	8.38	9.12	7.79	7.94	8.61	9.12	9.66
75	7.64	8.25	8.94	9.72	8.33	8.49	9.19	9.72	10.29
78	8.14	8.78	9.50	10.31	8.87	9.03	9.75	10.31	10.91
81	8.67	9.33	10.07	10.91	9.41	9.58	10.33	10.91	11.54
84	9.21	9.90	10.66	11.53	9.98	10.16	10.94	11.53	12.18
87	9.77	10.48	11.27	12.17	10.57	10.75	11.55	12.17	12.85
90	10.34	11.08	11.90	12.83	11.17	11.36	12.19	12.83	13.53
93	10.94	11.69	12.54	13.51	11.79	11.98	12.85	13.51	14.24
96	11.56	12.34	13.22	14.23	12.44	12.64	13.54	14.23	14.99
99	12.21	13.03	13.95	15.00	13.13	13.34	14.27	15.00	15.80
102	12.89	13.75	14.72	15.83	13.86	14.08	15.06	15.83	16.68
105	13.59	14.49	15.52	16.71	14.60	14.84	15.89	16.71	17.63
Girls									
45	1.74	1.91	2.11	2.33	1.94	1.98	2.18	2.33	2.49
48	2.19	2.40	2.64	2.91	2.43	2.48	2.72	2.91	3.11
51	2.65	2.91	3.19	3.51	2.94	3.00	3.29	3.51	3.74
54	3.26	3.56	3.89	4.27	3.59	3.67	4.01	4.27	4.55
57	3.91	4.26	4.65	5.09	4.30	4.39	4.79	5.09	5.42
60	4.59	4.99	5.43	5.93	5.04	5.14	5.59	5.93	6.30
63	5.27	5.71	6.20	6.75	5.77	5.88	6.37	6.75	7.16
66	5.89	6.37	6.91	7.51	6.43	6.55	7.09	7.51	7.95
69	6.46	6.97	7.55	8.19	7.04	7.17	7.75	8.19	8.67
72	6.98	7.52	8.13	8.82	7.59	7.73	8.35	8.82	9.33
75	7.46	8.03	8.67	9.39	8.10	8.25	8.90	9.39	9.93
78	7.93	8.53	9.20	9.95	8.61	8.76	9.44	9.95	10.52
81	8.43	9.05	9.75	10.54	9.13	9.29	10.00	10.54	11.13
84	8.95	9.60	10.33	11.16	9.68	9.85	10.59	11.16	11.78
87	9.48	10.17	10.94	11.80	10.26	10.43	11.21	11.80	12.45
90	10.06	10.78	11.58	12.50	10.87	11.05	11.87	12.50	13.18
93	10.67	11.42	12.27	13.24	11.52	11.71	12.57	13.24	13.96
96	11.30	12.10	12.99	14.02	12.20	12.40	13.31	14.02	14.79
99	11.94	12.78	13.74	14.82	12.89	13.11	14.07	14.82	15.64
102	12.58	13.47	14.48	15.64	13.58	13.81	14.84	15.64	16.52
105	13.21	14.16	15.24	16.48	14.28	14.53	15.62	16.48	17.43

gradually being replaced by BMI percentiles because of obsolete data sets (measured in 1985) and the significant differences with other PEM defining criteria (Department of Exercises, Health and Art Education, Ministry of Education 2003).

Table 181.4 Weight-for-height for Chinese children aged under 7 years (65–125 cm) (kg) (Data source: Ministry of Health of China et al. (2009). With permission)

	Weight-for-height (kg)								
	Z-scores				Percentiles (kg)				
Height (cm)	-3 SD	-2 SD	-1 SD	Median	3rd	5th	25th	50th	75th
Boys									
65	5.91	6.44	7.02	7.67	6.50	6.64	7.22	7.67	8.15
68	6.52	7.08	7.70	8.40	7.15	7.29	7.92	8.40	8.91
71	7.07	7.66	8.32	9.05	7.74	7.89	8.55	9.05	9.60
74	7.59	8.20	8.89	9.66	8.28	8.44	9.13	9.66	10.23
77	8.09	8.73	9.44	10.25	8.81	8.97	9.70	10.25	10.85
80	8.61	9.27	10.02	10.85	9.36	9.53	10.28	10.85	11.47
83	9.15	9.84	10.60	11.47	9.92	10.10	10.88	11.47	12.12
86	9.71	10.42	11.21	12.11	10.51	10.69	11.49	12.11	12.78
89	10.29	11.01	11.84	12.77	11.11	11.29	12.13	12.77	13.46
92	10.88	11.63	12.48	13.44	11.73	11.92	12.78	13.44	14.17
95	11.49	12.27	13.15	14.15	12.37	12.57	13.46	14.15	14.91
98	12.15	12.95	13.87	14.92	13.06	13.27	14.20	14.92	15.72
101	12.82	13.67	14.64	15.75	13.78	14.00	14.98	15.75	16.59
104	13.52	14.41	15.44	16.62	14.53	14.76	15.80	16.62	17.53
107	14.21	15.16	16.26	17.54	15.28	15.53	16.65	17.54	18.53
110	14.90	15.92	17.11	18.50	16.06	16.33	17.54	18.50	19.59
113	15.61	16.72	18.01	19.54	16.86	17.15	18.48	19.54	20.75
116	16.33	17.54	18.95	20.66	17.69	18.01	19.47	20.66	22.01
119	17.08	18.40	19.96	21.87	18.57	18.92	20.54	21.87	23.41
122	17.87	19.31	21.05	23.19	19.50	19.89	21.69	23.19	24.95
125	18.69	20.28	22.21	24.64	20.49	20.92	22.94	24.64	26.66
Girls									
65	5.83	6.31	6.84	7.43	6.37	6.49	7.02	7.43	7.88
68	6.41	6.92	7.48	8.12	6.98	7.11	7.68	8.12	8.60
71	6.93	7.47	8.08	8.76	7.54	7.68	8.29	8.76	9.26
74	7.41	7.98	8.62	9.33	8.05	8.20	8.84	9.33	9.87
77	7.89	8.48	9.15	9.90	8.56	8.71	9.38	9.90	10.46
80	8.38	9.00	9.70	10.48	9.08	9.24	9.94	10.48	11.07
83	8.89	9.54	10.27	11.10	9.63	9.79	10.53	11.10	11.71
86	9.43	10.11	10.87	11.74	10.20	10.37	11.14	11.74	12.38
89	10.00	10.71	11.52	12.42	10.80	10.99	11.80	12.42	13.11
92	10.60	11.36	12.20	13.16	11.45	11.64	12.50	13.16	13.88
95	11.24	12.03	12.92	13.94	12.13	12.33	13.24	13.94	14.70
98	11.88	12.71	13.66	14.74	12.82	13.04	14.00	14.74	15.56
101	12.52	13.40	14.41	15.56	13.51	13.74	14.76	15.56	16.43
104	13.15	14.09	15.16	16.39	14.21	14.45	15.54	16.39	17.34
107	13.79	14.79	15.94	17.27	14.92	15.18	16.35	17.27	18.29
110	14.45	15.51	16.74	18.18	15.65	15.93	17.19	18.18	19.29
113	15.13	16.27	17.60	19.15	16.42	16.72	18.08	19.15	20.37
116	15.84	17.07	18.50	20.20	17.23	17.55	19.02	20.20	21.54
119	16.59	17.91	19.46	21.32	18.08	18.43	20.03	21.32	22.79
122	17.39	18.80	20.49	22.52	18.99	19.37	21.10	22.52	24.15
125	18.22	19.74	21.57	23.79	19.94	20.35	22.24	23.79	25.60

Table 181.5 Height-for-age (cm) for Chinese children aged 6–17 years

		Height (cm)						
				Percentiles				
Age (years)	n	Mean	SD	3rd	5th	25th	50th	75th
Boys								
6	216	121.5	5.1	112.3	113.0	117.8	121.8	125.1
7	227	126.5	5.1	117.8	118.6	123.2	126.4	129.8
8	210	131.7	5.3	121.4	124.2	128.0	131.2	136.0
9	214	136.4	5.7	126.3	127.7	132.7	136.1	139.6
10	200	141.4	5.5	131.1	132.1	138.1	141.5	144.5
11	210	146.9	6.7	135.6	136.5	142.4	146.5	151.0
12	204	155.4	8.6	139.7	140.5	149.1	155.3	161.6
13	204	162.2	6.6	148.3	150.5	158.0	162.7	166.4
14	207	168.1	6.1	156.1	157.9	164.1	168.4	172.1
15	210	170.2	6.5	158.1	160.3	165.9	170.0	174.6
16	188	172.1	6.4	158.8	160.6	168.0	172.1	176.7
17	156	173.2	6.3	160.7	163.3	168.1	173.4	177.6
Girls								
6	206	120.1	5.0	110.4	112.1	116.4	120.2	123.4
7	248	125.5	5.2	115.1	116.9	122.4	125.3	129.2
8	198	131.6	5.1	122.1	122.7	128.0	131.1	135.1
9	214	136.3	5.8	126.1	127.6	132.1	136.0	139.9
10	202	142.3	6.9	131.1	131.8	137.2	142.0	146.0
11	200	148.6	6.3	138.0	139.4	144.3	148.0	152.9
12	211	154.8	6.4	141.1	142.7	151.3	155.0	159.1
13	207	158.1	5.4	147.7	149.1	154.3	158.0	161.7
14	208	160.6	5.3	151.1	152.6	157.1	160.4	164.0
15	199	160.3	5.0	151.4	152.3	156.7	160.1	163.7
16	203	160.9	4.8	151.7	153.0	158.0	160.7	164.0
17	156	160.9	5.6	149.8	151.8	157.4	160.7	165.0

Data were from samples of Beijing children in 2000

Table 181.6 Weight-for-age (kg) for Chinese children aged 6–17 years

		Weight (kg)						
				Percentiles (%)				
Age (years)	*n*	Mean	SD	3rd	5th	25th	50th	75th
Boys								
6	216	23.2	4.4	17.7	18.0	20.5	22.5	24.5
7	227	25.8	5.1	19.1	19.7	22.3	24.5	28.1
8	210	28.5	5.3	21.6	22.1	24.5	27.5	31.2
9	214	31.8	6.9	23.5	24.5	26.6	30.4	34.6
10	200	34.0	6.4	25.3	26.3	29.8	32.9	36.9
11	210	39.2	8.6	27.7	28.7	32.7	37.0	44.7
12	204	45.9	11.1	30.7	31.6	37.6	43.7	51.5
13	204	51.1	10.9	35.1	36.8	43.9	49.9	56.2
14	207	57.3	11.5	40.3	42.9	49.5	54.5	63.8
15	210	58.7	10.3	41.6	43.0	52.0	57.3	63.9
16	188	62.3	11.0	47.3	48.8	54.0	60.7	67.8
17	156	64.0	10.2	45.3	47.5	56.7	63.1	71.3

(continued)

Table 181.6 (continued)

		Weight (kg)						
				Percentiles (%)				
Age (years)	*n*	Mean	SD	3rd	5th	25th	50th	75th
Girls								
6	206	21.8	3.1	17.1	17.6	19.5	21.4	23.5
7	248	24.3	4.8	17.6	18.5	21.2	23.5	26.7
8	198	27.4	4.6	20.4	21.6	24.2	26.5	29.7
9	214	30.1	5.9	20.9	22.0	26.4	29.2	32.7
10	202	34.6	7.8	23.5	24.9	29.2	33.0	38.5
11	200	38.4	7.0	27.2	28.7	32.8	37.9	43.2
12	211	44.4	8.9	29.9	32.5	38.1	42.8	48.8
13	207	47.7	8.9	34.6	35.8	41.9	45.7	51.4
14	208	50.4	8.0	38.4	40.5	45.0	49.4	53.5
15	199	51.5	7.4	40.3	41.8	46.0	49.8	55.6
16	203	53.3	7.8	41.0	42.8	47.6	51.8	58.3
17	156	53.2	7.2	42.0	42.8	48.3	52.1	57.4

Data were from samples of Beijing children in 2000

Table 181.7 Mean (SD) and percentiles of BMI (kg/m^2) for Chinese children aged 6–17 years

		BMI (kg/m^2)						
				Percentiles (%)				
Age (years)	n	Mean	SD	3rd	5th	25th	50th	75th
Boys								
6	216	15.7	2.3	13.4	13.5	14.3	15.1	16.3
7	227	16.0	2.3	13.2	13.5	14.4	15.4	17.0
8	210	16.4	2.2	13.5	13.6	14.8	15.7	17.6
9	214	16.9	2.6	13.5	13.8	15.2	16.3	17.9
10	200	16.9	2.4	13.7	13.9	15.3	16.6	17.9
11	210	18.0	2.9	14.3	14.6	15.8	17.3	19.6
12	204	18.8	3.4	14.4	15.0	16.3	18.1	20.7
13	204	19.3	3.3	15.1	15.5	17.3	18.5	20.9
14	207	20.2	3.5	15.2	15.7	17.8	19.4	21.8
15	210	20.2	3.2	16.0	16.3	18.0	19.4	21.8
16	188	21.0	3.3	16.5	17.0	18.7	20.4	22.5
17	156	21.3	3.1	16.2	16.7	19.1	20.8	23.3
Girls								
6	206	15.1	1.5	12.8	13.0	14.2	14.8	15.8
7	248	15.3	2.2	12.6	13.0	13.9	15.0	16.3
8	198	15.8	2.1	13.0	13.3	14.3	15.4	16.5
9	214	16.1	2.4	12.8	13.1	14.5	15.7	17.3
10	202	16.9	2.7	13.4	13.5	15.0	16.4	18.4
11	200	17.3	2.4	13.7	13.9	15.3	17.0	18.8
12	211	18.4	3.0	14.2	14.5	16.3	18.0	19.9
13	207	19.1	3.2	14.8	15.3	16.8	18.3	20.3
14	208	19.5	2.8	15.7	16.0	17.6	19.0	20.7
15	199	20.0	2.8	16.1	16.3	18.0	19.5	21.8
16	203	20.6	2.7	16.0	16.7	18.7	20.2	22.1
17	156	20.6	2.6	16.1	16.7	18.7	20.4	22.1

Data were from samples of Beijing children in 2000

181.4 Protein–Energy Malnutrition in Japanese Children

181.4.1 Prevalence of Malnutrition

Malnutrition in Japanese children has long been kept very low (less than 4%) since 1980. For children and adolescents aged over 5 years, the prevalence of PEM (thinness) in 2008 was estimated using the data sets of the annual school health check. It was less than 4% in all children (Fig. 181.5). Thinness in children was defined as body weight less than 20% of the standard weight-for-height (criterion for Japanese). Secular trends in thinness have also been below 4% since 1980 (School health statistics 2008).

181.4.2 Risk Factors of Child Malnutrition in Japan

Although there are many reasons for the thinness of Japanese children, voluntary dieting cannot be excluded from the reasons for the malnutrition of adolescent Japanese girls. In general, more Japanese adolescents diet for weight management and control. In addition, fad foods and an unhealthy eating pattern might have contributed to the thinness of Japanese children and adolescents.

181.4.3 Defining Criterion of PEM for Japanese Children

For defining malnutrition in childhood, the percentage overweight (POW), or percentage of standard weight-for-height, has been adopted as a parameter in screening malnutrition in all children. POW is based on the differences between the measured weight and the age- and sex-specific standard weight-for-height (Please see calculation in Box 181.2). The undernutrition/thinness is defined as *POW < 20%* for Japanese children of all ages (School health statistics 2008).

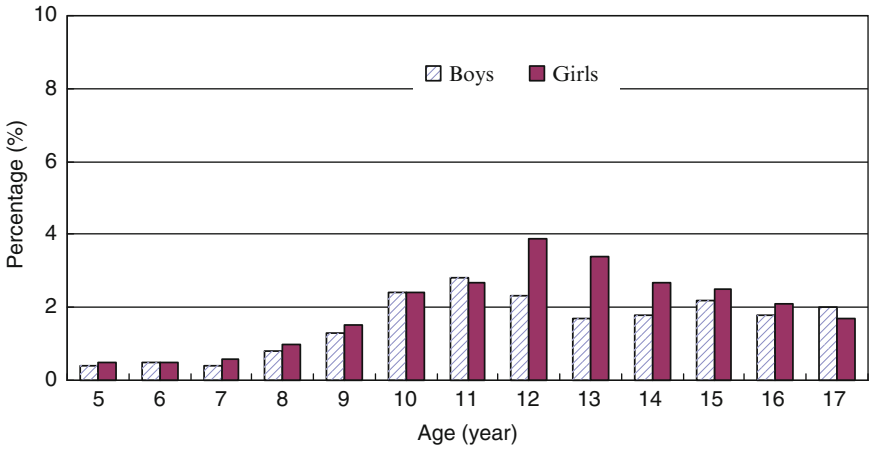

Fig. 181.5 Prevalence of thinness in Japanese children aged 5–17 years in 2008. Prevalence of thinness was less than 4% in Japanese children aged 5–17 years in 2008 (School health statistics 2008)

Box 181.2 Calculation for POW (%OW)

$$\text{Percentage overweight}\left(\text{POW},\%\text{OW}\right)=100\cdot\ (\text{measured weight}-\text{standard weight for height})\ /\ \text{standard weight for height}$$

Standard weight-for-height can be calculated by either using the following formula or searching from the website of the Japanese government (School health statistics 2008)

$$\text{Standard weight - for - height}\left(\text{kg}\right)=a\cdot\ \text{measured height}\ \left(\text{cm}\right)-b$$

The constants '*a*' and '*b*' are coefficients for calculating the *standard weight-for-height (kg)*. The values of '*a*' and '*b*' for children of a specific age and gender can be searched from the website of the Japanese government (School health statistics 2008).

181.4.4 Anthropometry of Japanese Children

The websites of the Japanese government display the percentiles for the length/height-for-age and the weight-for-age for Japanese children and the standard weight-for-height (Department of Maternal and Child Health 2000; School health statistics 2008).

Tables 181.8 and 181.9 display the mean (SD) and percentiles of BMI for Japanese children aged two to 18 years (Inokuchi1 2007).

Table 181.8 Mean (SD) and percentile references of BMI for Japanese boys aged 2–18 years (BMI in kg/m^2) (Data source: Inokuchi1 et al. (2007). With permission)

	Mean (SD) (BMI in kg/m^2)				Percentiles (BMI in kg/m^2)				
Age (years)	-2.5 SD	-2 SD	-1 SD	Mean	3rd	5th	25th	50th	75th
2	13.8	14.3	15.3	16.5	14.4	14.6	15.7	16.5	17.3
3	13.6	14.0	14.9	16.0	14.1	14.3	15.3	16.0	16.8
4	13.3	13.7	14.5	15.6	13.8	14.0	14.9	15.6	16.4
5	13.1	13.5	14.3	15.4	13.6	13.8	14.6	15.4	16.2
6	13.0	13.4	14.2	15.3	13.5	13.7	14.6	15.3	16.2
7	13.0	13.4	14.3	15.4	13.5	13.7	14.6	15.4	16.3
8	13.1	13.5	14.4	15.6	13.6	13.8	14.7	15.6	16.7
9	13.3	13.7	14.7	16.0	13.8	14.0	15.1	16.0	17.2
10	13.5	14.0	15.0	16.5	14.1	14.3	15.5	16.5	17.8
11	13.8	14.3	15.4	17.0	14.4	14.7	15.9	17.0	18.4
12	14.1	14.6	15.9	17.5	14.8	15.0	16.3	17.5	19.0
13	14.6	15.1	16.4	18.1	15.2	15.5	16.9	18.1	19.7
14	15.1	15.6	17.0	18.7	15.8	16.1	17.5	18.7	20.3
15	15.6	16.2	17.6	19.3	16.4	16.7	18.1	19.3	20.9
16	16.2	16.7	18.1	19.9	16.9	17.2	18.6	19.9	21.5
17	16.6	17.2	18.6	20.4	17.3	17.6	19.1	20.4	22.0
18	16.9	17.5	19.0	20.8	17.7	18.0	19.5	20.8	22.4

Table 181.9 Mean (SD) and percentile references of BMI for Japanese girls aged 2–18 years (BMI in kg/m^2) (Data source: Inokuchi1 et al. (2007). With permission)

	Mean (SD) (BMI in kg/m^2)				Percentiles (BMI in kg/m^2)				
Age (years)	-2.5 SD	-2 SD	-1 SD	Mean	3rd	5th	25th	50th	75th
2	13.5	14.0	15.1	16.2	14.1	14.4	15.4	16.2	17.1
3	13.3	13.8	14.8	15.9	13.9	14.1	15.1	15.9	16.7
4	13.1	13.5	14.5	15.6	13.6	13.8	14.8	15.6	16.4
5	12.9	13.3	14.2	15.3	13.4	13.6	14.5	15.3	16.2
6	12.7	13.1	14.0	15.1	13.2	13.4	14.3	15.1	16.0
7	12.6	13.0	13.9	15.1	13.1	13.3	14.3	15.1	16.1
8	12.6	13.0	14.0	15.3	13.1	13.4	14.4	15.3	16.4
9	12.7	13.2	14.3	15.7	13.3	13.5	14.7	15.7	16.9
10	13.0	13.5	14.7	16.3	13.6	13.9	15.2	16.3	17.6
11	13.3	13.9	15.2	16.9	14.0	14.3	15.7	16.9	18.3
12	13.8	14.4	15.8	17.6	14.5	14.8	16.3	17.6	19.1
13	14.4	15.0	16.6	18.4	15.2	15.5	17.1	18.4	20.0
14	15.1	15.7	17.3	19.2	15.9	16.2	17.9	19.2	20.9
15	15.7	16.3	17.9	19.9	16.5	16.9	18.5	19.9	21.5
16	16.1	16.8	18.4	20.3	17.0	17.3	19.0	20.3	21.8
17	16.4	17.1	18.6	20.5	17.3	17.6	19.2	20.5	22.0
18	16.6	17.3	18.8	20.6	17.5	17.8	19.4	20.6	22.0

181.5 Applications to Other Areas of Health and Disease

Assessment of nutritional status is the primary step in the evaluation of all children whose growth differs from the norm and should be an integral part of the evaluation and management of all children with acute and chronic diseases. Almost all chronic medical conditions in a child can result in poor weight gain through a number of factors. These include decreased energy/nutrient intake (anorexia, food withholding, and altered mental status), increased caloric requirements (fever and infections), and/or inefficient utilization of ingested calories and nutrients (maldigestion and malabsorption). The common factors and diseases relating to child malnutrition are:

- Any chronic medical condition resulting in:
  - Inadequate intake (e.g., swallowing dysfunction and anorexia);
  - Increased metabolic rate (e.g., congenital heart disease and fevers); and
  - Maldigestion or malabsorption (e.g., AIDS and celiac disease);
- Premature birth (e.g., intrauterine growth retardation);
- Developmental delay;
- Congenital anomalies;
- Intrauterine toxin exposure (e.g., alcohol);
- Plumbism and/or anemia; and
- Lead intoxication.

181.6 Practical Methods and Techniques in Calculating Percentages and *Z*-Scores

Calculation of percentage and *Z*-scores of the anthropometric indices is the basic step in the nutrition evaluation of an individual or a group. Box 181.3 presents the method.

Box 181.3 Calculating Percentages and *Z*-Scores

Percentage of the median:

The percentage of the median is calculated as follows:

$$\text{Percentage} = \left[\text{observed value/median reference value}\right] \cdot 100$$

For example, if the child's weight is 8.0 kg and the reference value is 10 kg, the percentage of the median is (8.0 kg/10 kg) × 100 = 80%.

Z-score (Standard Deviation):

The *Z*-score of an observed point is calculated as follows:

$$Z\text{ - score} = [(\text{observed value}) - (\text{median reference value})] / Z\text{ - score of the reference population}$$

Summary Points

- Protein–energy malnutrition remains a problem in Chinese children, especially in rural areas. But, the prevalence of child malnutrition has been kept very low in Japan.
- An appropriate mix of nutrition-related indicators should be selected to measure nutritional status as well as to identify causes of malnutrition.
- The most commonly used anthropometric indicators of PEM in children are wasting, stunting, and underweight, which are determined respectively by low weight-for-height, low height-for-age, and low weight-for-age. Low body mass index (BMI) can be used for some age groups in children.
- Identification of PEM in Chinese children is in accordance with the WHO (2006) recommendations.
- Identification of child protein–energy malnutrition in Japan is based on percentage overweight (POW).
- Ranges of malnutrition vary greatly across populations. Thresholds may be used for guidance by decision makers to select nutrition-related interventions. However, they must be used with caution, taking into consideration contextual and trend analyses.
- Anthropometric measurements can assess growth cross-sectionally or longitudinally. If children are measured once, their growth status for age can be assessed by comparing this measurement with the appropriate reference. If children are measured more than once, growth-velocity data reflecting change can be obtained.

Key Points or Features of Moderate and Severe Malnutrition

Stunting, wasting, and underweight can have different levels of severity. Box 181.4 describes the cutoff points for different levels of PEM in children.

Box 181.4 The cutoff points for different levels of PEM

Index	Level of severity	Cutoff points
Stunting	Severe growth failure	Height-for-age index below -3 *Z*-scores or below 80% of the median
	Moderate growth failure	Height-for-age index between -2 and -3 *Z*-scores or between 80% and 90% of the median
Wasting	Severe acute malnutrition	Weight-for-height index below -3 *Z*-scores or below 70% of the median and/or presence of bilateral edema
	Moderate acute malnutrition	Weight-for-height index between -2 and -3 *Z*-scores or below 70% and 80% of the median
Underweight	Severe underweight	Weight-for-age index below -3 *Z*-scores or below 70% of the median
	Moderate underweight	Weight-for-age index between -2 and -3 *Z*-scores or between 70% and 80% of the median

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Part XXVI
Biomechanical and Ergonomic Aspects

Chapter 182
Anthropometry in Bipedal Locomotion: The Link Between Anatomy and Gait

Franck Multon, Guillaume Nicolas, Robin Huw Crompton, Kristiaan D'Août, and Gilles Berillon

Abstract Bipedal locomotion is a key point in many scientific domains including medicine, palaeoanthropology, biomechanics, physiology, neuroscience, robotics, computer animation and so on. The link between an anatomical property and its impact on gait relies on accurate anthropometrical data. While human bipedal locomotion and animal motion in general is often well depicted biomechanically, neurologically or physiologically, relatively little is known about the relationships between the normal bipedal gaits and the anthropometric data and its variation. In this chapter, we aim at describing recent work and knowledge concerning this problem. With regard to bipedal gait, we believe that considering humans among primates in a wider comparative framework would enable us to identify the fundamental relationship between anthropometry and biomechanics. It provides us with an original and complementary point of views to other approaches addressed in this volume. Indeed, it provides us with enlarged fundamental knowledge that could be reused in many application domains, such as explaining gait patterns in normal and pathological human locomotion. In this chapter, we propose a synthesis of relevant contributions addressing this assumption for the specific case of human and non-human primates bipedal gaits. We will address the common features and the main differences of this movement from the anthropometrical and functional point of views. General bipedal gait patterns are depicted with regards to biomechanical parameters including kinematics, dynamics and energy expenditure. We thus identify common properties of bipedal locomotion that seem to be independent from anatomical parameters. We conclude this chapter by describing modern approaches based on computer simulation in order to identify the use of anthropometry in understanding normal and pathological gait in humans.

Abbreviations

BHBK	Bent Hip Bent Knee
COM	Centre of mass
CT-images	Computed tomography images
NPP	Natural Pendular Period
SLR	Step Length Ratio
vGRF	Vertical component of the Ground Reaction Force

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_182,

182.1 Introduction

Bipedal locomotion is a key point in many scientific domains including medicine, palaeoanthropology, biomechanics, physiology, neuroscience, robotics, computer animation and so on. The link between an anatomical property and its impact on gait relies on accurate anthropometrical data. While human bipedal locomotion and animal motion in general are often well-depicted biomechanically, neurologically or physiologically, relatively little is known about the relationships between locomotor habits and anatomical traits. In this chapter, we aim at describing recent work and knowledge concerning this problem. We believe that considering humans among primates in a wider comparative framework would enable us to identify the fundamental relationship between anthropometry and biomechanics. It provides us with an original and complementary point of view to other approaches addressed in this volume. Indeed, it provides us with enlarged fundamental knowledge that could be reused in many application domains, such as explaining gait patterns in normal and pathological human locomotion.

Indeed, bipedal walking is a locomotor mode that is used by numerous taxa that are phylogenetically distant from each other, from humans (committed bipedal with a hyperspecialised locomotor anatomy) to macaques or baboons (anatomically specialised to terrestrial quadrupedalism). Analyses demonstrate that bipedal walking in primates differs both kinematically and kinetically from one taxon to another.

In this chapter, we propose a synthesis of relevant contributions addressing this assumption for the specific case of human and non-human primate bipedal gaits. We will address the common features and the main differences of this movement from the anthropometrical and functional point of view. General locomotor patterns are depicted with regard to biomechanical parameters including kinematics, dynamics and energy expenditure. We thus identify common properties of bipedal locomotion that seem to be independent from anatomical parameters. We conclude this chapter by describing modern approaches based on computer simulation in order to identify the use of anthropometry in understanding normal and pathological gait in humans.

182.2 (Comparative) Locomotor Anatomies of Human and Non-human Primates: Habitual Versus Facultative Bipedalism

The literature on primate locomotor anatomy has been steadily increasing, but studies focussing on bipedal locomotion are relatively limited. We will focus on the subset of morphological features associated with this particular locomotor mode.

182.2.1 Comparative Anatomies and Bipedal Walks

A prerequisite for static equilibrium is that the vertical projection of the body centre of mass should lie within the support polygon. The latter is strongly reduced in the case of bipedal locomotion, making static equilibrium (and probably, dynamic equilibrium) more challenging. In humans, a unique body arrangement is associated with balance and upright posture (e.g. Kummer 1962): a head positioned obliquely onto the neck, an upright trunk, extended hip joints, adducted and extended knee joints, a horizontal talocrural joint axis, a stiff plantigrade foot and a centre of gravity located in the mid-pelvis during habitual stance.

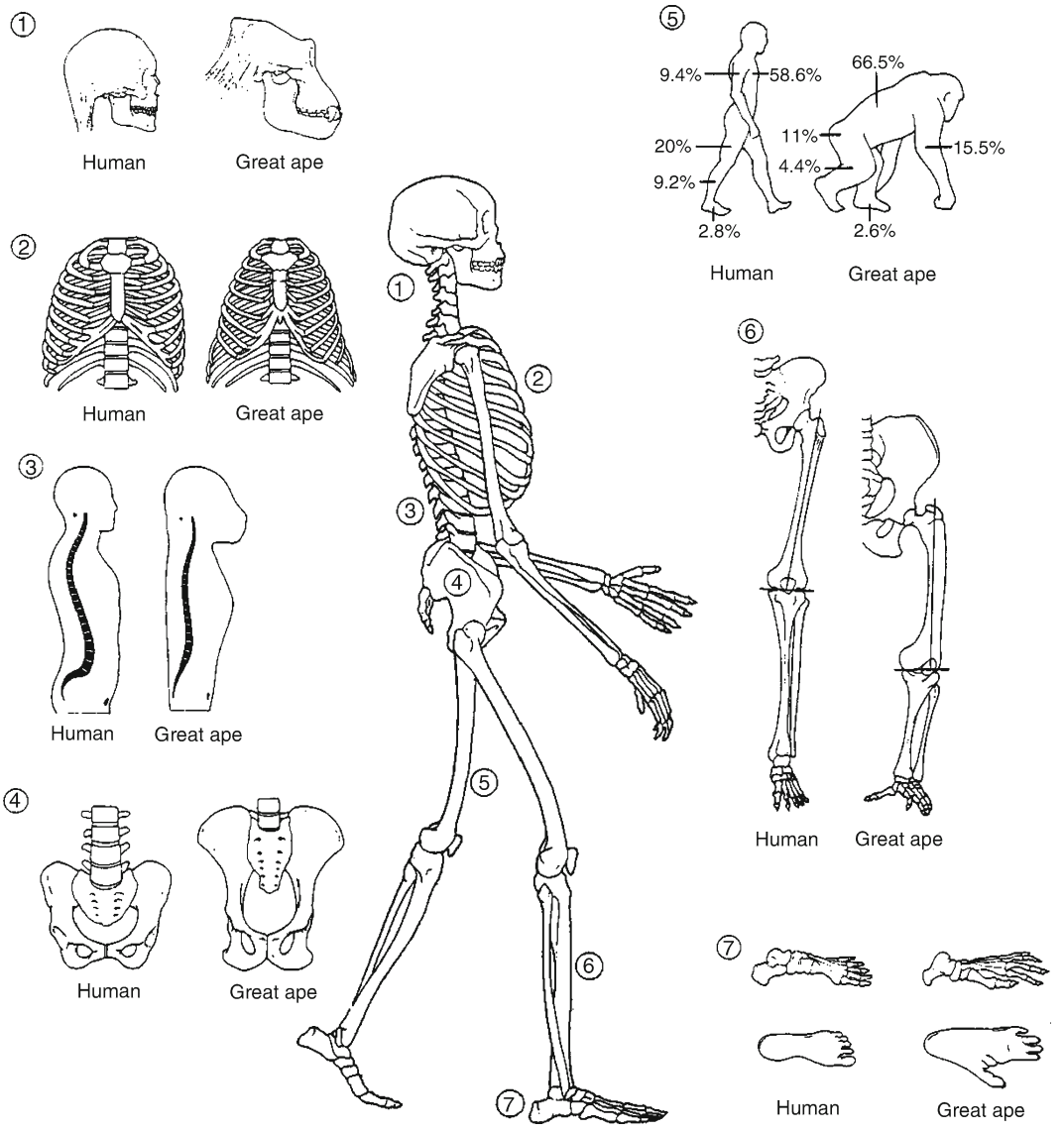

Fig. 182.1 Comparative features of bipedal locomotion in human and non-human primates (Modified from Jones et al. (1992))

In humans, several characteristic features are observed with regard to mass distribution and anatomy. We introduce some of these features identified on the spine, the pelvic girdle and hind limbs (Fig. 182.1):

- On average, body mass is distributed as follows: hind limbs: 32%, head and trunk (59%) and forelimbs (9%). Compared to other hominoids, the neck–head segment and the hind limbs are relatively long and the forelimbs are relatively short.
- The vertebral column displays four curvatures: two lordoses (lumbar and cervical) and two kyphoses (thoracic and sacral).

- The pelvic girdle is short and basin-shaped, with stout ilia on which well-developed gluteal muscles originate.
- The diameter of the anatomical hip joint (acetabulum and femoral head) is large and the femoral neck is relatively long.
- Concerning the general shape of the femur, the femoral diaphysis is elongated and straight, the angle of femoral torsion is large as is the bicondylar angle, which adducts and orients the knee axis in a frontal plane. At the knee level, the femoral condyles are antero-posteriorly elongated, the patellar field is deep, the tibial plates are slightly concave and perpendicular to the tibial shaft and the lateral meniscus has two areas of attachment. Such arrangement stabilises the knee during push-off and provides « locking » at maximal extension. In addition, knee motion is mainly parasagittal.
- At the shank level, tibial and fibular shafts are elongated and straight. Together, the distal tibia and fibula form a mortise which accommodates the talar trochlea, which widening distally, stiffens the talocrural joint as the foot dorsiflexes. The overall movement of the talocrural joint is in the parasaggital plane, and plantarflexion is powered by a well-developed triceps surae muscle inserting at the tuber calcanei by a long Achilles tendon.
- At the foot level, the joints of the tarsometatarsal complex are very congruent due to the joint areas' shape and the ligament arrangement. The tarsus and the metatarsus form an arch-like structure, both longitudinally and transversally. Proximally, this arch is delimited by a long calcaneus with an enlarged (due to a lateral process) plantar base. Distally, this arch is delimited by roughly parallel metatarsals. The first metatarsal is adducted with a very limited medio-lateral range of motion. The metatarso-phalangeal joint allows for a great degree of dorsiflexion. The base of calcaneus and the phalanges are mechanically coupled by means of a well-developed plantar aponeurosis.

The arrangement outlined here allows for a habitual bipedal locomotor mode and contrasts to non-human primates (Fig. 182.1). In their occasional bipedalism, the latter tend to have a head connected roughly in line with the neck, a forward inclined trunk, flexed hips and knees and compliant feet (see Aiello and Dean 1990, for a review), but this is not universally the case (see later).

Numerous variations are observed with regard to the degree of joint compliancy, knee abduction, foot orientation and type of foot contact to the ground (plantigrady or semiplantigrady). In African apes, it has been proposed that certain anatomical features are related to their proper type of bipedal locomotion (e.g. Jenkins 1972). Distally, the varus position of the foot and the extreme exorotation of the lower leg over the heel during push-off have a morphological basis in the arrangement of the talocrural joint: for example, a relatively wider lateral trochlea margin compared to the medial one, the oblique orientation of the distal tibia (Latimer et al. 1987) as well as an ovoid calcaneal tuberosity (no plantar lateral process). At push-off, a mid-tarsal break is observed (Elftman 1935), although this too may sometimes occur in clinically normal humans.

The way in which posture and bipedal walking is achieved in primates varies markedly between species. The anatomical differences between humans and other primates, outlined earlier (Fig. 182.1), help us understand why non-human primates cannot engage in habitual bipedalism. Nevertheless, with the exception of African apes, very few studies explore potential links between anatomy and bipedal locomotion. However, new experimental data in less-well-studied species are acquired, along with the use of numerical techniques (see Sect. 182.5).

182.3 (Comparative) Biomechanics of Bipedal Walking in Humans and Non-human Primates

182.3.1 In Humans

Most experimental approaches enabled the provision of many fundamental parameters linked to the bipedal locomotion: spatiotemporal, kinematic, dynamic and energetic parameters.

182.3.1.1 Spatial and Temporal Parameters

People walk when travelling slowly but run when wishing to go faster, while moving the legs alternately, half a cycle out of phase with each other. Kinematics of human bipedalism is commonly depicted via various spatiotemporal parameters of the gait cycle (Fig. 182.2). A stride (or gait cycle) is a complete cycle of leg movements involving one step by each leg. The stride length λ is the distance travelled in a stride, and the stride frequency f is the number of strides taken in unit time. Thus, the speed is defined as $\lambda * f$ (Alexander 2003). Bipedal locomotion is composed of a succession of stance and swing phases that can be expressed as a percentage of the total duration of the gait cycle (Fig. 182.2). In humans, swing and stance phases represent approximately 40% and 60% of all of the gait cycle. This leads to two double-support phases, each of them representing around 10% of the gait cycle. A human gait cycle can therefore be considered from the duty factor β, that is, the fraction of the duration of the stride for which a particular foot remains on the ground. If the duty factor is greater than 0.5, there are periods of the stride in which both feet are simultaneously on the ground, and the gait is described as a walk. Otherwise, the gait is described as a run. In other species, such as the gibbons, it may be appropriate to use other criteria for separating running and walking; thus, Vereecke et al. (2006) describe running as that bipedal locomotion which uses a spring-mass not pendular-energy-saving mechanism, since the gibbon bipedal gait is compliant and high speed, but lacks a floating phase.

The step length is the distance travelled while a particular foot is on the ground and is approximately equal to $\beta * \lambda$ (it would be exactly equal to $\beta\lambda$ if the speed remained constant throughout the stride) (Alexander 2003).

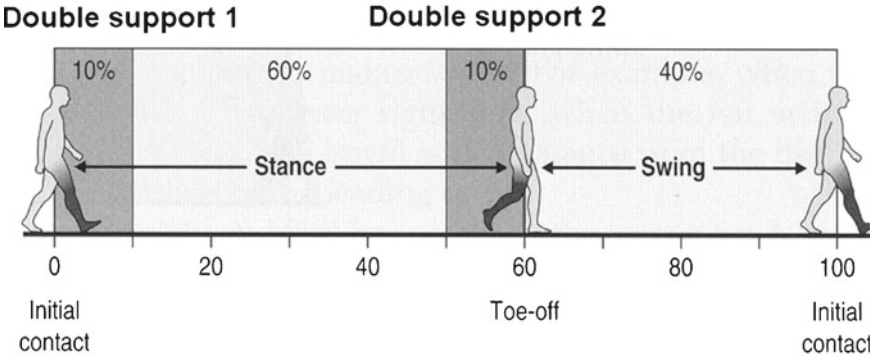

Fig. 182.2 Main phases of a gait cycle (Modified from Kirtley (2006))

Table 182.1 Interpretation of temporal spatial parameters in gait disorders (From Kirtley 2006)

Speed	Stride length	Cadence	Interpretation
N	N	N	Normal gait
N	↓	↑	Compensated gait
↓	↓	↑	Inadequately compensated gait
↓	↓	↓	Severe gait impairment

The spatial and temporal parameters of gait are recognised to be of clinical relevance in the assessment of motor pathologies. Consequently, they are considered as important functional measures (or *vital signs*) of gait (Kirtley 2006), the main applications of which are:

- Screening (e.g. detect elderly people at risk of falling);
- As a performance measure (e.g. to grade a patient's level of disability);
- Monitoring the efficacy of therapy (i.e. as a measure of outcome); and
- Normalisation of other gait measurements (in order to compare results from people walking at different speeds for example).

In order to compose a detailed and precise clinical report, complementary parameters have to be considered. For example, age (effect of maturation) or the size of the subject may potentially modify several of the gait characteristics. In order to highlight the fundamental and general aspects of locomotion, many researchers have proposed techniques to normalise the gait parameters (Alexander 2003). It was formally proposed that the motion of one animal could be predicted from that of another animal of different body size, if the two animals were geometrically and dynamically similar (see Alexander 2003 for a review). Two animals moving in a dynamically similar manner will have equal ratios of all lengths, times and forces. Because velocity is simply distance (a length) per unit time, two animals moving in a dynamically similar manner should also have equal ratios of their velocities. In this way, many parameters of one animal can be related to those of another. To allow direct comparison of motions of two animals which may be of different size or shape, a parameter called the Froude number (*Fr*) is used to compensate for differences in velocity, body size and gravity:

$$Fr = \frac{V^2}{g.L}$$

where g is the gravity (9.81 m s^{-2}) and L is a characteristic length (in m). The use of *Fr* to relate the motion of disparate animals is based on the mechanics of the pendulum, to which human walking has been likened. The characteristic length of choice is leg length or the distance from the acetabulum or greater trochanter to the ground. *Fr* can be shown to be equal to the ratio of potential and kinetic energy, when *h* is the characteristic length (Alexander 2003). From this description, it appears that the temporal–spatial parameters stabilise at around 4–5 years of age (Sutherland 1994). However, Li et al. (1996) found that the path of the centre of pressure under the foot and ground reaction forces as a whole do not mature until 7–8 at least.

In clinics, most gait problems result in decreased stride length, and increased cadence is a common compensation to maintain speed. In some diseases (e.g. Parkinson's disease), the increase in cadence is very marked (Morris et al. 1999). It is therefore best to measure all three parameters (Table 182.1).

