

# Muscle and Exercise Physiology

Edited by Jerzy A. Zoladz



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Edited by

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# Dedication

We, the contributing authors, would like to dedicate this book to the memory of our former colleagues, mentors, and friends—outstanding muscle and exercise physiologists: Erling Asmussen, Per-Olof Åstrand, John E. Greenleaf, Peter W. Hochachka, John O. Holloszy, Rodolfo Margaria, Bengt Saltin, Brian J. Whipp, and Roger C. Woledge, for their seminal contributions to our understanding of muscle and human exercise physiology.

The Authors,  
August 15, 2018

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# Preface

Human exercise physiology has a long history of research dating back to the pioneering works carried out at the beginning of the 20th century by the research teams of Archibald Vivian Hill and Schack August Steenberg Krogh (August Krogh)—Nobel Prize winners in Physiology or Medicine. Some of their fundamental discoveries concerning exercise physiology, such as the concept of oxygen uptake kinetics and oxygen deficit, are still valid and constitute a background and challenge for deeper understanding of muscle energetics and human physiology. At that time, some other crucial discoveries in muscle physiology were reported, notably the force-velocity relationship proposed by A.V. Hill and the concept of the motor unit as a population of muscle fibers activated by a common nerve, proposed by Sir Charles Scott Sherrington—Nobel Prize winner in Physiology or Medicine. These discoveries are among the most important achievements in this area of research. However, one more theory has been of fundamental importance for our understanding of muscle and exercise physiology, namely the sliding filament theory of muscle contraction postulated in 1954 in *Nature*, independently by two teams of scientists: Sir Andrew F. Huxley (Nobel Prize winner in Physiology or Medicine) and Rolf Niedergerke on the one hand, and Hugh Huxley and Jean Hanson, on the other hand.

The studies concerning human exercise physiology carried out at the beginning of the 20th century were originally associated almost exclusively with physical exercise capacity of healthy people and athletes. At this point, it is worth mentioning Henry Briggs for his studies of exercise tolerance of industrial workers (miners) and athletes as early as in 1920. He was the first to use the time course of expired CO<sub>2</sub> during graded exercise as the criteria of the so called “crest point”—the predecessor of the “anaerobic” or, more appropriately, the lactate and gas exchange thresholds. On a greater scale, testing of human exercise capacity has been successfully introduced into occupational physiology and to the United States Army by David Bruce Dill from the Harvard Fatigue Laboratory in the 1930s. Some of the first researchers to successfully introduce exercise testing to evaluate exercise tolerance in patients were Malcolm B. McIlroy and Karlman Wasserman in the 1960s. Later, together with Brian J. Whipp, protocols, instrumentation, and interpretation were honed into the clinical cardiopulmonary exercise tests that we know today.

Human exercise physiology is present in various areas of medicine, such as cardiology, pulmonology, endocrinology, gerontology, psychiatry, and rehabilitation, and constitutes a solid pillar of medical sciences. Nevertheless, studies involving top-class athletes and healthy people exposed to exercise performed in extreme conditions, such as hyperthermia, hypothermia, high altitude, diving, or low gravity, are still very important as they provide insight into the mechanisms limiting human exercise tolerance in various conditions. The following key discoveries in exercise physiology should be pointed out: (1) the finding by John O. Holloszy that endurance training increases activities of mitochondrial enzymes (cytochrome oxidase, COX, and citrate synthase, CS), which leads to an increase in muscle metabolic stability during exercise and to an enhancement of exercise tolerance; (2) the discovery by Greta Vrbová, Stanley Salmons, and Dirk W.G. Pette of the potential of muscle phenotypic adaptability to various external stimulus, e.g., chronic low-frequency stimulation (known as muscle plasticity); (3) the demonstration by Bengt Saltin that in healthy active individuals, oxygen supply by the cardiovascular system is limiting to whole-body oxygen uptake (e.g., during cycling) and, therefore, defines mechanistically the maximum oxygen uptake ( $\dot{V}O_{2\max}$ ); (4) the recognition, by Peter D. Wagner, that, in healthy individuals,  $\dot{V}O_{2\max}$  depends on the integration of perfusive and diffusive O<sub>2</sub> conductances along the O<sub>2</sub> transport pathway between the lungs and mitochondria; (5) the demonstration by Brian J. Whipp, the role of other variables, apart from  $\dot{V}O_{2\max}$ , defining oxidative metabolism and exercise tolerance during exercise, such as the  $\dot{V}O_2$  kinetics and its components, the gas exchange threshold, and critical power; and (6) the proposal by George A. Brooks of the concept of the lactate shuttle, which changed our understanding of the meaning of lactate production/utilization during exercise.

The enormous progress of knowledge achieved in the past few decades in various aspects of human physiology, especially in skeletal muscle physiology, provides new background for the enhancement of our understanding of various mechanisms determining human exercise tolerance in health and disease, as well as the effects of physical training. It would be very difficult for a single person to make a satisfying synthesis of the knowledge in this field. This is why

*Muscle and Exercise Physiology* textbook is presented to the reader, written by a group of 60 leading international experts who share their knowledge mainly based on their own recent scientific research in a given topic. This book contains 25 chapters organized in five sections, and presents the current state of knowledge concerning both basic facts in a given field as well as the most recent advances in research as documented by about 4000 relevant references.

This book, as expressed by its title, is focussed on different aspects of muscle and exercise physiology, including muscle morphology, energetics, efficiency, performance, fatigue, adaptation to physical training, and aging. Moreover, the book is devoted to various responses of the human body as an integrated system to physical exercise and training, as well as to heart muscle physiology, including heart morphology, energetics, efficiency, and the regulation of its functioning during exercise in health and disease. This book aims to be a useful source of information for students of medical and sport sciences, medical doctors and sports physicians, as well as scientists interested in the range of aspects that encompass mechanisms determining human exercise tolerance in health and disease. This book also presents contemporary knowledge concerning the factors limiting exercise performance of top athletes. Therefore, the book could be recommended to athletes, trainers, physiotherapists, and sport scientists interested in the mechanisms determining human physical performance.

As the editor of this book, I would like to express my deepest thanks to Prof. dr Charles Tipton—emeritus professor of the University of Arizona, Tucson, United States, for the long-lasting friendship and his unique advice on how to successfully accomplish the publication of this book. I would also like to thank the distinguished professors: Roberto Bottinelli, Veronique Billat, Paolo Cerretelli, Bruno Grassi, John O. Holloszy, David A. Jones, Arnold de Haan, Hans A. Keizer, Preben K. Pedersen, Dirk W.G. Pette, Kent Sahlin, Anthony J. Sargeant, Ronald L. Terjung, and Brian J. Whipp for sharing with me and my colleagues their knowledge on muscle and exercise physiology, either during my visits in their laboratories or during their visits to Kraków, Poland over the past few decades.

Prof. Jerzy A. Zoladz (Ph.D., D.Sc.)  
Kraków, August 15, 2018

Section I

# **Skeletal Muscle Morphology**





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# Human Body Composition and Muscle Mass

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## 1.1 INTRODUCTION

Body shape has attracted the attention of artists since the beginning of mankind. In Antiquity, proportions of the human body inspired artists, especially sculptors and painters. At that time, the so-called perfect proportions of the human body were defined (the “Polykleitos’ Canon” of the human figure). The greatest breakthrough in introducing human anatomy into art was made by Michelangelo Buonarroti (1475–1564, known as Michelangelo), a spectacular Renaissance artist whose work has been inspiring others until now (Hilloowala, 2009). In contrast to body shape, however, body composition that focuses on quantitative relationships between body components appeared in medicine in modern times, and nowadays it is an important branch of human biology (Wang et al., 1992).

The components of body composition significantly change during a life span in the process of growing, ageing, pregnancy, or during disease (“non-interventional” chronic biological processes). Moreover, body composition is dependent to a major extent on two unavoidable, “interventional” activities, namely nutrition and physical activity. Both may significantly change body composition, mainly in such extreme conditions as that of malnutrition, overfeeding, immobilization, and prolonged strenuous physical training.

Since body composition can independently influence health, it has become a matter of interest for various specialists in medical sciences—such as endocrinology, rheumatology, surgery, pediatrics, or geriatrics—who deal with a variety of medical conditions, including the metabolic syndrome, degenerative diseases, reaction to injury, osteoporosis, or sarcopenia. Studies on body composition seem to be particularly important for prediction,

prevention as well as management of obesity, type 2 diabetes, and cardiovascular disease—the latter being the main factor that increases morbidity and mortality in modern societies (Buskirk and Mendez, 1984; Duda, 2012; Lee et al., 2012; Aleman-Mateo and Ruiz Valenzuela, 2014; NCD Risk Factor Collaboration, 2016). Additionally, body composition is an important topic in sport sciences, not only when considering the selection of candidates for different sports disciplines, but also when evaluating the impact of training, recovery from injuries, and ageing on athletes. Moreover, monitoring body composition changes resulting from combined effects of microgravity and energy imbalance is one of the key problems to be considered during long-term space flight (Bartok et al., 2003; Smith et al., 2005). This is why this chapter will aim at presenting the current state of knowledge concerning human body composition, with a special focus on muscle mass.

## 1.2 THE ASSESSMENT OF THE SYSTEM AS A WHOLE

From the beginning of humanity, people were interested in expressing length in standardized units. For this purpose, human body size variables such as the width of the human palm (lat. *palmus*), the length of the foot (lat. *pes*), the length of the ell (lat. *cubitum*, i.e., the distance from the elbow to the tip of the middle finger), and fathom (i.e., the span of man’s outstretched arms) have been used in daily life as units of length. Nowadays, although advanced techniques of determining body characteristics are available, some traditional, basic human body measures—such as body mass (BM) and body height

(with regard to gender and age), body circumferences (e.g., waist circumference, hip circumference), skinfold thickness (used to estimate regional adiposity), body surface, and body volume (BV)—are still in use in clinical practice as well as in large population studies.

### 1.2.1 Body Mass, Basal Metabolic Rate, and Total Daily Energy Expenditure

BM is one of the fundamental physical characteristics of the human body. In physics, mass is the amount of “matter” that an object has, whereas weight (also referred to as the force of gravity) is the effect of the gravitational pull on the mass of the object and, according to Newton’s second law (see Eq. (1.1)), it is measured in newtons:

$$F \text{ (N)} = M \text{ (kg)} \times a \text{ (m s}^{-2}\text{)} \quad (1.1)$$

where Newton (N) is the unit of force, M, mass, and  $a$ , acceleration (Sir Isaac Newton, 1687).

However, weight is commonly expressed in kilograms, which consciously omits multiplication of mass by the gravitational acceleration, approximately constant on the entire surface of the Earth (average value:  $9.81 \text{ m} \cdot \text{s}^{-2}$ ). In this chapter, we used the term “body mass” (expressed in kg), whereas the term “weight” (expressed in N) was used only in the part dedicated to hydrodensitometry.

BM measurement and its monitoring is the starting point for controlling the energy balance of the human body. The relationship between BM and basal metabolic rate (BMR) has been intensively examined by European physiologists and zoologists from the beginning of the 19th century. BMR—the steady-state rate of heat production by an entire organism under a set of standard conditions (an individual is adult, awake, but resting, stress-free, for at least 12 hours after his/her last meal, maintained at a temperature that elicits no thermoregulatory effect on heat production)—represents the minimal metabolic activity of all tissues in a body at rest (Rolfe and Brown, 1997). It is usually expressed as heat production (direct calorimetry) or oxygen consumption (indirect calorimetry) per unit of body size (Rolfe and Brown, 1997; Henry, 2005). BMR or easier-to-assess resting energy expenditure (REE) (typically evaluated with indirect calorimetry in thermoneutrality, supine position at least 4 hours after the last meal) in most sedentary individuals accounts for about 1 kcal per 1 kg of BM per hour and constitutes of about 60%–80% of total daily energy expenditure (TDEE). Two other components of TDEE are: the rather stable cost of diet-induced thermogenesis (DIT) (10%–12% of TDEE) and the most changeable energy cost of physical activity (physical activity energy expenditure, PAEE) (Lowell and Spiegelman, 2000; Heymsfield et al., 2012a).

Organs in the human body differ according to resting metabolic rate and they may be divided into organs with high or low metabolic rate (Elia, 1992; Gallagher et al., 1998; Wang et al., 2001; Heymsfield et al., 2012a). For example, the energy cost of high metabolic rate organs such as kidneys and heart is similar and amounts to  $\sim 440$  kcal per kg per day. In another high metabolic rate tissue such as brain it amounts to  $\sim 240$  kcal per kg per day, whereas the energy cost of skeletal muscle (SM) at rest (low metabolic rate organ) amounts to about 13 kcal per kg per day (Elia, 1992; Wang et al., 2001). The energy cost of organs with high metabolic rate (brain, kidneys, heart, endocrine glands, that weigh only about 3.5 kg, i.e.,  $\sim 5\%$  of body weight of a standard man) constitutes about 60% of the REE. Organs with low metabolic rate such as: (1) SMs at rest, weighting about 28 kg ( $\sim 40\%$  of BM) accounts for about 20% of the REE; and (2) bones, fasciae, and extracellular fluid (ECF), weighting about 21 kg ( $\sim 30\%$  of BM) contribute to about 1% of the REE. Moreover, the energy cost of the digestive system, lungs and the immune system (that weight about 3.5 kg) accounts for 15% of the REE. The remaining part of the REE (about 4%) is completed by metabolism of adipose tissue weighting about 15 kg ( $\sim 20\%$  of BM). It should be underlined that, during strenuous physical exercise, SM metabolism can increase more than 100 times above its rate at rest and it constitutes about 90% of the total energy used by the human body (for overviews see Chapter 5: Muscle Energetics by Kemp and Chapter 18: Metabolic Transitions and Muscle Metabolic Stability: Effects of Exercise Training by Zoladz et al.).