Step-length differences are useful as a measure of symmetry. For example, the step length ratio (SLR) of the shorter to the longer step length is useful for tracking a patient's progress through their rehabilitation, the ratio rising to closer to 1 as the gait improves. Other symmetry indices have been described using variables, such as right and left stride times or double support times, but the SLR is probably the most widely used (Kirtley 2006).

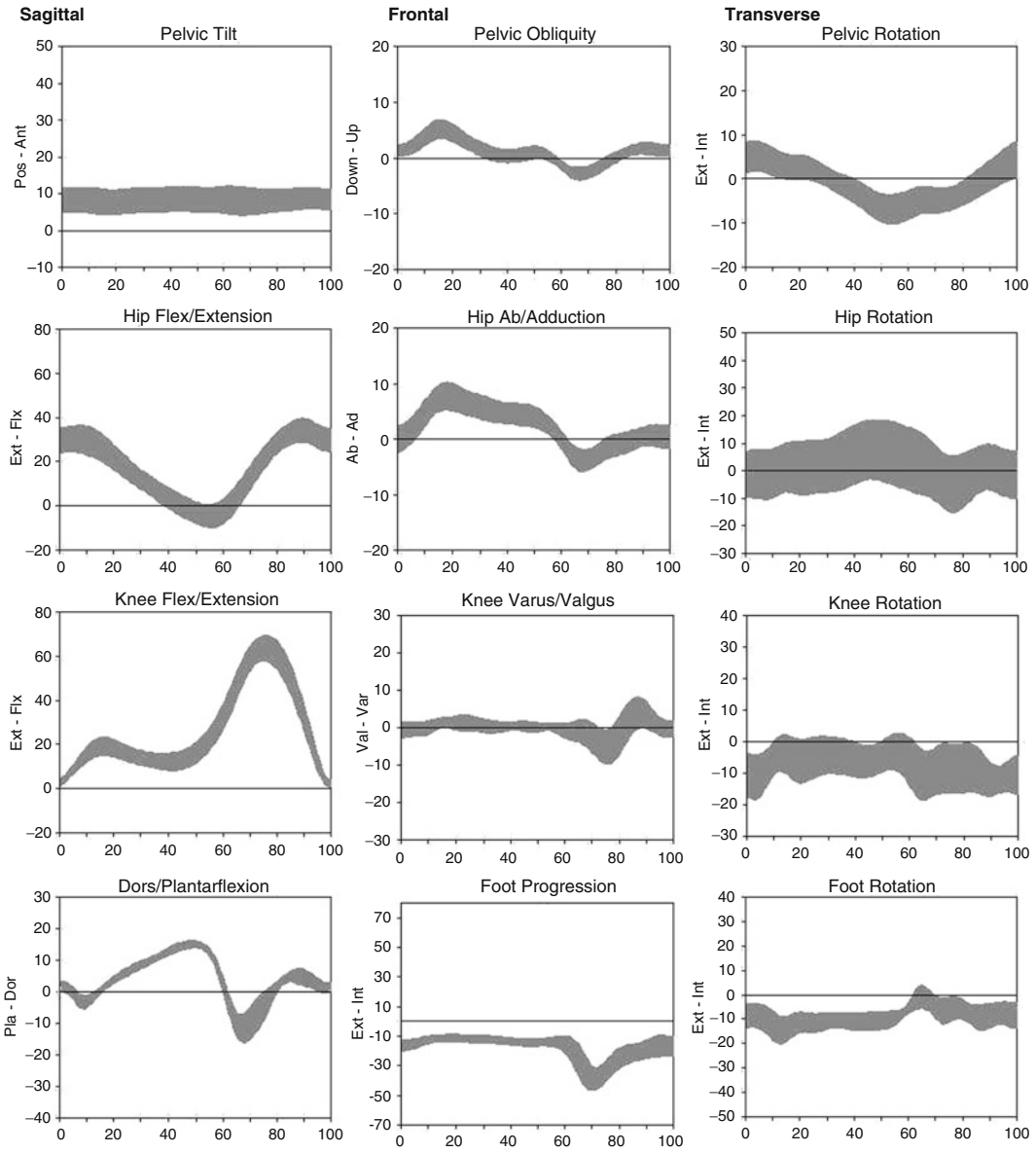

Fig. 182.3 Normative values of 3D joint angles during gait (Adapted from Kirtley (2006))

182.3.1.2 Joint Angles

Gait is also often described via 3D joint angles obtained by tracking the motion of a specific joint throughout the gait cycle. Many previous works depicted joint angles in all three planes (see Kirtley 2006 for a review); and it has been found that, during normal gait, the majority of motion occurs in the sagittal plane, whereas, in pathological gait, there is typically reduced motion in the sagittal plane and much greater motion in the coronal and transverse planes (see Fig. 182.3 for a normative range

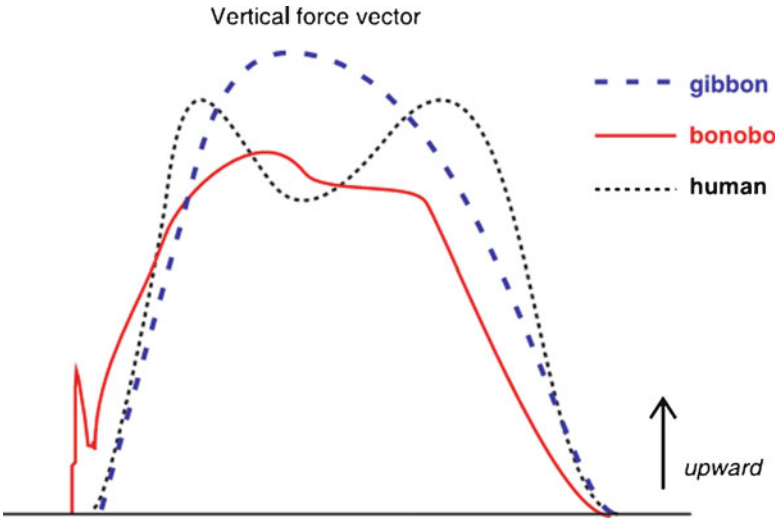

Fig. 182.4 Graph showing the average vertical ground-reaction force (scaled to body weight) for humans (*dotted line*), bonobo (*bold line*) and gibbon (*dashed line*) bipedalism. Ninety percent of voluntary bipedal walking by bonobos produces a single-humped vertical ground reaction force curve, 10% gives a mildly double-humped form. Gibbon bipedal running produces a single-humped curve, but, unlike human running, there is usually no floating phase. Note that gibbons do not show a heel-strike transient, which appears to be a great-ape feature. Also note the abrupt drop in vertical force prior to toe-off in humans and the more gradual decrease in vertical force in both apes (Crompton et al. 2008)

of joint angles during normal gait). Motion in these two planes is a function of compensation needed as coping responses for limited motions and deviations in the sagittal plane or as a direct result of the underlying conditions (Spivack 1995).

182.3.1.3 Dynamics and Energetics

During gait, relatively stiff lower limbs are used in such a way that our centre of mass is at its lowest point at heel-strike and rises to its highest point at midstance (Cavagna et al. 1977). This inverted pendulum-like gait allows for an effective exchange of gravitational potential and kinetic energy (Cavagna et al. 1977). The same style of walking is employed by other bipeds and probably by most quadrupeds (see Alexander 2003 for a review).

However, when people are asked to walk with minimal oscillations of the centre of mass, they adopt deeply flexed lower-limb postures like those of most apes (Schmitt 1999). Limb compliance leads to smaller oscillations of the centre of mass and alters the magnitude of the peak vertical substrate reaction force and the shape of the force–time plot. During normal walking, humans generate a vertical ground reaction force curve with two distinct peaks that are both greater than body weight (Crompton et al. 2008). This force pattern is characteristic of a stiff-legged gait in which the centre of mass is highest at midstance and lowest at double support (Fig. 182.4). By contrast, in most non-human primates, bipedal walking generates single-peaked force curves in which the peak is much closer to body weight (Fig. 182.4) (Kimura 1996).

As previously presented, gait kinematics is influenced by speed. Both in walking and in running, stride length increases with speed. From measurements of oxygen consumption, it can be shown that the adjustments of kinematic parameters aim at minimising the energy cost of locomotion at each

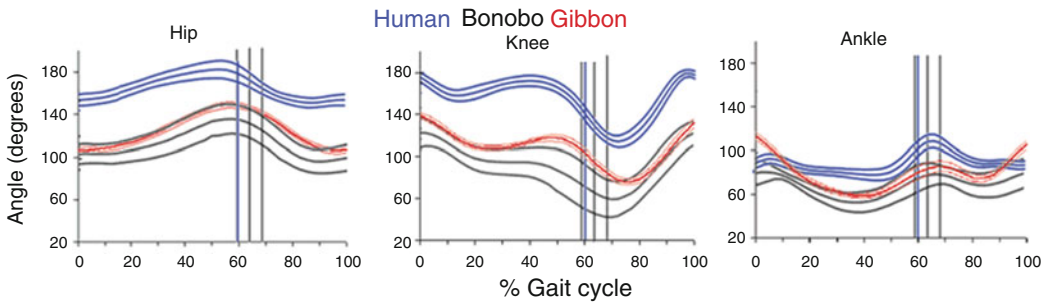

Fig. 182.5 Bonobos and gibbons: bent-hip, bent-knee gait; humans: 'stiff'-legged walking gait; gibbons have more extended hindlimb joints and more erect trunk position than bonobos (Adapted from Crompton et al. (2008), D'Aout et al. (2004))

particular speed. Transition from walking to running is made at approximately the speed at which walking and running have equal energy costs: walking is more economical than running below this energy cost, whereas running becomes more economical above (see Alexander 2003; Crompton et al. 2008). The stride length that is normally used at any given walking speed is the one that minimises energy consumption (see Alexander 2003).

182.3.2 In Non-human Primates

Biomechanical aspects of bipedal walking have been addressed in several non-human primate species, often with different questions in mind and with different techniques. Because of their close phylogenetic relationship to humans (Groves 2001), many studies have focussed on hominoids, especially the genus *Pan* (chimpanzees and bonobos). Other primate species are more distally related to humans but are particularly relevant for specific research questions and are essential in a broad comparative approach (D'Août and Vereecke 2010).

Many techniques used in human biomechanics have been applied to non-human primates as well (Schmitt 2003). These common techniques provide data from which human biometrics and biomechanics can be understood in a comparative framework, thanks to accurate comparisons with non-human primate biomechanics. Here, we will present general anthropometric and biomechanical characteristics of bipedal walking in non-human primates, even though this locomotor mode and the primate anatomy are variable. This aims to identify what (anthropometrically and biomechanically) in the human walking is shared by other primates and can be seen as "invariants" of the primate bipedal walker, and what is proper to the human walker.

Many studies have addressed spatiotemporal characteristics and joint motions during walking. Such studies typically use laboratory or captive setups, but some field data are available as well (see D'Août and Vereecke 2010).

One of the most striking aspects of bipedal walking in non-human primates is that they, unlike humans (who use extended hip and knee joints during walking), often adopt a relatively flexed (bent-hip bent-knee) and more compliant limb posture (Schmitt 1999) (Fig. 182.5). The trunk is typically inclined forward and bipedal strides are smaller (but at a higher frequency for a given velocity, e.g. Aerts et al. 2000) than quadrupedal ones, the latter being particularly long in primates when compared to other mammals (Reynolds 1987). Orangutans are again an exception, with bipedal strides being long and frequencies low, probably as an adaptation for dealing with support compliance.

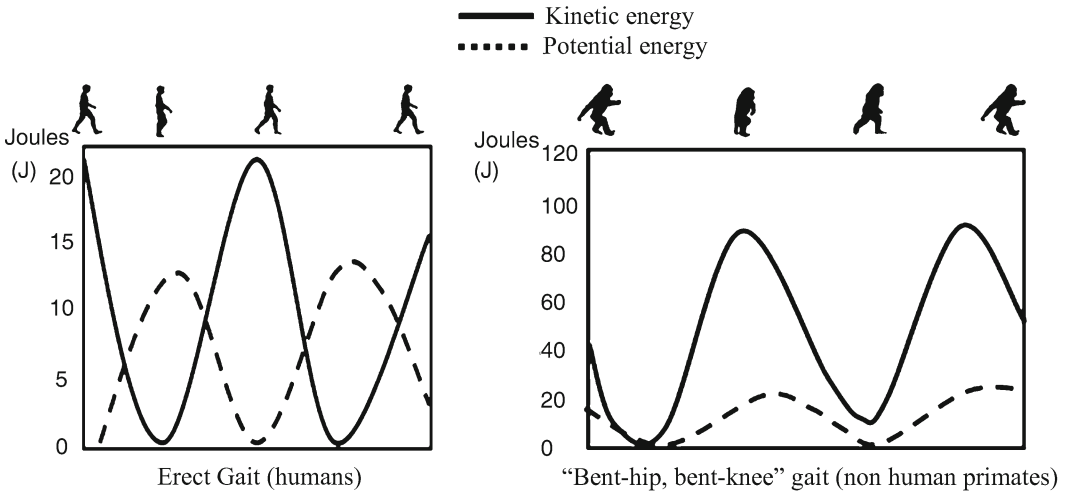

Fig. 182.6 Potential and kinetic energy during erect and 'bent-hip, bent-knee' walking in human and non-human primates

One aspect of locomotion in primates is the preferred use of diagonal-sequence gaits (Vilensky and Larson 1989), in which the left hindlimb moves in synchrony (albeit mostly, not perfectly) with the right forelimb. Whereas this is, obviously, a characteristic of quadrupedal gaits, such interlimb timing is often retained during bipedal locomotion, most clearly in the arm swing of humans.

Ground-reaction forces have been measured in several non-human primate species during bipedal walking (e.g. Kimura et al. 1977; D'Août et al. 2004; Sockol et al. 2007).

Bipedalism of untrained chimpanzees lacks the typical double-humped profile of the vertical force component seen in human walking (but not running) and does not show the associated "inverted pendulum" gait (Cavagna et al. 1977; Alexander 1991), in which mechanical energy can be conserved by the exchange of kinetic and potential energy as the centre of mass moves up and down while, respectively, decelerating and accelerating. However, bipedalism of untrained orang-utans, in at least 25% of cases, does show a double humped vGRF curve and one which overlaps in form with that in slow walking of humans, resulting in energy-exchange savings of some 50% versus 8% for untrained chimpanzees (Wang et al. 2003; Crompton et al. 2008). Further, some 10% of bipedalism of untrained bonobos shows a mildly double-humped curve (see Crompton et al. 2008).

With the data presently available, the general picture for non-human primates is that bipedalism has the same energetic cost as quadrupedalism and that the energetic cost of primate locomotion is similar to that of a generalised endotherm (Steudel-Numbers 2003) but higher than that of human bipedalism (Fig. 182.6).

182.3.3 Common Principles of Bipedal Walking

Gaits, that is, patterns of movement, may be expressed in terms of kinematics, where each limb has a stance phase, when it is in contact with the ground and a swing phase, when it is out of contact with the ground. The duty factor of a limb is the proportion of each complete cycle when it is in contact

with the ground, as described earlier. For bipeds, three kinds of gait are in common use, walking, running and hopping, while in human children, we may also recognise skipping. In hopping, either one limb at a time or both limbs at the same time exert propulsive (aft) force against the ground, with sufficient force to lift the whole body into a floating phase where there is no ground contact. There may also be a floating phase in running, and, in humans, the term 'running' is often limited to cases where there is a floating phase. However, in gibbons, running generally (but not always) lacks a floating phase (Vereecke et al. 2006). Minetti (1998) notes that most human children at some time voluntarily utilise skipping, a high-speed bipedal gait in which one foot has both stance and swing phases, followed by a small double-stance phase, then by the stance and swing phase of the opposite foot. Among our own Order, the primates, only humans and gibbons appear to be able to sustain non-hopping bipedalism.

Kinematic descriptions of gait are of particular value in the analysis of neural control mechanisms but, for an understanding of the mechanical work and cost of gaits, descriptions of gait based on force are more appropriate and, thus, recently more common. The best-established categorisation differentiates gaits that save energy by pendular mechanisms and the exchange of more or less out-of-phase potential and kinetic energies of the body centre of mass (COM) from those that save energy by spring–mass mechanisms, where energy is stored in elastic tissue. Modern human bipedalism is unique primarily for the extended or 'stiff' postures of the lower limb that characterise walking (Alexander 1991). It has been shown that in humans, 'stiff' limb postures allow for a high degree of energy recovery between strides by the exchange of nearly completely out-of-phase kinetic and potential energies of the COM (Cavagna et al. 1977). At speeds below about 2.2 m/s, human adults normally use such 'stiff' bipedal walking, which is accompanied by characteristic double-humped vertical ground-reaction forces, as the COM rises and falls twice within each complete gait cycle (Li et al. 1996). Such stiff gaits may conserve as much as 70% of energy between strides (Wang et al. 2003). Above nearly 2.2 m/s, humans switch to compliant running gaits, which by contrast produce higher peaks but single-humped vertical ground-reaction forces. The higher acceleration needed to lift the body off the ground is substantially paid back by elastic recoil (comparable with a bouncing ball) in tissues, such as the Achilles' tendon (tendo calcaneus). While humans are unique among the African apes (humans, chimpanzees and gorillas) in possessing a marked Achilles' tendon, the presence of a strongly marked Achilles' tendon in gibbons rather surprisingly does not seem to be related to its running bipedalism. As with several other mammals, gibbons may utilise a combination of pendular and spring-mass mechanisms, although the latter tend to predominate at higher speeds. Ruina and colleagues (2005) proposed a new model which concentrates on the energy of collisions of the limbs with the ground; it shows that energy of the COM may be substantially conserved by aligning the path of the COM to the trajectory of the ground-reaction force. A combination of several mechanisms is thus likely to contribute to energy conservation during bipedalism.

182.4 The Role of Anthropometry in Analysis of Locomotor Function

At the simplest level, bones act as levers which apply forces at joints. Their length therefore affects their effort or load arm with respect to the joint centre. The forces which they transfer are derived either from ground – and ultimately joint-reaction forces, or muscular contraction. Since most biological surfaces are curved, in most cases also joint motion is rotatory rather than linear, and so the forces exerted about joints are primarily turning forces: rotatory moments or torques. The torque which a muscle exerts at a joint is a function of the physiological cross-sectional area of a muscle and the

perpendicular distance from the line of action of a muscle about the joint's instant centre of rotation to that centre or moment arm. The joint's centre or axis of motion is rarely immobile but itself follows a curved path. The changing position of the origin and insertion of a muscle with respect to a joint centre throughout the physiological range of motion of a joint will thus change the moment arm through the range of motion. Further, the moment arm of a muscle will be affected by the passage of the muscle over bony protuberances, by the diameter of any sesamoid bones within the muscles' tendons, by its passage over deeper muscles which may bulge underneath it when they are activated, and even by passage of its tendons through pulleys comprised of bony or soft-tissue structures – or both.

Measurement of bone geometry may be done by linear measurements made with callipers, but, more recently, it is increasingly performed by building virtual models of bones by laser scanning or by reconstruction of CT imaging, which have the advantage that bone geometry may be recorded in articulation with other bones or even on the intact body. (Further, this approach allows the skeleton to be rigged with simulated muscles in forward dynamic modelling, see below).

These measurements require to be augmented with measurement of muscle moment arms, usually done by the tendon-travel method, simultaneously with measurement of joint angle and measurement of physiological cross-sectional area of muscles. A further parameter, which affects the range of motion over which forces may be effectively applied to joints, is the length of fibres within the muscle. All these parameters are normally gathered by dissection (for methods, see e.g. Thorpe et al. 2006), but digital goniometers and linear displacement recording can greatly aid data collection. Medical imaging may also be of value.

Motion of a limb segment, and, in particular, the forces which must be exerted to change its motion, are however affected by its mass distribution: not only its raw and relative mass but the geometric distribution of mass within the segment, and its inertial properties. In analyses based on pendular mechanics, for example, since the period of a pendulum is affected by its mass distribution, not its raw mass, analysis of stride frequency must take account of mass distribution; again, the inertial properties of a segment will affect the mechanical cost of bringing about changes in its angular motion. Although the forces exerted externally by any limb during the stance phase to power and control gait may be measured accurately for any living animal, calculation of the internal forces, such as joint torques from external forces, still requires inverse dynamic analysis, and, this in turn, necessitates knowledge of segment inertial properties.

Newton's second law states that the resultant force acting on a body, F, is the product of the mass of the body, m, and its acceleration, a:

$$F = ma$$

Forces acting on a body can thus be calculated from knowledge of its mass and acceleration. However, we have mentioned that, in biological entities, most motions are rotatory or angular rather than linear. Newton's second law can be restated in angular form:

$$T = I\acute{a}$$

where T is the torque acting on the body, I the moment of inertia of the body, and $\acute{a}$ its angular acceleration. In a three-dimensional analysis, torques, moments of inertia and angular accelerations must be resolved into their plane of rotation about X-, Y- and Z axes.

Thus, segment centres of gravity, moments of inertia and radii of gyration must be assessed three-dimensionally. While segment mass can be measured by use of balances, and simple water-displacement methods used for volumes, mass distribution of segments is much more demanding

to assess reasonably accurately. The three most important parameters are segment centre of gravity (the mean of the mass distribution of a segment), the radius of gyration (essentially, the standard deviation of mass distribution) and moment of inertia (the characteristic pattern of mass distribution acting to resist angular acceleration in a given plane of mass acting to resist a given angular acceleration). Methods for derivation of these parameters from complex pendulum experiments on segmented specimens, or from intact – and hence even living – specimens using external measurements (based on the uniform density assumption), via construction of geometric models, are provided by Crompton et al. (1996, and see also Isler et al. 2006). These data are essential for construction of computer simulation by dynamic modelling but can themselves provide direct insights: Isler et al. (2006) found that while all other non-human great apes show a mismatch of natural pendular period (NPP) between fore- and hindlimbs, the common chimpanzee alone has reduced distal mass in the forelimb and thus achieved a better match between fore- and hindlimb, suggesting that the common crown-hominoid ancestor was not a mechanically effective quadruped, but that the chimpanzee has undergone selection to enhance its effectiveness in quadrupedalism.

Whereas the description of translational inertia is straightforward (i.e. mass), rotational inertia can be presented in several ways, for example, moment of inertia around the proximal joint and principal moment of inertia (i.e. around the centre of mass), and it can be recalculated as the radius of gyration (which, in turn, can be expressed as a percentage of segment length). The latter measure does not directly relate to rotational inertia (it only does so after accounting for segment length and mass), but it allows for a comparison between subjects of different size, shape and mass.

Comparative and evolutionary biomechanics, especially that focussing on the origin of bipedal locomotion in humans, has been a fruitful study field. Various methods are being employed, and quantitative anatomical knowledge has been integrated in such studies. More specifically, studies have used segment inertial properties, muscle moment arms and architecture data and the general architecture of the articular chain.

As described earlier, the inertial properties of a segment document to what extent it resists accelerations and therefore have a substantial impact on the biomechanics and energetics of movements (including locomotion, although probably less than does joint kinematics). Energy is needed to propel the body (represented by its centre of mass) as a whole – this is external energy. Energy is also needed to move the body segments relative to each other – this is internal energy. By measuring or calculating inertial properties per segment, both types of energy can be calculated. The overall architecture of the body, as a linked-segment "skeletal" model, can be established either by imposing a specific posture, for example, erect or 'bent-hip, bent-knee' (e.g. Crompton et al. 1998) or it can be obtained by medical imaging techniques (e.g. Ogihara et al. 2009). Additionally, it can be reconstructed from isolated bones if available (e.g. Nicolas et al. 2009) (Fig. 182.7).

The muscles are often represented as functional units of which attachment may be measured directly on cadavers or from medical imaging (e.g. Ogihara et al. 2009).

Articulations have typically been represented as simplified 2D or 3D hinge joints (e.g. Nicolas et al. 2007), as they lead to a small set of variables which enables us to obtain reliable dynamic variables. However, recent studies increasingly account for anatomical complexity, for example, in the development of musculoskeletal models of the foot in a comparative perspective (Wang and Crompton 2004). However, the resulting set of variables is so large that it is difficult to obtain reliable dynamic data: the redundancy of the actuators leads to using hypotheses/constraints in computing muscle activation instead of measurements. Hence, according to the studied problem, one has to select the most appropriate model.

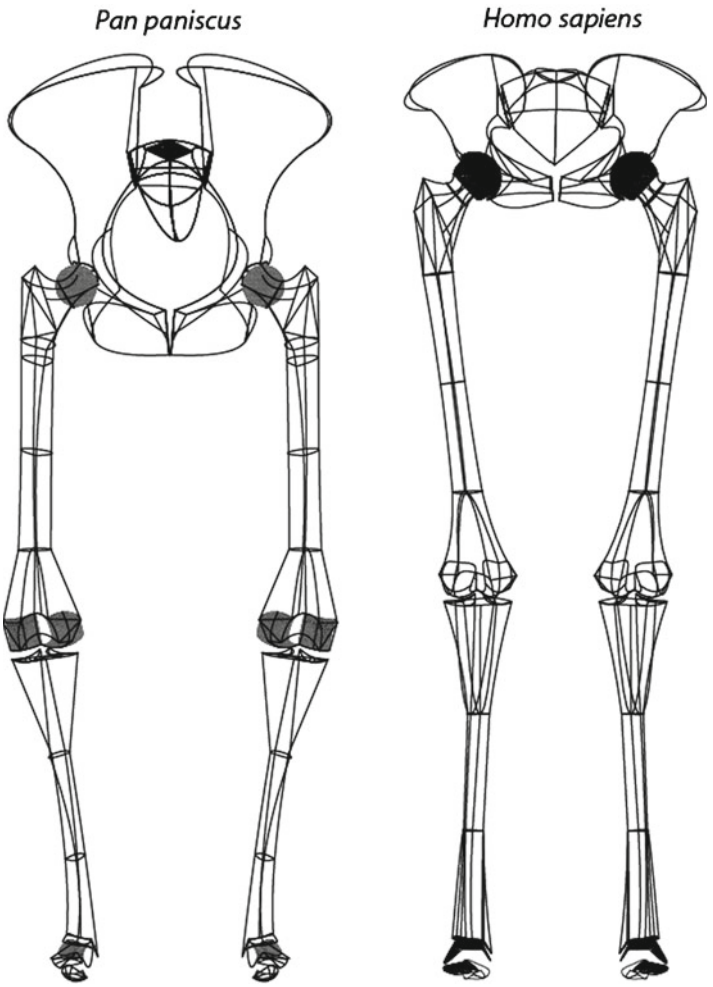

Fig. 182.7 Reconstructed pelvic girdle and hindlimbs in bonobo and human. They highlight the main architectural differences between human and bonobo. These articulated chains have been built using a procedure specifically designed for modelling and simulating analysis of bipedal locomotion in human and non-human primates (Nicolas et al. 2009)

182.5 Simulation for Associating Anthropometry and Bipedal Walking

182.5.1 Numerical Models of the Locomotor System

Simulating the locomotion of bipedal creatures by computer modelling requires an accurate modelling of the locomotor system. This modelling process has been widely explored in robotics (Shabana 1998) and computer animation (Badler 1999) for many years. The most accepted approach consists of modelling the locomotor system as an articulated multibody system composed of isolated bodies connected by idealised joints. These joints allow rotations and translations in order to capture all the possible geometric transformations between two adjacent bones.

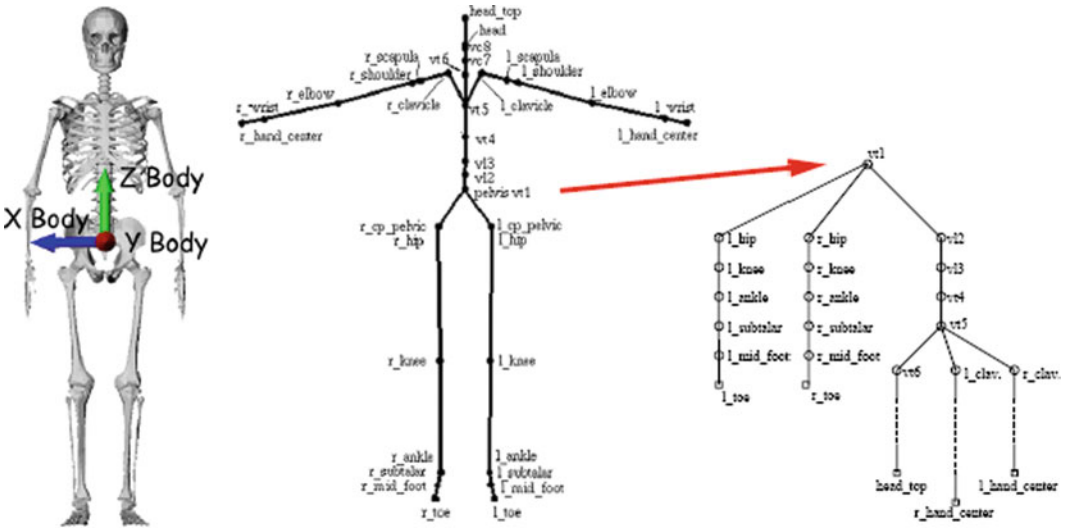

Fig. 182.8 Digital description of a human. This figure depicts how a digital human is represented. *Left*: A reference frame is placed on the pelvis in order to provide the global position and orientation of the subject. *Middle*: A set of connected bodies is used to model the subject and the joint. *Right*: A tree is used in order describe the relationships between adjacent bodies

Each isolated body is modelled with a set of biomechanical parameters, such as the mass, the location of the centre of mass and inertia that are generally obtained using anthropometric tables (e.g. Dempster and Gaughran 1967; Zatsiorsky et al. 1990, Crompton et al. 1996; Isler et al. 2006). This kind of modelling is based on the assumption that each body is rigid and cannot change shape during motion. For some populations, such as the obese, this assumption is too simple, and more complex models are required (Grüber et al. 1998). Equally, where structures such as the plantar aponeurosis are to be considered, models may require including compliant elements (e.g. Caravaggi et al. 2009). Whatever the type of model, bodies do not accurately correspond to actual bones but sometimes model a set of bones (such as a group of vertebrae, ribs and soft tissues for the abdomen and the torso). However, note that, for example, if the goal of the simulation is to study the load exerted on the lumbar region during a given motion, the anthropometric model of the trunk should include a complex description of the spine; conversely, if the goal of the study is to analyse knee rotations during gait, a single body may adequately model the trunk. Such adaptation of the model according to the aim of the study is a key point in anthropology.

Whatever the level of detail, the resulting model is generally presented as a hierarchy or tree: the nodes correspond to isolated bodies, while the links are associated with joints. If the pelvis is the parent of the femur in this hierarchy or tree, the femur inherits from the pelvis all the transformations applied to the pelvis, as depicted in Fig. 182.8. Using this tree structure enables us to provide only the relative geometric transformation between two adjacent bodies. In the previous example, whatever the orientation of the pelvis in space, the link to the femur only contains the local rotations of the hip, as generally employed in anatomy and biomechanics.

Thanks to this representation, a pose $q(t)$ at time t of the whole body is a simply a vector containing all the degrees of freedom for an n-joint multibody system:

$$q(t) = \left(x_r, y_r, z_r, \psi_r, \theta_r, \varphi_r, \left[x_i, y_i, z_i, \psi_i, \theta_i, \varphi_i\right]_{i=1\ldots n}\right)$$

where x, y and z stand for the three possible translations, and ψ, θ and φ stand for the three possible rotations either for the root global displacement (subscript r) or a joint (subscript i).

182.5.2 Numerical Methods for Simulation

As a pose is modelled with such a vector, the main role of the simulation is to calculate how this vector changes with time. A wide set of methods has been introduced to perform such a simulation for bipedal locomotion (see Multon et al. 1999 for a survey). The most intuitive approach consists in directly applying predefined locomotion data that generally come from motion capture. This so-called 'inverse dynamics' approach is mainly used to test a hypothetical motion on a given locomotor system, to check if it is mechanically plausible (Crompton et al. 1998). However, motion from one species may not be suitable to another, again a key point in anthropology.

Another method called 'inverse kinematics' consists in displacing the extremity of the locomotor system at each time step of the simulation and to calculate a pose which is compatible with this new constraint. In that case, the resulting motion is fully adapted to the anatomical structure. Hence, it is possible to check the influence of changes in anthropometric data on the resulting motion, as suggested in Nicolas et al. (2007). This method takes energy minimisation into account but does not consider other dynamic variables, which could lead to some unrealistic motions from the mechanical point of view.

To overcome the limitations of the two previous techniques, the 'forwards dynamics' approach predicts the dynamic equations of the mechanical system, which optimally correspond to the anthropometric data (this usually employs code from a physics engine, such as ODE 'Open Dynamics Engine'), together with code which systematically searches through parameters, such as simulated muscle-activation patterns to locate combinations which can achieve preselected optima, such as fastest possible speed or minimum possible cost. This approach allows computation of the motion of the system according to all external and internal forces that are acting on it. Although the resulting motion takes both anthropometric data and dynamic laws into account, it is computationally very demanding to obtain the most likely parameters to achieve a biologically likely motion, and it is in all cases necessary to validate such models by reference to real-world experimental measurements. Many approaches have been proposed to solve this problem, but it remains a research challenge. The next subsection presents some such approaches in work applied to anthropology.

182.5.3 Application to Anthropometry in Locomotion

As mentioned earlier, the mechanical costs of given gaits can be predicted from a knowledge of body proportions and estimates of masses and mass distributions, using inverse dynamic analysis. Equally, kinematics can be predicted from a knowledge of forces, by forwards dynamic analysis. These techniques are vital elements in the analysis of internal force and motion in biomechanics as a whole but, more recently, have begun to be accepted as powerful tools in reconstruction of the behaviour of extinct species, known only from fossils. This capability is particularly important in analysing the evolution of human bipedalism, where the traditional approach of reconstruction by analogy to living animals with similar morphologies is more or less impossible, in the absence of any living mammal other than humans with a similar habitual adaptation to striding terrestrial bipedal walking.

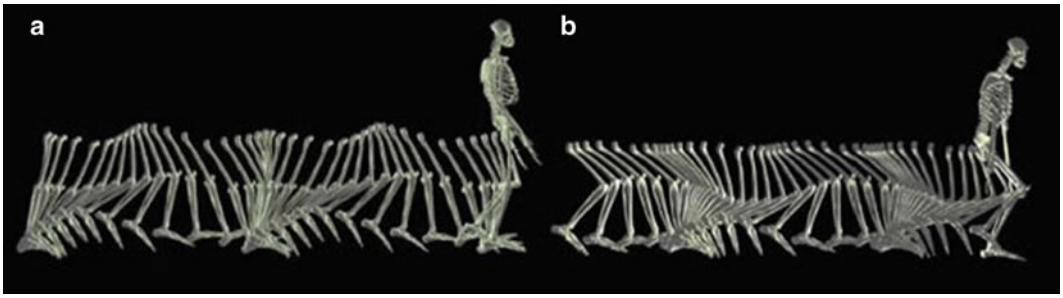

Fig. 182.9 Simulation of walking by Lucy (AL 288-1): (**a**) with motion functions derived from erect human walking; (**b**) with motion functions derived from 'bent-hip, bent-knee' human walking (Crompton et al. 1998)

The first such studies with a comparative focus were performed by workers, such as Yamazaki et al. (1996), who generated simulated bipedal gaits by forwards dynamics using a neuromuscular model with a pattern generator to generate muscle-activation patterns. A more overt application of dynamic modelling to gait reconstruction was that of Crompton et al. (1998), who used inverse dynamics to predict the mechanical energy cost (judged by the parameter of mechanical joint power) of the alternative hypotheses of bipedal gait in *Australopithecus afarensis*: upright, with extended hips and knees (see e.g. Latimer 1991) or 'bent-hip, bent-knee' (see e.g. Stern and Susman 1983) (Fig. 182.9).

This study ran sets of joint motion derived from humans walking upright and 'bent-hip, bent-knee' (BHBK) and from voluntary bipedalism of common chimpanzees through alternative inertial models representing *A. afarensis*' proportions but either common chimpanzee or human mass distribution (Fig. 182.9). The study suggested that BHBK walking by this early hominin would have lead to a doubling of the mechanical cost of locomotion and because of local imbalances in positive and negative joint power, would have lead to heat load. They also found, as did Yamazaki and colleagues (1996) that mass distribution seems to have a considerably smaller influence on costs than kinematics. This study was criticised, particularly by Stern (1999, 2000), who pointed out that the model was not validated and who argued for a more marginal difference in costs, based on studies of metabolic costs in humans walking in sand and snow and supposed advantages of compliant gait in lower peak reaction forces operating at the pelvis. However, Kramer (1999) independently performed an inverse dynamic modelling study of upright walking in *A. afarensis*, based on human-like kinematics, showing that, despite the short legs of this species, it could have been a very effective upright biped. Carey and Crompton (2005) carried out detailed physiological measurements on upright and BHBK walking in humans, which confirmed that the mechanical effects predicted for *Australopithecus afarensis* by Crompton et al. (1998) were reflected in metabolic costs of locomotion and increased heat load. In a series of studies, Wang et al. (e.g. 2004) extended inverse dynamic modelling to a consideration of the significance of evolutionary changes in body proportions on stability and effectiveness in carrying, showing that the changes in body proportions between *A. afarensis* and *Homo ergaster* give the latter major advantages in load carrying and walking over long distances. However, there is a limitation in the utility of inverse dynamic approaches, inasmuch as that they cannot readily generate optimal gaits for a given morphology. Forwards dynamic modelling can and, given a suitable muscle model, can directly predict metabolic energy costs from simulated muscle activity. This allows direct validation by comparing predicted costs in models of real humans to experimentally measured costs in the same individuals (e.g. Sellers et al. 2004). However, the computational demands of forwards dynamics models are very high compared to inverse dynamics, particularly during optimisation.

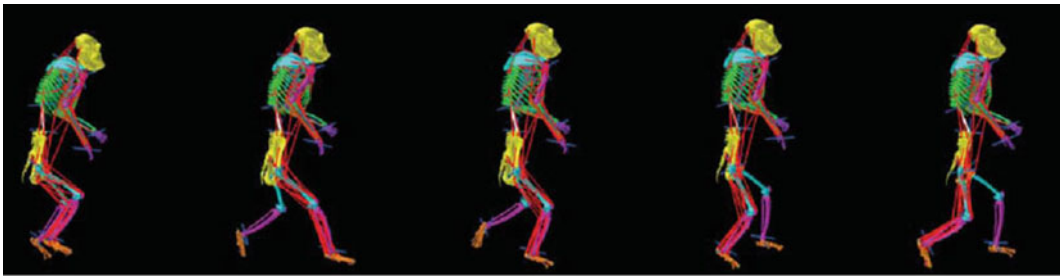

Fig. 182.10 Whole-body musculoskeletal kinematics of a Japanese macaque in bipedal walking (Ogihara et al. 2009)

Inverse dynamic models also require optimisation, but primarily to hone the smoothness of gait. Forwards dynamics models are usually searching for muscular-activation patterns that generate gaits which perform best according to preset optimisation targets: maximising speed, minimising energy costs, etc. Since forwards dynamics models are 'muscle'-driven, they are, therefore, more biorealistic than inverse dynamic models, and, despite utilising sophisticated optimisation techniques such as genetic algorithms, compromises are often necessary: either modelling in 2D only (e.g. Sellers et al. 2004) or limiting the number of cycles of locomotion modelled (e.g. Nagano et al. 2005). All these models have been based on rigid skeletons, with muscles simulated by force actuators and have not directly predicted the mechanics of compliant components (Fig. 182.10).

Even so, analyses may iterate 2,000 times or more and take several days on multiprocessor clusters. However, it is notable that Sellers et al. (2004) and Nagano et al. (2005) obtained very similar metabolic costs for simulated upright walking in *A. afarensis*, confirming Crompton et al. (1998) and Kramer's (1999) findings that this species could have been an effective upright biped. Sellers et al. (2004) found that the additional metabolic costs of BHBK locomotion would indeed have been near double but that total metabolic rates would have been less different in the two gaits. They went on to show (Sellers et al. 2005) that, at energetically optimal speeds, matching predicted stride lengths in *A. afarensis* to the stride lengths represented by the 3.75-Ma. Laetoli G footprint trails, if *A. afarensis* was indeed the maker, it was walking at absolute speeds within the human range, despite the difference in stature. Improvements in code and in processor availability have lead to progressively more sophisticated and more biorealistic models. Commercial code is readily available, well validated and powerful, allowing for example, for the first time, analysis of compliant effects in soft tissue, such as Caravaggi et al. (2009) study using MSC ADAMS of tension in human plantar aponeurosis.

With such type of tools, it is possible to define accurate musculoskeletal models of the locomotor system which have been successfully applied to studying pathological gaits. For example, it has been used to analyse the excessive tibial torsion, a rotational deformity about the long axis of the tibia, which is common in patients with cerebral palsy who walk with a crouch gait. Hicks et al. (2007) used a musculoskeletal model to simulate the effect of a range of tibial-torsion deformities on gait. Analysis of this model demonstrated that excessive external torsion reduces the extension capacity of soleus, which might be a significant contributor to crouch gait. Hence, using musculoskeletal models and dynamic analysis enables researchers to provide fundamental knowledge about the functionality of anatomical properties. In addition to this fundamental knowledge, this type of musculoskeletal-based analysis can help clinicians when making treatment decisions for such type of pathologies.

182.6 Discussion/Perspectives

In this chapter, we have described recent works and knowledge concerning the link between an anatomical property and its impact on gait. We have chosen to consider humans in a wider comparative framework to identify the fundamental relationship between anthropometry and biomechanics, instead of explaining gait patterns in normal and pathological human locomotion. We specifically focussed on the common features and the main differences of gait from the anthropometrical and functional point of views for human and non-human primates. One of the most promising approaches for the future consists of using simulation to identify the anatomical properties that are responsible for a given motor pattern. It could enable researchers to evaluate the role of a wide range of anatomical properties, including the consequence of some pathologies, on gait disorders.

To date, the available models allow for adequate descriptions of the upright walking in humans and compliant gait of non-human primate (e.g. Alexander 2003; Crompton et al. 1998; Sellers et al. 2004; Nicolas et al. 2009). Nevertheless, when accounting for the observed kinematic and kinetic variations within humans as well as differences between primate species (e.g. bipedal walking in bonobos, gibbons, macaques or baboons), it appears obvious that bipedal gaits cannot simply be categorised into these two single types: erected versus compliant gaits. As highlighted by the comparative anatomy, the anthropometric parameters that are potentially useful for locomotor modelling are numerous. The characterisation of general locomotor patterns (such as erected and compliant bipedal walks) are based on relatively simple anatomical model (built with few anatomical parameters). However the biomechanical characterisation of the varied patterns of bipedal gait should imply, in future developments, the use of anatomical models that are more complex and more faithful to the available anatomical data. In that perspective, the comparative approach provides some interesting ways of investigations: it increases the range of variation of the anatomical/anthropometric model and provides a functional interpretation of this variation in the frame of a normal functional pattern. In future studies, aiming at a more refined analysis of bipedal walking, the integration of additional and detailed taxon-specific anthropometric data, as well as larger ranges of variation will constitute a significant bonus. To date, their integration appears to be limited by at least: (1) the scarce kinematic and kinetic comparative data concerning normal bipedal gaits; and (2) tools of calculation which do not yet allow integration of sufficient parameters simultaneously to produce a truly biorealistic model. Research in both fields is in full development (cf. this chapter). The road to a modelling and simulating procedure that fully integrates all required anthropometric data is still long. Yet, it is not an Utopian dream to expect that anthropometric data will be increasingly used in the context of particular research, as it is already engaged in humans. We believe that a wide multidisciplinary research would constitute the ideal context in which to fill this gap.