In clinical practice, it is important to know BMR (as minimum energy required to exist) to determine caloric needs for energy balance and body weight maintenance (Henry, 2005; Heymsfield et al., 2012b), including weight loss programs in obesity management. Although much of the BMR, which is a main component of TDEE, is accounted for by the activity of organs with high metabolic rate, variations in BMR are related mainly to differences in body size.

One of the earliest formulas showing the relationship between BMR and BM was developed in 1932 by Max Kleiber (1893–1976) (Kleiber, 1932), the leader in animal nutrition and metabolism research. He showed that BM raised to three-fourth power is the most reliable basis for the prediction of the BMR of mature mammals (Eq. (1.2)):

$$\text{BMR} = a \times \text{BM}^{0.75} \quad (1.2)$$

where BMR is basal metabolic rate (kcal per day), BM is body mass (kg),  $a$  is proportionality constant or normalizing coefficient (the intercept, when the equation is graphed in log–log coordinates, for mammals, the average value of “ $a$ ” is 71.8), 0.75 is scaling exponent for

mature mammals (the slope of regression line in log–log coordinates) (Lindsted and Schaeffer, 2002).

Kleiber's classic equation was formulated at the whole-body level. Wang et al. (2001) proposed a new perspective on Kleiber's law by reconstructing it at the organ–tissue level. Interestingly, REE values of individual components (liver, brain, kidneys, heart, and remaining tissues) do not scale equally, but their combined formula was similar to that observed by Kleiber (Wang et al., 2001).

In the past century, many formulas were used to predict BMR in clinical practice, including Harris and Benedict equations, Schofield, Roberston and Reid equations (see, e.g., in Heshka et al., 1993). Roberston and Reid equations are recommended for obese individuals, since most equations developed to predict BMR overestimate its value in this particular group (Heshka et al., 1993).

A method of estimating BMR in larger groups of men and women belonging to varied age ranges (0–3, 3–10, 10–18, 18–30, 30–60, >60), based only on the BM and the so-called “Oxford equations” (Eqs. (1.3–1.8)), were presented by Henry (2005):

BMR for men:

18 – 30 years old ( $n = 2821$ ):

$$\text{BMR (kcal per day)} = 545 + 16.0 \times \text{BM (kg)} \quad (1.3)$$

30 – 60 years old ( $n = 1010$ ):

$$\text{BMR (kcal per day)} = 593 + 14.2 \times \text{BM (kg)} \quad (1.4)$$

> 60 years old ( $n = 534$ ):

$$\text{BMR (kcal per day)} = 514 + 13.5 \times \text{BM (kg)} \quad (1.5)$$

BMR for women:

18 – 30 years old ( $n = 1664$ ):

$$\text{BMR (kcal per day)} = 558 + 13.1 \times \text{BM (kg)} \quad (1.6)$$

30 – 60 years old ( $n = 1023$ ):

$$\text{BMR (kcal per day)} = 694 + 9.74 \times \text{BM (kg)} \quad (1.7)$$

> 60 years old ( $n = 334$ ):

$$\text{BMR (kcal per day)} = 569 + 10.1 \times \text{BM (kg)} \quad (1.8)$$

The estimation of TDEE includes two major components: BMR and physical activity energy expenditure (Westerterp, 2013). Based on the FAO nutrition studies (FAO, 1957), two simplified empirical equations were developed for the first time to predict total daily energy requirements. Those equations are easy to use since they involve only BM measurements (Eqs. (1.9) and (1.10)):

$$\text{for men: } E = 152 \times \text{BM}^{0.73} \quad (1.9)$$

$$\text{and for women: } E = 123 \times \text{BM}^{0.73} \quad (1.10)$$

where  $E$  represents total daily energy requirement (kcal per day) and BM represents body mass (kg).

An important issue in TDEE is the assessment of the energy cost of physical activity. According to FAO/WHO/UNU recommendations the physical activity level (calculated as TDEE/BMR) for sedentary and light activity lifestyles ranges between 1.40 and 1.69; for moderately active lifestyles between 1.70 and 1.99 and for strenuous or heavy leisure activity between 2.0 and 2.4 (Westerterp, 2013, 2017). Hence, TDEE might be expressed as a multiple of BMR or REE (measured by indirect calorimetry or calculated based on the prediction equations) by using adequate factor related to physical activity level.

The generally accepted and indicated method of TDEE measurements is doubly labeled water (DLW) method, which allows the measurement of energy expenditure under daily living conditions including exercise and extreme environment (Westerterp, 2013, 2017). The DLW method (method of indirect calorimetry) is based on the difference between the apparent turnover rates of the hydrogen and oxygen of body water as a function of carbon dioxide production after a loading dose of water labeled with the stable isotopes of  $^2\text{H}$  and  $^{18}\text{O}$  (Westerterp, 2017). Based on this method Redman et al. (2014) presented normative equations to calculate TDEE for nonobese men and women using the following basic variables: BM, age, and sex. In this study involving a group of 217 healthy subjects (aged 21–50 years; BMI:  $22\text{--}28 \text{ kg} \cdot \text{m}^{-2}$ ), they showed that the mean TDEE amounts to  $2443 \pm 397$  kcal per day and is on average 20% (580 kcal per day) higher in men than in women (see Eq. (1.11)):

$$\begin{aligned} \text{TDEE (kcal per day)} &= 1279 + 18.3 \times \text{BM (kg)} \\ &+ 2.3 \times \text{age (years)} - 338 \times \text{sex} \end{aligned} \quad (1.11)$$

where TDEE represents total daily energy expenditure (kcal per day), BM represents body mass (kg), and the sex variable may assume the following values: 1 = female, 0 = male.

## 1.2.2 Body Mass Index

BM and body height allow one to calculate other measures frequently used in epidemiology and clinical research, namely the BMI and the body surface area (BSA).

The BMI was introduced for the first time in whole-body assessment in 1832, by a Belgian polymath, Adolphe Quetelet (1796–1874), who was looking for an index of relative BM and introduced the Quetelet Index,

i.e., the ratio of BM in kilograms divided by the square of height in meters (Eq. (1.12)):

$$\text{BMI} = \text{BM} \times \text{H}^{-2} \quad (1.12)$$

where BM is body mass (kg) and H is height (m).

Ancel Keys (1904–2004), an American pioneer in biostatistics and a physiologist, confirmed 140 years later the validity of the Quetelet Index in epidemiological studies and named it (in 1972) “body mass index” (Eknoyan, 2008). From then on, BMI has become a standard formula for establishing, heuristically, ideal BM. The BMI for adult underweight people is lower than  $18.5 \text{ kg} \cdot \text{m}^{-2}$ ; for normal weight people it ranges from 18.5 to  $25 \text{ kg} \cdot \text{m}^{-2}$ , for the overweight from 25 to  $30 \text{ kg} \cdot \text{m}^{-2}$ , and it is higher than  $30 \text{ kg} \cdot \text{m}^{-2}$  for the obesity. The BMI above  $25 \text{ kg} \cdot \text{m}^{-2}$  is associated with an increased the risk of morbidity and mortality.

BMI may be understood as a simple sum of body fat mass (FM) and fat-free mass (FFM) component of BM (Eq. (1.13)), each of which divided by the square of height in meters (Van Itallie et al., 1990):

$$\text{BMI} = \text{FM} \times \text{H}^{-2} + \text{FFM} \times \text{H}^{-2} \quad (1.13)$$

BMI is often used in obesity studies as a measure of FM, since a high correlation between BMI and total body fat as well as BMI and the percentage of body fat have been reported during childhood and in adult individuals. However, BMI is neither a specific marker of body fat or a good marker of abnormal fat accumulation (Adler et al., 2017) and its applicability as body fat marker is questionable, since individuals of the same age, height, and weight (hence the same BMI) can have different body shape, body composition, and metabolic profile. For example, Asian people have higher body fat percentage than Western populations with the same value of BMI (Choo, 2002). In children, BMI is not a good index of body fatness because of their growth. Hence, the calculated BMI should be compared against the percentile for children of the same sex and age (Reilly, 2010; Laurson et al., 2011). In other situations—when FM and FFM may get altered due to ageing, physical training, or several diseases—BMI alone might lead to false conclusions and should be used with caution. Therefore, it is proposed nowadays to extend the description of body composition with other measures, which are based on more advanced techniques and better describe FM and FFM in the human body.

Recently, Peterson et al. (2017) found that in the group of non-Hispanic whites aged 8–29 ( $n = 2285$  participants) percent body fat scales to height with an exponent closer to 3. Therefore, they proposed tri-ponderal mass index (BM divided by height cube) as an alternative for BMI and more accurate measure of body fat for the group of non-Hispanic white adolescents (aged 8–17 years).

### 1.2.3 Body Circumferences and Skinfolts Measurements

It is generally accepted by clinicians and researchers that not total amount of adipose tissue, but rather the distribution of its excess correlates better with the risk of the occurrence of diabetes and/or cardiovascular disease.

It has been agreed that individuals with fat distribution of the central type (android *vel* “apple shape”) are at greater health risk (greater prevalence of metabolic syndrome, arterial hypertension, heart disease, stroke, type 2 diabetes) than those with peripheral fat distribution (gynoid *vel* “pear shape”) (Vague, 1996). The use of imaging techniques (computed tomography, CT; magnetic resonance imaging, MRI) indicated that unhealthy “apple shape” is associated with an internal, visceral fat deposition rather than external subcutaneous fat depots (Browning et al., 2010; Schneider et al., 2010). Therefore, simple anthropometric indices that allow one to describe regional adiposity—such as waist circumference (WC), waist-hip ratio (WHR) and waist-to-height ratio (WHtR)—might be used as a screening tool to predict diabetes and cardiovascular disease. WC was found to strongly correlate with abdominal fat measurement by means of advanced imaging techniques.

The WHtR—as another measure of relative fat distribution—was introduced by Japanese researchers in 1995 as predictor of coronary heart disease (Hsieh and Yoshinaga 1995a; Hsieh and Yoshinaga, 1995b) and it has received more attention in the past few years (Rodea-Montero et al., 2014; Lo et al., 2016; Choi et al., 2017). WHtR corrects the WC for the height of individuals and, similarly to WC, it shows a strong positive correlation with abdominal fat measured by means of imaging techniques (Soto González et al., 2007). WHtR as a proxy for central obesity was found to be a better predictive marker of “early health risk” than BMI (Schneider et al., 2010; Ashwell et al., 2014; Ashwell and Gibson, 2016). The WHtR assuming the value of 0.5 (“keep your waist to less than half your height”) has the character of a global boundary. When exceeded, it indicates an increased risk across different age groups (also in children and adolescents) as well as sex and ethnic groups (Browning et al., 2010; Mehta, 2015) (Table 1.1).

Skinfold measurements, which also belong to simple anthropometric measurements, are typically performed at 3–9 standard anatomical sites (e.g., “triceps,” “biceps,” “chest,” “subscapular,” “abdominal,” “suprailiac”), on the right side of the body, by means of caliper with constant pressure of  $10 \text{ g mm}^{-2}$ . The correct position of the calipers is critical for the accuracy of the measurement and the anatomical site should be accurately determined and then marked. The sum of skinfolds allows one to estimate (by means of an adequate equation) the amount of body fat (Jackson and Pollock, 1985).



**TABLE 1.1** Boundary Values of WC, WHR and WHtR

Index Value	Waist Circumference (cm)		Waist-hip Ratio		Waist-to-Height Ratio
	Men	Women	Men	Women	
No “health risk”	<94	<80	<0.90	<0.85	<0.5
“Health risk”	≥ 94 and ≤ 102	≥ 80 and ≤ 88	–	–	≥ 0.5 and <0.6
Very high “health risk”	>102	>88	≥ 0.90	≥ 0.85	≥ 0.6

### 1.2.4 Body Surface Area

Accurate determination of BSA is the essential issue in several medical fields. The use of BSA enables standardization of certain physiological parameters, such as cardiac function or glomerular filtration. BSA is also used to assess drug dosage.

Typically, in clinical practice, BSA is indirectly estimated on the basis of empirical formulas (Redlarski et al., 2016). Direct methods of BSA measurement—such as coating, surface integration, linear geometry, and touchless measurement (3D laser scanning) in the different groups of subjects (varied age, sexes, ethnic populations, different regions)—constitute the starting point for fitting model equations for the obtained data.