182.6.1 Applications to Other Areas of Health and Disease

As discussed earlier, anthropology and bipedal locomotion have several applications. We know that anthropometric data reflect features which have some consequences for gait that could lead to some diseases. This is the case for obese people who exert high loads on the joints and require more muscle power to walk. Repetitive loading on the feet and other parts of the lower extremity may have structural consequences, such as musculoskeletal pain, tenderness over the calcaneal tuberosity at the point of attachment of the plantar fascia, or osteoarthritis of the knee (Hill and Cutting 1989). Just as for obese people, compensatory strategies can be found during gait in elderly people.

Table 182.2 Key facts of anthropometry in bipedal locomotion

1. The anatomical parameters that are potentially useful for locomotor modelling are numerous.
2. Thus, the biomechanical characterisation of the varied patterns of bipedal gait in primates should imply, in future developments, the use of complex anatomical models, such as the integration of detailed taxon-specific anatomical and anthropometrical data.
3. To date, their integration appears to be limited by at least: (1) the scarce kinematic and kinetic data concerning the bipedal locomotion of non-human primates; and (2) tools of calculation which do not yet allow integration of sufficient parameters simultaneously to produce a truly biorealistic model.
4. A wide multidisciplinary research would constitute the ideal context for developing more detailed models to understand the link between anatomical and anthropometrical parameters and corresponding movements for a wide range of species.

This table lists the key facts of anthropometry in locomotion and especially how anatomy could be taken into account in understanding and simulating human locomotion

These adaptations can be caused by strength and mobility impairment, rheumatic (arthritis) and orthopaedic (low back pain and joint replacement) pathologies. A walking style which engenders increased energy expenditure by the low-back- and hip muscles could result in either chronic muscle fatigue or increase the articular forces acting on the hip and spine, leading to degenerative changes in joint cartilage, both of which can lead to a sedentary lifestyle and thus further increase functional limitations.

Musculoskeletal models have been initially introduced in medicine and especially surgery for rehabilitation. Hence, shortening a muscle, a tendon or modifying the tibial plateau, etc., is performed in order to modify the movement of the patient. The software OpenSim (http://simtk.org/home/opensim) has been developed to help researchers and doctors to carry out our experiments on virtual patients to simulate the impact of changing anatomical data of the subjects on gait. Many works cited in the last section are based on the same type of approaches (reported in Table 182.2).

Summary Points

- The link between an anatomical property and its impact on gait relies on accurate anthropometrical data. Considering human among primates in a wider comparative framework would enable us to identify the fundamental relationship between anthropometry and biomechanics.
- The spatial and temporal parameters of gait are recognised to be of clinical relevance in the assessment of motor pathologies. Consequently, they are considered as important functional measures (or *vital signs*) of gait.
- Limb compliance leads to smaller oscillations of the centre of mass and alters the magnitude of the peak vertical substrate reaction force and the shape of the force–time plot. During normal walking, humans generate a vertical ground reaction force curve with two distinct peaks that are both greater than body weight. This force pattern is characteristic of a stiff-legged gait in which the centre of mass is highest at midstance and lowest at double support. By contrast, in most non-human primates, bipedal walking generates single-peaked force curves in which the peak is much closer to body weight.
- One of the most striking aspects of bipedal walking in non-human primates is that they, unlike humans (who use extended hip and knee joints during walking), often adopt a relatively flexed (bent-hip bent-knee) and more compliant limb posture.
- In biomechanics, the three most important parameters for a body segment are segment centre of gravity (the mean of the mass distribution of a segment), the radius of gyration (essentially the

standard deviation of mass distribution) and moment of inertia (the characteristic pattern of mass distribution acting to resist angular acceleration in a given plane of mass acting to resist a given angular acceleration).

- Recent studies increasingly account for anatomical complexity, for example, in the development of musculoskeletal models of the foot in a comparative perspective. However, the resulting set of variables is so large that it is difficult to obtain reliable dynamic data: the redundancy of the actuators leads to using hypotheses/constraints in computing muscle activation instead of measurements.
- A combination of several mechanisms are likely to contribute to energy conservation: pendular mechanisms involving exchange of out-of phase potential and kinetic energies, spring-mass mechanisms where energy is stored in elastic tissue and aligning the path of the COM and the trajectory of the GRF.
- Movement, including bipedal locomotion, depends on numerous anatomical parameters that affect the way turning forces are exerted about joints: physiological cross-sectional area of a muscle, moment arm of this muscle, the moving joint's centre or axis of motion, position of the origin and insertion of a muscle…
- Inverse and forward dynamic analysis are vital elements in the analysis of internal force and motion and have begun to be accepted as powerful tools in reconstruction of the behaviour of extinct species, known only from fossils.
- With these various advances in computer simulation, this approach is now a recognised technique in studies of the evolution of the human locomotor system and is likely to become increasingly a core element in the toolkit of biological anthropology and anthropometry.

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Chapter 183
Use of Anthropometry for the Measurement of Lower Extremity Alignment

Annegret Mündermann

Abstract The measurement of lower extremity alignment is an important component of the diagnosis and prognosis of musculoskeletal diseases. In addition, poor lower extremity alignment has been identified as a risk factor for incurring injuries during physical activities. Relating anthropometric information and limb alignment to joint loads during daily activities enables the identification of risk factors for musculoskeletal injuries and diseases.

Lower extremity alignment can be assessed directly using medical imaging techniques or indirectly using established clinical measures. Palpation of anatomical landmarks and anthropometric information is currently used for many indirect methods assessing the alignment of the lower extremity. Current clinical methods for the measurement of lower extremity alignment include visual observation and methods using callipers, inclinometers or goniometers. A recent study showed the potential of using position capture similar to what is typically performed during gait analysis as an alternative method for the assessment of lower extremity alignment. Mechanical axis alignment assessed using this method correlated with radiographic measurements, the current gold standard, and with disease severity in patients with medial compartment knee osteoarthritis (OA). In addition, novel technology including functional joint center determination and markerless motion capture has a great potential in providing objective and thus reliable assessments of lower extremity alignment especially in populations that would not routinely undergo radiographic examination.

Indirect assessment of lower extremity alignment can be challenging in obese patients and in the elderly. Establishing relationships between anthropometric information, limb alignment and detailed information measured using novel techniques is an important step in increasing the relevance of simple and quick clinical measurements for a larger range of sub-populations in health and disease.

Abbreviations

ACL	Anterior cruciate ligament
ASIS	Anterior superior iliac spine
ICC	Intraclass correlation coefficient
OA	Osteoarthritis
MRI	Magnetic resonance imaging

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_183,

183.1 Introduction

Proper alignment of the skeleton during stance, ambulation, and occupational and sports activities is critical for optimal function, energy, efficiency and preservation of a healthy musculoskeletal system. During static and dynamic activities, the lower extremity fulfills a range of biomechanical tasks, including supporting the trunk, force production, load transfer, and maintaining balance. Sub-optimal alignment of the lower extremity during these tasks increases the risk for acute injury to the musculoskeletal system and the development of chronic tissue damage and degeneration, leading to excessive wear and loosening of the prosthetic implant in total joint replacement patients. The importance of this fact is widely recognized in the areas of orthopedics, ergonomics, physical therapy, sports, and other disciplines concerned with the prevention, rehabilitation, and treatment of musculoskeletal injuries and diseases.

A range of methods have been developed for the measurement of lower extremity alignment. For instance, the use of radiographic images facilitates the direct measurement of skeletal alignment but is limited to specific static or quasi-static postures. While other methods allow for the measurement of lower extremity alignment in different postures or even in dynamic situations, these methods rely on the accurate palpation of anatomical landmarks and the use of anthropometric information to estimate skeletal alignment indirectly.

In this chapter, common definitions of lower extremity alignment are given, and the role of lower extremity alignment for injury and disease development and for the aging population is discussed. Established and novel methods for the measurement of lower extremity alignment are described with a focus on methods that use anthropometric information. In the final section of this chapter, challenges and limitations of applying these methods and the use of anthropometric information to specific patient groups, including obese persons and the elderly, are considered.

183.2 Common Measures of Lower Extremity Alignment

For optimal function, the lower extremity should be properly aligned in all three planes, which are the frontal, sagittal, and transverse planes. Common measures describing the alignment of the femur and tibia in the frontal plane are the *anatomical axis*, the *mechanical axis*, and the *quadriceps angle* (*Q*-angle). The *sagittal plane mechanical axis* describes the alignment of the lower extremity in the sagittal plane in full extension. Lower extremity alignment in the transverse plane is described by the *natural foot position* during stance. While these measures are applicable to the general population, they might not be appropriate measures for the assessment of limb alignment in patient groups with severe limb deformities. Table 183.1 summarizes the definitions of these parameters.

183.2.1 Anatomical Axis

The anatomical axis of a bone is the mid-diaphyseal line represented by a line through the medullary cavity of the bone. The angle between the anatomical axis of the femur and the anatomical axis of the tibia represents the anatomical axis angle which normally is 6° of valgus (Schünke et al. 2005).

The anatomical axis of a long bone can only be measured accurately using imaging methods such as radiography, magnetic resonance imaging (MRI), or ultrasonograms. While the anatomical axis

Table 183.1 Key features of measures describing lower extremity alignment

Parameter	Definition	Anatomical plane
Anatomical axis of a bone	Mid-diaphyseal line represented by a line through the medullary cavity of the bone	Sagittal and frontal
Anatomical axis angle	Angle between the anatomical axis of the femur and the anatomical axis of the tibia	Frontal
Mechanical axis of a bone	Straight line connecting the joint centers of the joints proximal and distal to the joint of interest	Frontal
Mechanical axis angle	Angle between a line from the center of the femoral head to the center of the femoral intercondylar notch, and a line from the center of the tips of the tibial spines to the ankle talus	Frontal
Quadriceps angle (Q-angle)	Angle formed by the longitudinal axis of the femur and a line from the center of the patella to the center of the tibial tuberosity	Frontal
Natural foot position	Angle formed by the longitudinal bisection of the foot and the posterior–anterior axis	Transverse
Leg length discrepancy	Difference in leg length	NA

This table lists the definitions of measures that describe lower extremity alignment and anatomical planes in which alignment is described by these measures

alignment is of great importance in malaligned limbs, such as recurvatum deformity of the tibia or flexion deformity of the femur, these deformities can be poorly assessed by methods using anthropometric measurements. Hence, methods to assess anatomical axes (for instance, Cooke et al. 1991) are not described in this chapter.

183.2.2 Mechanical Axis

The mechanical axis of a bone is defined as the straight line connecting the joint centers of the joints proximal and distal to the joint of interest. The mechanical axis of the lower extremity is defined by a line running through the center of the hip joint to the center of the ankle joint. In a neutrally aligned leg, this line passes through the center of the knee joint. The mechanical axis angle is defined as the angle between a line from the center of the femoral head to the center of the femoral intercondylar notch, and a line from the center of the tips of the tibial spines to the ankle talus (Fig. 183.1) (Moreland et al. 1987). In the normal femur, the mechanical and anatomical axes deviate, whereas, in the normal tibia, the mechanical and anatomical axes are essentially represented by the same line.

In a varus knee, the mechanical axis passes medial to the center of the knee joint resulting in positive values for the mechanical axis angle, and, in a valgus knee, the mechanical axis passes lateral to the center of the knee joint resulting in negative values for the mechanical axis angle. The mechanical axis angle in normal volunteers is 1.3° ± 2° (Hsu et al. 1990; Moreland et al. 1987). In older females, the mechanical axis angle measures 0° (Glimet et al. 1979). Patients with OA of the medial compartment have varus aligned knees with mechanical axis angle of 6.0° ± 4.5° (Mündermann et al. 2004). As the disease progresses, mainly cartilage in the medial compartment deteriorates leading to gradually increasing varus alignment.

The distance between the line of action of the ground reaction force and the knee joint center increases with greater varus alignment for a given patient. This change in the geometric alignment typically translates into a greater dynamic knee varus moment. The greater the varus moment, the more load is transferred through the medial compartment of the knee, leading to a faster deterioration

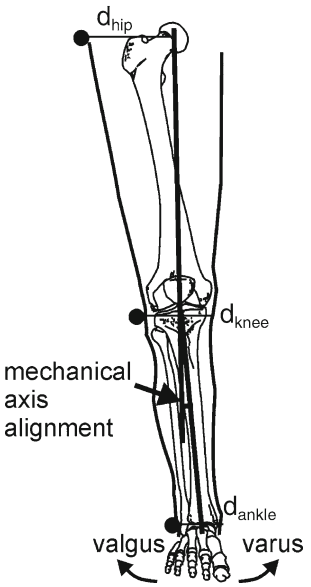

Fig. 183.1 Definition of the mechanical axis alignment of the lower leg in the frontal plane. Mechanical axis alignment was defined as the angle between a *line* from the *center* of the femoral head to the *center* of the femoral intercondylar notch, and a *line* from the *center* of the tips of the tibial spines to the ankle talus (Moreland et al. 1987). Joint centers were determined based on skin markers on the greater trochanter, lateral joint line of the knee, and lateral malleolus combined with measured joint correction factors. Positive values indicate varus alignment, and negative values indicate valgus alignment. The limbs were aligned with the laboratory coordinate system for the position capture method (Reprinted from Mündermann et al. (2008) with permission of Elsevier)

of cartilage (Andriacchi et al. 2004). This vicious cycle can be broken by interventions aimed at realigning the lower extremity such as osteotomies (Schipplein and Andriacchi 1991), braces, or footwear (Fisher et al. 2007).

In full extension, the normal sagittal plane mechanical axis passes anterior to the center of rotation of the knee joint allowing the knee to be locked in full extension and the quadriceps muscle to relax. In patients with a hamstring contracture, the mechanical axis runs posterior to the knee joint center requiring continuous quadriceps muscle effort to maintain upright stance. In hyper-extended knees, the mechanical axis runs anterior to the knee joint center placing additional load on soft-tissue structures to stabilize the joint in this position. However, because the knee moves in the sagittal plane during locomotion and other physical activities, static sagittal plane alignment generally provides limited value for lower extremity function during dynamic activities in healthy persons. By contrast, a pathological hamstring contracture prevents full extension of the knee that can be assessed statically and is manifested dynamically as crouch gait (Rab 1992).

183.2.3 Quadriceps Angle (Q-Angle)

The quadriceps angle or *Q*-angle is defined as the angle formed by the longitudinal axis of the femur, representing the line of action of the quadriceps muscle, and a line that represents the direction of the

patellar tendon. Clinically, the angle is obtained as the angle between a line connecting the center of the patella with the anterior iliac spine above and a line connecting the center of the patella with the tibial tuberosity. The *Q*-angle is normally 11.5° ± 2.4° in men and 13.9° ± 2.6° in women, with their quadriceps in a relaxed position (Medina McKeon and Hertel 2009). The angle becomes smaller when the quadriceps muscle is contracted.

Among other factors, the *Q*-angle is affected by foot position (Olerud and Berg 1984), and thus foot position should be controlled during its assessment. While a greater *Q*-angle is commonly associated with an increased likelihood of the quadriceps pulling the patella laterally, its importance for the risk of knee disorders such as patellofemoral pain syndrome or anterior knee pain is controversial (Fredericson and Yoon 2006). One main concern with using the *Q*-angle as an estimate of patella alignment is that in cases of lateral patellar subluxation, the *Q*-angle decreases. Hence, lateral subluxation masks the measurement that is designed to evaluate it.

183.2.4 Natural Foot Position

The natural foot position is defined as the angle formed by the longitudinal bisection of the foot and the posterior–anterior axis and is usually assessed during natural bipedal stance. The longitudinal bisection of the foot normally falls between the center of the plantar heel and the second and third metatarsals (Aharonson et al. 1980). Dynamically, the alignment in the transverse plane is assessed as the foot progression angle, which is the angle formed by the longitudinal bisection of the foot and the line of forward progression.

The natural foot position and foot progression angle show a large variability even in normal populations ranging from 6° to 21° (Seber et al. 2000). Several factors can influence the natural position and foot progression angle, including hip external rotation, femur torsion, and tibia torsion. Thus, these parameters can indicate a range of pathologies or functional abnormalities, such as muscle paresis or tibia torsion following fracture. Excessive internal or external rotation of the foot during gait affects the mechanical load placed on the joints of the lower extremity.

183.2.5 Leg Length Discrepancy

Leg length discrepancy is defined as a difference in leg length. Normally, both legs have close to the same length, facilitating symmetry during stance and dynamic activities. Leg length discrepancy can be caused by a true structural difference between the tibiae or the femora. This discrepancy can simply be a natural variation between the two sides of the body. Other causes for anatomical leg length discrepancy include injury to a bone, bone infection, bone dysplasias, arthritis, or neurological conditions. In addition, leg length discrepancy can have functional reasons such as joint dysfunction or be caused by differences in muscle mass.

However, even with two legs of the same length, the patient may present with functional leg length discrepancy because of a pelvic tilt, curvature in the back, or other parameters (see Chap. 44). While leg length discrepancy can be assessed using anthropometric measurements as described below, it is frequently assessed dynamically during a symmetric functional task.

183.3 Common Methods for the Measurement of Lower Extremity Alignment

183.3.1 Direct Measurement Methods

Direct methods for the measurement of lower extremity alignment are based on imaging of the skeleton itself using radiography or MRI techniques and subsequent manual or automatic measurement of the angle between the line connecting the hip and knee joint centers and the line connecting the knee and ankle joint centers (Table 183.2).

183.3.1.1 Radiographic Measurements

Lower extremity alignment is typically measured from frontal plane radiographs of the entire lower extremity during double-support standing. Using the gold standard or traditional method for the measurement of lower extremity alignment, single weight-bearing radiographs including the hip, knee, and ankle joints are captured (Moreland et al. 1987). To minimize measurement variation related to limb rotation, each patient is positioned with the tibial tubercle anterior. Using a ruler, lines are then drawn on the film from the center of the femoral head to the center of the femoral intercondylar notch, and from the center of the tips of the tibial spines to the ankle talus. Subsequently, a goniometer is used to measure the angle between these two lines on the X-ray film. These full-limb radiographs require administration of radiation to the pelvis, a grid, and a large film, as well as the expertise of the personnel to overcome the technical difficulties such as choice of radiation dose because of the considerable difference in the amount of soft tissue at the hip and the ankle joints in most patients.

In some cases, partial radiographs are sufficient for obtaining acceptable estimates of lower extremity alignment. For instance, Kraus et al. (Kraus et al. 2005) measured the anatomical axis angle on a fixed-flexion posterior–anterior knee radiograph with the feet 10° externally rotated, the knees and thighs touching the vertical platform anteriorly, and the X-ray beam angulated 10° caudally. The anatomical axis was defined as the angle formed by the intersection of two lines originating from points bisecting the femur and tibia and converging at the center of the tibial spine tips. The origin of these lines was 10 cm from the knee joint surfaces. The angle of the anatomical axis was also determined on an anterior–posterior full-limb radiograph using the same landmarks, originating 10 cm from the knee-joint surfaces. The anatomical axis angles obtained using these partial-view radiographs correlated moderately with the mechanical axis angle obtained from full-limb radiographs. However, an offset between anatomical axis angles and mechanical axis angles of 3.5° in women and 6.4° in men was found. This fact must be taken into consideration when choosing an appropriate method for determining lower extremity alignment.

Advances in computer technology allow capturing radiographs in digital formats. Electronic drawing tools are commonly used to superimpose lines onto the digital image and for the automatic calculation of the angle between these lines (Sailer et al. 2005). However, to achieve acceptable reproducibility with these methods, a standardized set of anatomic landmarks is required (Wong et al. 2009). Recently, fully automated methods for the measurement of lower extremity alignment from digital radiographs have been introduced (Fakhrai et al. 2009) that eliminate errors potentially introduced by the tester, thus improving the measurements' reproducibility.

Table 183.2 Key features of measurement of lower extremity alignment

Method	Description	Reliability – Comments
Direct methods		
Full limb weight-bearing radiographs	Lines are drawn on the X-ray films connecting joint centers; the angle between these lines is measured using a goniometer.	1 – gold standard
Partial limb weight-bearing radiographs	Lines are drawn on the X-ray films extrapolating the orientation of the bones; the angle between these lines is measured using a goniometer.	2 – tester is guessing the orientation of the bone
Magnetic resonance images	Lines are drawn on the images connecting joint centers; the angle between these lines is measured using software.	2 – potential image distortion; generally non-weight bearing
Indirect methods		
Visual observation	Classification of alignment based on the criteria during adducted stance: varus – medial malleoli touch first; valgus – knees touch first; neutral – knees and ankles touch simultaneously.	Not available – no grading within alignment category
Caliper	Adducted stance. For varus knees: distance between the medial knee joint lines; for valgus knees: distance between the medial malleoli.	1 – combined measurement for both knees
Plumb line	Plumb line positioned between knees. For varus knees: distance between the plumb line and the medial knee joint line; valgus knees: distance between plumb line and medial malleolus	1 – separate assessment of each knee
Inclinometer	Gravity inclinometer attached to calipers. Shoulder width foot position. Angle between a line connecting tibial tuberosity and neck of talus with respect to the vertical.	1 – orientation of the tibia
Goniometer	Shoulder width foot position. Origin of goniometer over center of patella, arms aligned with mid-thigh and with patellar tendon. Angle between goniometer arms.	2 – patellar tendon estimation difficult because of its short length
Novel methods		
Photogrammetry with palpation	Calculation between lines connecting adjacent joints determined by anatomical landmarks and joint correction factors with skin markers.	2 – depends on palpation of anatomical landmarks
Photogrammetry with functional joint center	Calculation between lines connecting adjacent joints determined by segment motion through joint range of motion with skin markers.	1 – tester independent joint centers, segment defined by tester
Markerless motion capture	Calculation between lines connecting adjacent joints determined by segment motion through joint range of motion without markers.	Not available – tester independent joint center and segment identification

This table lists direct and indirect methods for the measurement of lower extremity alignment. Direct methods are measurements of the alignment of the bone themselves using imaging techniques. Indirect methods are measurements utilizing anthropometric information for the estimation of joint center locations or bone orientation. The reliability of each method is graded where *1* good reliability; *2* acceptable reliability; *3* poor reliability

183.3.1.2 Magnetic Resonance Imaging (MRI) Measurements

Compared to radiography, MR imaging systems do not emit any radiation, and are thus considered safer for the patient. The main advantage of using MRI techniques for the assessment of lower extremity alignment is the fact that musculoskeletal structures can be evaluated in three dimensions. However, only open-bore MRI systems allow the patient to be positioned in an upright weight-bearing

position that is similar to the patient's position during the traditional radiographic method. Hinterwimmer et al. (Hinterwimmer et al. 2008) developed and applied a uniform radiation-free measurement technique for the analysis of leg geometry. MR images of the hip, thigh, knee, shank, and ankle were obtained sequentially in matching imaging planes and without artificial shortening. Reproducible results were obtained using a phantom leg. In patients, leg length was generally underestimated compared to values obtained from reference radiographs. Long-range measurements across the entire field of view produce an underestimation of acquired distances because of lower strength gradients at the imaging margins. Mechanical axis alignment angles in all knees were generally underestimated with a significant underestimation of −3.6° in knees with valgus alignment. While this technique entails a cumbersome setup to align the patient's limb in the magnet, it does not expose the patient to radiation and imaging time is around two minutes. Moreover, using additional axial images along the femoral head and neck, the knee and the ankle facilitate torsion measurements of the femur and tibia, and thus allows the assessment of lower extremity alignment in all three anatomical planes.

183.3.2 Indirect Measurement Methods

Indirect methods for the measurement of lower extremity alignment are based on estimating joint center positions through palpation and anthropometric correction factors and the subsequent measurement of the angle between the line connecting the hip and knee joint centers and the line connecting the knee and ankle joint centers using tools including inclinometers, calipers, goniometers, and, more recently, photogrammetric systems. All indirect measurement methods for the assessment of lower extremity alignment are typically validated against the traditional radiographic method before being established in clinical practice or research.

183.3.2.1 Joint Center Determination

Joint centers of lower extremity joints cannot be readily identified. However, databases of cadaveric and radiographic data link joint center positions to anatomical landmarks that can be *palpated* under the skin. For instance, a variety of essential anatomical landmarks has been proposed for locating the hip joint center. The method proposed by Andriacchi et al. (Andriacchi et al. 1980, 1982; Andriacchi and Strickland 1985) identifies the medio-lateral hip joint center coordinate 2.5 cm inferior to the point halfway between the anterior superior iliac spine (ASIS) and the pubic tubercle with the anterior–posterior and proximal–distal coordinate defined by the greater trochanter. Alternate methods (Bell et al. 1989, 1990; Seidel et al. 1995; Tylkowski et al. 1982) locate the hip joint center as a percentage of the distance between the ASIS and various anatomical landmarks. Methods based on greater trochanter position have been criticized for unacceptable accuracy (Cappozzo 1991; Neptune and Hull 1995). Only few methods have been validated in large sample sizes that include both men and women and, in some cases, children. The Andriacchi and Strickland method (Andriacchi and Strickland 1985) has been validated against radiographs in a cohort of 39 normal-weight children and 31 normal-weight adults resulting in a maximum error of 3.6 cm with 95% certainty (Bell et al. 1989). The Tylkowski method (Tylkowski et al. 1982) alone resulted in 3.3 cm mean error with 95% certainty, while the combination of the Andriacchi and Strickland method and the Tylkowski method resulted in an improved accuracy of 2.6 cm error with 95% certainty (Bell et al. 1989; Bell et al. 1990). Seidel et al. (Seidel et al. 1995) measured pelvic bones from 30 male and 35 female cadavers to develop an alternate palpation method that locates the hip joint center as a percentage of

pelvic depth, height, and width. Other studies reported validations of palpation methods for as few as two subjects using radiography (Kirkwood et al. 1999; Tylkowski et al. 1982), roentgen stereophotogrammetric analysis (Leardini et al. 1999), computer tomography scanning (Fieser et al. 2000), and MRI (Aguinaldo et al. 2003).

Similarly, different definitions of the knee and ankle joint center locations exist. For the knee, the joint center for radiographic measurements is defined as the femoral intercondylar notch (Moreland et al. 1987). Using palpation methods, the knee joint center has been defined as the midpoint between the most medial and lateral aspects of the tibia plateau or as the midpoint between the most prominent medial and lateral aspects of the femur epicondyles (Andriacchi et al. 1998; Schipplein and Andriacchi 1991). For the ankle joint, the joint center for radiographic measurements is defined as the center of the tips of the tibial spines to the ankle talus (Moreland et al. 1987). Using palpation methods, the ankle joint is typically defined as the midpoint between the tips of the medial and lateral malleoli (Wu et al. 2002). While the effect of using any of these definitions on mechanical axis angle measurements is negligible, the proper definition of the joint centers is very critical for other applications such as the estimation of joint loads using kinetic analysis and anatomical modeling.

183.3.2.2 Goniometer, Inclinometer or Caliper Measurements and Visual Observation

Clinically, several non-radiographic methods for the measurement of knee alignment have been used, including visual observation, goniometry, and caliper and inclinometer methods of measurement. *Visual observation* is used for the method described by Magee (Magee 1992) to categorize varus, valgus, or neutral alignment. Patients are asked to adduct their lower limbs slowly until either the knees or ankles touch. If the medial malleoli touch first, the participant is classified as having varus malalignment. If the knees touch first, the participant is classified as having valgus malalignment. If knees and ankles touch simultaneously, alignment is considered neutral. Malalignment that is evident using Magee's method can be quantified using a *caliper* marked in 1-mm increments (Hinman et al. 2006). In patient with varus knees, the distance between the left and right medial knee joint lines is recorded (Fig. 183.2a). In patients with valgus knees, the distance between the left and right medial malleoli is recorded. Because the caliper method is influenced by the alignment of both knee joints, a modification of this method can be used to more accurately assess alignment of the affected knee only. A *plumb line* is positioned between the lower limbs (Hinman et al. 2006; Jonson and Gross 1997). For varus knees, the distance between the plumb line and the symptomatic medial knee joint line is measured using a caliper (Fig. 183.2b). For valgus knees, the distance between the plumb line and the medial malleolus of the symptomatic side is measured using a caliper.

A novel method for assessing lower limb alignment has been recently introduced by Hinman et al. (Hinman et al. 2006) to assess orientation of the tibia with respect to the vertical. A *gravity inclinometer* is attached to a set of calipers. Patients are positioned with their weight distributed equally over both feet with their feet shoulder width apart. The tibial tuberosity and neck of talus are identified. The caliper arms are placed on these landmarks (Fig. 183.2c). The angle of the tibia with respect to the vertical (180°) is recorded.

For the measurement of alignment using a long-arm *goniometer*, patients are asked to stand with their weight distributed equally over both feet with their feet positioned shoulder width apart (Kraus et al. 2005). The origin of the goniometer is positioned over the center of the patella, and the arms are aligned with the mid-thigh above the knee and with the patella tendon below the knee (Fig. 183.2d).

The inclinometer, caliper, and plumb line methods have been shown to be reliable in patients with knee OA (ICC > 0.94; (Hinman et al. 2006). The goniometer method was slightly less reliable with an ICC of 0.84, and reliability for the visual observation method has not been reported. All of these

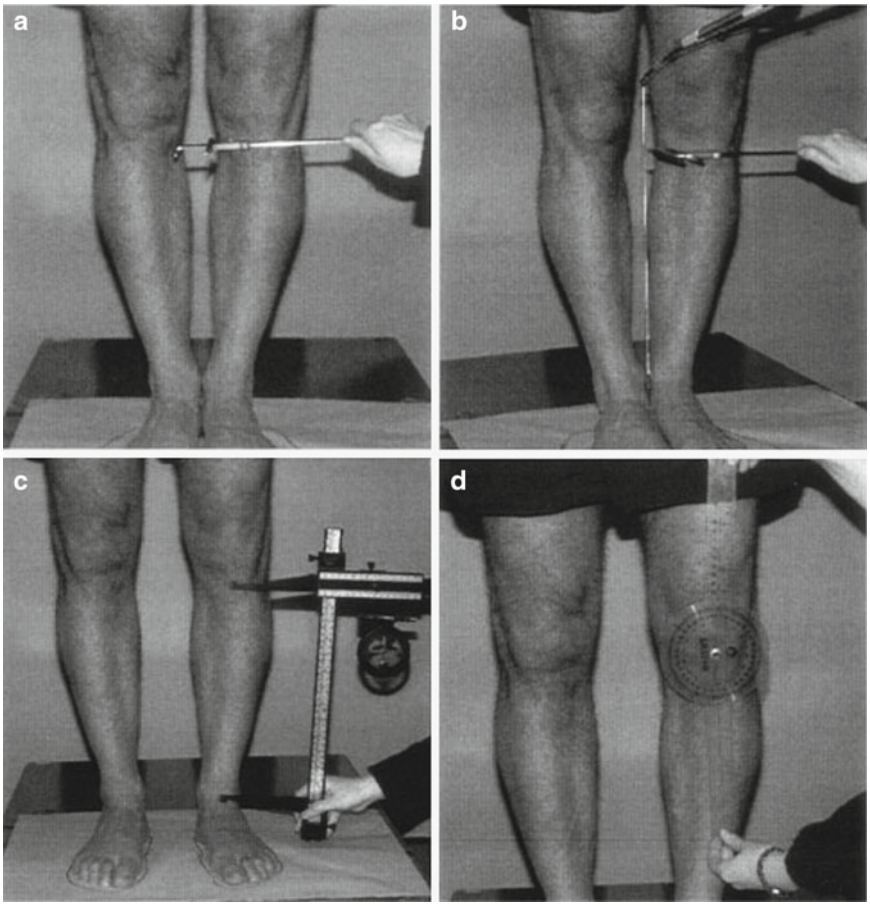

Fig. 183.2 Determination of knee alignment using common clinical measures. Determination of knee alignment using (**a**), the caliper method (for a varus knee), (**b**), the plumb-line method (for a varus knee), (**c**), the inclinometer method, and (**d**), the goniometer method (Reprinted from Hinman et al. (2006) with permission of John Wiley & Sons, Inc.)

Table 183.3 Key features of calipers, goniometers, and inclinometers

1. Calipers are devices that measure distances between two points or two landmarks.
2. Goniometers consist of two arms that are connected in a hinge joint.
3. The arms of goniometers are typically aligned with two body segments to measure the angle between these two segments.
4. Inclinometers measure the angle between the device arm and the vertical (inclination).
5. The angle between two segments can be calculated from the inclination of both segments.
6. These tools are common clinical tools mainly because of their low cost, because they are simple and provide instant results.
7. The reliability of these tools depends on the clinician's ability to locate anatomical landmarks correctly.

This table lists the key facts of clinical tools for measuring lower extremity alignment including calipers, goniometers, and inclinometers

methods offer great clinical application with regard to cost, simplicity of use, and speed of result. However, these methods require considerable tester training and experience to achieve acceptable results. Hence, the use of objective methods for the assessment of lower limb alignment is advised to allow for comparisons between studies and centers (Table 183.3).

183.3.3 Novel Measurement Methods

183.3.3.1 Photogrammetry Measurements

Joint motion and joint load during walking are commonly assessed using gait analysis based on stereophotogrammetric systems and reflective markers attached to the skin. Frequently, anthropometric measurements of patients' lower extremity joints are taken to determine the joint center locations relative to these skin markers. The knowledge of the joint center location is a prerequisite for the calculation of joint load during dynamic activities.

The goal of a recent study (Mündermann et al. 2008) was to investigate if the mechanical axis alignment can be estimated using anatomical landmarks and anthropometric measurements during stance and a stereophotogrammetric system and if the association with OA severity is similar for both measurements. It was hypothesized that the mechanical axis alignment measured from standing radiographs can be predicted from the mechanical axis alignment measured using anatomical landmarks and anthropometric measurements, and that mechanical axis alignment predicted from anatomical landmarks is associated with OA severity.

Reflective markers were placed by the same tester on the proximal aspect of the greater trochanter, the most lateral aspect of the joint space between tibia and femur, the most lateral aspect of the lateral malleolus, and the 5th metatarsal head in 62 patients with bilateral OA in the medial compartment of the knee. Marker data were captured using four high-speed cameras (120 frames/s; MCU240, Qualisys Medical AB, Gothenburg, Sweden). Anthropometric measurements were taken to determine the distance from the skin markers to the joint centers in the frontal plane. In this study, the hip joint center was assumed to be located 2.5 cm distal of the midpoint of a line connecting the ASIS to the pubic tubercle (Andriacchi and Strickland 1985). The hip joint correction factor was measured as the distance between this point and the most lateral aspect of the skin overlying the greater trochanter. The knee joint center was assumed to be located at the midpoint of the knee joint line. The knee joint correction factor was measured as half the distance between the skin overlying the medial and lateral joint line. The ankle joint center was assumed to be located at the midpoint of the trans-malleolar line. The ankle joint correction factor was measured as half the distance between the skin overlying the medial and lateral malleoli. The marker radius (0.5 cm) was taken into consideration when determining the joint center locations.

The mechanical axes alignment of all knee joints was calculated as the angle between a line from the hip joint center to the knee joint center, and a line from the knee joint center and the ankle joint center from a single standing trial taking into account the radius of the skin markers. To minimize measurement variation related to limb rotation, the patient's position was aligned to the laboratory coordinate system. The angle γ between the vector from the heel to the fifth metatarsal head (v_{foot}) and the anterior–posterior axis (y) was calculated as

$$\gamma = 180 / \pi * \arccos(v_{foot} \bullet y / (|v_{foot}| * | y |)$$

The entire limb was then rotated by γ about a rotation axis passing through the ankle and hip joint centers. The mechanical axis δ was then calculated as

$$\delta = 180 / \pi * \arccos(v_{femur,zx} \bullet v_{tibia,zx} / (|v_{femur,zx}| * | v_{tibia,zx} |),$$

where $v_{femur,zx}$ was the vector connecting the knee joint center with the hip joint center and $v_{tibia,zx}$ was the vector connecting the ankle joint center and the hip joint center projected into the zx-plane. Neutral alignment was defined as zero, varus alignment as positive angles, and valgus alignment as negative angles.

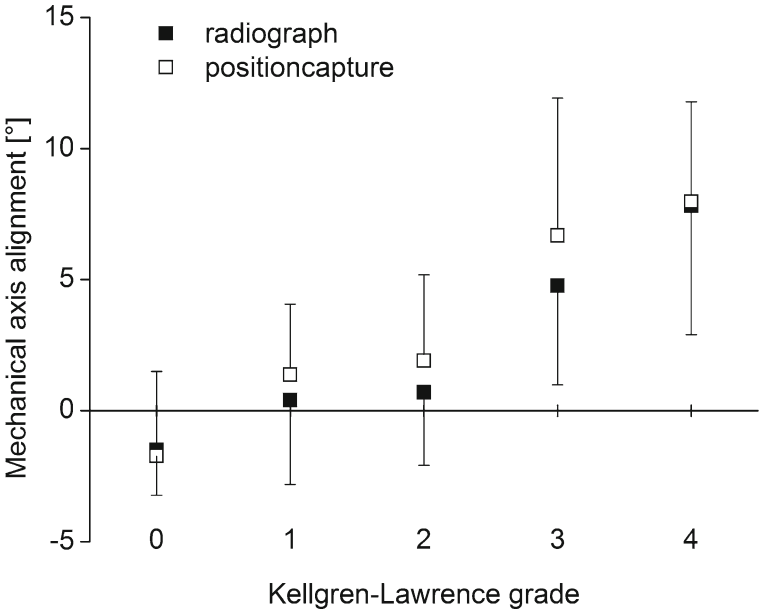

Fig. 183.3 Association between mechanical axis alignment and severity of knee osteoarthritis. Varus alignment based on mechanical axis alignment from radiographs and from position capture increased with increasing osteoarthritis severity (Kellgren–Lawrence grade; *0* no signs of osteoarthritis to *4* complete loss of articular cartilage). Values are mean values ± one standard deviation (Reprinted from Mündermann et al. (2008) with permission of Elsevier)

The mechanical axis alignment measured from radiographs ranged from −6° to +15° (6° valgus to 15° varus alignment). The average mechanical axis alignment based on position capture was 1.2° greater than the average mechanical axis alignment based on radiographs (position capture: 3.8 ± 4.7°; radiograph: 2.6 ± 4.4°; $P = 0.001$). A significant correlation was found between the mechanical axis alignment measured by position capture and by radiographs ($R = 0.738$; $P = 0.001$). The mechanical axis alignment based on position capture was not associated with age ($P = 0.902$), sex ($P = 0.849$), or BMI ($P = 0.568$), but was associated with Kellgren–Lawrence grades ($R^2 = 0.807$; $P < 0.001$). Varus malalignment measured from position capture increased with increasing OA severity (Fig. 183.3).

The strength of estimating the mechanical axis from position capture is that the measurement can be taken automatically during a reference trial in gait analysis. In addition, the information presented in this study could also be obtained from two-dimensional frontal view still images of the subject's lower extremity with markers on anatomical landmarks and anthropometric measurements. The measurement of the mechanical axis alignment using anatomical landmarks and anthropometric measurements would allow the estimation of the mechanical axis alignment in populations that are typically not subjected to a full-limb radiograph including healthy control subjects, subjects after anterior cruciate ligament (ACL) or meniscus injury or surgery, and even children when they undergo gait analysis. Information on limb alignment in these publications will allow the determination of the role of limb alignment as a risk factor for injuries and for the development and progression of degenerative joint diseases. However, the possibility of varying results depending on the marker set chosen for the measurements warrants the use of a consistent marker set such as the one used in this study.

183.3.3.2 Functional Joint Center Determination

Because of the difficulty of palpating anatomical landmarks for locating joint centers, joint center positions have been defined *functionally* in recent years. These methods require motion analysis equipment that is used to record the motion of one segment (e.g., the high) relative to an adjacent

segment (e.g., the pelvis). These methods have been shown to produce more reproducible results than methods based on palpation of anatomical landmarks (Besier et al. 2003).

All functional methods identify a joint center as the functional center of rotation between two adjacent segments. The various functional algorithms require data describing rotations of the specific joint being studied throughout its range of motion. For instance, in order to estimate the hip joint functional center of rotation, the thigh and pelvis are equipped with markers and the movement of the segments are recorded while the thigh is actively or passively rotated relative to the pelvis. Algorithms proposed for functional methods using reconstructed marker positions are based on the assumption that the distance between femoral markers, or their centroid, and the center of rotation does not vary. Methods that entail no geometric constraints between markers include quadratic best sphere fitting (Cappozzo 1984), quartic best sphere fitting (Gamage and Lasenby 2002), and quasi-intersection between mid-orthogonal planes and vectors connecting each marker position in two arbitrarily chosen instants of time (Halvorsen et al. 1999). Other methods impose that the distance between femoral markers must be invariant, that is, the femoral marker cluster must be rigid (Holzreiter 1991; Woltring 1990). Other factors including stereophotogrammetric error, type and amplitude of the relative movement between the pelvis and femur, number of markers used, and geometry and location of the femoral marker cluster may influence the performance of functional methods.

Similar to the palpation methods, only few functional methods have been validated against hip joint center locations measured using three-dimensional medical images. Bell et al. (Bell et al. 1989; Bell et al. 1990) reported that functional methods were less accurate than palpation methods when compared against dual radiographic images in ten able-bodied males. However, in these studies, the thigh segment was defined by a single marker. By contrast, Leardini et al. (Leardini et al. 1999) defined the thigh segment by a minimum of three markers and found that functional methods were more accurate than palpation methods when compared to dual radiographic images in 11 able-bodied males (8–16 mm vs. 25–30 mm error, respectively). Functional methods have been suggested for use in populations in which the anatomical landmarks required by palpation techniques are difficult to find and mark during activity (Besier et al. 2003).

183.3.3.3 Markerless Motion Capture

While the use of a functional joint center definition using traditional motion capture methods requires extensive patient preparation time, novel methods for motion capture have been introduced. The most significant technical advance has been the development of a markerless motion capture system (Corazza et al. 2006; Mündermann et al. 2006). This novel technique requires no preparation time. Multiple synchronized video sequences are captured while the patient performs the task of interest. The patient's silhouette is identified in each image, and the three-dimensional body surface is reconstructed for each frame. An anatomical model is then fit to the surface, and joint motion, forces, and moments are computed. Similar to the functional determination of the joint centers using skin markers, the functional joint centers can be identified by capturing markerless data of the patients while moving each joint throughout its range of motion (Corazza et al. 2007). Using the information on joint center location, limb alignment can be calculated as described above.