The first measurements of BSA were made in England during experiments on insensible perspiration by anatomist William Cruishank (1745–1800) in 1778 and by surgeon John Abernethy (1764–1831) in 1793. Abernethy, by applying the coating method (with paper) and linear geometry, calculated BSA as 2700 square inches (which equals 1.74 m<sup>2</sup> in the metric system) (Abernethy, 1793). Interestingly enough, both of them were searching for the proportion between hand area and BSA. Currently, it is agreed that the palm (i.e., the palmar surface area, which is the area between the interstyloid line and the palmar digital crease of each digit) represents 0.5% of the total BSA and the hand (i.e., the sum of the palmar surface area and the areas of the fingers and the thumb) represents around 0.8% of the total BSA. Both measures (hand and palm surface areas) are suitable for assessing the size of minor burns (<10% of total body surface) (Rhodes et al., 2013; Thom, 2017).

In 1879, German physiologist Karl Meeh suggested, on the basis of geometric considerations, that the BSA of mammals could be expressed with the following equation (Eq. (1.14)):

$$BSA \text{ (m}^2\text{)} = k \times BM \text{ (kg)}^{2/3} \quad (1.14)$$

where BM is the body mass,  $k$  is Meeh’s normalizing coefficient that varies slightly between species and

amounts to 0.1053 for humans (Meeh, 1879). Nowadays, this formula is used only in veterinary medicine.

Meeh’s formula remained a standard of BSA assessment until 1916, when E.F. DuBois and D. DuBois (cousins) published a new formula for BSA assessment, where they introduced height (H) as a variable (Eq. (1.15)):

$$BSA \text{ (m}^2\text{)} = 0.007184 \times BM \text{ (kg)}^{0.425} \times H \text{ (cm)}^{0.725}$$

(the originally used form)

or

$$BSA \text{ (m}^2\text{)} = 0.20247 \times BM \text{ (kg)}^{0.425} \times H \text{ (m)}^{0.725}$$

(SI units)

(1.15)

The estimation of the model coefficient in BSA assessment turned out to be an important issue. As it was found out, DuBois’ formula underestimated BSA in obese patients by 3%–5% (Verbraecken et al., 2006). After almost 100 years, the DuBois and DuBois BSA equation was corrected (Shuter and Asiani, 2000), based on a greater number of examined persons and application of modern statistical methods (Eq. (1.16)):

$$BSA \text{ (m}^2\text{)} = 0.00949 \times BM \text{ (kg)}^{0.441} \times H \text{ (cm)}^{0.655}$$

(the originally used form)

or

$$BSA \text{ (m}^2\text{)} = 0.19376 \times BM \text{ (kg)}^{0.441} \times H \text{ (m)}^{0.655}$$

(SI units)

(1.16)

Since BSA scaling plays a key role in medicine—for example, in pharmacology, toxicology, cytotoxic chemotherapy, nephrology, transplantology, extracorporeal circulation, burns assessment and fluid resuscitation—many studies in subsequent years tried to find more precise BSA formulas based on more accurate methods (including three-dimensional (3D) laser scanning techniques) and higher numbers of subjects (see Redlarski et al., 2016). As 3D full scan is a very fast technique that takes from a dozen seconds up to several dozens, depending on the type of equipment, the number of objects tested is generally much higher than in previously applied methods.

It should be mentioned that the method is unable to recognize overlapping parts of human skin.

Based on 3D full scanning measurements, [Schlich et al. \(2010\)](#) proposed the following formula for European men ( $n = 49$ ) aged 21–68 (Eq. (1.17)):

$$\text{BSA (m}^2\text{)} = 0.000579479 \times \text{BM (kg)}^{0.38} \times \text{H (cm)}^{1.24}$$

(the originally used form)

or

$$\text{BSA (m}^2\text{)} = 0.1750 \times \text{BM (kg)}^{0.38} \times \text{H (m)}^{1.24}$$

(in SI units)

(1.17)

and for women ( $n = 132$ ) aged 20–84 (Eq. (1.18)):

$$\text{BSA (m}^2\text{)} = 0.000975482 \times \text{BM (kg)}^{0.46} \times \text{H (cm)}^{1.08}$$

(the originally used form)

or

$$\text{BSA (m}^2\text{)} = 0.1410 \times \text{BM (kg)}^{0.46} \times \text{H (m)}^{1.08}$$

(in SI units)

(1.18)

Similarly, [Yu et al. \(2003\)](#) proposed the following formula for a population of Taiwanese workers (Eq. (1.19)):

$$\text{BSA (m}^2\text{)} = 0.015925 \times \text{BM (kg)}^{0.5} \times \text{H (cm)}^{0.5}$$

(the originally used form)

(1.19)

or

$$\text{BSA (m}^2\text{)} = 0.15925 \times \text{BM (kg)}^{0.5} \times \text{H (m)}^{0.5}$$

(in SI units)

which was based on 3D measurements of a group of 3951 women and men, aged 20–91. Additionally, [Yu et al. \(2003\)](#) showed different coefficients dedicated to various subgroups, i.e., separately for men and women within different age ranges.

Determination of BSA is an important issue from the point of view of diagnostic and therapeutic aspects of pediatric medicine, since BSA increases from 0.2 m<sup>2</sup> at birth up to 1.73 m<sup>2</sup> in adulthood. Only few formulas, however, have been validated for children ([Feber and Krásnicánová, 2012](#)). [Haycock et al. \(1978\)](#) developed a formula based on the measurements of a group of subjects, comprising the range from premature infants to adults, where (Eq. (1.20)):

$$\text{BSA (m}^2\text{)} = 0.024265 \times \text{BM (kg)}^{0.5378} \times \text{H (cm)}^{0.3964}$$

(the originally used form)

or

$$\text{BSA (m}^2\text{)} = 0.1506 \times \text{BM (kg)}^{0.5378} \times \text{H (m)}^{0.3964}$$

(in SI units)

(1.20)

According to the authors, this formula gives a good fit for all values of BSA within the range from less than 0.2 m<sup>2</sup> up to over 2.0 m<sup>2</sup>.

In 1987, [Mosteller \(1987\)](#) presented a simple formula for BSA calculation for adults, small children, and infants

(Eq. (1.21)), which is commonly accepted due to its precision and simplicity.

The originally used form:

$$\text{BSA (m}^2\text{)} = \sqrt{\frac{\text{H (cm)} \times \text{BM (kg)}}{3600}}$$

or in SI units:

$$\text{BSA (m}^2\text{)} = \sqrt{\frac{\text{H (m)} \times \text{BM (kg)}}{36}} \quad (1.21)$$

In clinical practice, the consequences of applying an inadequate BSA formula might be severe, including inappropriate drug dosage. The choice of an adequate BSA formula is important not only for children, but also for people from different geographical regions and for people with nonstandard body proportions, for example, in the case of obesity, cachexia, or massive bone structure ([Redlarski et al., 2016](#)).

## 1.2.5 Body Volume and Body Density

The total BV is an indicator of body size, which is subsequently used to calculate body density (BD) (Eq. (1.22)):

$$\text{BD} = \text{BM} \times \text{BV}^{-1} \quad (1.22)$$

and in consequence, body FM.

BV can be assessed by the water-displacement technique, also called “underwater weighting” or “hydrodensitometry,” or the air-displacement technique, also called “air-displacement plethysmography” ([Duren et al., 2008](#)). Both techniques are time-consuming, laborious and requires demanding laboratory conditions.

Hydrodensitometry is regarded as the most reliable of available techniques used to estimate BD. Archimedes’ principle is applied by comparing the mass of a subject in the air ( $M_a$ ) with the “mass underwater” ( $M_w$ ), which is calculated from the gravitational force ( $F_w$ ) exerted on a submerged object according to the Newton’s law (Eq. (1.23)):

$$M_w = F_w \times g^{-1} \quad (1.23)$$

where  $g$  is gravitational acceleration of 9.81 m · s<sup>-2</sup>. During underwater measurement, total expiration is necessary and account is taken of the residual gas volume remaining in the lungs ( $V_r$ ), and an estimated volume of gas in the intestine ( $V_i$ ). Temperature, which influences water density (WD), should be also taken into account. BD is calculated with the following equation (Eq. (1.24), [Brodie et al., 1998](#)):

$$\text{BD} = \frac{M_a}{((M_a - M_w)/\text{WD}) - (V_r + V_i)} \quad (1.24)$$

The volume of gas in the intestine ( $V_i$ ) included in the calculation is usually assessed to amount to about

100 mL, but this value should be increased for large adults and decreased for children.

Underwater weighting (UWW)—considered to be the “golden standard” for BV measurements—is actually replaced by the DEXA method which does not require lung volume measurement for body fat determination.

BV can be estimated with classic formulae. In 1959, Sendroy and Cecchini (1959), developed a formula (Eqs. (1.25) and (1.26)) based on the data collected for 446 men and adolescent boys [the ratio of BM (kg) to height (cm) is between 0.2 and 0.8] as:

$$BV \text{ (L)} = BSA \text{ (m}^2\text{)} \times 60.20 \times (BM/H)^{0.562} \quad (1.25)$$

and for 113 adult women and adolescent girls (the ratio of BM to  $H$  is between 0.2 and 0.8) as:

$$BV \text{ (L)} = BSA \text{ (m}^2\text{)} \times 62.90 \times (BM/H)^{0.578} \quad (1.26)$$

BSA and BV can be assessed on the basis of digital data recorded with the computer tomography, magnetic resonance imaging, or 3D scanning methods. The main advantage of these techniques is shorter time of acquisition, resulting in less measurement noise.

### 1.3 BODY COMPOSITION AT VARIED LEVELS OF COMPLEXITY

Since 1990s, a research team at Columbia University (St. Luke’s Roosevelt Hospital) has been developing a new concept of body composition research (Heymsfield and Waki, 1991; Wang et al., 1992; Wang et al., 2008). The so-called five-level model of body composition introduced by them (now widely accepted) organizes body components into a sequence of increasing complexity, namely: (1) the atomic level, where body composition is assessed in terms of the content of elements, including potassium, sodium, chlorine, phosphorus, calcium, nitrogen, and carbon; (2) the molecular level, at which chemical compounds such as fat, water, proteins, minerals, and glycogen are assessed; (3) the cellular level that accounts for the presence of cell membranes and describes extracellular and intracellular spaces; (4) the tissue–organ level, where the distribution of adipose, SM, bone and other tissues is described, and (5) the whole-body level, which describes the system as a whole (presented above) (Wang et al., 1992; Wang et al., 1998; Wang et al., 2008).

#### 1.3.1 Body Composition at the Atomic Level

Virtually 99% of BM is constituted by the mass of 6 elements, namely: oxygen (61%), carbon (23%), hydrogen (10%), nitrogen (2.6%), calcium (1.4%), and phosphorus (0.83%). The content of none of the remaining macroelements exceeds 0.5% of BM: potassium 0.4%, sulphur

0.3%, sodium and chloride 0.2% each, and magnesium 0.1% (Fig. 1.1).

The atomic body composition is measured primarily with two techniques: the whole-body counting that measures natural body radioactivity (i.e., the measurement of natural  $^{40}\text{K}$  isotope) and the neutron activation analysis (NAA) that uses neutron flux to activate atomic nuclei (reaching excited state). The measurement of characteristic gamma radiation of radionuclides enables quantitative assessment of the content of elements—such as hydrogen, carbon, oxygen, nitrogen, sodium, calcium, phosphorous, and chlorine—in the human body (Kehayias et al., 1991; Mattsson and Thomas, 2006).

##### 1.3.1.1 Total Body Nitrogen

Nitrogen is one of the main body components, required for protein synthesis and production of several nitrogenous compounds such as hormones, neurotransmitters, and components of antioxidant defense. The measurement of TBN, using in vivo NAA, allows one to assess body protein content, while it is assumed that all body nitrogen is incorporated into proteins. There is a close relationship between TBN and body proteins: every 6.25 g of protein contains 1 g of nitrogen. Proteins are mainly located in FFM, hence the evaluation of TBN is an indirect measure of FFM, and especially SM mass.

In healthy individuals (age range: from 24 to 72 years) TBN increases with BM and decreases with age, and it can be calculated with the following formula (Eq. (1.27)) developed on the basis of in vivo NAA measurements (Ryde et al., 1993):

$$\begin{aligned} \text{TBN (kg)} = & 1.42 \text{ kg} + 0.0109 \times \text{BM (kg)} - (\text{A (years)} \\ & \times 0.008 \text{ kg year}^{-1}) - (\text{gender} \times 0.46 \text{ kg}) \end{aligned} \quad (1.27)$$

(gender: male = 0, female = 1).