The main strength of these novel techniques is the objectivity of the measurement. Because this technique does not require the palpation of anatomical landmarks, the result will be independent of the tester or the laboratory. However, this technique is yet to be validated against standard radiographic assessments of lower limb alignment. This methodology can be expanded to assess the alignment of other segments of the body.

183.4 Challenges and Limitations of the Measurement of Lower Extremity Alignment in Sub-populations

183.4.1 Obese Population

Soft tissue overlying anatomical landmarks as it is present in overweight and obese subjects may greatly increase the error associated with correct palpation of these landmarks. While functional methods represent a promising advancement in the estimation of the hip joint center location in populations where the palpation of anatomical landmarks is difficult, their accuracy has not been quantified in an obese or overweight population.

183.4.2 Elderly Population

Special considerations must be undertaken in the selection of the most appropriate method for the measurement of lower extremity alignment in the elderly population. For instance, bone quality decreases with increasing age, and, hence, additional exposure to radiation may have detrimental consequences in patients who already present with poor bone quality. Further, functional methods for the determination of joint center locations may not be feasible in this subpopulation because of the limited active range of motion in some joints of the lower extremity and the reduced balance capability when performing required motion tasks.

183.5 Applications to Other Areas of Health and Disease

183.5.1 Joint Loading

During walking, the ground reaction force vector passes medially to the knee joint center causing an external adduction moment (Fig. 183.4). This represents greater forces being transferred through the medial than through the lateral compartment of the knee (Schipplein and Andriacchi 1991). Typically for a knee with varus malalignment, the line of action of the ground reaction force likely passes more medially to the knee joint center, thus creating a greater external knee adduction moment during single limb support (Fig. 183.4). Naturally, static alignment of the lower extremity is even more important for activities involving quasi-static postures.

The knee adduction moment is one component describing joint loading during physical activities such as walking. Joint loading in general is important for maintaining healthy tissue and is affected by the proper functioning of the entire musculoskeletal system. Specifically, muscle strength, neuromuscular coordination, balance, integrity of passive structures including ligaments and joint capsulae, and skeletal alignment are among the most important components affecting joint load.

183.5.2 Injury Mechanisms in Sports and Physical Activity

Static and dynamic alignment plays an important role in identifying the risk of an athlete or person for getting injured while playing sports or being physically active. For instance, a greater knee valgus

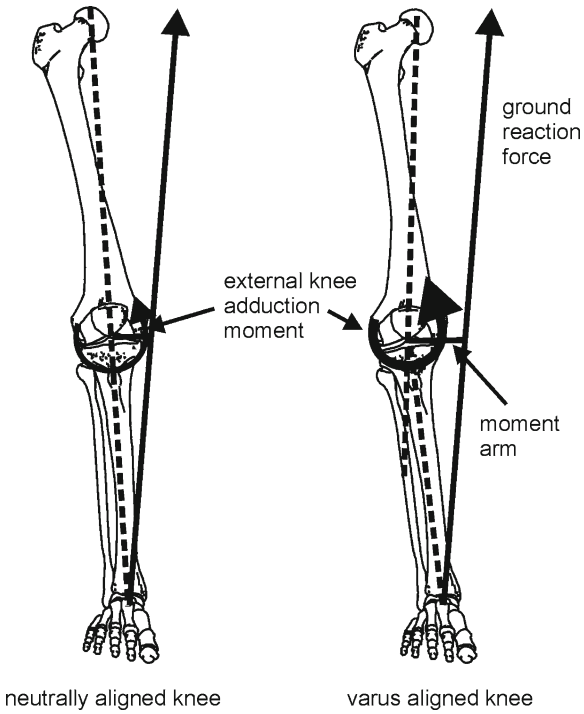

Fig. 183.4 Implications of longer moment arms of the ground reaction force in varus versus neutrally aligned knees. The external knee adduction moment tends to be greater in varus-aligned knees (*right*) compared to neutrally aligned knees (*left*) due to a greater moment arm of the ground reaction force about the knee joint center (Reprinted from Mündermann et al. (2008) with permission of Elsevier)

angle has been associated with greater knee valgus load during landing or sidestepping activities (McLean et al. 2005). Knee valgus load during sports movement is viewed as an important predictor of non-contact ACL injury risk, particularly in females. Hence, lower extremity alignment in athletes or in the generally physically active population may be used for assessing a person's risk for incurring an ACL injury.

183.5.3 Disease Development and Progression

In clinical practice, the static alignment of the osteoarthritic knee is frequently measured as the mechanical axis alignment using full-limb radiographs with the goal to estimate the load distribution between the medial and lateral compartments of the knee. Indeed, the dynamic load distribution at the knee measured as the external knee adduction moment is related to the mechanical axis alignment (Hurwitz et al. 2002). Dynamic alignment or the knee adduction moment during walking is related to the mechanical axis alignment (Hurwitz et al. 2002) and is a strong predictor for the presence (Baliunas et al. 2002), severity (Mündermann et al. 2004), and rate of progression (Miyazaki et al. 2002) of medial compartment knee OA. In addition, patella cartilage volume decreases with increasing varus alignment assessed using radiographs (Teichtahl et al. 2008). This association might be even more critical in obese patients because of their excessive weight.

In diseases or conditions involving severe malalignment such as recurvatum deformity of the tibia or flexion deformity of the femur, the specific alignment of the skeleton will affect the line of action

and hence the function of individual muscles. The contribution of aforementioned components to the overall function cannot be generalized for patients with these conditions.

183.5.4 Obesity

Despite the technical difficulties in assessing lower extremity alignment in the obese population, these measurements presumably are highly relevant in the context of comorbidities such as degenerative joint disease, or bone diseases that are associated with an altered metabolism, disuse, and overloading the musculoskeletal system. For instance, limited information is available on gait mechanics and joint loading during walking in obese subjects. Obese subjects walk at slower self-selected speeds and reduced step length and cadence than non-obese subjects (DeVita and Hortobágyi 2003; Spyropoulos et al. 1991). When walking at similar speeds, obese subjects experience similar sagittal plane joint moments and power at the ankle, knee, and hip (DeVita and Hortobágyi 2003). While joint kinetics in the secondary planes of motion have not been reported for obese subjects, these subjects step with their feet twice as far apart than non-obese subjects during walking (Spyropoulos et al. 1991). This greater base of support may result in a greater lever arm of the ground reaction force (distance of the ground reaction force to the knee joint center), thereby increasing the knee adduction moment and the load on the medial compartment of the knee. Thus, to date it is not clear if obese subjects are at greater risk for OA primarily because of mechanical or biological differences to a healthy population.

183.5.5 Aging

Radiographic evidence of OA increases with increasing age (Felson et al. 1987). Biological tissues undergo significant changes during the aging process and these biological changes, for instance, in cartilage may be the cause for decreased tensile stiffness and strength (Kempson 1982). Articular cartilage aging does not cause OA, but the age-related metabolic and phenotypic decline of the chondrocytes increases the risk of articular cartilage degeneration and limits the ability of the cell to repair the tissue once degenerative changes occur (Martin and Buckwalter 2002). Similar changes have been observed in menisci and ligaments. Simultaneously, reduced muscle activation, cross-sectional area, force per cross-sectional area, and maximum muscle strength have been observed (Jubrias et al. 1997; Stackhouse et al. 2001).

The primary changes in gait that occur with increasing age are slower walking speeds, reduced step length, and increased double-support time (Winter et al. 1990). It has been suggested (DeVita and Hortobágyi 2000) that age causes a redistribution of joint torques and powers, with the elderly using their hip extensors more and their knee extensors and ankle plantar flexors less than young adults when walking at the same speed. This shift in power generation could be caused by the physiological changes in muscle (Jubrias et al. 1997), where the knee extensor muscles in the elderly are simply not capable of producing similar forces than in young adults. However, due to a lack of information on joint kinetics in the secondary planes of motion little is known about how these changes affect mechanical load at the joints of the lower extremity, especially at the knee. It has been proposed (Andriacchi et al. 2004) that kinematic changes associated with aging may lead to a shift in the normal load-bearing regions in a manner similar to the kinematic changes following ACL injury.

183.6 Guidelines for the Use of Anthropometry for the Measurement of Lower Extremity Alignment

While anthropometric information is used for many methods for the measurement of lower extremity alignment described above, the importance of using valid information cannot be emphasized enough.

- Appropriate anthropometric information should be selected based on the primary purpose of the lower extremity alignment measurement.
- Advantages and disadvantages of using direct versus indirect methods for the measurement of lower extremity alignment, including exposure to radiation, ease of use, technical requirements, and comparability across studies and users, must be considered.
- Direct measurements of lower extremity alignment should be used in patients with severe limb malalignment and in conditions that require capture of radiographic imaging for other diagnostic purposes justifying the exposure to radiation.
- Indirect measurements of lower extremity should be taken using the inclinometer in settings where position capture equipment is not available.
- Indirect measurements of lower extremity alignment should be included in all studies and protocols utilizing motion capture equipment and should be performed using the functional method.
- For two-dimensional position capture systems, an alignment of the subject with the laboratory coordinate system is critical since rotation about the vertical axis could lead to cross-talk between the flexion–extension angle and the mechanical axis alignment.

Summary Points

- Lower extremity alignment can be assessed directly using medical imaging techniques or indirectly using established clinical measures.
- Palpation of anatomical landmark and anthropometric information is currently used for many indirect methods assessing the alignment of the lower extremity.
- Novel technology enables more objective and thus more reliable assessment of lower extremity alignment.
- Relating anthropometric information and limb alignment to joint loads during daily activities enables the identification of risk factors for musculoskeletal injuries and diseases.
- Lower extremity alignment plays an important role in the presence, severity, and rate of progression of knee OA and in injury mechanisms of ACL rupture.
- Indirect assessment of lower extremity alignment can be challenging in obese patients and in the elderly.
- Establishing relationships between anthropometric information, limb alignment, and detailed information measured using novel techniques is important to increase the relevance of simple and quick clinical measurements for a larger range of sub-populations.

Acknowledgments The author would like to express her appreciation to Prof. Thomas Andriacchi and Chris Dyrby for their contribution to the study on measuring mechanical axis alignment using position capture.

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Chapter 184
Anatomical Reference Frames for Long Bones: Biomechanical Applications

Luca Cristofolini

Abstract The definition of anatomical reference frames is necessary both for *in vitro* biomechanical testing, and for *in vivo* human movement analyses. Different reference frames have been proposed in the literature, for the different applications. Reference frames for *in vivo* use must rely on anatomical landmarks that can be accessed non-invasively in living subjects. This limits the operator to certain regions of the bone segments, and possibly to anatomical landmarks that are scarcely reproducible. Conversely, when the bone is fully accessible *in vitro*, direct measurements are possible of diameters, lengths, and angles. This enables the selection of anatomical reference planes that rely upon anatomical landmarks that are better reproducible. In this section, anatomical reference frames are discussed for the most important long bones of the human skeleton: femur, tibia, fibula, metatarsal bones, humerus, radius, ulna, metacarpal bones, and phalanges. The different reference frames proposed for each bone segment are discussed: this includes the guidelines proposed by the Standardization and Terminology Committee of the International Society of Biomechanics (ISB) for *in vivo* movement analysis, and also reference frames proposed by different authors for *in vitro* testing. Optimal reference frames are proposed for each bone segments. Detailed guidelines (including suggested materials and methods) are provided to correctly identify the anatomical landmarks and the anatomical frames. For each bone segment, an estimate of the intra-operator repeatability (i.e. when the same operator repeatedly identifies the reference frame on the same specimen) and of the inter-operator repeatability (i.e. when different operators identify the reference frame on the same specimen) is reported for the recommended reference frame. This confirms the reliability of the approach proposed.

Abbreviations and Acronyms

3D	Three-dimensional
BLF	Biomechanical length of the femur
BLH	Biomechanical length of the humerus
BLR	Biomechanical length of the radius
BLT	Biomechanical length of the tibia-fibula complex

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_184,

BLU	Biomechanical length of the ulna
CLT	Landmark for the humerus: center of the most lateral part of the humeral trochlea
CMT	Landmark for the humerus: center of the most medial part of the humeral trochlea
CT	Computed tomography
DFL	Landmark for the femur: on the distal femoral diaphysis in the center of the concavity present on the anterior surface, proximal to the lateral epicondyle
HF	Landmark for the shank: apex of the head of the fibula
IM	Landmark for the shank: midpoint of the line joining MM and LM (coincides with MPM)
ISB	International Society of Biomechanics
LC	Landmark for the shank: most medial point on the edge of the lateral tibial condyle
LFC	Landmark for the femur: posterior side of the lateral femoral condyle
LHDL	Living Human Digital Library
LM	Landmark for the shank: apex of the lateral malleolus
LTC	Landmark for the tibia: centre of the lateral tibial condylar plateau
MC	Landmark for the shank: most medial point on the edge of the medial tibial condyle
MFC	Landmark for the femur: posterior side of the medial femoral condyle
MM	Landmark for the shank: apex of the medial malleolus
MP	Landmark for the tibia: medial point between MTC and LTC
MPM	Landmark for the shank: midpoint of the line joining MM and LM (coincides with IM)
MTC	Landmark for the tibia: centre of the medial tibial condylar plateau
PFL	Landmark for the femur: on the proximal diaphysis, center of a flat region immediately distal to the lesser trochanter
SP	Landmark for the radius: most distal point of the styloid process
TAS	Landmark for the tibia: centre of the talar articulation
TN1, TN2, TN3	Landmark for the ulna: three points in the trochlear notch in the proximal ulna
TT	Landmark for the shank: tibial tuberosity
UN	Landmark for the radius: central point of the ulnar notch
VPH-OP	Virtual Physiological Osteoporotic Human

184.1 Introduction

Univocal definition of reference frames (Table 184.1) is extremely important in musculoskeletal biomechanics (Currey 1982; Fung 1980; Van Sint Jan and Della Croce 2005). During in vivo motion analysis, reference frames enable tracking of segments and joint motion and calculation of joint moments (Cappozzo et al. 1995). Reference frames in vitro enable correct alignment of specimens and the test loads and the definition testing conditions so that these can be replicated (O'Connor 1992; Cristofolini 1997). In general, anatomical reference frames are based on anatomical landmarks (Table 184.2) that must be identified on the bone(s). This applies to all bone segments.

In general, two types of errors can affect measurements in general (Taylor 1997), and also the identification of anatomical landmarks, as well as the associated anatomical reference frames:

1. Lack of repeatability: The same operator will indicate slightly different points (and will consequently define slightly different reference frames) if he observes the same specimens a number of times.

Table 184.1 Key facts of anatomical reference frames

1. Reference frames are needed for the sake of measurement methodology and data comparability
2. Anatomical reference frames are useful in biomechanics to univocally identify the relative pose (i.e., position and orientation) of the different parts of the body (e.g., the forearm with respect to the arm or with respect to the trunk)
3. Anatomical reference frames are also fundamental for in vitro tests involving bone segments, in order to identify univocally the pose of the specimen on the testing system, the position and direction of the applied loads, the position of the transducers, etc
4. Anatomical reference frames consist (like most other reference frames) of a system of three planes, which must be perpendicular to each other (Cartesian frames)
5. In general, the planes of an anatomical reference frame related to a bone segment are aligned (or nearly aligned) with the frontal, sagittal, and coronal planes of the entire body
6. Definition of anatomical reference frames for a bone segment relies on the identification of reference points on the bone (anatomical landmarks, see Table 184.2)

This table lists the key facts of anatomical reference frames, including their most general features, their identification, and application

Table 184.2 Key facts of anatomical landmarks

1. A landmark literally means a geographic feature used by explorers to find their way back or through an area
2. In anatomy and in biomechanics, anatomical landmarks are used to provide some reference point in a structure that is otherwise too irregular in shape to enable quantitative location of relative positions and orientations
3. Anatomical landmarks in in vivo musculoskeletal biomechanics are generally based on bony prominences that can be easily located by palpation
4. In vitro, more choices are possible through the anatomical landmarks that can either be based on bony prominences (like those used in vivo), but also on special points that can be easily located/measured on the bone surface
5. In all cases, anatomical landmarks must be defined based on features that: (1) are consistent in different subjects/specimens and (2) can be consistently located by different operators on the same subject/specimen
6. Landmarks are generally the starting point for the definition of anatomical reference frames

This table lists the key facts of anatomical landmarks, including their definition and use in biomechanical testing

2. Lack of reproducibility: Different operators will possibly interpret definitions in slightly different fashions and will perceive the bone surface in a subjective way. This leads to inter-operator differences in the identification of anatomical reference frames.

Depending on the type of application, reference frames are defined to meet different needs and facing different constraints:

- Reference frames intended for in vivo use (such as motion analysis) are based on anatomical landmarks that need to be palpable in living subjects (Cappozzo et al. 1995; Van Sint Jan and Della Croce 2005). Original identification of bony prominences rather than anatomical planes and axes leads to more repeatable measurements in gait analysis (Leardini et al. 2007). Similar criteria are also adopted in case virtual palpation is adopted, although in this case, also, points that are not directly accessible in vivo (noninvasively) (Salvia et al. 2009) can be included. A systematic approach to the consistent definition of skeletal anatomical landmarks using manual and virtual palpation was recently proposed (Van Sint Jan 2007). In all in vivo cases, direct physical measurement of lengths, widths, or thicknesses of bone segments are not possible. Hence, identification of anatomical landmarks and of the associated reference frames is affected by errors due to the uncertainty in identifying such points.
- Reference frames intended for in vitro use (e.g., mechanical testing of cadaver bones) can be based on anatomical landmarks that can only be accessed invasively. In addition, direct measurement of lengths, diameters, widths, cross sections, and angles using calipers, goniometers, etc., is feasible as the surface of the physical specimen is directly accessible. Hence, in general, measurement

of such dimensions is more accurate in vitro than in vivo. This generally enables a more accurate identification of anatomical landmarks, which has the potential to define reference frames with better repeatability and reproducibility.

As a consequence, it is clear that optimal anatomical landmarks (and associated reference frames) will generally be different for in vivo and in vitro studies (Wu et al. 2002).

In the biomechanics community, there is strong awareness of the need for defining unambiguously the anatomical reference frames, which was voiced by the International Society for Biomechanics (ISB) (ISB 1995; Wu and Cavanagh 1995). This has generated an effort toward standardization, led by the Standardization and Terminology Committee of the ISB: a consensus was slowly reached on reference frames for the lower limb and spine (Wu et al. 2002) and for the upper limb (Wu et al. 2005). All such reference frames are mainly intended for in vivo use, having as a priority consistent reporting of kinematic data.

Definition of anatomical reference frames for in vitro testing is somewhat less consolidated. While reference in vitro frames have been recommended for specific bone segments, no concerted action was developed such as that for in vivo reference frames. For instance, whereas a number of definitions have been discussed for the femur (Della Croce et al. 2003), little has been reported for the tibia and fibula, and even less has been reported for the upper-limb bones. One of the first reference frames for the lower-limb bones was proposed by (Ruff 1981; Ruff and Hayes 1983). This frame was based on identification of anatomical landmarks and geometrical measurements that are possible only in vitro on dissected femur and tibia segments. Although this method was originally intended for anatomical analyses, it was adopted successfully for in vitro biomechanical tests both on the femur (Cristofolini 1997) and tibia (Cristofolini and Viceconti 2000; Gray et al. 2007, 2008; Heiner and Brown 2001).

184.2 General Guidelines

184.2.1 Ideal Definition of Anatomical Reference Frames for Biomechanical In Vitro Testing

It is clear that an ideal reference frame should be based on anatomical landmarks that are easily and reproducibly identified in all subjects and in case of severe bone deformity. For instance, anatomical landmarks associated with bony prominences that strongly vary between subjects (such as those related to the insertion of muscle with different possible insertions between subjects) should be avoided. Similarly, reference systems based on specific points on the edge of the articular cartilage should be avoided as much as possible as aging can cause deformities associated with arthritis, calcification, etc. Serious implications of incorrect identification of anatomical landmarks and reference frames have been reported both in vitro (Gray et al. 2007; Cristofolini and Viceconti 2000) and in vivo (Della Croce et al. 2005; Thewlis et al. 2008).

As a general approach, identification of reference frames includes the following steps:

1. Coarse alignment of the bone specimen: This step allows subsequent measurements for accurate identification of anatomical landmarks and reference planes.
2. Identification of the neutral position about the long axis of the bone (this typically corresponds to identifying the neutral position in internal/external rotation. Such anatomical landmarks lie in a plane that is perpendicular to the long axis of the bone [i.e., at a relatively small distance from

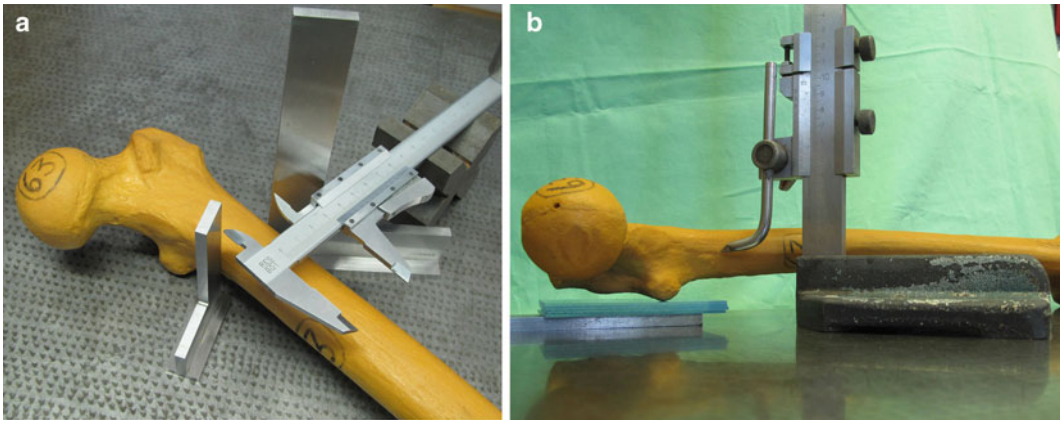

Fig. 184.1 Tools for accurately measuring anatomical dimensions. Tools for accurate measurement of anatomical landmarks and identification of reference frames: (**a**) vernier calipers and square block and vertical rulers used to measure the width of the femoral diaphysis using a level surface; and (**b**) scribing block and supports used to mark the reference planes on a femur, using a level surface

such axis]): Anatomical landmarks that are as far as possible from such an axis should be adopted to minimize errors related to their inaccurate identification.

3. Alignment of the bone in the two planes passing from the bone long axis (typically defining the neutral position in flexion/extension and abduction/adduction): Anatomical landmarks close to the opposite bone extremities should be chosen to minimize errors in identification of such planes.

184.2.2 Recommended Tools and Methods

Once the reference frame and the associated anatomical landmarks are defined, the problem of identifying them on the bone specimen remains. The easiest and most inexpensive method is based on building an osteometric board (Ruff 1981; Ruff and Hayes 1983). This provides accuracy of the order of 1 mm, which is sufficient for many applications, especially on large bones. To improve measurement accuracy, the osteometric board should be used in combination with metal angled squares, scribing blocks, surface gauge, and Vernier calipers (Cristofolini 1997) (Fig. 184.1). Identification and marking of anatomical landmarks and reference planes involves holding the bone specimen at an assigned position and orientation; to avoid undesirable movements during specimen preparation, dedicated clamps and fixtures can be extremely useful.

In our laboratory, we developed a clamp that allowed rotating the bone specimen in a controlled fashion about three axes and translating it along three axes with accuracy of the order of 0.1 mm (Fig. 184.2).

With the recent development of accurate three-dimensional (3D) digitizers (Fig. 184.3), acquisition of coordinates has become more accurate (of the order of 10 μm). Digitizers consist of a probe that is mounted on an articulated arm with several degrees of freedom (typically five or six), each equipped with an accurate electrogoniometer, enabling the exploration of complex three-dimensional space and recording the spatial coordinates of selected points. Thus, 3D digitizers help marking reference frames more accurately and, at the same time, relation of the reference frame on the physical specimen with the geometry of computer models that are built based on the same specimen (Schileo et al. 2008; Schileo et al. 2007).

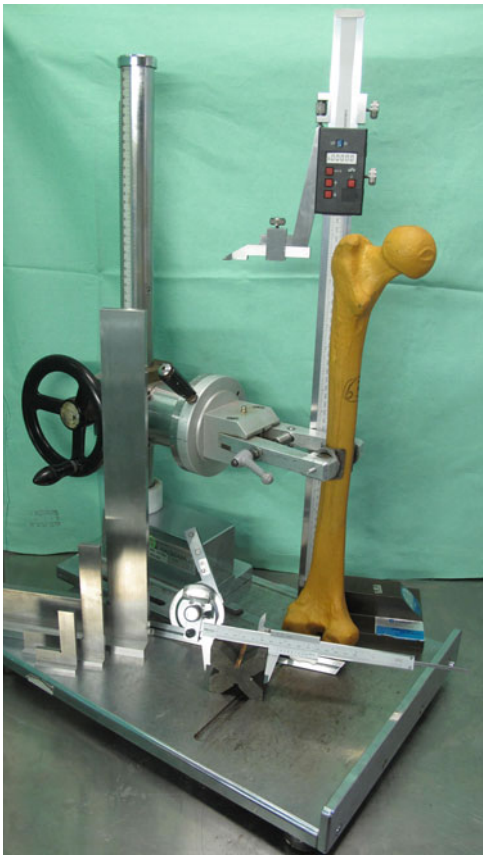

Fig. 184.2 Clamp and tools to control the alignment of a bone specimen. Picture of a clamp that allows rotating the bone specimen (a femur, in this instance) in a controlled fashion about three axes and translating it along three axes. Also shown are a scribing block, Vernier calipers, a vertical gauge, and a goniometer

Fig. 184.3 Three-dimensional digitizer. Points on the bone surface can be acquired with a 3D digitizer with an accuracy of microns. In this instance, a tibia, prepared with proximal and distal pots and strain gauges is being digitized (Mod. Gage-Plus-V1.5, Faro-Europe, Stuttgart-Weilimdorf, Germany, in this instance). This can assist in accurately measuring planes and measuring spatial coordinates

Relative orientation of reference frames can be expressed using the same approach used by Grood and Suntay (1983) for referring one anatomical segment to the other. This entails defining flexion/extension as the relative orientation about the medio-lateral axis of a first frame, internal/external rotation as the relative orientation about the vertical axis of the second frame, and abduction/adduction as the relative orientation about a 'floating' axis orthogonal to the previous two.

184.3 The Femur

184.3.1 Review of Published Reference Frames for the Femur

Although countless anatomical studies address the femur, apparently no agreement has ever been sought on the reference frame to be adopted for biomechanical testing. Probably the most extensively defined first reference frame for the femur was proposed by Ruff (1981) and Ruff and Hayes (1983). This method was originally intended for anatomical analyses; it was adopted successfully for in vitro biomechanical tests and numerical simulations on the femur (Cristofolini 1997; Waide et al. 2001; Schileo et al. 2006).

For completeness, an alternative reference frame must be discussed: the Standardization and Terminology Committee of the International Society of Biomechanics proposed a slightly different reference frame (Wu et al. 2002). It is based on the center of the head and on the (palpable) lateral and medial femoral epicondyles. Such a reference is quite different from that defined by Ruff (1981) and Ruff and Hayes (1983), especially in the proximal part, the rationale being that, in this case, markers that are palpable or easily identifiable in movement analysis were preferred. Such method is also valuable for anthropometric measurements in living subjects (see the chapter by Annegret Mündermann).

184.3.2 Guidelines for Identifying the Reference Frame for the Femur

In several studies (e.g., Harman et al. 1995; Cristofolini 1997), it was chosen to define the longitudinal diaphyseal axis as that axis passing through the mid-section at two well-defined levels of the diaphysis following Ruff and Hayes (1983) and Ruff (1981). The reference frame proposed by Ruff (1981) and Ruff and Hayes (1983) and consistent with past definitions of the femoral axis Backman (1957), identifies the axis of the femur with the diaphyseal axis. The procedure proposed by Ruff (1981) and Ruff and Hayes (1983) and later modified (Cristofolini 1997) is as follows (Fig. 184.4):

1. The biomechanical length of the femur (BLF) is defined as the minimal distance between the trochanteric fossa and the condylar notch.
2. The femur must be laid on a level board, posterior side down. The posterior sides of the two femoral condyles (LFC and MFC) must be resting on the board; the proximal part resting on the lesser trochanter. Such alignment already defines the neutral rotation as far as internal/external rotations are concerned.
3. Two sections must be identified along the diaphysis, which are later used for identifying the frontal and sagittal planes.
4. A landmark (DFL) is located on the distal femoral diaphysis in the center, or lowest point, of the concavity present on the anterior surface, just proximal to the lateral epicondyle.

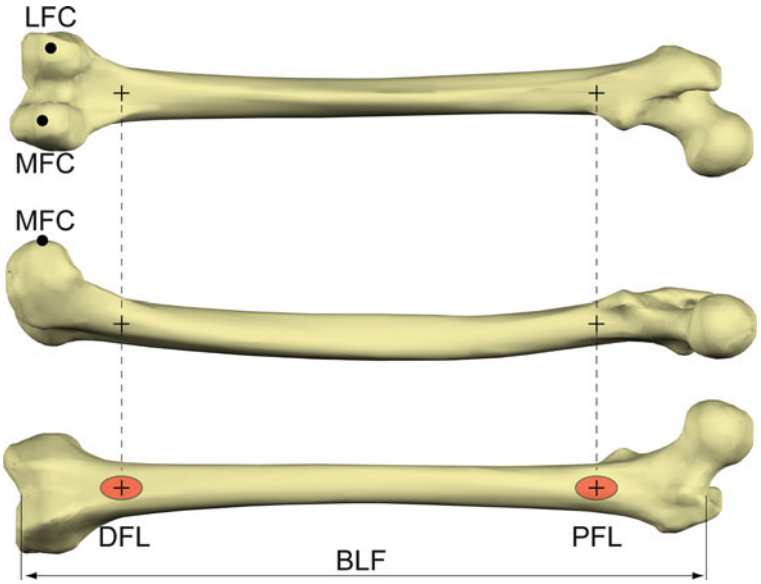

Fig. 184.4 Anatomical landmarks and dimensions of a human femur. Posterior, medial, and anterior view of a *left* femur. The most posterior points on the lateral and medial condyles (*LFC* and *MFC*) are used to define a neutral position about the long axis of the femur. The biomechanical length of the femur (*BLF*) is defined as the minimal distance between the trochanteric fossa and the condylar notch. Two anatomical landmarks must be identified (*PFL* and *DFL*), where a small depression (*highlighted in dark*) is visible on the proximal and distal portions of the anterior face

5. A second landmark (PFL) is located on the proximal diaphysis, at a site immediately distal to the lesser trochanter, where a similar depression is found.
6. The mid-section at two such levels must be found using Vernier calipers and a vertical ruler, both in the frontal and in the sagittal plane (Fig. 184.1a).
7. The frontal plane is defined as a plane parallel to the one tangent to the posterior side of the condyles (LFC and MFC), and passing through such two center points.
8. The sagittal plane is a plane perpendicular to such a frontal plane and passing through such two center points.

To mark such planes and axes, clay or an adjustable clamp should be used to hold the femur by aligning the reference points described earlier in a vertical/horizontal plane, as needed (Fig. 184.5).

184.3.3 Assessment of the Reference Frame for the Femur

The reference system proposed by Ruff (1981) and Ruff and Hayes (1983) and later adapted by Cristofolini (1997) has been extensively tested after refinement. Based on the extensive experience on over 100 composite and over 50 cadaveric femurs (Cristofolini 1997; Waide et al. 2001; Cristofolini et al. 2007a, b, c), it is possible to assess:

- the intra-operator repeatability (i.e., when the same operator repeatedly identifies the reference frame on the same specimen); and
- the inter-operator repeatability (i.e., when the different operators identify the reference frame on the same specimen).

The intra-operator repeatability in identifying the individual anatomical landmarks was 0.1–0.5 mm; the inter-operator repeatability was 0.3–1.0 mm. The largest errors were associated with the axial position of the two sections along the diaphysis (however, this was found to have a lesser effect on the final alignment of the reference frame). The smallest errors were associated with the position of the two points on the posterior side of the condyles (LFC and MFC).

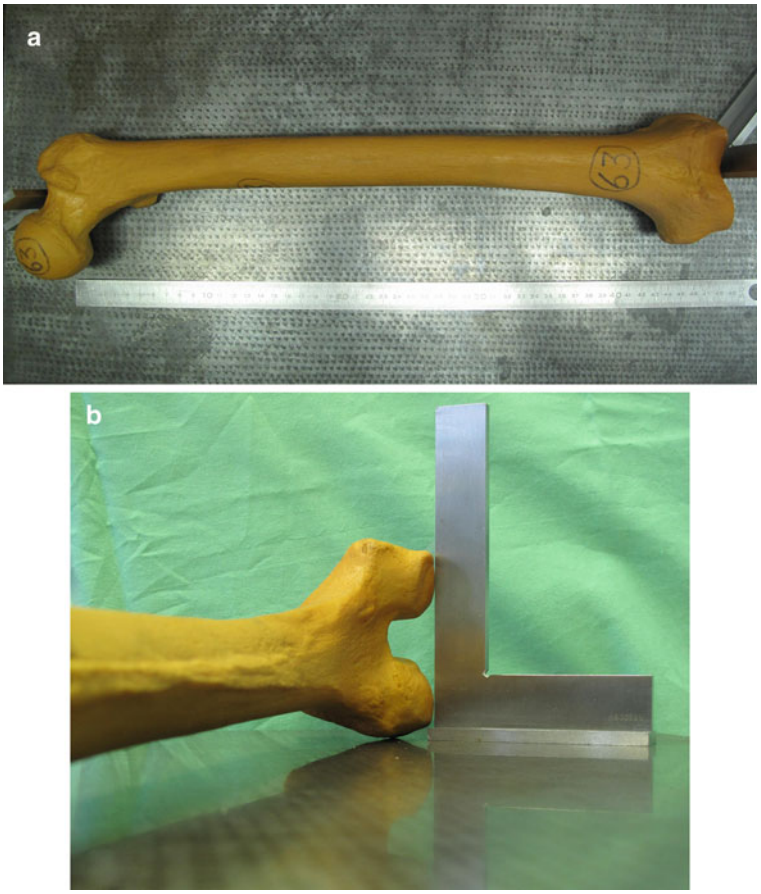

Fig. 184.5 Femur ready for identification of anatomical planes. (**a**) Picture of a femur resting on the posterior side of the condyles and the lesser trochanter (anterior face up), ready for measuring the biomechanical length (between two metal angles). (**b**) Detail of the distal femur being aligned so that the posterior side of the condyles rest on a right angle to ensure correct alignment in internal/external rotation

Table 184.3 Repeatability of the reference frame for the femur

Intra-operator repeatability	Abduction/adduction	0.05–0.15°
	Flexion/extension	0.05–0.15°
	Internal/external rotation	0.20–0.60°
Inter-operator repeatability	Abduction/adduction	0.10–0.30°
	Flexion/extension	0.10–0.30°
	Internal/external rotation	0.3–1.10°

Repeatability for the same operator and between different operators for the identification of the reference frame for the femur according to Ruff and Hayes (1983) and Ruff (1981). The range is reported based on extensive experience on over 100 composite and over 50 cadaveric femurs (Cristofolini 1997; Waide et al. 2001; Cristofolini et al. 2007a, b, c)

The intra-operator repeatability was nearly one order of magnitude better than the inter-operator repeatability (Table 184.3). The largest errors were always associated with the correct identification of the reference frame in internal/external rotation. In fact, the anatomical landmarks used to identify such an angle are close to each other, thus, even a small error in the identification of such anatomical landmarks propagates to a large error in terms of rotation. Errors were smaller for the flexion/extension and abduction/adduction angles, with similar repeatability in both planes.

Introduction of the reference frame proposed by Ruff and Hayes (1983) and Ruff (1981) improved repeatability and reproducibility of strain measurements in the femur by nearly one order of magnitude (Cristofolini 1997).

184.4 The Tibia and Fibula

184.4.1 Review of Published Reference Frames for the Tibia and Fibula

One of the first reference frames for the tibia was proposed by Ruff (1981) and Ruff and Hayes (1983). Although this method was originally intended for anatomical analyses, it was adopted successfully for in vitro biomechanical tests on the tibia (Cristofolini and Viceconti 2000; Gray et al. 2007, 2008; Heiner and Brown 2001). The reference frame *Ruff-coord* (Fig. 184.6) proposed by Ruff (1981) and Ruff and Hayes (1983) is based on the centers of the articulating cartilage areas at the proximal and distal tibia, with no anatomical landmarks on the fibula. The *Ruff-coord* can only be

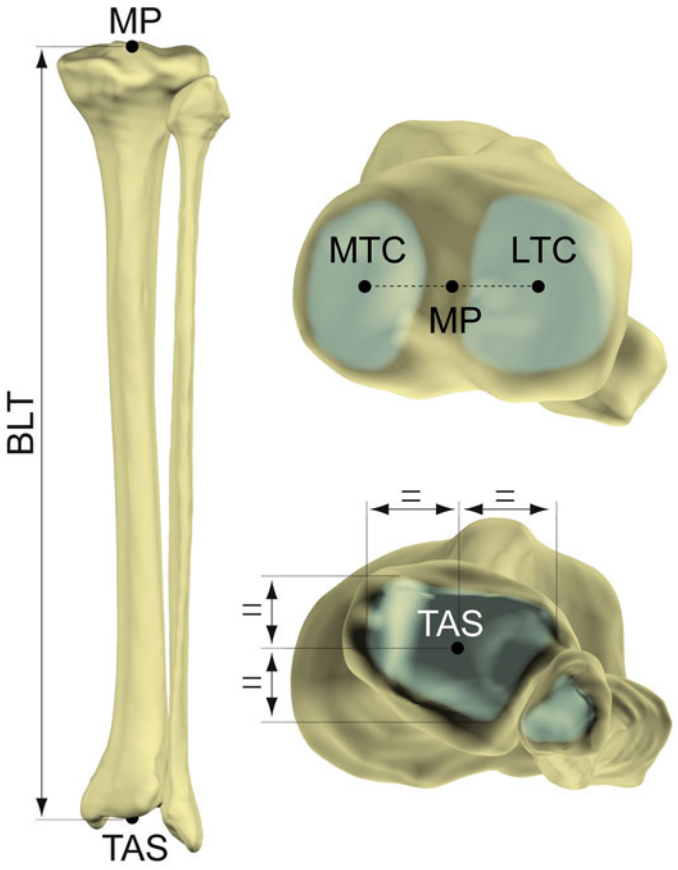

Fig. 184.6 Anatomical landmarks proposed by Ruff 1981 and Ruff and Hayes 1983 for the tibia–fibula complex. Anatomical reference frame proposed by Ruff 1981 and Ruff and Hayes 1983 for a left tibia–fibula complex: anterior view, transverse view from *above*, and transverse view from *below*. The centers of the two tibial condyles (*MTC* and *LTC*) and of the surface articulating with the top of the talus (*TAS*) are initially identified. This is performed by locating (with calipers) the midpoints in the antero-posterior and medio-lateral directions on each cartilage surface (as this procedure relies on an estimated provisional alignment, the procedure must be iteratively repeated – typically twice – until no significant further correction is needed). As an example, the location of TAS is shown in (**c**). The midpoint (*MP*) between the two tibial condyle center points (*MTC* and *LTC*) is then calculated. The frontal plane is the one passing through *MTC*, *LTC*, and *TAS*; the sagittal plane is perpendicular to the frontal plane and goes through points *TAS* and *MP*. Also indicated is the biomechanical length of the tibia (*BLT*)

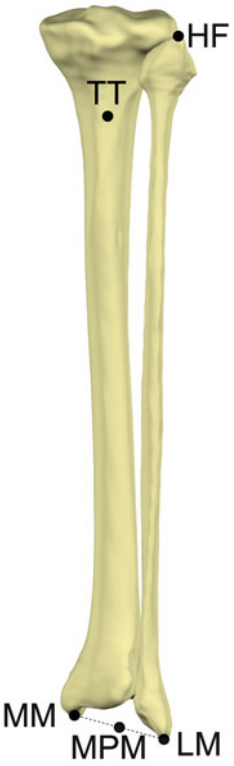

Fig. 184.7 Anatomical landmarks proposed by Cappozzo et al. (1995) for the tibia–fibula complex. Anatomical reference frame proposed by Cappozzo et al. 1995 for a left tibia–fibula complex (anterior view). First, the tibial tuberosity (*TT*), the apex of the head of the fibula (*HF*), and the distal apices of the medial and lateral malleoli (*MM* and *LM*) are identified. The midpoint (*MPM*) of the line joining *MM* and *LM* is then calculated (this point coincides with IM of the reference frame proposed by the *ISB* (Wu et al. 2002)). The frontal plane passes through *HF*, *LM*, and *MM*; the sagittal plane is perpendicular to the frontal plane and goes through points *TT* and *MPM*

identified in vitro when the bone surface is visible. As Ruff (1981) and Ruff and Hayes (1983) did not suggest a separate reference for the fibula, we propose to use the same reference frame for the entire tibia–fibula complex (Conti et al. 2008).

For completeness, other reference frames must also be described: a different anatomical reference frame was proposed by Cappozzo et al. (1995) to provide consistent identification of anatomical landmarks for a more repeatable motion analysis. The reference frame *Cappozzo-coord* (Fig. 184.7) proposed by Cappozzo et al. (1995) is based on anatomical landmarks of the tibia and fibula that need to also be palpable in vivo. Later, the Standardization and Terminology Committee of the International Society of Biomechanics (ISB) proposed a slightly different reference frame (Wu et al. 2002) (Fig. 184.8): it is based on the same anatomical landmarks as *Cappozzo-coord* distally, but on different anatomical landmarks proximally (with anatomical landmarks over only the tibial plateau). Both *Cappozzo-coord* and *ISB-coord* rely on the anatomy of the entire tibia–fibula complex. It must be stressed that the *Cappozzo-reference* and the *ISB-reference* are designed for in vivo use. A similar reference is also proposed for anthropometric measurements in living subjects (see chapter by Annegret Mündermann).