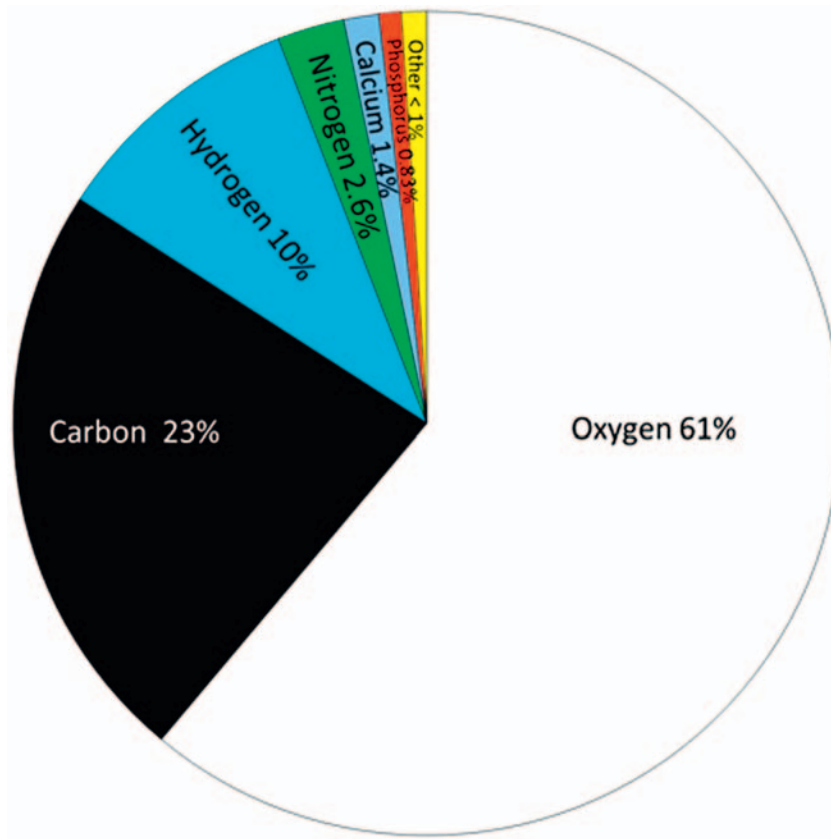
It was postulated that the amount of nitrogen in FFM is biologically constant and the TBN/FFM relation can be formulated as follows (Eq. (1.28), Ryde et al., 1993):

$$\text{TBN (kg)} = 0.031 \times \text{FFM (kg)} - 0.0009 \text{ kg} \quad (1.28)$$

##### 1.3.1.2 Total Body Potassium

The measure of the total amount of potassium in the body [total body potassium (TBK)] is based on the activity of the natural  $^{40}\text{K}$  isotope (with 1.46 MeV gamma radiation) as the isotope constitutes 0.0118% of potassium ion. TBK amounts to about 47 and 36 mmol·kg<sup>-1</sup> in men and women, respectively. TBK increases with BM and body height ( $H$ ), and decreases with age ( $A$ ). According to the formula Eq. (1.29), (Wang et al., 1992), TBK might be estimated as follows:





**FIGURE 1.1** Body composition at atomic level in the reference man. Based on the data from Snyder, W.S., et al., 1984. Report of the task group on Reference Man. Oxford, Pergamon Press; Wang, Z.M., et al., 1992. *Am. J. Clin. Nutr.* 56, 19–28.

The originally used form:

$$\text{TBK (mmol)} = 77.8 + 27.3 \times \text{BM (kg)} + 11.5 \times \text{H (cm)} - 21.9 \times \text{A (years)} \quad (1.29)$$

or

$$\text{TBK (mmol)} = 77.8 + 27.3 \times \text{BM (kg)} + 1150 \times \text{H (m)} - 21.9 \times \text{A (years)} \quad (\text{in SI units})$$

TBK can be used to assess the body cell mass (BCM), as noticed by Francis D. Moore (1913–2001) in the mid-20th century (see Section 1.5.3).

### 1.3.1.3 Total Body Calcium

The total body calcium (TBCa) content can be measured in vivo by the delayed  $\gamma$ -NAA and amounts to about 1100 g in men and 800 g in women (Reid, 1986).

Based on the TBCa and TBK, it is possible to calculate the total body phosphorus (TBPh, Eq. (1.30)), (Wang et al., 1992):

$$\text{TBPh (kg)} = 0.456 \times \text{TBCa (kg)} + 0.022 \times \text{TBK (mol)} \quad (1.30)$$

Since calcium constitutes a relatively constant fraction of bone minerals (38%–39%), its content can also be

used to evaluate total body bone mineral content (see Eq. (1.58)).

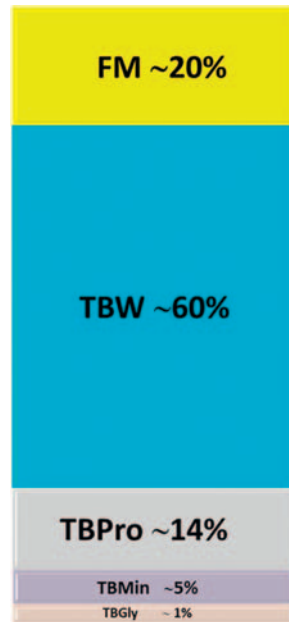
## 1.3.2 Body Composition at the Molecular level

Measurements at the level of chemical molecules concern water, fat, protein, salts and glycogen (Fig. 1.2).

### 1.3.2.1 Total Body Water

At the chemical level, the two largest compartments of the system are water (approximately 60% of BM) and anhydrous fat (20%–30% of BM). Mean values of TBW have been reported to range from 38 to 50 L in men (~60% of BM), whereas in women, it is between 26 and 40 L (~50% of BM), (Chumlea et al., 2001). Women and elderly individuals have less body water, due to greater adiposity and lower muscle mass. TBW decreases with age. For instance, in individuals around 60 years of age, it comprises 55% of BM in case of males, and 45% in females.

The TBW, determined on the basis of the dilution principle by means of labeled water isotopes (e.g.,  $^2\text{H}_2\text{O}$ ,  $^3\text{H}_2\text{O}$ ,  $\text{H}_2^{18}\text{O}$ ), was used as the starting point to derive equations that predict TBW from anthropometric measurements (Watson et al., 1980; Chumlea et al., 2001).