184.4.2 Guidelines for Identifying the Reference Frame for the Tibia and Fibula

As remarked, we propose to use the same reference frame for the entire tibia–fibula complex (Conti et al. 2008). Therefore, the ligaments of the proximal and distal tibiofibular articulations (syndesmosis) must be left intact to preserve the original relative position and orientation. Thus, once the reference

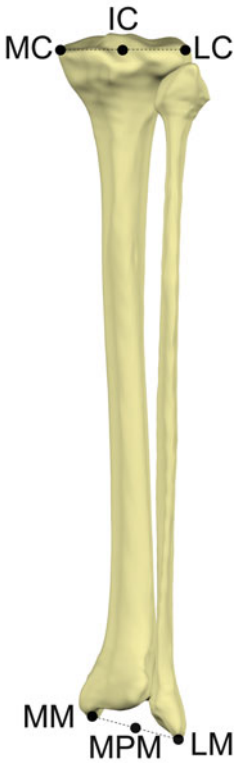

Fig. 184.8 Anatomical landmarks proposed by the International Society of Biomechanics (Wu et al. 2002) for the tibia–fibula complex. The anatomical reference frame proposed by the Standardization and Terminology Committee of the International Society of Biomechanics (Wu et al. 2002) for a left tibia–fibula complex (anterior view). First, the most medial and lateral points on the edge of the relevant condyles (*MC* and *LC*) and the tip of the medial and lateral malleoli (*MM* and *LM*) are identified. The inter-malleolar point (*IM*, which coincides with *MPM* in the reference frame proposed by Cappozzo et al. 1995 located midway between *MM* and *LM* and the inter-condylar point (*IC*) found midway between the *MC* and *LC* are calculated. The frontal plane passes through *IM*, *MC*, and *LC*; the sagittal plane is perpendicular to the frontal plane and containing the points *IC* and *IM*

frame is marked on the femur, it can immediately be projected on the fibula as well. The procedure proposed by Ruff (1981) and Ruff and Hayes (1983) is as follows (Fig. 184.6):

1. Provisionally aligning the tibia on a level surface;
2. Identifying (by means of calipers and rulers) the centre of the talar articulation (TAS) and of the two tibial plateaus (MTC and LTC);
3. Identifying the midpoint (MP) between the two centers of the tibial condyles;
4. The biomechanical length of the tibia–fibula complex (BLT) is defined as the distance between TAS and MP;
5. The frontal plane of the tibia is the plane containing the talar (TAS) and the two plateau center points (MTC and LTC); and
6. The sagittal plane of the tibia is perpendicular to such frontal plane and goes through the midpoint of the tibial condyles (MP).

In addition, we suggest the following steps to identify the reference planes on the fibula (while still rigidly connected to the tibia):

7. Identifying two sections that are respectively 20% of the biomechanical length of the tibia–fibula complex (BLT) from the distal and proximal extremity;

8. In such sections, by means of a caliper and a vertical ruler the mid-point of the cross-sections in the antero-posterior and medio-lateral directions must be identified; and
9. The frontal and sagittal planes of the fibula go through the center points just identified (in general, these planes will not be parallel to the corresponding one previously identified for the tibia).

To mark such planes and axes, clay or an adjustable clamp should be used to enable aligning of the bone by aligning the reference points described earlier in a vertical/horizontal plan, as needed.

184.4.3 Assessment of the Reference Frame for the Tibia and Fibula

As such, reference frames were defined independently from each other, the relative orientation of one system respect to the other is unknown. A study was recently carried out (Conti et al. 2008) to compare these three reference frames for the tibia–fibula complex (Ruff and Hayes 1983; Cappozzo et al. 1995; Wu et al. 2002), with the following goals:

- Assess the intra-operator repeatability;
- Assess the inter-operator repeatability; and
- Assess if the three reference frames overlap and, if not, to assess the relative poses.

Six specimens, consisting of intact tibia–fibula complexes were visually inspected and CT-scanned to document bone quality and lack of abnormality or defects (Conti et al. 2008). The anatomical landmarks described earlier were acquired with a 3D digitizer (Mod. Gage-Plus-V1.5, Faro-Europe, Stuttgart-Weilimdorf, Germany) with an accuracy of 10 μm. The specimens were held in space by an adjustable vice. From these anatomical landmarks, the position and orientation of the three reference frames (*Ruff-coord*, *Cappozzo-coord*, and *ISB-coord*) were obtained for each specimen.

To assess the intra-operator repeatability, each reference frame was identified ten times by the same operator on one randomly selected specimen. To assess the inter-operator repeatability, three operators with a good knowledge of musculoskeletal biomechanics were asked to identify the anatomical landmarks of the three reference frames on each specimen.

For *Ruff-coord*, the intra-operator repeatability in identifying the individual anatomical landmarks was 0.58–0.98 mm; the inter-operator repeatability was 1.64–2.34 mm. For *Cappozzo-coord*, the intra-operator repeatability for the anatomical landmarks was 1.17–2.19 mm; the inter-operator repeatability was 3.18–6.96 mm. For *ISB-coord*, the intra-operator repeatability for the anatomical landmarks was 0.94–1.42 mm; the inter-operator repeatability was 3.18–7.07 mm.

The intra-operator repeatability was of the same order of magnitude for the three reference frames (Table 184.4). In abduction/adduction, *Cappozzo-coord* was significantly less repeatable than *Ruff-coord* and *ISB-coord*. The repeatability was similar for the three reference frames in flexion/extension. In internal/external rotation, *Cappozzo-coord* was more repeatable than *Ruff-coord* and *ISB-coord*. The inter-operator repeatability of the reference frames was worse than the intra-operator repeatability (Table 184.4). In the frontal plane (abduction/adduction), *Cappozzo-coord* was one order of magnitude less repeatable than *Ruff-coord* and *ISB-coord*; the difference between *Ruff-coord* and *ISB-coord* was not significant. In the sagittal plane (flexion/extension), *Ruff-coord* was more repeatable than *Cappozzo-coord* and *ISB-coord*. In the transverse plane (internal/external rotation), the only significant difference was that *Ruff-coord* was more repeatable than *ISB-coord*.

The most obvious difference was the external rotation of *Cappozzo-coord* with respect to the other two reference frames (Fig. 184.9). This is accounted for by the definition of the frontal plane of *Cappozzo-coord*, which includes the two apices of the malleoli, with the lateral malleolus being much more posterior than the medial one. No significant difference existed between the pose of *Ruff-coord*

Table 184.4 Repeatability of the reference frame for the tibia–fibula complex

		Ruff-coord (Ruff and Hayes 1983)	*Cappozzo-coord* (Cappozzo et al. 1995)	*ISB-coord* (Wu et al. 2002)
Intra-operator repeatability	Abduction/adduction	0.06°	0.39°	0.07°
	Flexion/extension	0.16°	0.27°	0.15°
	Internal/external rotation	0.88°	0.30°	1.11°
Inter-operator repeatability	Abduction/adduction	0.25°	1.55°	0.29°
	Flexion/extension	0.27°	0.68°	0.54°
	Internal/external rotation	2.78°	3.51°	5.71°

Repeatability for the same operator and between different operators for the identification of the three reference frames examined for the tibia–fibula complex

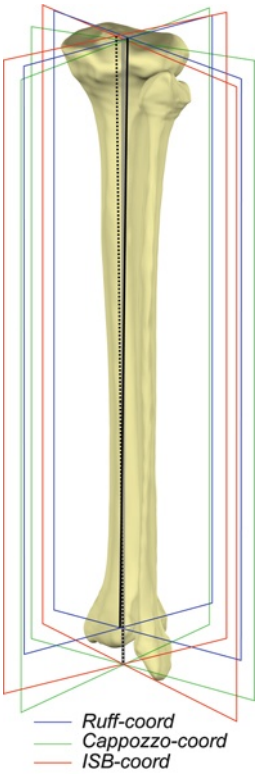

Fig. 184.9 Comparison of three reference frames for the tibia–fibula complex. Comparison of the alignment of the three reference frames on a left tibia–fibula complex in an antero-lateral view. The three frames had similar alignments in the sagittal and transverse planes. However, *Cappozzo-coord* was translated laterally and externally rotated with respect to *Ruff-coord* in the frontal plane. No significant rotation existed between *Ruff-coord* and *ISB-coord*

and *ISB-coord* (Fig. 184.9). *Cappozzo-coord* was significantly flexed and externally rotated with respect to *ISB-coord*. *Cappozzo-coord* was significantly flexed and externally rotated with respect to *Ruff-coord*. The fact that the two malleoli (used in *Cappozzo-coord*) are more posterior than the points on the tibial tray identified by *Ruff-coord* and *ISB-coord* explains such differences.

Ruff-coord was more repeatable because it relied on anatomical landmarks that could be accurately measured (i.e., by calipers) on the bone surface. In fact, *Ruff-coord* (Ruff and Hayes 1983) is intended for in vitro use, where the bone surface can be easily accessed and measured. The main problem reported with *Cappozzo-coord* (Cappozzo et al. 1995) was with point TT on the tibial tuberosity. The main problem reported with *ISB-coord* (Wu et al. 2002) was the identification of the most medial and lateral points on tibial condyles (MC and LC), which were quite subjective because of the large and nearly linear crest; this affects the repeatability in identifying internal/external rotation.

Thus, the reference frame proposed by Ruff and Hayes (1983) is preferable when the full bone surface is accessible, typically during in vitro tests. No clear advantage of one system over the others appeared for mixed conditions, where the proximal part of the shank bones is accessible directly and the distal part is covered by soft tissue (surgical navigation of total knee replacement) or vice versa (surgical navigation of total ankle replacement).

184.5 The Humerus

184.5.1 Review of Published Reference Frames for the Humerus

Apparently, no reference frame for the humerus has ever been conceived to provide optimal accuracy for in vitro measurements and biomechanical testing. Conversely, different reference frames have been proposed for in vivo use. The Standardization and Terminology Committee of the International Society of Biomechanics (ISB) has recently issued a recommendation concerning the entire upper limb (Wu et al. 2005). The reference frame for the humerus put forward by the ISB is based on palpable markers (Wu et al. 2005): the most caudal points on the medial and lateral epicondyles and the centre of rotation of the glenohumeral articulation must be identified; alignment of the reference planes is based on the midpoint of the two epicondylar points and the center of the glenohumeral articulation. While this reference is certainly suitable for in vivo use, identification of such points in vivo is associated with errors that can be avoided by using other anatomical landmarks. In fact,

- The precision of different in vivo palpation methods for the humerus has recently been assessed (Salvia et al. 2009): the repeatability when the same observer was identifying the two epicondylar points was of the order of 2–4 mm; such error doubled between different observers.
- The glenohumeral center of rotation can be identified, even using the most sophisticated multiple regression approaches, with an error greater than 2.5 mm (Sholukha et al. 2009).

Therefore, in vitro reference frames for the humerus should be based on different anatomical landmarks than the in vivo ones. Dunlap et al. (2008) recently tested the structural properties of composite models of the humerus. They provide a partial indication of the alignment they used: it is not clear what criterion was used to define the long axis of the humerus; they defined the frontal plane as a plane between the medial and lateral epicondyles (only two points were indicated for identifying one plane in space).

As in vivo definitions are not fully satisfactory for in vitro use and in vitro reference frames are only partially defined, we made an effort to define an unambiguous reference frame for the humerus that can be accurately implemented in vitro, and (a) is as compatible as possible with the ISB recommendations (Wu et al. 2005), and (b) is as consistent as possible with the criteria previous adapted from Ruff and Hayes (1983) and Ruff (1981) for the lower limb.

184.5.2 Guidelines for Identifying the Reference Frame for the Humerus

The reference frame proposed below for the humerus adopts some of the criteria proposed by Ruff (1981) and Ruff and Hayes (1983) for the femur and tibia (measurement of the center of cross sections of the diaphysis at a given position along the diaphysis). In addition, as the humerus articulates with the ulna as a hinge joint, its neutral position in internal/external rotation is defined in a way that

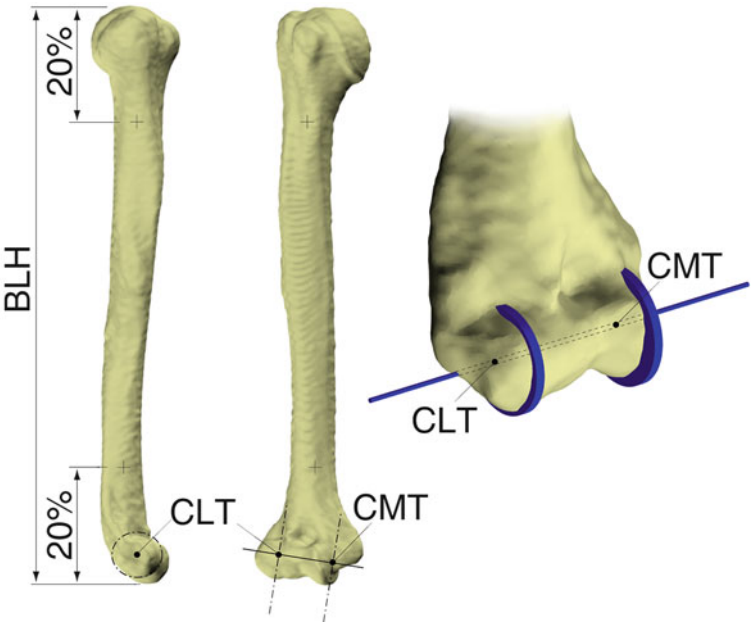

Fig. 184.10 Anatomical landmarks and dimensions of a human humerus. Lateral and anterior views of a right humerus, showing the biomechanical length (*BLH*) and the two sections where the center point must be identified. The detail (antero-lateral view) shows the circular shape of the most medial and lateral parts of the trochlea: the centers (*CMT* and *CLT*) of such circles define the frontal plane

can also be reported on the ulna (see later). The procedure can be summarized as follows (Figs. 184.10 and 184.11):

1. First, the biomechanical length of the humerus (BLH) must be measured (this is the full length of the bone).
2. Two levels along the bone, each at 20% of BLH from the most proximal and distal extremity, must be identified and marked.
3. The humerus must be laid on a level board, resting on the two posterior surfaces of the epicondyles and on the posterior face of the humeral head (posterior face up, Fig. 184.11a).
4. The centers of the cross sections at two such levels must be identified and marked both in the antero-posterior and in the medio-lateral views.
5. As the articulation between the humerus and the ulna operates as a perfect hinge joint, the trochlea is nearly perfectly circular when seen laterally (although the radius varies from lateral to medial). Therefore, the diameter of the most medial and lateral part of the trochlea can be measured. The centers of the most medial and lateral portions can be accurately identified (CMT and CLT, Fig. 184.10, detail).
6. Clay or plates of assigned thickness must be inserted underneath one of the two parts of the trochlea (typically the lateral part, which is smaller) so as to place the two centers of the trochlea on the same plane.
7. Similarly, clay or plates of assigned thickness must be inserted under the head of the humerus so that the centers of the two cross sections (point 4 above) lie in the same plane.
8. The frontal plane is defined as the plane passing through two such center points and parallel to the line joining the centers of the trochlea (CMT and CLT).
9. The sagittal plane is defined as a plane perpendicular to the frontal plane and passing through two such center points (Fig. 184.11b).

Fig. 184.11 Humerus ready for identification of anatomical planes. (**a**) Medial view of right humerus resting posterior side up: plates of the desired thickness (*arrow*) were placed below the anterior side of the lateral trochlea to ensure that the medial and lateral centers of the trochlea (*CMT* and *CLT*) lie in the same plane; another plate (*arrow*) is placed under the head, to align the diaphysis to the level plane; a scribing block can be used to mark the frontal plane. (**b**) Left humerus resting on its medial side; blocks and plates of constant thickness (*arrow*) are used near the lateral part of the trochlea to ensure that the frontal plane lies vertical; thus, a scribing block can be used to mark the sagittal plane

184.5.3 Assessment of the Reference Frame for the Humerus

The reference system described earlier has been tested in vitro to assess:

- The intra-operator repeatability (i.e., when the same operator repeatedly identifies the reference frame on the same specimen): the same bones were prepared with anatomical landmarks and reference planes ten times by the same operator. Each time, the reference frame was acquired with a digitizer and erased to avoid bias between repeats.
- The inter-operator repeatability (i.e., when the different operators identify the reference frame on the same specimen): the same bones were prepared with anatomical landmarks and reference planes by three independent operators. Each time, the reference frame was acquired with a digitizer and erased to avoid bias between operators.

Table 184.5 Repeatability of the reference frame for the humerus

Intra-operator repeatability	Abduction/adduction	0.18°
	Flexion/extension	0.13°
	Internal/external rotation	1.65°
Inter-operator repeatability	Abduction/adduction	0.50°
	Flexion/extension	0.17°
	Internal/external rotation	1.98°

Repeatability for the same operator and between different operators for the identification of the reference frame for the humerus

The inter-operator repeatability was larger but comparable to the intra-operator repeatability (Table 184.5). The largest errors were always associated with an incorrect identification of the reference frame in internal/external rotation. In fact, the anatomical landmarks used to identify such an angle are close to each other; thus, even a small error in the identification of such anatomical landmarks propagates to a large error in terms of rotation. Errors were smaller for the flexion/extension and abduction/adduction angles, with similar repeatability in both planes.

184.6 The Radius and Ulna

184.6.1 Review of Published Reference Frames for the Radius and Ulna

In fact, the radius and ulna have seldom been tested in vitro, and few methodological details have been reported. For this reason, no detailed reference frame has ever been proposed to provide optimal accuracy for in vitro measurements and biomechanical testing of the radius and ulna. Hsu et al. (1993) investigated the ulna and radius together. They defined the mechanical axis of the forearm, based on the radius, as the line passing through the center of the radial head and the middle of the interfossa ridge, between the scaphoid and lunate fossae on the distal radial articular surface.

Conversely, reference frames have been proposed for in vivo use. The recommendation recently issued by the Standardization and Terminology Committee of the International Society of Biomechanics (ISB) (Wu et al. 2005) includes details for the forearm. In this reference frame (like in any other for in vivo use), the forearm is most of the time treated as a whole, as it is difficult to accurately identify the radius and ulna noninvasively. Moreover, for most in vivo purposes (e.g., movement analysis), modeling the forearm as a whole provides satisfactory results.

The reference frame for the forearm proposed by the ISB is based on palpable markers (Wu et al. 2005): distally, the most caudal points on the ulnar and radial styloid must be identified; proximally, the reference frame is based on the two epicondyles of the humerus. Therefore, identification of anatomical axes of the radius and ulna is possible only in a whole upper limb, according to this recommendation (Wu et al. 2005). While this reference is certainly suitable for in vivo use, identification of such points in vivo is associated with errors that can be avoided by using other anatomical landmarks. In fact, even using the most sophisticated multiple regression approaches, the glenohumeral center of rotation can be identified, with an error greater than 2.5 mm (Sholukha et al. 2009).

Therefore, in vitro reference frames for the radius and ulna should be based on different anatomical landmarks than the in vivo ones. However, in the very few in vitro studies involving either the radius or the ulna (e.g., Edmonds et al. 2000) no clear definition of an anatomical reference frame has been provided.

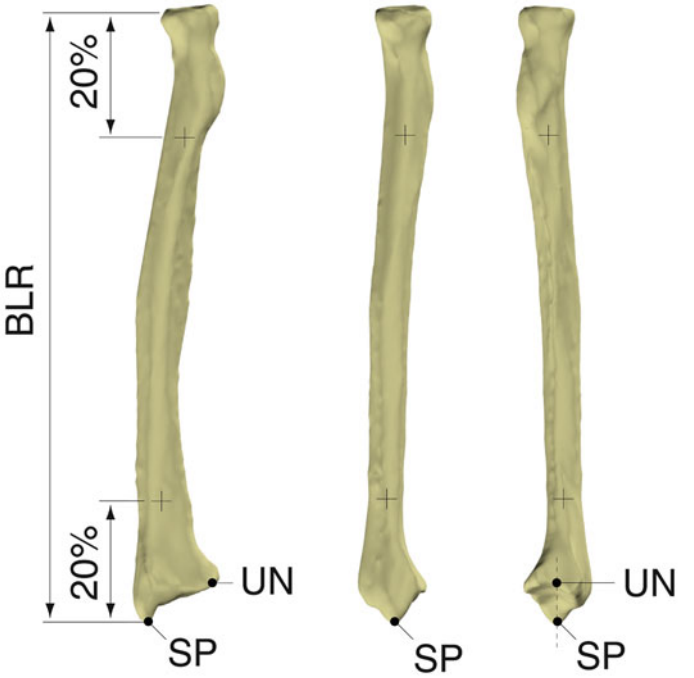

Fig. 184.12 Anatomical landmarks and dimensions of a human radius. Anterior, lateral, and medial views of a right radius, showing the biomechanical length (*BLR*) and the two sections where the center point must be identified. The anatomical landmarks used to identify the frontal plane are indicated: the most distal point of the styloid process (*SP*) and the center of the ulnar notch (*UN*)

As reference frames of the forearm intended for in vivo use are not fully satisfactory for in vitro use, and in vitro reference frames are only partially defined, we made an effort to define unambiguous reference frames for the radius and ulna that can be accurately implemented in vitro, and (a) are compatible with the ISB recommendations (Wu et al. 2005), and (b) are consistent with the criteria previous adopted by Ruff and Hayes (1983) and Ruff (1981) for the lower limb.

184.6.2 Guidelines for Identifying the Reference Frame for the Radius

Because of its curved shape, reference planes for the radius should be centered at selected sections along the diaphysis, as opposed to some center point in the epiphyses (in order to ensure that the long axis does not lie outside the bone contour at some section along the (curved) diaphysis). The description of the procedure to define the reference frame for the radius follows (Figs. 184.12 and 184.13):

1. The biomechanical length of the radius (BLR) is defined as the full length from the center of the nearly flat proximal surface of the head to the most distal point of the radial styloid process.
2. Two levels along the bone, each at 20% of BLU from the most proximal and distal extremity, must be identified and marked.
3. The centers of the cross sections at two such levels must be identified and marked both in the antero-posterior and in the medio-lateral views.
4. The most distal point of the styloid process (SP) and the central point of the ulnar notch (UN) must be marked (Fig. 184.13). Such points define the alignment of the frontal plane.
5. The radius must be laid anterior face up, either on a level plane (using clay to support it) or using adjustable clamps. The most distal point of the styloid process (SP) and the central point of the

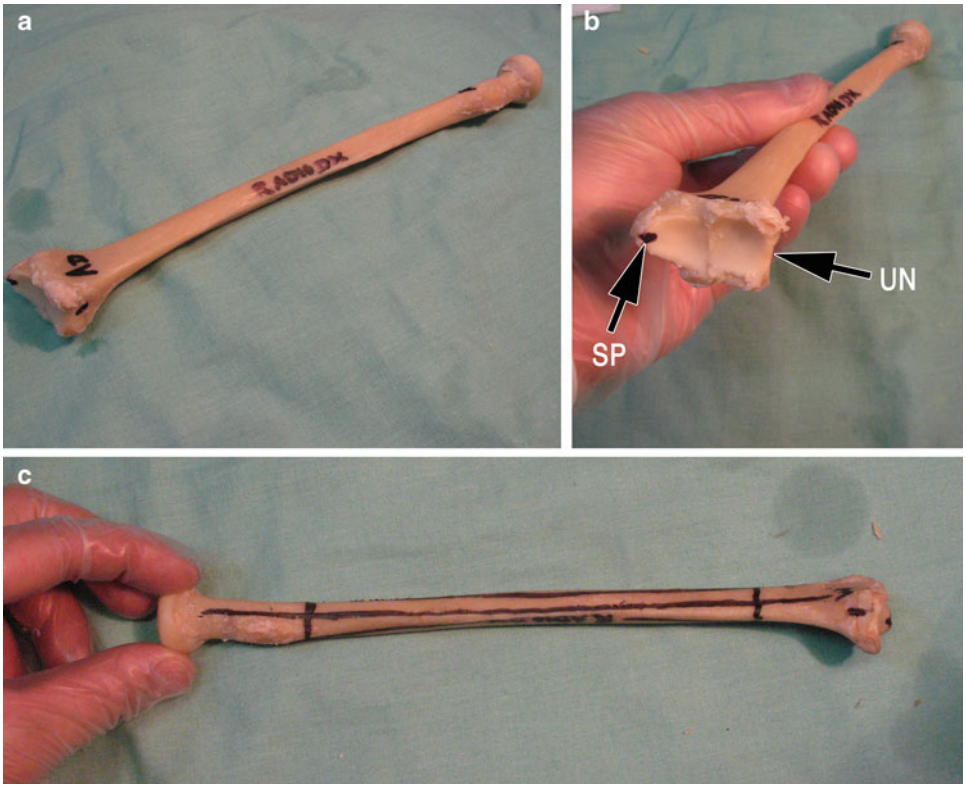

Fig. 184.13 Radius ready for identification of anatomical planes. (**a**) Medial and (**b**) distal views of right radius resting anterior side up: the tip of the styloid process (*SP*) and the center of the ulnar notch (*UN*) are visible. (**c**) Medial view of the radius, where the *black lines* indicate the frontal and sagittal planes

ulnar notch (UN) must be used to identify the neutral position in internal/external rotation: when both lie in a vertical plane, the radius lies in a neutral position.

6. Clay or plates of assigned thickness must be inserted under the two extremities so that the centers of the two cross sections (point 3 above) lie in the same plane.
7. The frontal plane is a plane parallel to the two distal points (SP and UN) and passing through the centers of the two sections above.
8. The sagittal plane is perpendicular to the frontal plane and goes through the center of the two sections above.

184.6.3 Guidelines for Identifying the Reference Frame for the Ulna

As the joint between the humerus and the ulna is a hinge joint, we chose to define the neutral position about the ulnar long axis in a way that is consistent with the frame adopted for the humerus. Therefore, the trochlear notch is used to identify the correct rotation about the ulnar long axis. Because of the curved shape of the ulna, reference planes should be centered at selected sections along the diaphysis, as opposed to some center point in the epiphyses (in order to ensure that the long axis does not

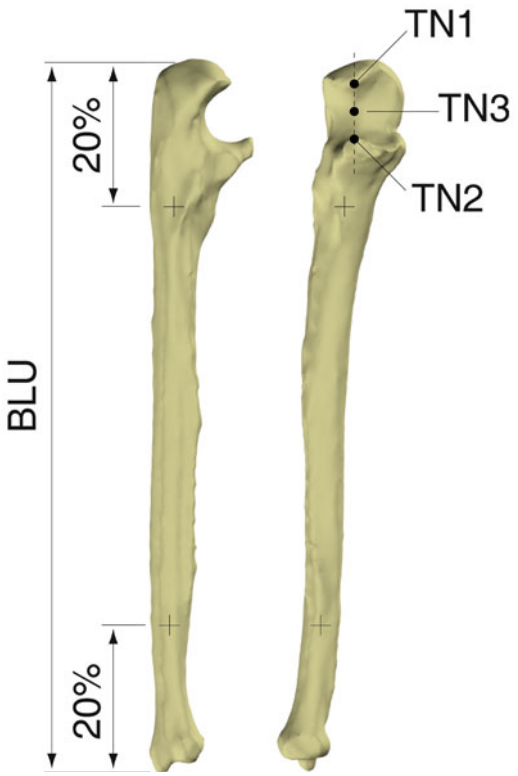

Fig. 184.14 Anatomical landmarks and dimensions of a human ulna. Lateral and frontal views of a right ulna, showing the biomechanical length of the ulna (*BLU*) and the two sections where the center point must be identified. Also shown are three points that must be identified on the ridge inside the trochlear notch (*TN1*, *TN2*, and *TN3*)

lie outside the bone contour at some section along the (curved) diaphysis). Following is a description of the procedure to define the reference frame for the ulna (Figs. 184.14 and 184.15):

1. The biomechanical length of the ulna (BLU) is defined as the full length from the proximal most point of the olecranon to the most distal point of the ulnar styloid process.
2. Two levels along the bone, each at 20% of BLU from the most proximal and distal extremity, must be identified and marked.
3. The centers of the cross sections at two such levels must be identified and marked both in the antero-posterior and in the medio-lateral views.
4. A ridge is visible in the trochlear notch, which runs in a frontal plane (it corresponds to the groove in the trochlea of the humerus). Three points must be marked in the trochlear notch (TN1, TN2, and TN3, Fig. 184.15), which are useful in the following steps.
5. The ulna must be laid anterior face up, either on a level plane (using clay to support it) or using adjustable clamps. The three points in the trochlear notch must be used to identify the neutral position in internal/external rotation: when all three points (TN1, TN2, and TN3) lie in a vertical plane, the ulna lies in a neutral position.
6. Clay or plates of assigned thickness must be inserted under the two extremities so that the centers of the two cross sections (point 3 above) lie in the same plane.
7. The sagittal plane is a plane parallel to the three points in the trochlear notch and passing through the centers of the two sections above.
8. The frontal plane is perpendicular to the sagittal plane and goes through the centers of the two sections above.

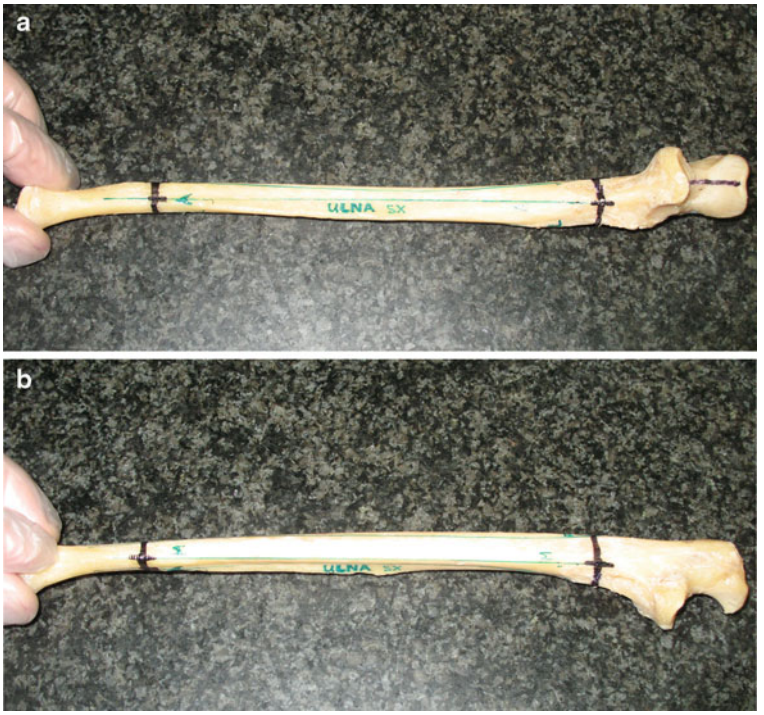

Fig. 184.15 Ulna ready for identification of anatomical planes. (**a**) Anterior view of left ulna: The *black line* in the trochlear notch was used to align the ulna so that its sagittal plane lies vertical. (**b**) Medial view of left ulna, where the anatomical planes are marked in *green*

184.6.4 Assessment of the Reference Frame for the Radius and Ulna

The reference frames described earlier for the radius and ulna have never been tested systematically. Based on past experience on the other bone segments, and on limited experience on the radius and ulna, it can be said that the intra-operator and the inter-operator variability are:

- Comparable to those reported for the humerus (Table 184.5) for the correct identification of the long axis of the radius and ulna in the frontal and sagittal plane and
- Nearly twice as large as those reported for the humerus (Table 184.5) for the correct identification of the neutral position in internal/external rotation about the axis of the radius and ulna.

184.7 The Metacarpal and Metatarsal Bones

184.7.1 Review of Published Reference Frames for the Metacarpal and Metatarsal Bones

To the author's best knowledge, no detailed anatomical reference frame has ever been proposed for the individual metacarpal and metatarsal bones. Conversely, reference frames have been proposed for in vivo use. However, in movement analysis, the hand and the foot are often described either as single bodies or divided in two or three parts. In fact, the recommendation issued by the Standardization and Terminology Committee of the International Society of Biomechanics (Wu et al. 2002) for the

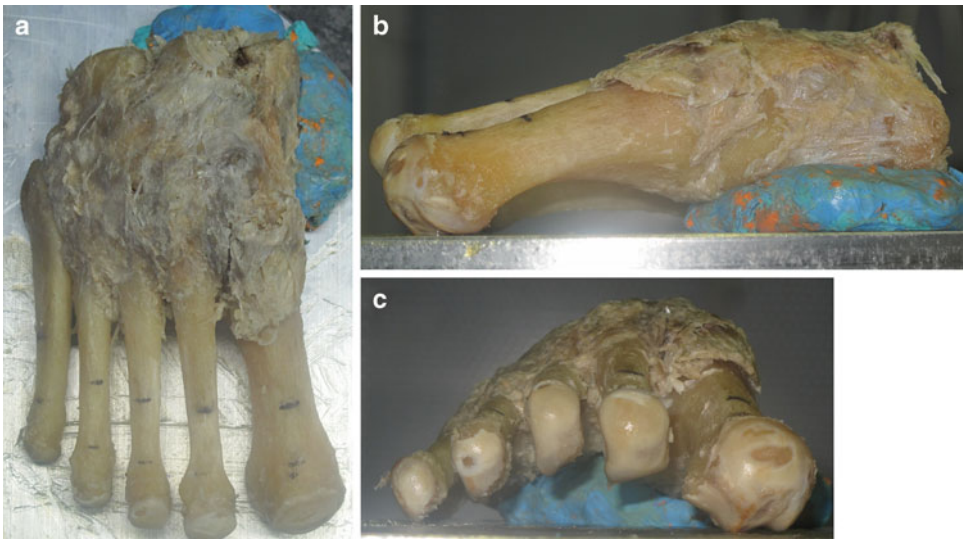

Fig. 184.16 Metatarsal bone preparation. Portion of a right foot including selected tarsal (cuneiforms, cuboid, and scaphoid) and all metatarsal bones: (**a**) view from above, (**b**) from medial, and (**c**) frontal. The medial part of the foot (medial cuneiform) is supported by clay to restore the natural curvature of the plantar arch

lower limb assigns a reference frame to the ankle joint complex and one to the calcaneus, with no further detail for the metatarsal region. The recommendation recently issued by the Standardization and Terminology Committee of the International Society of Biomechanics (Wu et al. 2005) for the upper limb provides some more detail for the metacarpal bones: the origin of the reference frame for each of the metacarpals is located midway between the base and head of each metacarpal. In the transverse plane, it will be at the approximate center of the tubular bone. The sagittal plane is defined as that plane that splits the metacarpal into mirror images.

As no reference frame has ever been proposed for in vitro applications, we devised a procedure to identify the reference frame of each metacarpal and metatarsal bone that is inspired by the ISB guidelines (Wu et al. 2005) and is compatible with the criteria adopted for the other bones, consistent with Ruff and Hayes (1983) and Ruff (1981).

184.7.2 Guidelines for Identifying the Reference Frame for the Metacarpal and Metatarsal Bones

A similar procedure is proposed for the metacarpal and metatarsal bones. For brevity, the procedure for the metatarsal bones is described below (only minor changes apply to the metacarpal ones). The metacarpal bones do not have sufficient detail or transversal dimension that enable accurate alignment about their longitudinal axis if they are removed from the rest of the foot. The procedure described below is designed to transfer the anatomical planes of the entire foot to each of the metatarsal bones (Figs. 184.16–184.18):

1. The foot can be freed of the most proximal part (calcaneus, etc.) while preserving the other tarsal bones (cuneiforms, cuboid, and scaphoid) and their ligaments to preserve the physiological alignment in internal/external rotation.

Fig. 184.17 Preparation of alignment pots for the metatarsal bones. Portion of a right foot including selected tarsal (cuneiforms, cuboid, and scaphoid) and all metatarsal bones: (**a**) The distal extremity of each metatarsal bone is included in bone cement while resting on a flat surface; (**b**) First metatarsal, after complete dissection: the flat pot on the distal extremity provides alignment about the long axis of the bone in the subsequent steps

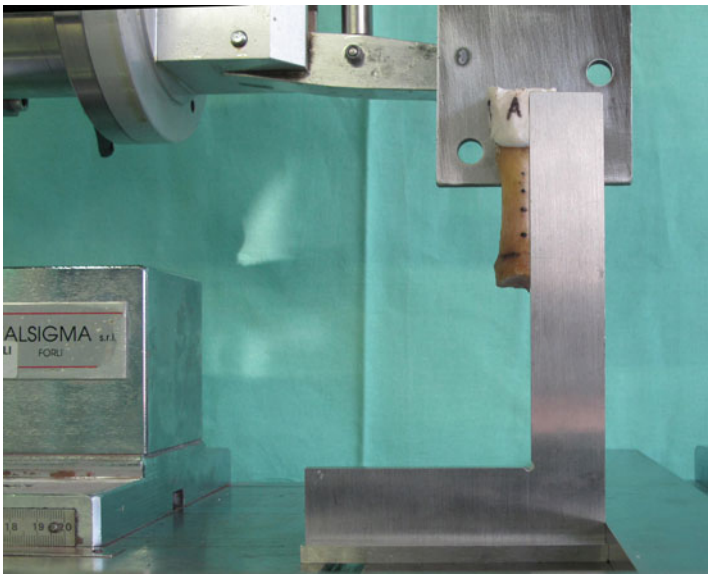

Fig. 184.18 Alignment of the first metatarsus. First metatarsal supported in an adjustable clamp: the acrylic pot is used to ensure correct alignment about its axis, while vertical alignment is checked using a vertical ruler

2. The biomechanical length of each metatarsal is defined as the full length from the most proximal point to the most distal point. As this is not measurable directly before dissection is completed, the distal portion should be measured first (while the proximal part is still included in the ligamentous structures) up to an arbitrary point that must be marked along the diaphysis. When the distal part is potted and the proximal part is free of all soft tissue, the remaining proximal length must be measured and summed to the previous measurement.
3. The medial part of the foot (medial cuneiform) must be supported by clay to restore the natural curvature of the plantar arch (Fig. 184.16).
4. The distal extremity of each metatarsal bone must be included in high-viscosity bone cement while resting on a flat surface to provide alignment about the long axis of the bone in subsequent steps (Fig. 184.17).
5. Two levels along the bone, each at 20% of biomechanical length from the most proximal and distal extremity, must be identified and marked.

6. The centers of the cross sections at two such levels must be identified and marked both in the antero-posterior and in the medio-lateral views.
7. With the aid of the flat surface of the distal pots of bone cement and the center points of the two sections (see point 6 above), the frontal and sagittal planes can be identified (Fig. 184.18).

184.7.3 Assessment of the Reference Frame for the Metacarpal and Metatarsal Bones

The reference frame described earlier has only provisionally been assessed. Because of the small dimension of the bones involved, alignment errors are larger (and more difficult to assess). It can be provisionally estimated that the uncertainty affecting rotation about the long axis of these bones is of the order of 5–10°, while the uncertainty affecting identification of the frontal and sagittal planes is of the order of 2–5°.

184.8 The Phalanges

184.8.1 Review of Published Reference Frames for the Phalanges

To the author's best knowledge, no detailed anatomical reference frame has ever been proposed for the phalanges for neither the hand or the foot. As already pointed out, the hand and the foot are often described either as single bodies in movement analysis or divided in two or three parts. In fact, the recommendation by the Standardization and Terminology Committee of the International Society of Biomechanics (Wu et al. 2002) for the lower limb does not suggest any specific reference frame for the phalanges of the foot. The recent recommendation by the Standardization and Terminology Committee of the International Society of Biomechanics (Wu et al. 2005) for the upper limb provides some more detail for the phalanges: similar to the metacarpal bones, the origin of the reference frame is located midway between the base and head of each phalanges. In the transverse plane, it will be at the approximate center of the tubular bone. The sagittal plane is defined as that plane that splits the phalanges into mirror images.

As no reference frame has ever been proposed for in vitro applications, we devised a procedure to identify the reference frame of each phalanges bone that is inspired by the ISB guidelines (Wu et al. 2005) and is compatible with the criteria adopted for the other bones, consistent with Ruff and Hayes (1983) and Ruff (1981).

184.8.2 Guidelines for Identifying the Reference Frame for the Phalanges

The procedure for the phalanges is quite similar to that described for the metacarpal and metatarsal bones and is consistent with the methods described for the other bones:

1. Because of the small size of the phalanges, accurate identification of the palmar plane is critical on isolated bones. Therefore, alignment of the phalanges about their long axis must be derived from that of the adjacent metacarpal or metatarsal bones prior to complete dissection (similar to the method explained for the metacarpal and metatarsal bones).

2. The biomechanical length of each phalanx is defined as the full length from the proximal most point to the most distal point.
3. Two levels along the bone, each at 20% of biomechanical length from the most proximal and distal extremity, must be identified and marked.
4. The centers of the cross sections at two such levels must be identified and marked both in the antero-posterior and in the medio-lateral views.
5. Clay or plates of assigned thickness must be inserted under the two extremities so that the centers of the two cross sections (point 4 above) lie in the same plane.
6. The sagittal plane and frontal planes can now be marked.

184.8.3 Assessment of the Reference Frame for the Phalanges

The reference frame described above has only provisionally been assessed. Because of the small dimension of the bones involved, alignment errors are larger (and more difficult to assess). It can be provisionally estimated that the uncertainty affecting identification of the frontal and sagittal planes is of the order of 2–5° (similar to that of the metacarpal and metatarsal bones). However, the uncertainty affecting rotation about the long axis of these bones is necessarily larger than that of the neighboring metatarsal and metacarpal bones, as alignment of the phalanges is only derived from such bones): errors greater than 10° should be expected.

184.9 Applications to Other Areas and Future Work

In the last few years, following the Physiome initiative that has been put forward by many research centers and grant agencies, the musculoskeletal system is often investigated using a multiscale approach (Viceconti et al. 2008). This implies that the same bone specimen has to be tested at different dimensional scales (see, for instance, the Living Human Digital Library project (LHDL: http://www.biomedtown.org/biomed_town/LHDL/users/repository/ and http://www.livinghuman.org/); or the Virtual Physiological Osteoporotic Human (VPH-OP: http://www.biomedtown.org/biomed_town/vphop and http://www.vphop.eu/). When a skeleton has to be investigated at different scales, first as a whole, by extracting individual bone specimens, down to the tissue and sub-tissue level, new reference frames and new methods for propagating them across the different dimensional scales are needed. As an example, in the LHDL project, the human femur was investigated as a whole, at the tissue level (mechanical properties of cortical and trabecular bone) and at the sub-tissue level (collagen orientation, etc.) (Cristofolini et al. 2009). To achieve this, specific references and practical tools to transfer them from one scale to the other had to be developed (Juszczyk 2009).

Summary Points

- Identification of reference frames based on anatomical landmarks is fundamental for the correct execution of reproducible in vitro tests on bone segments.
- While reference frames for in vivo use must rely on anatomical landmarks that are accessible noninvasively by palpation, reference frames for in vitro use can rely upon physical points on the bone surface and direct measurement of bone dimensions.

- The possibility of directly accessing the bone surface in vitro enables more accurate identification of anatomical landmarks and reference frames than when the same task is performed in vivo.
- Bone anatomical landmarks for in vitro use should be defined so that they rely upon points, features, and dimensions that are available in all subjects and are not altered during aging.
- For long bones, the most critical alignment is that about the long axis of the bone: inaccurate identification of such anatomical landmarks causes large error in internal/external rotation because of the small dimensions in a direction perpendicular to the long axis.
- For most long bones, reliable anatomical landmarks for the identification of the long axis are based upon the mid-section at two well-defined levels, both in the frontal and sagittal plane. Direct measurement of cross section by means of Vernier calipers enables accurate identification of such points (typical error: 0.2–0.4 mm).
- Similar criteria are proposed to define consistent reference frames of most long bones (femur, tibia, fibula, humerus, radius, ulna, metatarsal and metacarpal bones, and phalanges).
- Typical inter-operator uncertainty in the identification of the neutral position about the long axis of long bones (internal/external rotation) is 0.5°–5°, the largest error being found for the smallest bones.
- Typical inter-operator uncertainty in the identification of the neutral position in the frontal plane (adduction/abduction) and in a sagittal plane (flexion/extension) is 0.1°–1°, the largest error being found for the smallest bones.

Acknowledgments The authors wish to thank Massimiliano Baleani, Mateusz Juszczyk, and Serge Van Sint Jan for the stimulating discussions. Giorgia Conti, Valentina Danesi, and Paolo Erani greatly contributed to the development of the reference frames. Andrea Malandrino, Doriana Lionetti, and Caroline Öhman patiently contributed to the inter-operator variability assessment. Luigi Lena provided the artwork. Daniel Espino carefully revised the script.

The European Community co-funded this study (grants: IST-2004-026932 "Living Human Digital Library - LHDL" and #223865 "The Osteoporotic Virtual Physiological Human – VPHOP").

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Chapter 185
Using Three-Dimensional (3D) Anthropometric Data in Design

Jianwei Niu and Zhizhong Li

Abstract With the emergence of 3D scanning technology, it is now possible to generate a large database of 3D models of humans from different demographic backgrounds. Unfortunately, one major drawback is that there is no clear link between 3D anthropometric data and engineering design. Sizing is regarded as an effective way to design properly fitted products. This chapter aims to show the usefulness of 3D anthropometry for the development of product sizing systems, taking helmet design using 3D head data as a case study. Current 3D scanning technology, the representative large-scale 3D anthropometric surveys, the diverse applications of 3D anthropometry in ergonomic product design, and the historical development of military helmet sizing systems were reviewed. Emphasis was then put on the proposed sizing method for helmet design by combining a multi-resolution representation of 3D anthropometric data and k-means clustering on the decomposed data. By using a novel block-based distance, each 3D head was transformed into a multi-dimensional vector. Clustering validation was implemented by using two measures, i.e., size-weighted variances and Clustering Validity Indices (CVI). The results show that the proposed block distance-based descriptor is superior to traditional sizing dimensions. Comparative studies were conducted as well to investigate the robustness of the proposed method. The proposed method provides a systematic method for properly grouping 3D anthropometric samples into clusters according to their 3D shape.

Abbreviations

3D	Three Dimensional
ANOVA	Analysis of Variance
CAD	Computer Aided Design
CAESAR	Civilian American and European Surface Anthropometry Resource
CMAR	Cluster Membership Accuracy Rate
CMM	Coordinate Measurement Machine
CVI	Clustering Validity Indices
HMD	Helmet-mounted display
NURBS	Non-Uniform Rational B-Spline
PCA	Principal Component Analysis
WEAR	World Engineering Anthropometry Resource

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_185,

185.1 Introduction

Anthropometry is a requisite for ergonomics and user-centered design (Liu et al. 2009). It has been recognized that anthropometric data could improve the quality of product design, usability, and workstation planning. Modern anthropometry can be traced back to 1870, when Quelet attempted to obtain measurements of the average man in order to provide better-fitting uniforms for Napoleon's army (CUErgo 2009).

Traditionally, anthropometric data were manually collected using tapes, calipers, and other such measurement tools. Traditional anthropometry has many sociological, logistical, and technical drawbacks. It takes prolonged time, requires a skilled researcher for consistency and accuracy during measuring, and brings about undesirable physical contact between the subject and the researcher (Deo 2006). Over the past few years in anthropometric research, it has been found that observer error – such as inaccurate instrument placement and readings, the subject's attitude, and the imprecise placement of landmark locations – is extremely problematic in traditional anthropometry (Gordon and Bradtmiller 1992). 3D anthropometry is the quantitative study of the regions of the human body and characteristics of the surfaces, volume, and shapes of organs using noninvasive methods (Vannier and Robinette 1995). As the cost of scanning technology declines, research utilizing 3D techniques is becoming widely accessible to academia and industry (Lerch et al. 2007).

An effective way to design properly fitted products is to analyze human body forms and to classify them into several groups (Mochimaru et al. 2000), commonly referred to as 'sizing' in anthropometry. A sizing system classifies a specific population into homogeneous groups by using certain key body dimensions, such as stature and waist girth (Chung et al. 2007). For a traditional sizing system, sizing programs are established by dividing the range of key dimensions into appropriate intervals.

There are some drawbacks in traditional sizing methods. The most important is that, in traditional univariate or bivariate sizing methods, only one or two dimensions are referenced. Geometric characteristics and the internal structure of human surfaces are not adequately considered. This leads to design deficiencies on fit and comfort.

The aim of this chapter is to summarize several previously published papers (Niu et al. 2007, 2008; Niu and Li 2008; Niu et al. 2009a, b, c) demonstrating the usefulness of 3D anthropometry with regard to sizing and ergonomic design requirements. A novel sizing method for helmet design by combining a multi-resolution representation of 3D anthropometric data and k-means clustering on decomposed data was presented. In order to understand the robustness of the new sizing method, several further comparative studies were conducted, for example, the sensitivity to the decomposition level.

185.2 3D Scan Technique and Large-Scale 3D Surveys

Even before 3D scanning technologies were available, there were several methods for capturing human body surfaces (Gordon et al. 1989; Li 2006). Nowadays, capturing human body surface data can be accomplished in many ways. They include, but are not limited to, coordinate measurement machine (CMM) technology, computed tomography (CT) scanning, optical scanning, industrial laser scanning, etc. Although 3D data can provide a rich array of information on human body shapes, researchers usually have to face the daunting task of first processing the data. Data processing work includes filling holes, data filtering, surface modeling, registration, and alignment of multiple scans, etc. Currently, one major part of 3D data processing focuses on landmark labeling and extraction of human body dimensions

from 3D scanning (Li 2006). No 3D systems are commonly used in anthropometry. An efficient, reliable, and non-contact solution to 3D data acquisition would be a very significant step forward.

Currently, a number of major ergonomic studies are underway, undertaken by consortiums of universities, governments, and industries to create large accurate 3D anthropometric data sets. CAESAR (Civilian American and European Surface Anthropometry Resource), regarded as the first large-scale civilian 3D survey in the West, was the result of a comprehensive research project that brought together representatives from various industries including apparel, aerospace, and automotive in order to assist these industries with their ergonomic needs by making anthropometric measurements of large populations of citizens (Robinette et al. 2002). SizeUK (www.fashion.arts.ac.uk) and SizeUSA (www.tc2.com) are two other representative 3D surveys. France, China, Korea, Mexico, and Brazil are also conducting or have conducted similar national 3D anthropometric surveys. WEAR (World Engineering Anthropometry Resource project, http://wear.io.tudelft.nl) brings together a wealth of different anthropometric data collected around the world as well as methods for the use of these data in a wide variety of innovative applications. Through collaboration between experts in anthropometry from ten countries in six continents, the project unifies access to 145 existing databases, including 3D body scans. Its aim is to develop data models and software tools of an on-line worldwide information system for utilization in the latest anthropometric databases in engineering environments (http://ovrt.nist.gov).

185.3 Application of 3D Anthropometry in Ergonomic Product Design

The large variety of working or living environments presents a challenging task for the designers. Fitted clothing, worn items, equipment, and/or workstations must be designed with careful consideration of the size and shape of the target population (Reed and Parkinson 2008). The interfaces between user and designed products can affect fit, safety, and other performances. For example, if an aircraft seat cannot be sufficiently adjusted for height, a pilot with short stature cannot see over the instrument panel (Vannier and Robinette 1995). The traditional design process is usually both costly and time consuming.

3D anthropometry has the potential to accelerate the design process using 3D data, and has inspired the interests of designers. Unfortunately, automatic processing of 3D scan data is still currently under development. This is why designers are often confused regarding how to use anthropometric theory to guide their designs (Kouchi et al. 1996). Therefore, development of new methods and tools for the exploitation of 3D anthropometric databases is urgently needed for designing and functional evaluation of products. Only in this way can the time and cost of launching products be reduced, the fit and comfort of products be improved, and design aspects such as protection, functionality, and style be integrated.

Computer-aided software systems have assisted in enhancing the efficiency of engineering design. Many researchers are working on developing a virtual environment to be used for product design where 3D anthropometric data are important. A number of 3D software tools have been developed for ergonomic design of consumer products, machines, workplaces, and occupational devices. For instance, Mochimaru et al. (2000) proposed a homologous modeling method. Well-fitted products can be designed by applying deformed control lattice points which convert a standard body form into other body forms. Brodeur and Reynolds (2004) presented a method for converting the CAESAR full-body scanned data into human body models for use in the ERL (a comprehensive automobile interior design tool). CAESAR data can be incorporated into the ERL software for ergonomic design and evaluation. McKean et al. (2005) presented the development and testing of a tool for designing

vehicle operator workstations using 3D anthropometry. Goonetilleke and his colleagues showed an approach to automating foot measurements using 3D scanned data, as well demonstrating how to model foot height and foot shape-related dimensions (Witana et al. 2006; Xiong et al. 2008). Veitch and Davis (2009) presented their use of 3D anthropometric data in the selection and design of life-like apparel fit manikins, which then resulted in 2D apparel blocks, patterns, and grading.

3D anthropometry also finds applications in the individualized design and fabrication of total-contact seating systems, etc. For example, Hsiao et al. (2007) evaluated the fit efficacy of fall-protection harnesses by using 3D anthropometric data to help reduce the number of fall-related injuries and fatalities among construction workers. Successive and increasingly revealing studies have resulted in improved specifications for new harness designs (National Fallen Firefighters Foundation and Total Contact Inc. 2008).

The design of airline and automotive interiors is also facilitated by the use of 3D human models. For the automotive industry, comfortable seating is considered a consumer requirement. High-resolution human models can provide ergonomic information regarding appropriate seat height and necessary legroom space and then generate a computerized pressure map (Reed et al. 2002). NIOSH recently completed a 3D anthropometric study of agricultural workers to enhance tractor safety and performance.

An important category of wearing products required to be extremely fitted are head and face-related products, such as masks, helmets, goggles, respirators, etc. Traditional helmet design usually depends on certain linear measurements, for example, head length, head breadth, or head circumference. During the 1990s, with the rapid development of scanning techniques, 3D head data became popular in helmet design. Meunier et al. (2000) proposed a method involving the use of 3D laser scanned geometry as a means of measuring helmet standoff distance (distance between the inside of the helmet and the skull). Their method provides a valuable tool to design ergonomic helmets by providing objective feedback for information regarding compatibility. By using 3D head data, a computer-aided tool based on a semi-parametric helmet shell model was proposed by Liu et al. (2007). This tool can quickly generate a helmet shell after several critical parameters are set. It speeds up the development of customized safety helmets and offers improved comfort and better protection for the wearer. Zhang and Molenbroek (2009) introduced their method to model and design the glasses based on 3D head scan data with the computer design software Rhinoceros (www.rhino3d.com).

In contrast with traditional linear anthropometry, 3D anthropometry brings tremendous benefits to accommodate various and diverse groups of users, and leads to much improvement in product ergonomic design.

185.4 Historical Development of Military Helmet Sizing Systems

Early during World War I and II, soft leather helmets were first designed and considered the headgear of choice for battle aircraft aviators. These soft helmets usually came in only one size and had a drawstring or cloth strap for adjustment around the face and neck for a closer fit. Face length served as the key dimension of a sizing system developed in 1942 (Randall and Damon 1942). In 1944, a new Four Size Head Circumference Program using the cadet anthropometric series was established (Koepnick and Benton 1944).

Subsequently, head breadth and head length as key dimensions were also considered when rigid crash helmets became a necessity with the advent of high-speed aircraft, and led to the 1954 Headform Series (Zeigen et al. 1960). A major drawback of the 1954 system was its complexity. Zeigen et al. (1960) reported a method for the sizing and design of rigid and semi-rigid helmets based on a single

key dimension: head circumference. Another early sizing system was the 1954 Head Length–Head Breadth System (Zeigen et al. 1960). As pointed out by researchers, helmets designed based on such sizing systems were usually bulky and uncomfortable.

More recently, Sippo and Belyavin (1991) described a method of sizing using three key dimensions: head length, head breadth, and pupil-vertex height. The authors used multivariate statistical analysis on anthropometric data from a 1970/1971 survey of 2,000 Royal Air Force Aircrew members. Robinette and Whitestone (1992) reported an approach for characterizing the human head in the design process. They selected head length and head breadth to divide the population into groups. They then arbitrarily selected target head length and head breadth points within these groups for selection of heads to represent the group. Bradtmiller and Beecher (1993) introduced their approach for helmet sizing. The authors developed vectors from a central point on the head to points on the surface from a data set of 475 males and 462 females in a nationwide survey. The authors stated that the vectors form variables that can be manipulated in traditional ways and that they were pursuing two analytical approaches with the radii. A similar concept was also adopted by Elliott (1998).

In conclusion, this brief survey clearly demonstrates that helmet sizing is a complex issue, and has been a hot spot in the research of anthropometry, especially with the rapid progress of 3D technique.

185.5 Use of 3D Anthropometric Data for Helmet Sizing

Helmets have become increasingly specialized for a variety of tasks and functions. Types of helmets include helmets used by construction workers, motorcyclists, football players, baseball players, divers, welders, bicyclists, fire fighters, wrestlers, aviators, etc. The issue of properly fitting helmets has been studied for a long time. Numerous reports have referred to the high incidence of head injuries and the resultant fatalities in aircraft accidents. The extreme complexity and variability of the head and face exaggerate the limitations of traditional linear dimensions.

The demand for new methods arose when traditional sizing systems proved to be inadequate for current helmet-design problems. Protective helmets that are too loose may become displaced from the wearer's head during an accident and even result in head injury. Conversely, too tight a protective helmet will be uncomfortable and may cause the wearer to position the helmet incorrectly on the head, or cause an unnecessary distraction. This is critical for jobs requiring a great degree of concentration. Operation of a fighter aircraft during wartime would be just one example where a poor-fitting helmet would be extremely undesirable.

Helmet-mounted displays (HMDs) are becoming increasingly popular for both military and civilian use. Medical operations, such as endoscopic surgery, and robotic applications, such as bomb disposal, are just a few examples of the use of HMDs where a poor-fitting helmet could reduce human performance and result in disaster (Elliott 1998). Properly fitting modern flight helmets means not only comfort, but also proper placement of accessorial components (e.g., headphones, helmet-mounted optics, etc.), stability, and proper location of the center of gravity on a helmet (Harrison and Robinette 2005).

A new attempt to implement sizing based on 3D anthropometric data is presented in our research. First, by using B-spline wavelet analysis, a multi-resolution description of 3D anthropometric data is established. Then, a block-division method is used to convert each 3D surface into a block-distance vector, which reflects both size and shape information. Next, such vectors become the input of the k-means clustering algorithm, which segments samples into groups according to inter-individual distances rather than range division of key dimensions. Finally, a case study on 3D head data demonstrates the effectiveness of the proposed method and provides results on sizing head shapes.

Fig. 185.1 NURBS surface of the head scan at decomposition level 3. This figure depicts THE NURBS (Non-uniform rational B-spline) surface of a head scan at decomposition level 3. The decomposition is based on B-spline wavelet decomposition algorithm

185.5.1 Data Acquisition and Preprocessing

Head data of 510 young male Chinese soldiers (ages 19–23) were collected with a computerized tomography (CT) scanner at a low dosage by a military department in 2002. However, the head postures of some subjects were not properly settled and stabilized for scanning, and thus the corresponding head scans were rejected for analysis. The final sample size dropped to 447. The slice-to-slice distance was set at 5.0 mm. The original data format was Digital Imaging and Communications in Medicine (http://medical.nema.org). Coordinates of head surfaces were calculated from the original data. The number of points varies from a minimum 38,420 to a maximum 56,200. Under the aid of the CAD software, Unigraphics, noise data on each section can be removed manually by visual check. Since we are mainly concerned with the shape of the whole head, the data for the ears, other than the shape and geometry of the ears, were not analyzed. Using Unigraphics software, the non-uniform rational B-spline (NURBS) surface of the head was generated, as shown in Fig. 185.1.

185.5.2 Multi-resolution Description of a 3D Head

To obtain a multi-resolution description of a 3D head, B-spline wavelet decomposition for heads in our database has been conducted with the aid of the Unigraphics user function developed by our research team.

Multi-resolution decomposition of a head sample is illustrated in Fig. 185.2. Surfaces (a), (b), (c), (d), (e), and (f) correspond to the original surfaces and the decomposed surfaces on the first, second, third, fourth, and fifth levels, defined by 17,161, 4,489, 1,225, 361, 121, and 49 control points, respectively. It can be seen that the decomposed surfaces can describe the main shape of the original ones. Quantitative approximation errors, which reflect the approximation of the decomposed surface to the original surface, have been investigated with respect to various decomposition levels and reported in Niu et al. (2007).

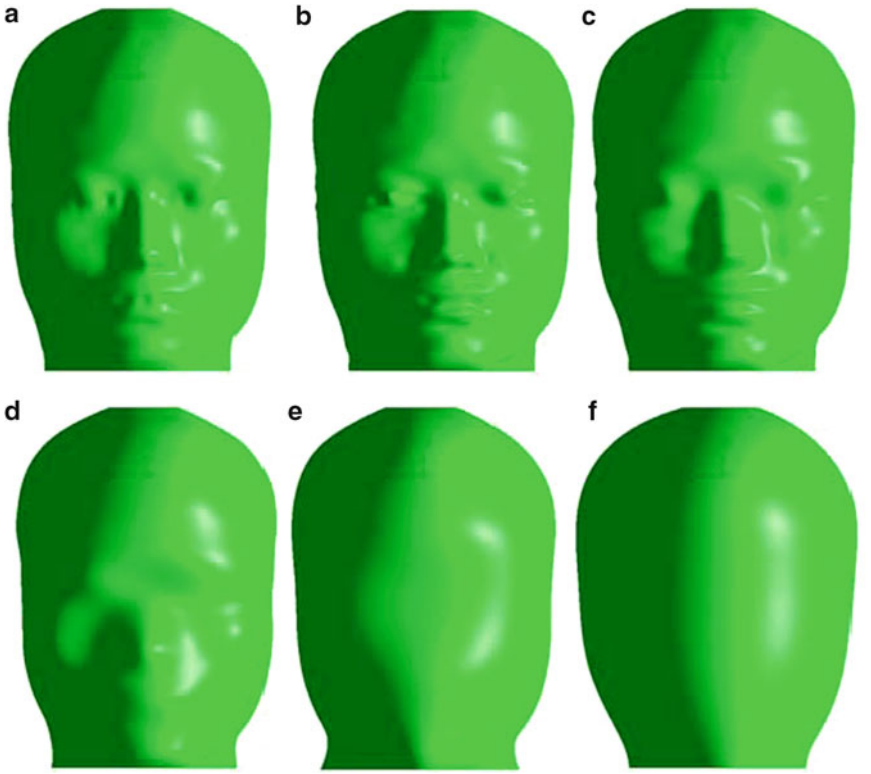

Fig. 185.2 Multi-resolution modeling of a sample (Niu et al. 2009a). This figure depicts multi-resolution modeling of a sample. The original head surface was decomposed based on B-spline wavelet decomposition algorithm. The main shape information can be preserved by the decomposed head surface, while the details were ignored

185.5.3 Block Distance-Based Vector Descriptor for 3D Head Surfaces

The sample surfaces are normally expressed in 3D Cartesian coordinates. To facilitate later shape analysis, a 'vector descriptor' is proposed. A vector descriptor consists of a number of block distances. Here, the term of block means a regular patch on the 3D surface. The block division result of a sample is shown in Fig. 185.3 with different colors and symbols in front and side views.

The distance between the two corresponding blocks on a sample surface i and the inscribed surface, namely $S(i)$, can then be constructed with two parts, namely $S_1(i)$ and $S_2(i)$, that reflect macro-size and micro-shape differences, respectively (Niu et al. 2009a). $S_1(i)$ can be calculated as

$$S_1(i) = \sum_{j=1}^{n_i} dis(p_{i,j}), \quad i = 1,2,3,\ldots,m \tag{185.1}$$

where $p_{i,j}$ is the jth point, and n_i represents the number of points falling into the ith block. Euclidean distance was used to calculate the distance between two corresponding points. $S_2(i)$ can be calculated as

$$S_2(i) = \sum_{j=1}^{n_i} \left| dis(p_{i,j}) - \frac{S_1(i)}{n_i} \right|, \quad i = 1,2,3,\ldots,\mathrm{m} \tag{185.2}$$

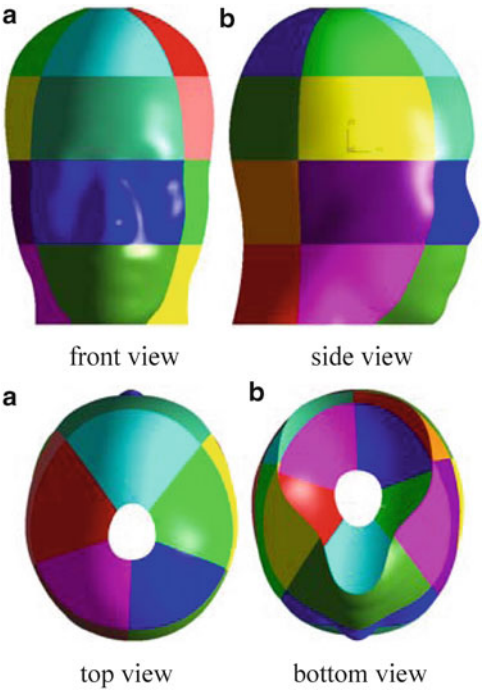

Fig. 185.3 Block division of a head (Adapted from Niu et al. 2009b). This figure depicts the result of block division of a head sample. The whole head surface was divided into 20 blocks, where the block number is 4 in the vertical direction and 5 in the horizontal direction respectively

S_2 describes the shape variation in the corresponding local areas of two 3D surfaces. Different local areas on a surface can have different shapes and geometrical characteristics; therefore, they contribute differently to dissimilarity of the entire shape between a sample surface and the inscribed surface.

Using the above method, the shape of a surface can be characterized by a vector (S_1 (1), S_2 (1), S_1 (2), S_2 (2),…, S_1 (m), S_2 (m)). The vectors are the input of the following k-means clustering algorithm.

185.5.4 K-Means Clustering for 3D Head Surfaces

Clustering has been applied to accommodate various demographic groups and designs for sizing systems. In the case study, k-means clustering was applied to different sets of sample data for comparison, including:

- The head length and head breadth data set.
- The top five PCA components of the proposed block distance-based vectors.
- Directly applied to the proposed block distance-based vectors.

The three clustering alternatives will be compared with two other criteria as described in the next section to see the difference of clustering on traditional sizing measurements and the proposed block distance-based vectors, as well as the necessity of PCA before clustering.

185.5.5 Evaluation of Clustering Results

Cluster evaluation is the process of assessing the quality and reliability of the cluster sets derived from various clustering processes. The Turi & Ray index (Ray and Turi 1999) was revised for clustering

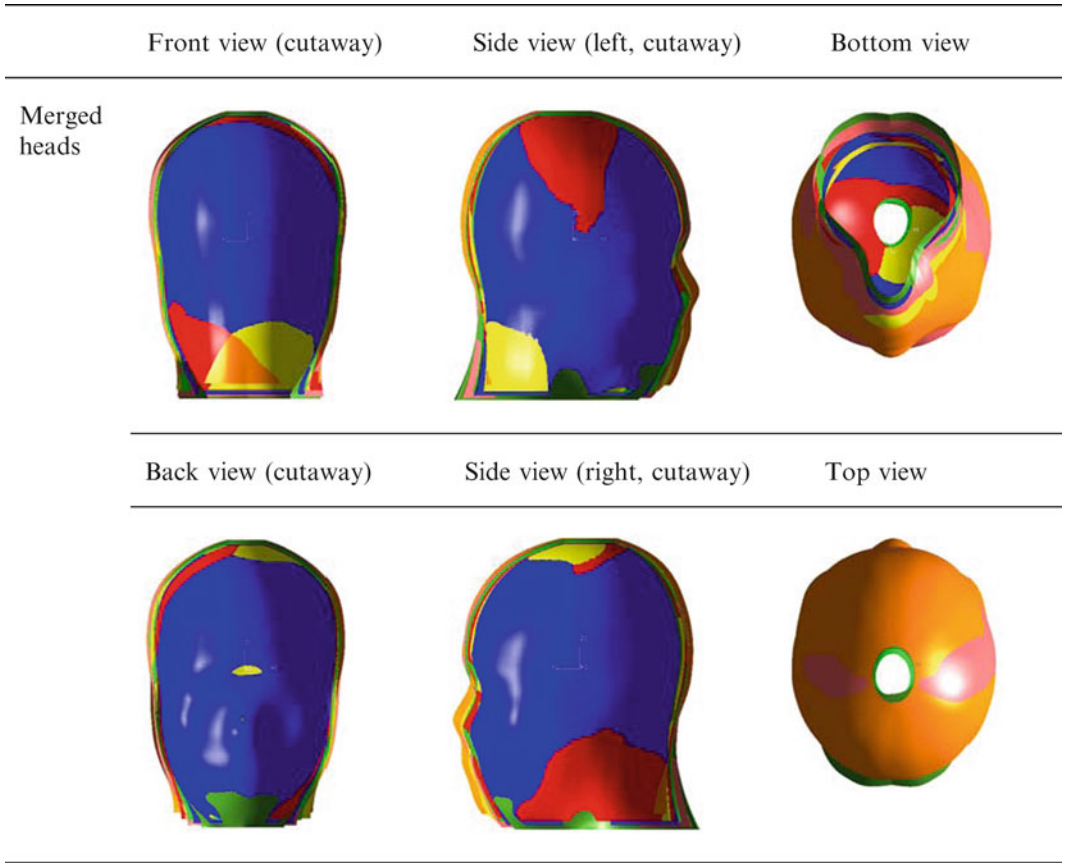

Fig. 185.4 Different views of the merged heads of clusters ($N = 447$, decomposition level = 3). This figure depicts the different views of the merged representative heads of clusters, where the sample size is 447, and the wavelet decomposition level is three. It can help readers distinguish the shape and size difference between different clusters more easily

evaluation (Niu et al. 2009a). Another criterion for clustering evaluation adopted is size-weighted variance. The statistical results of the size-weighted variances of the variables in different clustering alternatives can be referred to in Niu et al. (2009a). Results show that all of the size-weighted variances of S_1 (i) and a majority of the size-weighted variances of S_2 (i) of block distances formed by clustering on the vector descriptor were smaller than those formed by clustering on the head length and head breadth. There is no obvious difference of size-weighted variances between clustering on the vectors with and without PCA. It can be concluded that PCA has little influence on the sizing results. Therefore, PCA can be used for dimension reduction and calculation efficiency improvements.

Different views of average heads of clusters ($N = 447$, decomposition level = 3) by clustering on block distances are shown in Fig. 185.4.

It must be mentioned that a validity index is not a clustering algorithm itself but a measure to evaluate the results of clustering algorithms and gives an indication of a partitioning that best fits a data set. After the cluster results were evaluated with CVIs, domain experts may further analyze the validation procedure results. Using this method, the appropriate partitioning scheme can be selected.

Table 185.1 Headform distribution of Chinese male soldiers (GJB5477-2006)

	Head height–length index (%)		
Head breadth–length index (%)	≤119.99	120–129.99	≥130
≤79.99	I (12.98%)	II (10.96%)	III (0%)
80–89.99	IV (18.79%)	V (43.62%)	VI (7.16%)
≥90	VII (0%)	VIII (3.80%)	IX (2.68%)

This table depicts the headform category accommodation rates of Chinese male soldiers adopted in the latest China military standard GJB5477-2006, where the head breadth–length index and head height–length index were used as the two key measures for head sizing system

185.5.6 Comparative Studies

Some subsequent comparative studies have been conducted to evaluate the effectiveness and robustness of the new methods.

It is interesting to compare sizing results by the proposed method and the current method adopted for the development of a Chinese national military standard of 3D head–face dimensions of male soldiers (GJB5477-2006) (Niu and Li 2009). Head breadth–length index (the ratio between head breadth and head length) and head height–length index (the ratio between head height and head length) are adopted as two key variables in GJB5477-2006. Based on the two indices, the population of Chinese male soldiers is divided into nine groups. The accommodation rate of each group is depicted in Table 185.1. If the 3D heads are classified by using our block distance-based sizing method, the representative heads of each size will fall into the fifth group where head breadth–length index ranges between 80 and 89.99, and head height–length index ranges between 120 and 129.99. However, this is not rational since actually the nine representative heads evidently vary in 3D shape between each other. This emphasizes the necessity to take shape information into consideration in the revision of the military standards in the future.

A case study was done to evaluate the sensitivity of clustering results on block-division number (Niu et al. 2009b). In the case study, each head surface was divided into 20 (5 × 4), 30 (6 × 5), and 90 (16 × 6) blocks, respectively. Multiple comparisons of the means of the proposed block-based distances between different block divisions were conducted using one-way ANOVA. Thus, no significant differences were found between the block-division numbers at the confidence level of 0.05. In other words, this reveals the robustness of the 3D clustering method with block division.

The influence of decomposition levels on clustering results of 3D head data sets was also investigated (Niu et al. 2009c). Cluster membership accuracy rates (CMARs) on different resolution levels, namely from the first to the fifth decomposition levels, were investigated. High CMAR values imply that the wavelet decomposition level does not have a significant influence on shape clustering before the decomposition level reaches five. Considering the difference of the product interface with the human body's surfaces, engineers could be encouraged to adopt the CMAR value as a valuable reference to select a proper decomposition level for the design of a specific product based on the corresponding fit requirements (Table 185.2).

Finally, the influence of alignment, that is, aligned at the centroid and aligned at the top of the head, was investigated (Niu et al. 2008). Cluster membership variation of different alignment methods indicated that the reference can greatly influence the k-means clustering results of 3D anthropometric data.

Table 185.2 Key points of this chapter

1. K-means is one of the simplest unsupervised clustering algorithms. It is to classify the samples based on attributes into K groups by minimizing the sum of squares of distances between data and the corresponding cluster centroid
2. Sizing system development aims to establish sizing systems of whole body or body segment types from the anthropometric data of population by using various approaches. The establishment of the standard sizing systems requires the anthropometric data as reference
3. Ergonomic fit evaluation is to evaluate fit of the wearing items, working places, and tools or equipments made for population with various anthropometric characteristics. It aims to improve the safety, fit, comfort, and other ergonomics levels of products or working places for the customers
4. Computer-aided ergonomic design is an engineering discipline using computers for the design of objects, real or virtual, to solve complex ergonomic problems involving interaction between the human body and its environment
5. Three-dimensional anthropometry is the science of measuring and quantifying the human body or body segments in a three-dimensional space

This table lists the key points of this chapter including k-means clustering, sizing system development, ergonomic fit evaluation, computer-aided ergonomic design, and three-dimensional anthropometry

185.6 Conclusions

In contrast with traditional linear anthropometry, 3D anthropometry brings tremendous benefits to accommodate diverse groups within a population, and leads to improvement in the product ergonomic design. However, researchers must recognize the gap between 3D anthropometric data and the design process. It is urgent to analyze 3D data and to present it to designers by means of anthropometric tools while satisfying design requirements in terms of ergonomics.

In this chapter, a method for analyzing 3D shape is introduced. A multi-resolution description of 3D anthropometric data, which enables data analysis progressively in a coarse-to-fine fashion, was established first. The fundamental properties of wavelets guarantee that the lower dimensionality is able to preserve the major information and describe the main shapes. The multi-resolution description of 3D anthropometric data makes use of not only the coordinates of data points, but also the geometric characteristics and internal structure among the points. Each decomposed surface was divided into a specific number of patches, namely blocks. Shape description was defined based on block distance. In this manner, each surface can be transformed into a block distance-based vector. K-means clustering was performed on the vectors. Clustering results were evaluated with two measures, that is, size-weighted variances and the revised Turi & Ray index. Some subsequent comparative studies, that is, comparison between sizing results by the proposed method and the current Chinese national military sizing standard for 3D head–face dimensions of male soldiers, as well as the sensitivity of clustering results on block-division number and the influence of alignment, have also been conducted. The results emphasize the necessity to take shape information into consideration in the development of future sizing systems.

It is necessary to point out that a sizing system design cannot merely rely on the clustering routine. The suggestions from domain experts and end users should also be considered. Cost and manufacturing issues must be taken into consideration as well. Utilization of 3D anthropometric data for use in design is still at an early stage of development.

185.7 Applications to Other Areas of Health and Disease

Beyond end-user design, 3D anthropometry can also be applied in numerous health and medical fields. It has been used in a number of different applications for comparing morphological differences, including craniofacial growth, craniofacial abnormality, and artificial cranial modifications.

As for rehabilitation treatment and aesthetics applications, 3D anthropometric shape comparison will aid to quantitatively describe and compare facial proportions in a virtual environment, especially from an aesthetic point of view. It can be utilized for investigating 3D facial changes for unilateral cleft lip repair, and for studying organ growth in organ transplants.

3D anthropometry also attracts attention from the forensic sciences, and is expected to be used in determining the identity of crime suspects. A system comparing 3D facial geometry and 2D facial imagery has been proposed by researchers (Kumhyr 2005). This system is capable of automatically scanning and analyzing suspects and will expedite the process of identification or the selection of suspects from a larger number of suspects. Undoubtedly, more and more successful applications in the health and medical fields will be accomplished by using 3D anthropometry. 3D anthropometry will surely also make rapid progress as applications accelerate.

Summary Points

- 3D anthropometry brings tremendous benefits to product ergonomic design.
- There is no clear link between 3D anthropometric data and the design process.
- A multi-resolution description of 3D anthropometric data, which enables data analysis progressively in a coarse-to-fine fashion, was established.
- A 3D sizing system was presented by conducting k-means clustering on block distance-based vectors. Clustering evaluation was performed by using two measures.
- The proposed method provides a systematic method for properly grouping samples into clusters according to their 3D shape.
- Use of 3D anthropometric data in design is still at the early stage of development. It is urgent to understand how to analyze 3D data and to present them to designers by means of computer-aided anthropometric tools.

Acknowledgments The authors of this chapter wish to express their appreciation for the support from the National Natural Science Foundation of China (No.70571045).

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Chapter 186
Use of Anthropometric Measures and Digital Human Modelling Tools for Product and Workplace Design

Lars Hanson and Dan Högberg

Abstract This chapter addresses and demonstrates the application of digital human modelling (DHM) tools to consider anthropometric diversity in product and workplace design. A number of additional methods for evaluating ergonomics conditions are also illustrated. Three cases show how DHM tools can be applied in different design settings and for different design undertakings, focusing on user variation in anthropometry. A number of methods for user representation in the DHM tool are briefly presented. Method selection depends on the design problem at hand, and the chapter exemplifies the use of different methods for different design tasks. Examples are the use of one-dimensional percentile based statistics data, the use of predefined collections of manikins, and the creation of representative cases by using multidimensional statistics. The chapter takes a designer's view of the uses of DHM tools for anthropometry-related issues and illustrates how the tools can be of value in the design process.

Abbreviations

CAD	Computer-aided design
CAE	Computer-aided engineering
DHM	Digital human modelling
H-point	Hip point
MTM	Methods-time measurement
PCA	Principal component analysis
PDM	Product data management
ROM	Range of motion
SAE	Society of automotive engineers
SgRP	Seating reference point
TSB	Task simulation builder
USB	Universal serial bus

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_186,

186.1 Introduction

The employment of user-centred approaches in design to understand and meet the variety of targeted users' needs and expectations is acknowledged as a path to successful business for companies that develop and produce products. Computer-aided engineering (CAE) tools can be utilised to support the consideration of some of these user-centred design issues. This chapter describes how digital human modelling (DHM) tools can be utilised to consider issues such as anthropometry, postural comfort and biomechanics in product and workplace design. DHM tools are particularly useful for proactive ergonomics consideration in design processes where computer-aided design (CAD) tools are used to define products and workplaces and where no physical prototypes exist or are to be produced (e.g. due to cost or time). Ergonomics is defined as the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data, and methods to design in order to optimise human well-being and overall system performance (Wilson 2000).

The DHM tools illustrated in this chapter consist of four essential parts: (1) a manikin: a digital replica of the human, including skeleton, segments, and (sometimes) muscles; (2) a CAD tool to build or import digital components describing products and process equipments/environment; (3) a manikin posture and/or motion generator; and (4) ergonomics evaluation methods. The DHM tools are applied in the design, modification, visualisation and analysis of human workplace layouts and/or product interactions. The simulations and visualisations are frequently used to provide information about body posture, biomechanics, human comfort, reachability, field of view and clearances for arms, hands and tools, to serve as a basis for ergonomics evaluations and design improvements.

The following three cases aim to illustrate how DHM tools can be applied in user-centred design processes for the consideration of anthropometric diversity in product and workplace design. The first case illustrates how vehicle designers work with the tool to determine an appropriate seat adjustment range. A wide variety of users occupies a vehicle cockpit, and some even have the cockpit as their place of work. These users all have their unique anthropometry and posture preferences. Hence, the objective is to design the vehicle interior so that all targeted users can find a safe, functional and comfortable arrangement in the vehicle. A DHM tool can support the designers in meeting that objective. The second case describes a scenario from the healthcare sector. The design engineers are to develop a foot support for a bathtub, which should accommodate elderly residents as well as be easy to handle by caregivers. The biomechanical load on the caregiver when bathing a resident is also analysed. The third case is from the vehicle industry, where DHM tool users are challenged to simulate a worker's wrist motions when performing a work sequence. The wrist motion analysis is intended to optimise the assembly workplace and minimise the biomechanical load on the worker. The three cases are fabricated but realistic examples of how DHM tools are used in product and workplace design.

186.2 Case 1: Seat Adjustment Range for a New Vehicle Platform

A large vehicle development project is launched where a number of car brands co-operate in order to develop a new common car platform. The mission is to create a platform suitable for a wide range of cars, from roadsters to sport utility vehicles. Alfred is responsible for seat-related issues in the platform project. After reading the newspapers and discussing with Lina, who is responsible for the platform's human factors characteristics, he is aware of the general anthropometric trends of people getting taller and more corpulent. With this in mind, Alfred and Lina have decided to conduct a deeper analysis of the seat adjustment range required to ensure that the targeted population will be accommodated by the proposed design. They discuss using the in-house test group in the flexible

buck (basically an adjustable car structure) and DHM tools to find a suitable adjustment range. They then contact Emil who is the human factors simulation engineer responsible for the use of the DHM tool *Ramsis* at the car company. We follow Alfred and Lina's first meeting with Emil where he guides them through a standardised ergonomics simulation ordering process (Hanson et al. 2006). After that, we follow Emil's thoughts and actions when he generates manikins, describes the physical environment, defines the tasks and runs the DHM tool. Finally, we depict Emil delivering the results to Alfred and Lina and storing the analysis report in a documentation database.

Emil, Alfred and Lina meet to begin the DHM analysis of an appropriate seat adjustment range for the platform. Their discussion is structured and follows the predefined ergonomics simulation process available through the company's intranet system. The meeting starts with Alfred and Lina describing the background: the new platform, the anthropometric trends and their uncertainties about the appropriate seat adjustment range. Emil takes notes and fills in the blanks in the process protocol. The protocol is linked to a database, to which all employees in the company have access. Emil summarises the background and enters the data in the protocol. He expresses the analysis objective as follows: "To describe the appropriate seat adjustment range for European and American vehicles launched in 10 years, as well as the location of the seat adjustment range relative to the accelerator heel point." Alfred and Lina agree upon this formulation. Emil adds his name and contact data as the one who is performing the analysis, and Alfred as the requester of the simulation. When all have a common picture of the aim, the desired output is discussed. Alfred is interested in illustrating differences and similarities with the proposed adjustment range and existing car models, for both their own cars and competitor cars. Lina highlights the importance of comparison with SAE (Society of Automotive Engineers) standards. She also suggests that the analysis should include comfort ratings as a complement to the hip-point locations predicted by the DHM tool. Emil confirms these requests by adding them to the protocol and promises to deliver tables and pictures for illustrative purposes. Finally, the group discusses the desired completion date. The agreed date, 2 weeks from today, is entered into the protocol. This concludes the first of three stages in the human simulation process. Before Alfred and Lina leave, Emil gathers the information required to perform the analysis properly, such as information about the targeted market segments and the physical environment as CAD geometry.

Emil is now left alone to start the analysis by searching the human simulation database on the intranet, hoping to find earlier similar studies to save time and gain from previous simulations. He uses "seat adjustment range" as a keyword. Unfortunately, he gets few hits. This is not surprising since DHM is a relatively new tool in the company and seat adjustment ranges are set when car platforms are designed, platforms that may last for decades. He finds one interesting investigation about adjustable pedals and how they affect the seat adjustment range. He also asks an experienced packaging engineer, who is responsible for the SAE requirements, how such studies have been performed previously. She tells Emil that the size and shape of the adjustment range and its location have been based on results from studies in the flexible buck and SAE seat adjustment curves, SAE J1100 ergonomics standard (Roe 1993). She also reminds him that ASPECT guidelines have been introduced and are now working in parallel with SAE recommendations (Schneider et al. 1999).

Emil continues the work by reading the market analysis report. There he finds that the premium mid-segment vehicle that Alfred, Lina and he chose as an example car is aimed at Western Europe and USA. The vehicle will be produced as a sports sedan and wagon, and is projected to attract young people and families. Emil understands the underlying marketing issues, because he knows that vehicle buyers are relatively brand faithful, and, consequently, it is good business strategy to attract younger people. With this in mind, Emil starts to search for updated anthropometric data for the countries with expected large market shares for the future vehicle. In the DHM tool *Ramsis*, he finds up-to-date American, German and Swedish anthropometric data. The American and German anthropometric data are standard in the tool. The Swedish anthropometric data are a company-specific feature developed to get information about a large market. He uses a tool feature that adjusts the anthropometric

data for secular trends so that the manikin sizes are likely to correspond to the customers' sizes when the car is eventually introduced on the market and throughout the car platform's market life cycle.

Emil uses a manikin collection suggested by Speyer (2005) to represent anthropometric diversity. This collection consists of manikins that represent anthropometric diversity suitable for occupant packaging in vehicle design. The collection consists of both central users and boundary users (elaborated in the Discussion section). Based on these data, he generates a set of manikins, six females and six males for each nationality of interest. In total, 36 manikins are generated by combining three key anthropometric variables in cockpit design: stature, waist circumference and sitting height. This approach is based on the assumption that the definition of the characterising properties of stature, corpulence and proportion (ratio of the sitting height to length of the legs) of an individual is sufficient to predict all other body dimensions for this person (Flügel et al. 1986; Bubb et al. 2006). The combinations of percentile values are presented in Table 186.1. The other body dimensions for each manikin are defined by the anthropometric functionality in the DHM tool itself, using existing correlation data to these three key dimensions.

Information about the manikin generation procedure is described in the process protocol that Emil utilises. He also decides to include manikins with the same anthropometrics as each person in the in-house test group, which is to facilitate comparison with the flexible buck study. He models Alfred, Lina and himself as well to support discussions between the people involved in ordering and performing the analysis.

Alfred, Lina and Emil decide to use a mid-segment vehicle as an example in the investigation. Emil enters the PDM (Product Data Management) system and searches the database for the latest CAD geometry definition of the vehicle. He imports floor, pedals with their motion line, steering wheel with its adjustment area, proposed seat adjustment area, inner roof and top of dashboard into *Ramsis*. He tries to keep a minimal description since exchange between computer systems is often time consuming and conversion errors sometimes occur. In addition, Emil believes that a simple description of the physical environment allows the viewer of the illustrations to focus on the ergonomics issues in terms of posture and accommodation. It also indicates that the analysis has been performed at an early design stage with relatively rough assumptions, and that design corrections are both possible and recommended if required. Before the physical environment definition is completed, he makes sure that the steering wheel adjustment areas are located for a quarter-to-three handgrip and moves the accelerator halfway down along the motion line.

Table 186.1 Speyer (2005) manikin family to represent anthropometric diversity

	Stature (percentile)	Waist circumference (percentile)	Sitting height (percentile)
Male 1	5.7	60.2	9.7
Male 2	50.7	47.6	52.5
Male 3	96.4	8.5	76.0
Male 4	94.0	35.7	89.7
Male 5	92.5	95.1	88.0
Male 6	94.3	81.6	98.8
Female 1	6.3	15.1	2.5
Female 2	6.6	48.2	10.9
Female 3	7.8	99.4	12.8
Female 4	4.6	94.2	29.8
Female 5	50.8	43.4	53.0
Female 6	95.1	38.0	91.2

Stature, waist circumference and sitting height as key anthropometric measures and a percentile value combination for a set of manikins

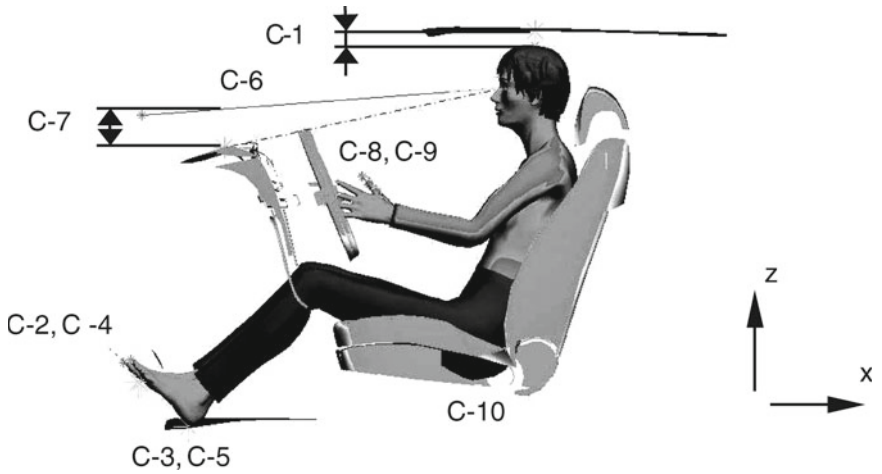

Fig. 186.1 Constraints used in Case 1. Clearance (e.g. C-1 head under ceiling), Line of sight (e.g. C-7 vision line above dashboard) and Fixation (e.g. C-8 hand on steering wheel) are constraints used to determine a seat adjustment area required. When investigating seat adjustment, C-10 (hip-point) is not used as a constraint

The next step in the process is to define the tasks: a normal driving task, which Emil usually defines with the following constraints in *Ramsis* (Fig. 186.1).

- Head clearance. Minimum 25 mm vertical distance between head top (vertex) and inner roof.
- Right pedal point on accelerator, pressed down halfway.
- Right heel point on floor.
- Left pedal point on foot support.
- Left heel point on floor.
- Line of sight. 5° down from horizontal line.
- Line of sight clearance. Minimum 70 mm vertically between line of sight and top of instrument panel.
- Right grasp point within steering wheel adjustment area.
- Left grasp point within steering wheel adjustment area.
- H-point (hip point) within greatly extended seating adjustment area (non-constraining in x and z direction).

Since he does not want to restrict the seating adjustment area in the simulation (that is the aim of the study), he greatly enlarges that area so that it will be non-constraining. With the constraints and physical geometry defined, Emil enters the *Ramsis* automatic analysis procedure. He inputs the manikins and the constraints to be used. In the output section, he describes that he is interested in receiving information about comfort and coordinates for the H-point. Before running the automatic analysis, he remembers that he should change the settings so that the company's unique posture descriptions are used instead of the default *Ramsis* values. When this is done, he pushes the start button and takes a coffee break while the computer is working. After the break, the computer calculation is ready and he has plenty of interesting output data to consider. However, he temporarily ignores the new information and instead starts to use the SAE packaging kit in *Ramsis*. By entering the accelerator heel point and the desired vertical distance between the heel point and the seating reference point (SgRP), that is, the H30 value (Roe 1993), seat reference curves automatically appear. He now has a very interesting picture (Fig. 186.2) with SAE seat reference curves, marks for each manikin's H-point (grey diamonds) and the previously proposed seat adjustment area for the platform.

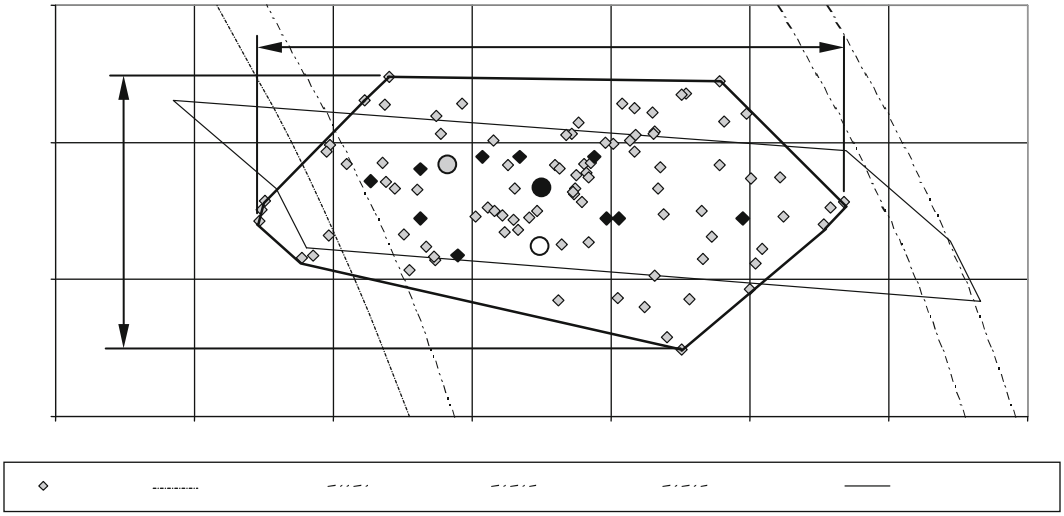

Fig. 186.2 Seat adjustment range and hip points. Example of illustration presented at the Case 1 meeting. *Grey diamonds* represent hip points from the manikin family. *Black diamonds* illustrate hip points for manikins representing the internal test group. *Circles* represent hip points for the key project members. The *dotted line* shows the proposed adjustment range from SAE guidelines. The *thin black line* is the current seat adjustment proposal

Table 186.2 Comfort data from the analysis

	Target population *Mean (SD)*	In-house test group *Mean (SD)*	Alfred	Emil	Lina	Previous car model *Mean (SD)*	Concept car with flexible pedals *Mean (SD)*
Overall	9.0 (2.2)	7.8 (1.8)	9.5	7.6	6.5	8.3 (1.9)	9.2 (2.1)
Neck	7.5 (1.9)	7.9 (2.0)	8.8	8.1	7.4	7.4 (1.6)	7.7 (2.0)
Arms	8.7 (1.3)	7.5 (1.1)	8.5	6.3	4.8	8.5 (1.2)	9.1 (1.4)
Back	9.5 (1.8)	8.1 (1.9)	10	8.0	7.1	9.1 (1.8)	9.9 (1.8)
Legs	6.9 (2.0)	6.9 (2.1)	7.1	6.9	4.6	7.1 (2.3)	8.8 (1.7)

Comfort data (mean and standard deviation) for Target population, in-house test group and key project members (Alfred, Emil and Lina) as well as results from previous studies (previous car models and concept cars with flexible pedals). Comfort data are presented on a ten graded scale, where ten is maximum comfort

Emil also arranges the comfort data in an illustrative table, showing mean and standard deviation values for the target population and the in-house test group (Table 186.2). Data for Alfred, Emil and Lina are also presented, as are data from a previous analysis. As further benchmarking, Emil uses the kind of drawings that vehicle companies share with each other to find out competitors' designs of seat adjustment ranges. With this information in hand, Emil contacts Alfred and Lina for a meeting to deliver the results.

Emil has stored all pictures and tables generated in the analysis in the database. He uses the unique project number, and pictures and figures together with his own comments. Emil starts the presentation by showing Alfred and Lina illustrations similar to Fig. 186.2.

He describes how the previously proposed seat adjustment range is shown by the thin line in the figure. The adjustment range required to accommodate the target group is represented by the thicker line. The black diamonds represent H-points for the in-house test group, and the white, black and grey circles represent Alfred, Emil and Lina's H-points, respectively. The SAE seat

adjustment range is presented with dotted lines. They discuss the differences and conclude that the previously proposed seat adjustment area is sufficient, at least in length. The size and the shape are also comparable to competitors in the premium mid-segment vehicles. Alfred and Lina are convinced that a horizontal extension of the adjustment range, which was their thought before seeing Emil's pictures, is not required. Instead, a decrease in length and increase in height seem preferable. However, Alfred's view is that even though obviously advantageous, a larger height adjustment range is likely to be complicated to realise and difficult to get approval for in the new platform. Alfred also believes that the decrease of the seat adjustment range in length may not be an option in a conservative design environment. Based on the discussion, they together update the comments and conclusions about the seat adjustment range. Lina who has short legs finds the comfort ratings interesting. Her ratings in Table 186.2 are lower than all others, indicating a lower comfort level. She admits that she has difficulty reaching the pedals without sitting too close to the steering wheel. Overall, the comfort ratings look promising, though, with high numbers close to the maximum of ten. However, the absolute comfort values are of minor interest. It is the value compared to different concepts that is interesting. In this case, the seat adjustment range proposed by the DHM tool is almost as good as the concept car with adjustable pedals, and better compared to the previous car model. The issues that come up during Emil, Alfred and Lina's final discussion are entered into the protocol as a complement to the comments that Emil stored earlier about the analysis results. Alfred and Lina thank Emil for a good job and sign their names and date in the approval section in the protocol, which concludes the digital human simulation and visualisation mission. Before leaving, they promise Emil that they will come back with information about H-point locations and comfort ratings from the tests with the in-house test group in the flexible buck, information that Emil can use for validation of the software.

After the meeting, Emil is satisfied with his job and the positive feedback. He thinks he showed the strengths of the DHM approach. He is glad that he was consulted since it indicates that the possibilities of the DHM tool are recognised and considered advantageous. Another positive point is that the study was initiated at an early design stage where it is possible and comparatively easy to perform design changes when necessary. An extra bonus was Alfred and Lina's assurance to provide him with H-point locations and comfort ratings from the tests with the in-house test group, information that Emil can use for validation of the software, in his work, and in convincing colleagues about the qualities and advantages of the DHM tool.

186.3 Case 2: New Bathtub Footrest Optimised for Elderly Home Residents and Caregivers

The project is initially aimed at designing a new footrest to be integrated into a new bathtub design, complementing the healthcare company's product portfolio. Three design engineers, Bork, Mattis and Lovis, attend the start-up meeting from the company, along with two DHM tool users, Ronja and Birk, from a university nearby (in this case, representing regular DHM tool users). The analysis follows the human simulation process proposed and used in the automotive industry (Hanson et al. 2006). The meeting starts with Mattis describing the background: the new bathtub, the anthropometric trends, their uncertainties about the appropriate footrest adjustment range as well as the high biomechanical loads on the caregiver when adjusting the footrest. Bork also presents the company's *Mobility Gallery* (Arjo 2005). This is a user characteristics representation approach that has proven to be successful in the way it supports descriptions and

communication about product users' abilities and requirements, for people inside and outside of the company. In the gallery, residents are classified according to their degree of functional mobility, from the most mobile and independent to the most dependent and entirely bedridden resident. Five mobility levels are described and labelled using alphabetical names: *Albert*, *Barbara*, *Carl*, *Doris* and *Emma*. Each resident is described with different personal characteristics and background details and an illustration. Residents can be represented by a female or male, regardless of their gender-specific names.

Birk takes notes and fills in the blanks in the prepared human simulation process protocol, which is linked to a database that all involved in the project have access to. After the discussion, the project group formulates the following objective for the analysis: "To analyse the bathtub ingress and describe an appropriate bathtub footrest position and adjustment range for typical residents, as well as a confirmation that the footrest is easily manually adjusted by typical caregivers. The footrest is to be designed for mobility levels represented by Albert, Barbara and Carl." They all agree upon this formulation. Birk adds his name and contact data as the person responsible for the analysis; one of the design engineers fills in her data as the requester of the analysis. When all have a common picture of the aim, the desired output is discussed. Mattis, Bork and Lovis are interested in illustrating differences and similarities with the proposed adjustment range and the current one, for both their own bathtub and competitors' designs.

Ronja and Birk ask for national and company design standards for comparison purposes. However, no such standards exist. Instead, the company has reports from tests of physical prototypes describing preferred bath postures, among other things. Ronja receives copies of the reports. The design engineers ask Ronja and Birk to utilise ergonomics evaluation methods integrated in the DHM tool when analysing the caregivers' situation when adjusting the footrest. This request is added to the protocol as confirmation, and they agree that the analysis results shall be complemented with tables and pictures for illustrative purposes. Finally, the group discusses the desired completion date. The agreed date, 2 weeks from today, is entered into the protocol. This concludes the first of three stages in the human simulation process. Before Ronja and Birk leave, they gather information required to perform the analysis properly, such as the targeted market segments and the physical environment as CAD geometry.

The DHM tool users, Ronja and Birk, are now left alone to start the analysis by searching the human simulation database on the intranet, hoping to find earlier similar studies to save time and gain from previous simulations. Ronja uses keywords such as "bathtub" and "footrest position." Unfortunately, she gets no hits. This is not surprising since DHM is a new tool at the company. Ronja continues the work by reading the market analysis reports. Here, she finds that the new bathtub is planned to be sold as a high-quality brand product and is aimed at Swedish people living in elderly service apartments. With this in mind, she starts to search for updated anthropometric data for mid-age and elderly Swedish people. Ronja finds up-to-date detailed data for Swedish people aged 18–65 (Hanson et al. 2009). Unfortunately, she does not find detailed anthropometric data for the elderly population when searching through research literature. Instead, she uses an article by Dey et al. (2001) where stature and weight have been studied.

Ronja uses the anthropometric information for the Swedish female working force and generates three female manikins to replicate the caregivers: one central user, 50th percentile in stature, as well as two boundary users, 5th percentile and 95th percentile in stature measure. Ronja only generates female manikins since the majority of caregivers are female. In the same manner, she calculates 5th percentile, 50th percentile and 95th percentile manikin data to represent residents (i.e. female and male Alberts, Barbaras and Carls). Ronja generates these 18 resident manikins in the DHM tool *Delmia V5*. Stature is selected as the key dimension in this case, and all other body measures are automatically calculated in the DHM tool to give the manikins normal proportions. Ronja is well aware that no "normal" proportions or mean persons exist when considering several anthropometric

measures together (Daniels 1952; Robinette and Hudson 2006). However, the approach with one key anthropometric variable (stature) is used to keep the problem simple and is considered good enough in this case. In addition to these manikins, Ronja creates manikins that are anthropometric replicas of the ones involved in the development project (e.g. the design engineers). She does this to support discussions about the analysis results among the people involved in ordering and performing the analysis.

To more accurately simulate elderly people, Ronja adjusts the joint flexibility of the manikins (exemplified in Table 186.3) based on range of motion (ROM) data from Older Adultdata (Smith et al. 2000). Three levels of mobility are relevant for this bathtub design (Albert, Barbara and Carl). The appearances of the residents are adjusted to the company standard described by the Mobility Gallery according to mobility level (Fig. 186.3) (Högberg et al. 2009). The default appearance and joint ranges of motion in the DHM tool are used for the caregivers. By using this method, Ronja cre-

Table 186.3 Range of motion data for Albert, Barbara and Carl

			ROM angle		
Resident	Gender	Percentile	Hip flexion	Shoulder extension	Shoulder flexion
Albert	Male	50	110	38	160
	Female	50	111	49	169
Barabara	Male	20	101	29	151
	Female	20	101	38	161
Carl	Male	10	96	24	146
	Female	10	96	32	157

Albert, Barbara and Carl are members of the Mobility Gallery. This table shows their range of motion in hip (flexion) and shoulder (extension and flexion) as examples of joint flexibility

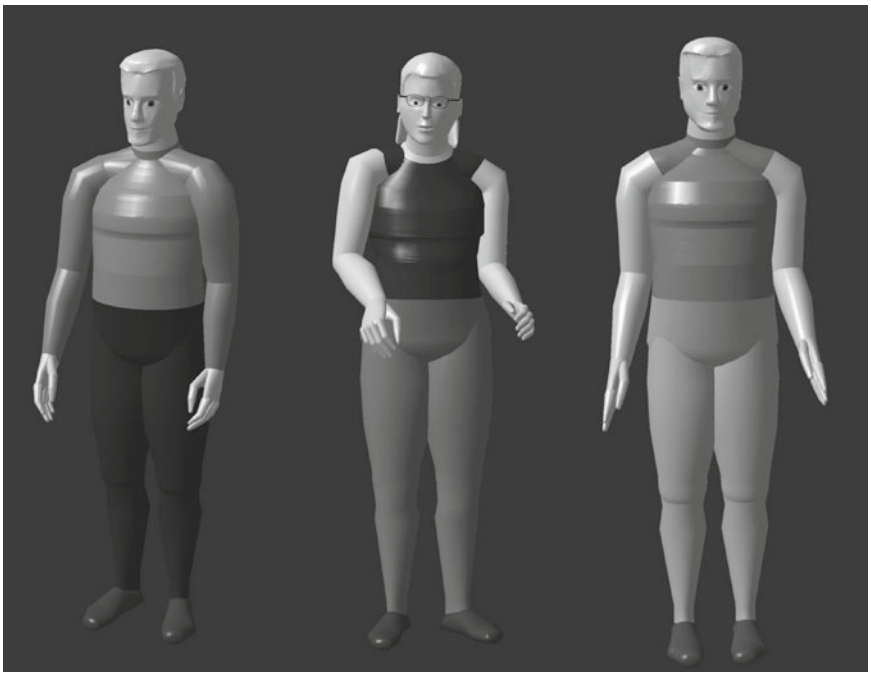

Fig. 186.3 Albert, Barbara and Carl, from *left to right*, members of the Mobility Gallery. Manikin representations of Albert, Barbara and Carl and their appearance

ates a set of 26 manikins: three mid-aged caregiver manikins, 18 elderly resident manikins and five manikin replicas of the team members.

The next step is to load the CAD geometry, and Ronja imports the bathtub and competitors' adjustable footrests from a USB memory stick. She tries to keep a minimal physical environmental description since exchange between computer systems still is quite time consuming and conversion errors sometimes occur, especially when using CAD and DHM systems from different suppliers. A simple description of the physical environment encourages the viewer of the illustrations to focus on the ergonomics issues. It also indicates that the analysis has been performed at an early design stage with relatively rough assumptions, and that design corrections are both possible and welcome if they improve the design.

The next step in the human simulation process is to define the tasks performed by the resident and the caregiver. Ronja performs a basic task analysis and defines the tasks in bullet form as follows:

Bathtub ingress task

Resident	Caregiver
• Sitting relaxed	• Standing relaxed
• Hands on the support handles	• Feet attached to floor
• Left leg straight forward	• Right hand on the lifting device control
	• Left hand lifting resident's leg
	• Eye focus on hand lifting leg

Footrest adjustment task

Resident	Caregiver
• Sitting in preferred posture	• Standing relaxed
• Head above water surface	• Feet attached to floor
• Back attached against bathtub backrest plane	• Right hand on foot adjustment device
• Buttocks attached against bathtub bottom plane	• Eye contact with resident

With the manikins, the physical geometry environment and the tasks defined, Ronja starts to manipulate the manikins. She saves the preferred bathing posture described in the report as a predefined posture in the DHM tool. She uses the preferred bathing posture as a starting point for residents. The manikin is moved to the bathtub and manikin joints are manipulated only when needed to fulfil the task description. This is done for all 23 manikins. Ronja then uses the relaxed standing posture as a starting point for the caregivers. The joints in the back, arms and neck are adjusted minimally to fulfil task criteria. After repeating this for the manikins representing caregivers, a more detailed ergonomics analysis can be made. The team member manikins act as both residents and caregivers.

Ronja generates plots of the position of the sole of the foot for each manikin representing residents (Fig. 186.4). As a benchmark, she inserts the adjustment range of the competitor product, and adds dots representing likely positions of the project group members. Joint comfort values for each manikin are automatically calculated by functionality in the DHM tool.

For caregivers, Ronja generates reach envelopes and calculates a RULA (Rapid Upper Limb Assessment) score (McAtamney and Corlett 1993) (exemplified in Fig. 186.5). All illustrations, tables and comments are stored in the database. With this information accessible, Ronja discusses the results with her university colleague Birk and they agree to arrange a meeting with the design engineers at the healthcare company to deliver the results. When at the healthcare company, they gather around a bathtub and open the project database. In the database, they study the foot sole positions of potential users. Mattis enters the bathtub and they visually compare his preferred foot position with the positions suggested by the DHM tool. It seems to match quite well and the design engineers conclude that they will base the prototype on the facts proposed by the DHM tool.

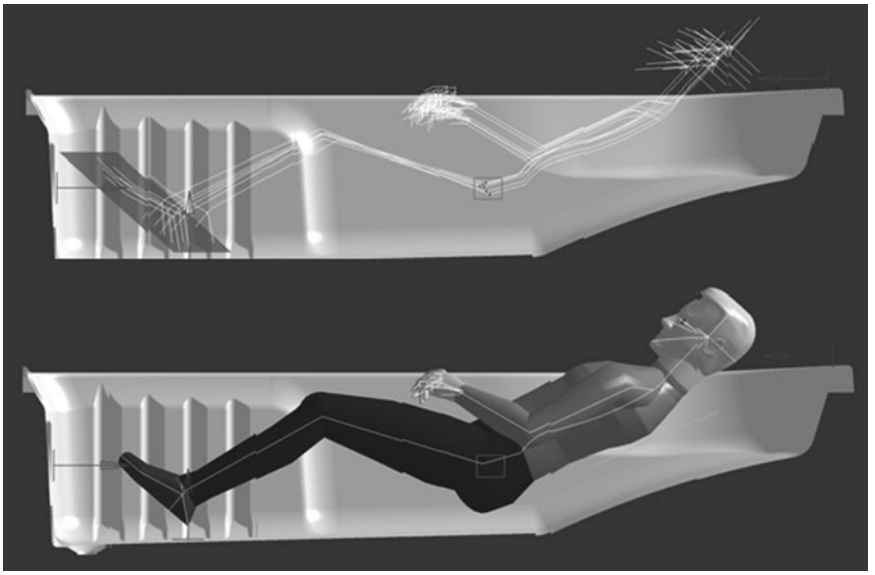

Fig. 186.4 Albert bathing and investigating required footrest adjustment range. Stick figures representing residents (*above*), and 50th percentile Albert in a preferred bathtub posture (*below*)

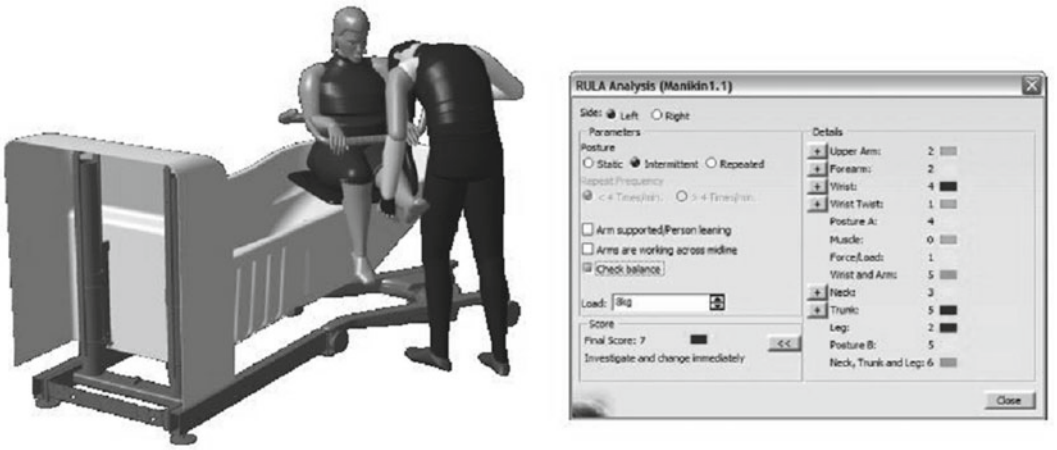

Fig. 186.5 Ergonomic analysis of caregiver when helping resident into bathtub. *RULA* Rapid Upper Limb Assessment analysis of a caregiver's working task when the resident enters the bathtub

Lovis imitates the caregiver, lifting her colleague's legs and adjusting an imaginable footrest with a similar adjustment solution as the competitors use. She admits that the posture feels a bit awkward and she can understand the high physical loads on the caregiver. Mattis, Bork and Lovis come to the insight that they have to rethink the adjustment principle used in order to reduce the workload on caregivers.

Birk enters all comments made at the meeting in the database. The design engineers thank Birk and Ronja for a good job and sign their names and date in the approval section in the human simulation protocol, which concludes the digital human simulation and visualisation mission. Ronja and Birk are satisfied with the job and the positive feedback. They think they showed the strengths

of the DHM approach. They are glad that they were consulted since it indicates that the possibilities of the DHM tool are recognised and considered advantageous. Another positive aspect is that the study was initiated at an early design stage where it is possible to affect the design of the product. The design engineers are very happy to find out that less adjustability seems to be needed to accommodate the target users. This enables the footrest to be designed smaller, lighter, more inexpensive and easier to handle than they first expected.

186.4 Case 3: Design of an Assembly Station to Minimise Wrist Injuries

Psychotherapist Prysselius and Dr. Kling work at a vehicle company. They have noticed an increase in assembly workers' complaints about wrist pain, and so have contacted the human factors specialist, Klang. Together they performed a wrist study with direct measurements to record the exposure. The study was carried out on one subject, who was mounting a sealing on a car. The results showed that the worker performed a task that included awkward and constrained wrist postures as well as repetitive movements with high wrist angular velocity. These postures and movements have been shown to be risk factors for musculoskeletal disorders (Wells et al. 2007). To reverse this trend of increasing wrist pain and injuries among assembly workers, an analysis and modification project of existing assembly stations is initiated. Another project is initiated that focusses on future assembly lines and how wrist problems among assembly workers can be detected and avoided proactively at early design phases. To initiate the second project, Prysselius, Kling and Klang invite Pippi, Tommy and Annika who are working as senior production engineers and DHM users.

The meeting starts with Dr. Kling describing wrist pain among assembly workers and Klang describing the results from their study for Pippi, Tommy and Annika. They ask if the company has any tool or process that could detect these problems at an early design phase before an assembly line is set up. The DHM users are interested since they realise that the DHM tool has the potential to find such ergonomics problems. Currently, however, the tool is mainly being used for analysing frozen postures. In order to predict angular velocity and other time-dependent measures, a dynamic simulation of the assembly worker performing the working task is needed. Pippi, Tommy and Annika like the challenge and agree to investigate the possibilities with DHM. Tommy logs in to a computer and enters the DHM web-based work process protocol. Pippi summarises the background and proposes the following project aim: "To illustrate how time sensitive wrist exposure data can be extracted from a manikin." The others in the group read simultaneously what Tommy is writing while the web protocol is projected on a large screen. They all agree on the text and set the project closure day to 6 months ahead. By then, Pippi, Tommy and Annika promise to deliver results in the same form as those retrieved in the pilot study, where goniometers were used to acquire objective measures of wrist joint angles, in addition to the company standard assessment method based on visual observations of joint angles. The expected result deliveries are entered in the protocol before the kick-off meeting is adjourned.

Pippi, Tommy and Annika return to their department. On the way back, they divide up the tasks. Tommy will develop a small computer program that transforms the output from the DHM tool *Jack* into the format used by the analysis tool for the direct measures. Annika will define manikins representing the assembly workers and define the tasks in order to generate a simulation of the work sequence. Senior engineer Pippi would support Tommy and Annika.

Tommy writes a MATLAB script that resamples data generated in *Jack* into a lower frequency (from 30 frames per second to 10 frames per second) and rotates the coordinate system to fit definitions in the wrist motion analysis software. The script also selects the relevant data from the *Jack*

Table 186.4 Boundary manikins generated by using PCA approach

Manikin family member	Body stature (cm)	Body weight (kg)
c1	178.2	72.6
c2	158.4	58.8
c3	155.2	56.6
c4	175.0	70.4
i1	180.8	74.4
i2	169.0	66.2
i3	152.7	54.9
i4	164.4	63.0

Body stature and Body weight for the eight boundary manikins generated by using principal component analysis (PCA) approach

output data and generates output files in a format recognised by the wrist angle analysis software. Annika begins her work of defining the users. She decides to use the anthropometrics and principal component analysis tool (PCA) available in the DHM tool. The PCA approach (Zehner et al. 1993) enables the generation of boundary manikins (Dainoff et al. 2003). Eight manikins, representing both females and males, are generated according to her settings (95% coverage and two principal components) and data available in the tool (a description file with detailed anthropometric measures of 100 Americans). The eight boundary manikins are expected to cover 95% of the anthropometric diversity of the population represented by the 100 Americans, both females and males, in the sample file (Table 186.4). The rationale for using boundary manikins in this case is that if the assembly work is studied using these eight boundary manikins (which might be seen as extreme cases), the assessment would cover other anthropometric configurations as well (i.e. cases within the multidimensional distribution enclosed by the eight boundary manikins).

Annika enters the manikin description in the web-based protocol and continues with the procedure. The following steps in the procedure are the definition and creation of the environment and the tasks. She searches the database after the rear part of the vehicle of interest. She uses the Task Simulation Builder (TSB) integrated in *Jack* (Raschke et al. 2005) to generate manikin movements. The TSB module enables animation sequences to be created simply by using basic MTM (Methods-Time Measurement) language. She uses the code *Touch* and selects the positions evenly distributed around the gasket. The DHM tool generates the manikin motion and Annika uses the data reporter to export wrist angles into a file. She lets all eight manikins perform the task, controlled by the same task description. A unique wrist motion file is generated for each manikin. Annika also uses the company-specific ergonomic evaluation method to get an indication about the workload when each manikin positions the sealing in the highest position. She uses the animation and stops the film sequence when the manikin reaches the point of interest. A screenshot from the animation is seen in Fig. 186.6. The manikin posture is exported to the company-specific ergonomics evaluation tool. Other information, such as weight of sealing and grip surface type, is added manually. The objective company-specific analysis results for the eight manikins are generated and stored in the database with supporting illustrations.

Annika sends the eight wrist angle files to Tommy, who has developed the script to convert the file to suit the analysis tool for the direct measures. The file conversion is successful and the wrist angle files are analysed by the software used for the direct measures. Tommy runs the software and calculates exposure data for the eight manikins. He compiles the data and calculates mean values for the eight manikins and corresponding standard deviations. Tommy creates a table (Table 186.5), where DHM output is placed next to the results from the psychotherapist, doctor and human factors engineer's study and determines if the results are significantly different using statistical methods.

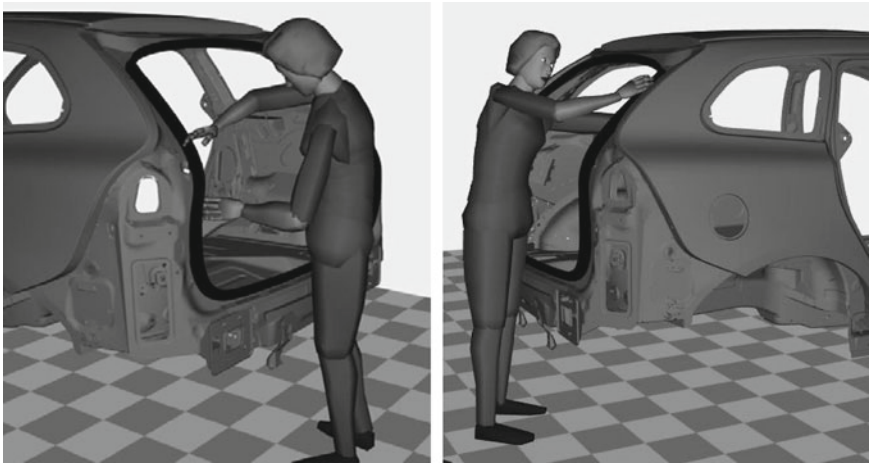

Fig. 186.6 Manikin applying a sealing. The manikin motion when applying a sealing is controlled by a motion database and wrist angles are exported to other software for in-depth exposure studies

Table 186.5 Exposure data for wrist

Wrist position, right hand (°)	Motion from field test (°)	Motion from *Jack* TSB (°)	*p*-Value for difference in means between wrist position from field tests and generated with *Jack* TSB
Flexion, 5th percentile	–51 (7.4)	–78 (2.6)	$p < 0.005$
Flexion, 50th percentile	–26 (3.9)	0 (0)	–
Flexion, 95th percentile	32 (6.3)	71 (5.9)	$p < 0.005$
Deviation, 5th percentile	–41 (9.4)	–43 (2.5)	$p < 0,05$
Deviation, 50th percentile	–3 (5.6)	0 (0)	–
Deviation, 95th percentile	18 (8.6)	44 (0)	–
Wrist velocity, right hand [°/s]			
Flexion, 10th percentile	2 (9.0)	0 (0)	–
Flexion, 50th percentile	18 (5.0)	1.4 (0.5)	$p < 0.005$
Flexion, 90th percentile	65 (9.0)	94 (5.9)	$p < 0.005$
Deviation, 10th percentile	3 (9.8)	0 (0)	–
Deviation, 50th percentile	25 (4.3)	1 (0)	–
Deviation, 90th percentile	105 (8.6)	62 (9.1)	$p < 0.005$

Wrist position (flexion and deviation) and Wrist velocity (flexion and deviation) from the field test for the manikins (mean value) guided via the Task Simulation Builder (TSB) in Jack. Standard deviations in brackets. Positive values denote extension

After completion, Tommy goes to Pippi and Annika to discuss the wrist angle study results as well as the results from the company standard. With all results stored in the database and a common idea of how to explain them, the DHM users arrange a meeting with the psychotherapist, doctor and human factors specialist.

Tommy, Pippi and Annika meet Prysselius, Kling and Klang. Annika shows an animation of the manikin worker applying the sealing. Prysselius, Kling and Klang state unanimously that the manikin motions look awkward. This statement initiates a long discussion about what a "natural/average" motion really is. The outcome of the discussion is that all agree that the manikin motions do look a bit awkward, but are ones that are possible for most humans to perform. They move on and look at the

tables. Now it become obvious that the manikin performed motions that differ from what the test subject did in the field test. The manikin used a larger joint range and centred the motions round a neutral wrist position. The real-life subject did not flex and extend his wrist as much and had his wrist slightly flexed all the time. Psychotherapist Prysselius, Dr. Kling and human factors specialist Klang are quite happy to see that the DHM simulation and visualisation tool is able to present measures that are in the same format as their objective field measures. This looks promising for the future. The DHM tool enables the use of the same methods in early design stages as in later field tests. Some years ago, the company-specific ergonomics assessment method was integrated into the DHM tool (Fig. 186.7); this evaluation method is mainly based on performing visual observations. Now it has been shown that the DHM tool can provide information that is comparable with data from direct measures. It will also be advantageous to be able to show that a manikin can perform an assembly task with a motion sequence that can be performed by humans, and that complies with ergonomics guidelines all the time. If the workers can be trained later on to use the same or a similar motion pattern as the manikin, musculoskeletal disorders can be reduced. This is a step forward from the common praxis of analysing static postures. All project members see the potential in starting to use ergonomics simulations. However, they are also aware that plenty of work is needed before such simulations can be used for all new workstations. Tommy concludes the discussion and summarises the essence in the web protocol. Before closing the meeting, they have a brief discussion about motion capture techniques, an alternative for manipulating the manikin. Tommy, Annika and Pippi leave the room. On the doorstep, Tommy remembers a large redesign project of an assembly line. He returns and asks the psychotherapists, doctor and human factors engineer if they would be interested in digging deeper into the problems identified in the case. They are, and Tommy promises to do everything he can to initiate a parallel project as soon as possible, including his new friends from the health sector.

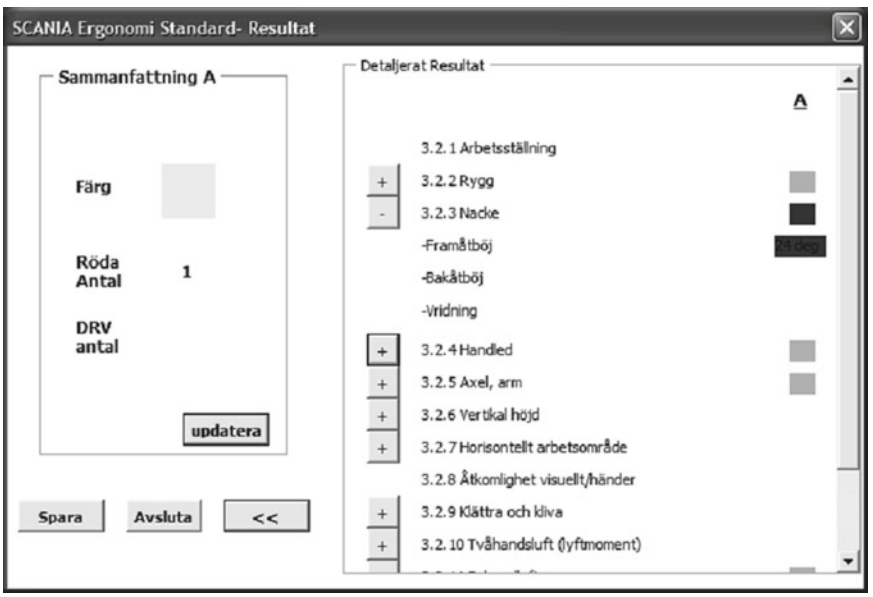

Fig. 186.7 Screenshot from the DHM integrated company-specific ergonomics evaluation method. The DHM integrated company-specific ergonomics evaluation method, based on an established observation method used for field tests. The method considers overall work posture and detailed neck, wrist, shoulder posture. Furthermore, the method considers accessibility, visibility and biomechanical load. The method gives result in terms of recommended actions: no action required (*green*), action required in near future (*yellow*) and action required at once (*red*)

186.5 Discussion

Human anthropometric diversity makes user-centred design processes challenging. A rule of thumb is that if the users of products or workplaces are few and known, designers prefer to take anthropometric measures of the actual users and create computer manikins representing them (Fig. 186.8). If the number of users is large and/or unknown, distributed or boundary manikins are preferred. According to the best practices of the Human Factors and Ergonomics Society (Dainoff et al. 2003), central manikins and boundary manikins based on one-dimensional percentile statistics (e.g. 1st percentile,

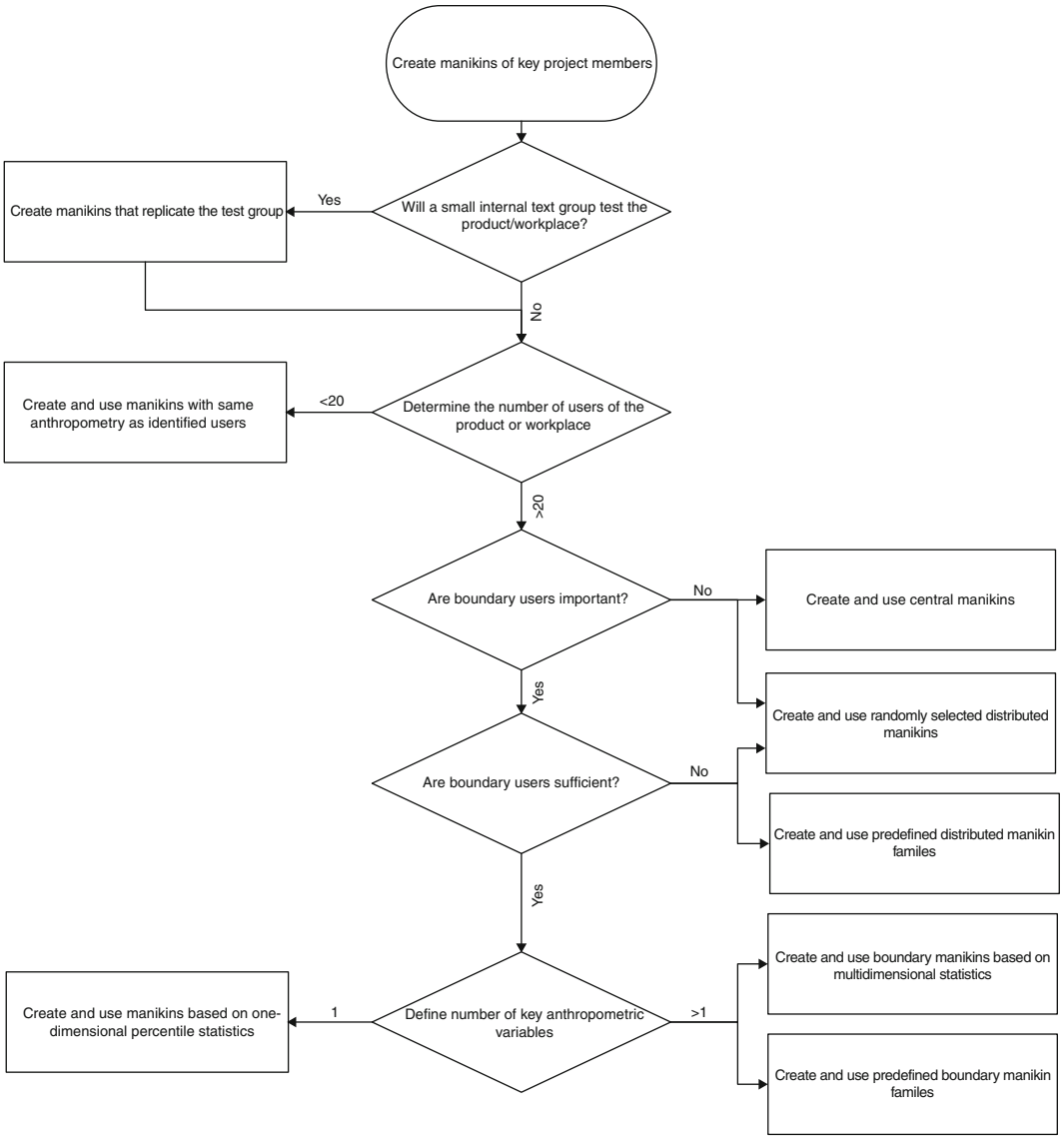

Fig. 186.8 Practical methods and techniques for anthropometric user representation. Modified decision tree from Dainoff et al. (2003). The tree is a guide to select user representation method: replicas of identified users, central, distributed or boundary manikins. The different methods are preferably combined

50th percentile and 99th percentile statures) can be used if one key anthropometric variable is considered important for the design problem at hand. If two or more key anthropometric variables need to be considered simultaneously (two-dimensional or multidimensional design problems), boundary manikins based on ellipse or ellipsoid statistics are preferred (such as those defined by using PCA in Case 3). For some design problems, it is appropriate to define manikins within the distribution as well (i.e. distributed cases) (Dainoff et al. 2003). As presented in this article, several different methods for user representation exist and a method can be used in isolation or combined with other methods.

As illustrated in the three cases, DHM tools are helpful in considering anthropometric diversity, and other ergonomic issues, at early stages of the design process. In the cases, three different DHM tools are presented: *Ramsis* (Case 1), *Delmia V5 Human* (Case 2), and *Jack* (Case 3). Other digital human modelling tools exist such as *Anybody*, *Pro/Engineer Manikin* and *Sammie*. The *Handbook of Digital Human Modeling* presents a detailed list of digital human modelling tools (Bubb and Fritzsche 2009). In addition, the following four user representation methods were applied in the three cases:

- Predefined manikins for user representation (Speyer's approach, Case 1).
- Boundary and central manikins to consider one key anthropometric variable (Case 2).
- Boundary manikins to consider several anthropometric variables (Case 3).
- Distributed manikins. Randomly selected persons were replicated (the project members were modelled in Cases 1 and 2).

DHM tools have great flexibility in that it is possible to generate manikins according to one's own settings (Fig. 186.9). However, the tools typically do have some ingenuity regarding manikin creation where extreme manikins with combinations of non-existing anthropometrics measures cannot be generated. The possibilities to create one's own manikins enable the use of predefined

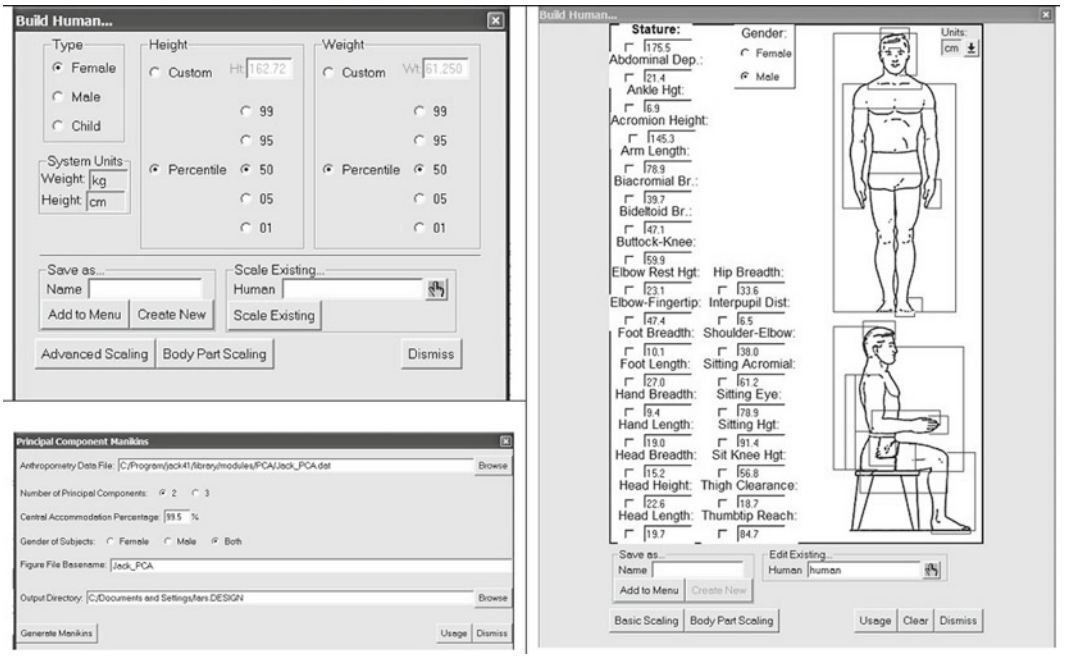

Fig. 186.9 User representation methods in a DHM tool. Screenshot from Jack illustrating (*1*) the possibility to define one's own manikin (*right*), (*2*) by defining height and weight percentiles (*top left*) and (*3*) method for creating boundary manikins (*bottom left*)

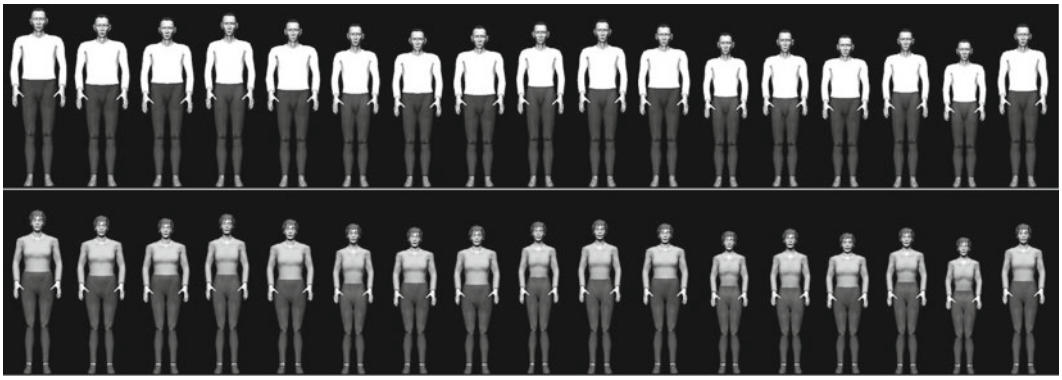

Fig. 186.10 A-CADRE, a manikin family to consider user diversity. A-CADRE, a manikin family configuration defined by Bittner (2000) for the evaluation of workplaces

manikin families and any other method for the consideration of users' anthropometric diversity. A-CADRE (Bittner 2000) is one example of a manikin family developed for this purpose in workplace design. Male and female manikins modelled according to the anthropometric data in A-CADRE are illustrated in Fig. 186.10. DHM tools also enable the creation of manikins that replicate test dummies (e.g. crash dolls and certification dolls used in the design and development process). In some DHM tools, the SAE standard test manikins are integrated.

In the user-centred design process, it is essential to define the users and their requirements and desires for products and workplaces. These requirements and desires include such aspects as being easily accessible, easy to handle, comfortable and the requirements are, preferably, transformed into measurable parameters, such as minimum clearances or maximum biomechanical loads. In the three cases presented, the following ergonomics analysis methods were illustrated: comfort values, reach, clearance, RULA and wrist angles. A number of different evaluation methods are integrated into the DHM tools such as field of vision, NIOSH lifting equation, OWAS, SSPP, Snook and Garg. A brief description of common ergonomics analysis methods is included in the *Handbook of Digital Human Modeling* (Lämkull et al. 2009). Companies frequently customise DHM tools by implementing their own standard ergonomics evaluation method in the tools (Chiang et al. 2008; Högberg et al. 2008). All these methods being integrated in the DHM tools give a quantitative measure in return. The results from the ergonomics assessment tools indicate whether the product or workplace is ergonomically acceptable or needs to be redesigned. It is acceptable if it fulfils the user requirements and desires. If not, this indicates that the users may experience discomfort or exposure to unacceptable workloads, and the design of the product or workplace then needs to be changed. The product or workplace is typically modified, and new analyses are performed on the redesigned product or workplace. The design, analysis, redesign, analysis loop continues until satisfying ergonomics results are retrieved for all manikins used in the user tests.

Summary Points

- Digital human modelling (DHM) tools are applied in the design, modification, visualisation and analysis of human workplace layouts and/or product interactions.
- A manikin is a digital replica of the human including skeleton, segments and (sometimes) muscles.
- In an initial state, define the users in terms of age and nationality and other factors that affect anthropometrics, and define key anthropometric variables for the design problem.

- Three main general user representation methods exist: boundary, central and distributed. DHM also enables the generation of manikins according to one's own anthropometric settings.
- In the DHM tools, a number of different ergonomics evaluation methods are integrated, such as field of vision, biomechanical analysis, collision and clearance analysis, comfort assessment, NIOSH and Snook lifting equations, posture evaluation methods such as OWAS, RULA, as well as Garg energy prediction.
- The user-centred design approach is a continuous, iterative design–analysis–redesign–analysis loop, carried out until satisfactory ergonomics results are retrieved for all manikins used in the user tests.

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Chapter 187
Anthropometric Indices in the Philippines for Manufacturing Workers

Jinky Leilanie DP Lu

Abstract This chapter discusses anthropometry among Filipino manufacturing workers and its application to the design of the workstation and personal protective equipment. The anthropometry is also discussed as to its importance to the prevention of work-related health problems. The data on anthropometry was taken from a study of the author of 1,805 manufacturing workers who were measured for their anthropometry and given survey questionnaires related to work hazards and illnesses. The study showed that those with poor posture were twice more likely to report exhaustion. The walk through survey revealed that workers assumed poor posture because of non- anthropometrically designed work equipment. Backache was common among assembly line workers because of the lack of application of ergonomics in workstation design and incorrect biomechanics. This chapter concludes by emphasizing the importance of anthropometry to workstation design, personal protective equipment design, worker's quality of work life, and prevention of work-related illnesses such as musculoskeletal disorders.

Abbreviations

PPE	Personal protective equipment
TNC	Transnational corporation
s.d.	Standard deviation
CAD	Computer-aided design
BMI	Body mass index
DBP	Diastolic blood pressure
BP	Blood pressure
WC	Waist circumference
cm.	Centimeters
kg.	Kilogram
n	Sample population
Mdn	Median
Std Dev	Standard deviation

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_187,

187.1 Introduction

Anthropometry is the science of measurement and the art of application that establishes the physical geometry, mass properties, and strength capabilities of the human body. The uses of anthropometry in the workplace include: (1) evaluating postures and distances to reach controls; (2) specifying clearances separating the body from hazards such as surrounding equipment; (3) identifying objects or elements that constrict movement; and (4) assisting in the biomechanical analysis of forces and torque.

An anthropometric measurement for Filipino manufacturing workers was conducted by the author, which was the first ever study conducted in the Philippines. Currently, there is increasing demand for this kind of information among researches and occupational health practitioners who develop measures to prevent occupational injuries. In the United States, they found that the body size or body segment measurements of some occupational groups differ significantly compared to others. This implies that caution must be exercised in selecting databases for the design and evaluation of machinery, human–machine interfaces, and personal protective equipment (PPE) (Barley et al. 2008). This chapter gives the anthropometric data of Filipino manufacturing workers in the Philippines.

Considering the great cost to human life, safety, and economy, it is worthwhile to look into possible measures to make the working environment hazard-free for the common worker. One way to do this is through the ergonomic design of workstations. Ergonomics has been described as "…the study of human characteristics for the appropriate design of the living and working environment (Kroemer 2002)." Meanwhile, the workstation is the immediate working environment of the individual, which includes working surfaces, tables, chairs, and equipment layout. It has been shown that proper design and layout of equipment that is tailored to the individual needs of the worker lead to lower physiological stress, increased efficiency, lesser workload, and, thus, greater productivity. In a study on carpet weavers whose posture was mostly constrained by the design of workstations, it was found that improving postural variables resulted in lesser occurrence of musculoskeletal disorders (Choobineh et al. 2004). A within-subject controlled experiment among bricklayers and bricklayers' assistants also found that the use of ergonomic measures significantly decreased lower back discomfort (van der Molen et al. 2004).

In dealing with machines in manufacturing, techniques can be designed to support both user interface development and workstation layout (Johnson 1996). Personnel, equipment, and environmental and systems ergonomics should be harnessed to maintain user acceptance and overall man–machine–system efficiency (Trispel 1982). He suggested a task approach in systems design that can create improved man–machine interfaces.

A survey was carried out among 31 different kinds of manufacturing industries in export zones in the Philippines. Export zones are important employment sites for Filipino workers. Export zones are special economic and social enclaves in developing countries where multinational companies operate with special benefits and privileges. The benefits given to transnational corporations (TNCs) in export zones in the Philippines include 100% ownership, free duties, exemption on taxes or license fees on imports to the zone, the privilege to borrow from Philippine banks, exemption from minimum investment requirement, and unrestricted repatriation of capital and profits (Rowbotham and Mitter 1994).

The sample for the anthropometric study consisted of 1,805 manufacturing workers. Body physique or anthropometric measurements were measured using tape measure, goniometers, calipers, and anthropometers in order to measure body segment length, height, breadth, depth, and circumference. Examples of such measurements included hip breadth, crotch length, functional leg length, buttock–knee length, knee height, and popliteal height, among others. A walk-through survey was also conducted to investigate the work equipment and workstation design in relation to standards. The walk-through survey included evaluation of postures and distance to reach controls, for example, whether person was seated too far or too near to the reach control. In order to assess the extent of hazard and injury exposure of the target population, 500 workers were also interviewed using a survey questionnaire in a subsequent study of the author from the same target population.

187.2 Anthropometric Data Among Filipino Manufacturing Workers

Among the 1,805 individuals selected, 53.3% were females while 46.7% were males. Majority were single (60.4%) and aged below 30 years (77%), indicating a relatively young working population. Majority (80.50%) of the participants were between 150 and 174 cm in height (s.d. = 8), with the shortest being 54 in. and the tallest 71 in. Most of respondents (92.7%) weighed less than 80 kg, with measurements ranging from 40 to as high as 170 kg.

The study showed the anthropometric measurements of the workers as shown in Tables 187.1–187.9. The mean standing height for males was higher than for females at 167.0 cm (s.d. = 8.03) and 153.9 (s.d. = 8.08) cm, respectively. Meanwhile, the mean sitting height was 84.8 cm for males (s.d. = 5.81) and 79.9 (s.d. = 4.5) cm for females.

187.3 Health Issues Related to Ergonomic Problems

A subsequent study showed that those with poor posture were twice more likely to report exhaustion. The walk-through survey revealed that workers assumed poor posture because of nonanthropometrically designed work equipment. Backache was also common among assembly-line workers because of the lack of application of ergonomics in workstation design and incorrect biomechanics.

Eyestrain was also associated with the type of work such as dealing with minute electronic part and detailed work. This was also aggravated by the slouching posture of the worker because the mounting table was far below the visual range. In this situation, there is a need for ergonomic design of the workstation.

In the study of the 31 industries, all workstations did not meet ergonomic standards. Working surfaces were too low for the workers and were cramped. Repetitive movements and prolonged posture were also prevalent. As for work activities, majority reported lifting objects weighing from 1 to 25 kg (47.1%), standing and carrying objects for prolonged periods (41.9% and 36.2%, respectively), and performing high-precision movements (33.7%). See Table 187.10.

The workers in the selected manufacturing industries were exposed to ergonomic hazards such as poor workstation design, poor biomechanics, and poor quality of air inside the work area. To address the problem on biomechanics and workstation design, anthropometric data of the manufacturing workers are necessary. This is also more pressing since most of the equipment in the Philippine manufacturing sector are imported and, thus, do not conform to the body physique of Filipino workers.

187.4 Application of the Anthropometric Data to Workstation and PPE Design for Filipino Workers

Based on these principles, equipment and workstation design should conform to the measurements culled from the study. For instance, a fit-tested hardhat and dust mask for Filipino workers should incorporate certain dimensions (Fig. 187.1). In the same manner, prototype design for computer-seated work for Filipino manufacturing worker using the 95th percentile (Fig. 187.2) should be incorporated. Figure 187.3 also shows the application of the anthropometry gathered in this study for the prototype design for personal protective equipment and protective clothing.

Table 187.1 Anthropometric measurement for standing (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.)	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Standing height	167.01	157.00	167.00	178.00	8.03	153.92	143.00	155.00	165.00	8.28
Eye height	155.01	145.00	155.00	166.00	6.92	143.05	134.00	143.00	153.00	6.15
Shoulder height	137.45	128.00	137.00	148.00	6.07	127.21	118.00	127.00	136.00	5.80
Shoulder width	44.67	39.00	44.00	49.40	7.33	40.24	34.00	40.00	46.00	8.29
Shoulder elbow length	33.05	28.00	33.00	37.00	3.97	31.39	27.00	31.00	35.00	10.28
Length of upper arm	25.99	20.00	26.00	31.00	4.54	24.92	20.00	25.00	29.00	8.38
Length of lower arm	25.83	21.10	25.00	30.00	4.41	24.16	20.00	24.00	30.70	4.18
Forearm hand length	44.06	40.00	44.00	48.00	4.12	40.47	36.00	41.00	45.00	5.39
Length of arm and hand	72.60	67.00	73.00	79.00	6.35	66.04	59.00	67.00	72.00	5.77
Elbow height	104.14	96.50	104.00	112.80	6.72	96.28	89.00	97.00	104.00	7.39
Knuckle height	72.51	66.00	73.00	79.00	5.80	67.77	62.00	68.00	74.00	6.33
Chest height	123.36	114.0	123.00	134.00	7.22	111.28	102.50	112.00	121.00	10.50
Chest breadth	36.35	29.00	35.50	47.00	6.17	32.63	25.00	31.00	47.43	7.22
Waist height	97.32	90.00	98.00	105.00	8.43	95.47	88.58	96.00	103.00	6.09
Waist hip length	10.11	5.00	9.00	15.00	6.44	10.19	6.00	9.00	14.00	6.32
Hip width	43.50	31.00	44.00	54.80	8.33	43.38	32.00	44.00	52.93	7.10
Hip height	87.66	81.00	89.00	96.00	8.57	85.34	79.00	86.00	94.00	9.01
Knee height	49.73	44.00	50.00	55.00	5.99	45.88	41.00	46.00	50.00	3.09
Popliteal height	46.35	41.50	47.00	51.00	2.99	42.05	37.00	42.00	47.00	4.02
Upper reach	193.40	175.00	190.00	208.00	10.8	190.19	177.00	191.00	204.00	10.28
Overhead fingertip reach	212.08	195.00	213.00	224.90	9.10	196.46	183.00	196.00	211.00	8.91
Arm span	167	154.20	169.00	181.00	9.15	153.18	141.00	153.00	165.00	8.53

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.2 Anthropometric measurement for sitting (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.)	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Sitting height	84.84	78.00	85.00	92.00	5.81	79.92	73.00	80.00	87.00	4.50
Eye height	73.36	67.00	73.00	80.00	3.83	68.38	62.00	69.00	74.00	4.85
Elbow height	22.23	17.00	22.00	27.00	4.21	21.89	17.00	22.00	26.43	4.09
Waist height, sitting	19.44	15.00	19.00	24.00	6.15	22.41	18.00	22.00	27.00	3.21
Hip height	13.28	10.00	13.00	18.00	4.06	15.29	11.00	15.00	20.00	6.71
Hip breadth, sitting	35.60	31.00	35.00	41.00	4.19	36.39	31.00	36.00	42.43	4.83
Thigh clearance height	13.49	10.50	13.00	16.50	4.45	12.82	10.00	12.00	16.00	6.97
Buttock knee length	54.80	49.00	55.00	61.90	5.21	52.73	47.00	53.00	59.00	4.56
Buttock popliteal length	46.40	41.00	46.00	52.00	3.72	45.14	40.00	45.00	51.00	3.69
Knee height, sitting	50.03	45.00	50.00	55.90	3.99	46.98	42.15	47.00	52.00	4.43
Popliteal height	43.33	39.00	43.00	47.00	2.57	40.34	36.00	40.50	44.00	2.90
Buttock width	48.45	35.10	48.00	59.00	7.40	47.66	35.00	48.25	58.00	6.85
Length of upper leg	36.80	29.20	36.00	46.50	6.12	35.96	28.00	36.00	45.00	5.25
Length of lower leg and foot	45.27	38.00	46.00	52.00	4.53	42.14	35.00	42.50	48.00	4.31
Thumbtip reach	71.30	61.00	72.00	79.00	7.12	65.44	56.00	66.00	74.00	7.63
Overhead fingertip reach, sitting	127.92	117.00	128.00	138.00	7.81	116.87	108.00	117.00	128.00	9.77

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.3 Circumference anthropometric measurement (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement	Male (n = 843)					Female (962)				
(cm.) circumference	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Head	55.28	53.00	55.50	58.00	3.086	53.88	51.00	54.00	56.43	2.63
Shoulder	106.67	96.00	106.00	120.00	9.243	94.52	85.00	95.00	107.85	10.86
Biceps	28.10	23.50	27.50	33.00	5.499	25.28	21.00	25.00	30.50	3.97
Lower arm	25.62	22.00	25.00	29.00	4.794	22.28	19.00	22.00	25.50	4.45
Buttock	92.69	83.00	93.00	105.00	9.035	92.53	83.00	92.00	104.85	7.52
Upper leg	46.14	37.00	46.00	54.40	6.401	45.46	38.00	45.00	54.00	5.21
Lower leg	35.68	30.00	35.00	42.00	5.292	33.83	29.00	33.00	39.00	4.59
Chest	86.66	76.10	87.00	100.80	9.344	84.42	74.00	84.00	98.43	9.31
Waist	79.42	66.00	79.00	94.00	8.566	72.74	60.00	71.00	90.00	9.05
Hips	88.34	79.00	88.00	100.00	7.934	86.64	75.00	86.00	101.00	9.44

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.4 Grip strength measurement for standing (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.) grip strength	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Standing (left)	38.53	23.00	39.00	53.00	8.56	20.72	11.00	20.85	29.00	7.00
Standing (right)	40.64	25.200	41.00	54.80	9.35	22.36	13.00	22.00	31.00	8.89
Sitting (left)	38.60	24.00	39.00	52.00	8.40	20.21	12.00	20.00	29.00	5.66
Sitting (right)	40.41	27.00	40.00	55.00	8.46	21.84	12.00	22.00	31.00	5.72

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.5 Depth anthropometric measurement (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.) depths	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Forward reach, functional	76.58	78.00	78.00	86.00	7.61	69.64	59.08	70.00	79.00	6.83

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.6 Breadth anthropometric measurement (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.) breadths	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Elbow to elbow breadth	30.57	32.00	31.00	48.00	2.07	28.85	30.00	29.00	46.00	1.68

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.7 Anthropometric measurement for standing (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.) head dimension	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Head breadth	17.22	14.60	17.00	19.40	6.21	16.50	14.00	16.00	18.50	6.96
Head length	20.53	17.50	20.00	26.00	7.48	19.23	16.50	19.00	23.00	2.76
Interpupillary distance	7.74	6.50	7.50	8.00	4.63	7.37	6.00	7.00	8.00	5.18
Bitragion subnasale arc	28.62	25.00	29.00	31.00	3.03	27.09	25.00	27.00	29.00	1.43
Bitragion chin arc	30.57	27.00	31.00	33.40	2.07	28.85	26.00	29.00	31.00	1.68

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.8 Hand anthropometric measurement (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.) hand dimension	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Sleeve outseam	54.02	48.00	4.72	60.00	4.72	49.38	44.50	50.00	55.00	4.65
Hand length	19.75	17.00	7.82	21.50	7.82	17.95	15.50	18.00	20.00	3.44
Hand breadth	9.80	8.00	4.07	11.00	4.07	9.23	7.50	8.50	10.00	6.97
Hand circumference	20.78	19.00	1.64	23.00	1.64	18.39	16.00	18.00	20.00	7.44
Wrist center of grip length	9.20	7.50	3.93	11.00	3.93	8.69	7.00	8.50	10.00	4.10

Mdn median; *Std Dev* standard deviation; *cm* centimeters

Table 187.9 Foot anthropometric measurement (Source: Int J Ind Ergon. 2007;37:497–503)

Anthropometric measurement (cm.) foot dimension	Male (n = 843)					Female (962)				
	Mean	5th percentile	Mdn	95th percentile	Std. Dev	Mean	5th percentile	Mdn	95th percentile	Std. Dev
Foot length	25.42	23.00	25.50	28.00	1.67	22.63	20.00	23.00	25.00	1.64
Foot breadth, horizontal	10.52	8.50	10.00	11.50	6.37	9.50	8.00	9.00	11.00	4.41
Ankle circumference	24.18	21.00	24.00	27.00	2.23	21.93	19.00	22.00	25.00	2.80
Functional leg length	93.34	88.00	93.00	100.00	4.08	90.70	83.00	90.00	98.00	4.60
Step height	27.67	16.00	28.00	40.00	7.79	25.63	14.58	25.00	37.00	9.11

Mdn median; *Std Dev* standard deviation, *cm* centimeters

Table 187.10 Frequency distribution of work activities (repetitive movements and prolonged posture) of workers (n = 500) (Source: Asian J Ergon. 2004;5:19–29)

Work activities (duration of 4–8 h)	Frequency	Percentage (%)
Sitting	137	27.4
Standing	218	43.6
Carrying light objects	74	14.8
Reaching	129	25.8
Bending to the side	77	15.4
Carrying objects in the hands	188	37.6
Leaning over	62	12.4
Pushing	33	6.6
Pulling	40	8.0
Climbing	7	1.4
Walking	154	30.8
Lifting (1–15 kg)	233	46.6
Handling difficult to grasp objects	40	8.0
Exertion of forces in awkward positions	59	11.8
High precision movements	175	35.0

n sample population; *kg.* kilogram

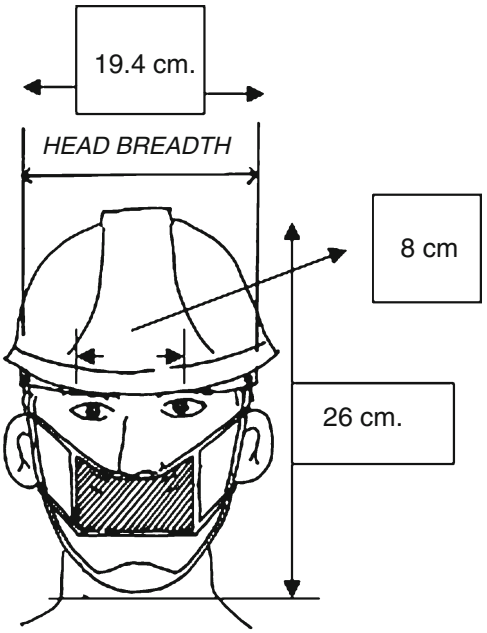

Fig. 187.1 Anthropometric measurement of filipino male workers for design of hardhat and gas mask using 95th percentile. *cm* centimeter (Source: Int J Ind Ergon. 2007;37:497–503)

187.5 Anthropometry and Workers' Quality of Worklife

For the past few years, ergonomic initiatives have been growing in Asia due to increasing local needs. A number of studies in some developing countries in the region have contributed in improving the working conditions of locals in terms of materials handling, workstation design, and work organization through utilization of locally available resources. This was done in Mexico where anthropometric database for the working population was produced for the manufacturing sector (Lavender et al. 2002). In Hong Kong, the increasing popularity of computer-aided design (CAD) prompted

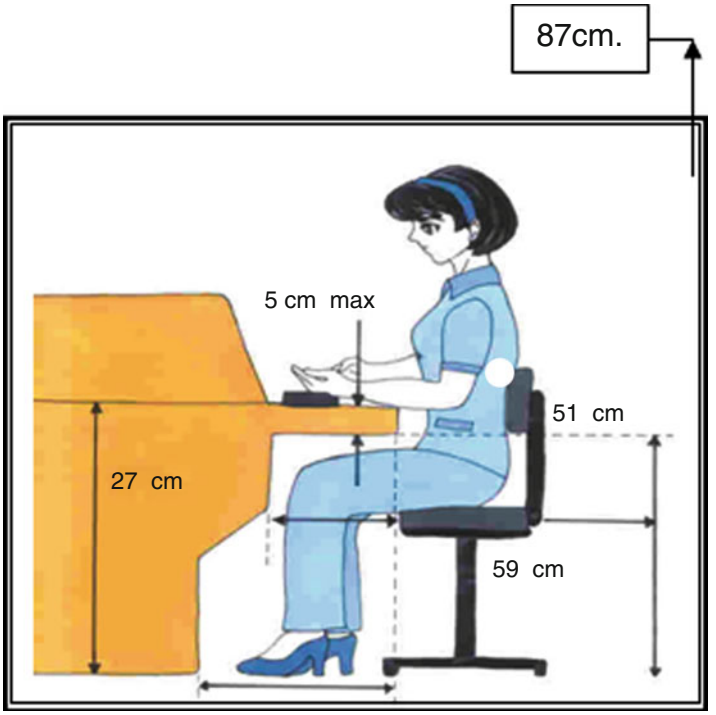

Fig. 187.2 Prototype design for computer-seated work for filipino manufacturing workers using 95th percentile. *cm* centimeter (Source: Int J Occup Saf Ergon. 2004;10:349–59)

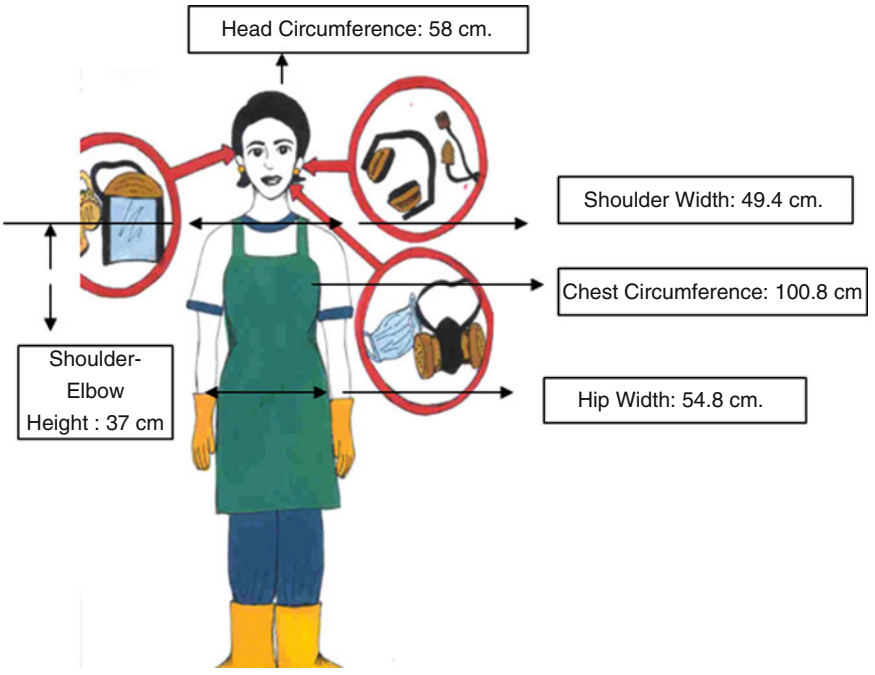

Fig. 187.3 Prototype design for personal protective equipment and clothing for filipino manufacturing workers using 95th percentile. *cm* centimeter (Source: Int J Occup Saf Ergon. 2004;10:349–59)

researchers to look into the design of a suitable workplace for CAD operators using anthropometric data to enhance performance and reduce musculoskeletal problems (Chan and Jiao 1996).

Industrial ergonomics uses much of anthropometric data in the design of machinery and interventions in the workplace. Use of anthropometric data can help in the proper design of equipment for better efficiency and more human comfort (Gite and Yadav 1989). Since mismatches in anthropometric dimensions have been postulated to be one of the main causes of work-related fatigue and occupational illness (Chan and Jiao 1996), steps must be taken to gather anthropometric data that can aid in the formulation of ergonomic interventions in the workplace.

The anthropometric data in the study can have many applications. It can be used as a reference for body mass index (BMI) and obesity index. This was done in a previous study (Eckhardt et al. 2003) where authors tried to look into the ability of BMI to predict body fat (BF) among youths in four Asian countries and identify the degree to which additional anthropometric measures improved this prediction. Data came from 456 Filipinos, Chinese, Russians, and black South African youths, with ages ranging from 6 to 16 years. Weight and height measures were collected and percentage body fat (BF) was regressed on BMI.

The anthropometric data gathered can also be used for the design of equipment and clothing for Filipino workers in manufacturing industries. This application was used in determining anthropometric characteristics of biologically admixed population in the United States (Yokota 2005). The purpose of this study was to examine multivariate craniofacial anthropometric distributions among biologically admixed male populations and single racial groups of Black and White males. The author suggested that nose breadth and lip length were different between Blacks and Whites. This was then used for the design of equipment and clothing for the US Army and other large organizations.

Adequate posture, work height, normal and maximum working areas, lateral clearance, and visual requirement provided a conceptual basis for a good workstation design (Das and Sengupta 1996). Those who worked in computer workstations that have ergonomic deficiencies reported eyestrain, shoulder pain, back pain, arm pain, wrist pain, and neck pain (Shikdar and Al-Kindi 2007).

The need for fitness testing of respirators was also reiterated (McKay and Davies 2003). Respirator fit testing is necessary before entering hazardous working environments to ensure that the respirator, when worn, satisfies a minimum fit and that the wearer knows when the respirator fits properly. Many countries do not have fit testing or total inward leak (Kim et al. 2003). In research facilities, specific regulations and guidelines define safety standards, along with medical evaluation, training, inspection, maintenance, and care.

187.6 General Application of Anthropometric Data

Anthropometric data have many applications and uses. The dimensions of the workplace, including furniture, machines, working tables, and protective equipment, can match the body physique and strength requirements through baseline anthropometric measurement. These anthropometric measures and the ergonomics aspects of objects and workplace provide elements that will allow the design and the implementation of surveillance programs for the control and the prevention of work-related musculoskeletal disorders, a relation to the personnel's inadequate selection and to the redesign of interior spaces, and the selection of the machinery and tools to use in the technological processes (González et al. 2000). The need to adopt school furniture was done among Turkey students aged 3–5 (Barli et al. 2005). A set of 18 body dimensions was taken from 154 males and 132 females to eventually design school furniture, fittings, and equipment, the purpose of which was to prevent or minimize musculoskeletal, visual, and circulatory problems resulting from badly designed elements.

In a study on hand anthropometrics, it was found out that Nigerian females' hands are wider and thicker but shorter than compared with those for females from the UK, Hong Kong, and from America. Such differences have implications for design and evaluation of hand tools for the Nigerian female population (Okunribido 2000). Anthropometric design was also used for automobile seat comfort and automobile seat design specifications (Kolich 2003).

Anthropometry is also helpful among farmers such as in human–tractor interface designs and well-accommodated operator enclosures (i.e., cabs and protection frames). One such study was done where authors found that knee height (sitting) was found to affect the cab-enclosure accommodation rating (Hsiao et al. 2005). The study also showed that multiple anthropometric dimensions interactively affected the steering wheel and gear-handle impediment.

Anthropometry can also be used in garment sizes. This was done among European women to adapt garment sizes with the changing body physique of new generations that may be different from previous ones (Ujevi et al. 2005).

Anthropometry can also be used, among other risk factors, in determining certain diseases such as blood pressure elevation. In a study, ethnic difference in blood pressure (BP) among British adolescents was observed (Harding et al. 2006). Results showed that apart from higher diastolic blood pressure (DBP) for Indian girls, BP in minority groups was generally lower than their white UK counterparts. The authors recommended that targeting intervention in adolescence may be a critical opportunity for preventing ethnic differences in BP in later life. In a similar study, body fat deposition between Japanese and Australian-Caucasian men was done (Kagawa et al. 2006). The authors concluded that Japanese men have greater body fat deposition than Australian-Caucasians at the same BMI value. Japanese men may, therefore, require lower BMI cut-off points to identify obese individuals compared to Australian-Caucasian men.

Conversely, simple and reliable anthropometric measurement tools were developed for multiple metabolic disorders for 361 Japanese and 252 Mongolians aged 30–60 years (Shiwaku et al. 2005). Mongolians of both genders had significantly higher values for all anthropometric measurements than did the Japanese. The study suggested that BMI (body mass index) and WC (waist circumference) were useful for predicting multiple metabolic disorders in non-diabetic Mongolians and Japanese. It also suggested that the use of plasma triglyceride and high-density lipid-cholesterol levels in combination with BMI and WC may enhance the ability of predicting metabolic parameters in the Japanese.

Even snoring can be predicted with anthropometric data. Anthropometric data, particularly neck, chest, and abdominal girth, were significantly associated with the snoring group in both men and women (Park and Shin 2005).

The anthropometric measurements gathered in this study can be applied in the improvement of manual materials handling, posture, interface and furniture design, workplace design, and workstation layout, among many others. The use of anthropometry and ergonomics in design systems has proven to reduce human error in system performance, minimized hazards to individuals in the work environment, reduced adverse health effects, and improved system efficiency.

187.7 Applications of Anthropometry to Other Areas of Health and Disease

The Filipino physique should be incorporated in the design of working equipment and working spaces in the manufacturing sector in particular, and in the wider working sector in general. Equipment that is difficult to operate leads to body strain and other musculoskeletal disorders that are debilitating and costly.

Table 187.11 Key points

Definition of anthropometry	Anthropometry is the science of measurement and the art of application that establishes the physical geometry, mass properties, and strength capabilities of the human body. The uses of anthropometry in the workplace include: (1) evaluating postures and distances to reach controls; (2) specifying clearances separating the body from hazards such as surrounding equipment; (3) identifying objects or elements that constrict movement; and (4) assisting in the biomechanical analysis of forces and torque
Results of the study conducted by the author	• In the study, 53.3% were females while 46.7% were males. Majority (80.50%) of the participants were between 150 and 174 centimeters in height (s.d. = 8), with the shortest being 54 inches and the tallest 71 inches • The mean standing height for males was higher than for females at 167.0 cm (s.d. = 8.03) and 153.9 (s.d. = 8.08) centimeters, respectively. Meanwhile the mean sitting height was 84.8 centimeters for males (s.d. = 5.81) and 79.9 (s.d. = 4.5) centimeters for females • Workers with poor posture were twice more likely to report exhaustion. • All the workstations in the study of the 31 industries did not meet ergonomic standards. Working surfaces were all too low for the workers and were cramped. Repetitive movements and prolonged posture were also prevalent
Applications of anthropometry in the study conducted	• Anthropometry can be used for design of personal protective equipment • Anthropometry can be used for workstation design • Anthropometry can be used for the prevention of work-related illnesses • Anthropometry can be used for improving worker's quality of work life

The use of personal protective equipment (PPE) is vital in protecting workers from hazards in the workplace. However, the PPE may not suit the body physique of the Filipino worker, thereby forfeiting the benefit of the PPE. For instance, gas masks do not snugly fit the worker's face, thus allowing hazardous substances to get into the breathing zone of the worker.

Reduction of occupational hazards can also be done through the use of personal protective equipment. However, many problems have been encountered in implementing compliance in the use of protective gears. Even in hospitals where a mandate exists requiring the use of universal precautions, it was observed that rate of compliance on the use of protective gadgets was very low, and protective equipment labeled as impenetrable or uncomfortable to wear had a high failure rate (Ahmad et al. 1998). This was also observed in the study conducted by the author. Table 187.11 shows the key points of this chapter.

187.8 Conclusion

The gathering of anthropometric data is a much needed and worthwhile pursuit in light of the increasing incidence of work-related accidents and injuries, as well as in response to the growing demand for safer and more ergonomic working conditions. The gathered data from the 1,805 workers in the study can be applied to the ergonomic design of workstations, tools, equipment, layout designs, and interventions that are uniquely well suited for Filipino workers. In addition, this information is envisioned to be used in the improvement of local working conditions, targeting key problem areas to minimize ergonomic problems.

Summary Points

- The uses of anthropometry in the workplace include: (1) evaluating postures and distances to reach controls; (2) specifying clearances separating the body from hazards such as surrounding equipment; (3) identifying objects or elements that constrict movement; and (4) assisting in the biomechanical analysis of forces and torque.
- Since mismatches in anthropometric dimensions have been postulated to be one of the main causes of work-related fatigue and occupational illness, steps must be taken to gather anthropometric data that can aid in the formulation of ergonomic interventions in the workplace.
- The anthropometric measurements gathered by the author can be applied in the improvement of manual materials handling, posture, interface and furniture design, workplace design, and workstation layout, among many others, for Filipino manufacturing workers.
- Anthropometry can be used for the prevention of work-related illnesses such as musculoskeletal disorders.
- Anthropometry can be used for improving worker's quality of work life.

Acknowledgment This is to acknowledge the funding support of the National Institutes of Health, University of the Philippines Manila, the valuable support and participation of the Bureau of Working Conditions, Department of Labor and Employment Manila through Engr. Jomar Batino, as well as publication of the study in Anthropometric Measurement of Filipino Manufacturing workers, International Journal of Industrial Ergonomics, 2007, 37:497–503, Asian Journal of Ergonomics, 2004, 5:19–29, and International Journal of Occupational Safety and Ergonomics, 2004, 10: 349–359.

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ERRATUM TO

Body Fat Measurement by Air Displacement Plethysmography: Theory, Practice, Procedures, and Applications

Mauro E. Valencia and Rosa C. Villegas-Valle

V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1_22,

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DOI 10.1007/978-1-4419-1788-1_188

In chapter 22, "Body Fat Measurement by Air Displacement Plethysmography: Theory, Practice, Procedures, and Applications" the following errors were found:

Page 403: Figure caption 22.3, part (d) is incorrectly displayed as:
"(d) To measure the lung volume, the person is instructed to breathe normally through the tube attached inside the instrument. The measurement is performed twice after the chamber is closed. The instrument will then calculate the final results"
The caption should read as:
"(d) To measure the lung volume, the person is instructed to breathe normally through the tube attached inside the instrument. The instrument will then calculate the final results"

Page 408, line 6: The value "±3.30%" is incorrect.
It should display as: "±3.39%"

Page 409, line 8, under head "22.14 Calculation of Body Density and % Body Fat by ADP" is incorrectly displayed as:
"In adults, D_{fm} is mostly constant…"
It shoud display as:
"In adults, D_{ffm} is mostly constant…"

Line 9 is incorrectely displayed as:
"Because D_{fm} changes during growth…"
It should display as:
"Because D_{ffm} changes during growth…"

Page 410, line 5 of the caption for table 22.4 is incorrectly displayed as:
"permission of WOHers"
It should display as:
"permission of Wolters"

Page 410, line 1 of the footnote at bottom of table 22.4 is incorrectly displayed as:
“Table 22.3 shows the densities of”
It should display as:
“Table 22.4 shows the densities of”

Page 412:
Reference line that begins with “Ruppell” is incorrectly spelled as “Ruppell”
It should be spelled as “Ruppel”

The online version of the original chapter can be found at
http://dx.doi.org/10.1007/978-1-4419-1788-1_22

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V.R. Preedy (ed.), *Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease*, DOI 10.1007/978-1-4419-1788-1,

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