**FIGURE 1.2** Body composition at the molecular (chemical) level in the 70 kg reference man (expressed as percentage of body mass, % BM). FM, fat mass; TBW, total body water; TBPro, total body proteins; TBMin, total body mineral; and TBGly, total body glycogen. *Based on the data from Snyder, W.S., et al., 1984. Report of the task group on Reference Man Oxford, Pergamon Press.*

Watson et al. (1980) formulated the following equations to calculate TBW (Eqs. (1.31) and 1.32):  
for men ( $n = 458$ ):

$$\text{TBW (L)} = 2.447 - 0.09516 \times A \text{ (years)} + 0.1074 \times H \text{ (cm)} + 0.3362 \times \text{BM (kg)}$$

(the originally used form)

(1.31)

or

$$\text{TBW (L)} = 2.447 - 0.09516 \times A \text{ (years)} + 10.74 \times H \text{ (m)} + 0.3362 \times \text{BM (kg)}$$

(in SI units)

for women ( $n = 265$ ):

$$\text{TBW (L)} = 0.1069 \times H \text{ (cm)} + 0.2466 \times \text{BM (kg)} - 2.097$$

(the originally used form)

(1.32)

or

$$\text{TBW (L)} = 10.69 \times H \text{ (m)} + 0.2466 \times \text{BM (kg)} - 2.097$$

(in SI units)

Chumlea et al. (2001) presented the following race- and gender-specific formulas (Eqs. (1.33)–(1.36)) based on a larger group of adult subjects (age between 18 and 90):  
for white men ( $n = 604$ ):

$$\text{TBW (L)} = 23.04 - 0.03 \times A \text{ (years)} + 0.50 \times \text{BM (kg)} - 0.62 \times \text{BMI}$$

(1.33)

for black men ( $n = 128$ ):

$$\text{TBW (L)} = -18.37 - 0.09 \times A \text{ (years)} + 0.34 \times \text{BM (kg)} + 0.25 \times H \text{ (cm)}$$

(the originally used form) (1.34)

or

$$\text{TBW (L)} = -18.37 - 0.09 \times A \text{ (years)} + 0.34 \times \text{BM (kg)} + 25 \times H \text{ (m)}$$

(in SI units)

for white women ( $n = 772$ ):

$$\text{TBW (L)} = -10.50 - 0.01 \times A \text{ (years)} + 0.20 \times \text{BM (kg)} + 0.18 \times H \text{ (cm)}$$

(the originally used form)

or

$$\text{TBW (L)} = -10.50 - 0.01 \times A \text{ (years)} + 0.20 \times \text{BM (kg)} + 18 \times H \text{ (m)}$$

(in SI units) (1.35)

for black women ( $n = 191$ ):

$$\text{TBW (L)} = -16.71 - 0.01 \times A \text{ (years)} + 0.22 \times \text{BM (kg)} + 0.24 \times H \text{ (cm)}$$

(the originally used form) (1.36)

or

$$\text{TBW (L)} = -16.71 - 0.01 \times A \text{ (years)} + 0.22 \\ \times \text{BM (kg)} + 24 \times H \text{ (m)} \text{ (in SI units)}$$

Total body water (TBW) consists of intracellular (ICW) and extracellular water (ECW). Since almost all body potassium is located in the ICW and ECW compartments, assuming stable intra- and extracellular  $K^+$  concentration of 152 and 4  $\text{mmol} \cdot \text{kg}^{-1} \text{H}_2\text{O}$ , respectively, the ICW and ECW can be calculated (Eqs. (1.37) and (1.38)) if TBK (determined by the whole-body counting) and TBW (determined with the dilution method) are known (Wang et al., 2003; Silva et al., 2007):

$$\text{ICW (kg)} = \frac{\text{TBK (mmol)} - 4 \times \text{TBW (kg)}}{148} \quad (1.37)$$

and

$$\text{ECW (kg)} = \frac{152 \times \text{TBW (kg)} - \text{TBK (mmol)}}{148} \quad (1.38)$$

It is worth highlighting that FFM hydration is strikingly stable in mammals; as noted already in 1945 by Pace and Rathbun (see in Wang et al., 1999). In a mature organism, hydration rests within the range between 70% and 75%, as confirmed by the formula for calculating the TBW in an adult human (Eq. (1.39), Ryde et al., 1993):

$$\text{TBW (kg)} = 0.733 \times \text{FFM (kg)} - 0.44 \text{ kg} \quad (1.39)$$

### 1.3.2.2 Total Body Fat

There are no direct methods of *in vivo* evaluation of body fat. Fat can be determined by measuring the effect fat has on physical properties of the body, such as BD (measured by UWW, see Section 1.2.5) and body impedance (Kehayias et al., 1991). Rough evaluation of body fatness in clinical practice can be performed through easily-accessible simple measures, namely BM, BMI, abdominal circumference, skinfold thickness measurements. The bioimpedance method—a low-cost and frequently used approach to body composition measurements—differentiates between FM, considered to be a non-conductor of electric charge, and FFM, considered to be a conducting volume that helps the passage of electric current, due to conductivity of electrolytes dissolved in body water (Lemos and Gallagher, 2017). Although bioimpedance is a simple, noninvasive approach to body composition measurements, it is not a reference method, as it relies on specific assumptions, the most important of which is constant body hydration (Lemos and Gallagher, 2017). Nowadays, methods acquiring higher precision—such as MRI, CT, DEXA—are implemented to determine body fat and muscle mass (Hellmanns et al., 2015).

Body fat is one of the most changeable elements of body composition. It can account for 7%–10% of BM in

well-trained endurance athletes and in some extremely well-trained marathon runners can account for less than 5% of BM (Costill, 1986; Noakes, 2003). On the other hand in case of pathological obesity, body fat can constitute up to 50% of BM (Alemán et al., 2017).

### 1.3.2.3 Total Body Protein

Total body protein (TBPro) accounts for about 14%–16% of BM, that is, ~11 kg in men and 9 kg in women. TBPro is comprised in BCM (~77%), but also in extracellular solids and ECF (~23%).

As mentioned above, TBPro can be calculated on the basis of the TBN (determined by the NAA), on the assumption that every 6.25 g of protein contains 1 g of nitrogen (i.e., the nitrogen-to-protein ratio amounts to 0.16).

TBPro can also be estimated on the basis of the value of TBK, measured by the whole-body counting ( $^{40}\text{K}$ ) method, and of the content of bone minerals assessed using the whole-body DEXA method (Eq. (1.40), Wang et al., 2003):

$$\text{TBPro (kg)} = 0.00252 \times \text{TBK (mmol)} \\ + 0.732 \times \text{bone mineral (kg)} \quad (1.40)$$

### 1.3.2.4 Total Body Mineral

Total body mineral (TBMin) (~4.5% of BM) consists of bone minerals (BoM, ~4% of BM) and soft-tissue minerals (STM, ~0.5% of BM). According to Beddoe et al. (1984) TBMin can be estimated as 6.22% of FFM (Eq. (1.41)):

$$\text{TBMin (kg)} = \frac{0.0622 \times \text{TBW}}{0.732} \quad (1.41)$$

STM (~0.5 vs 0.38 kg, respectively, for men and women) is a small molecular component which consists of soluble minerals and electrolytes (6 main:  $K^+$ ,  $Na^+$ ,  $Mg^{2+}$ ,  $Cl^-$ ,  $H_2PO_4^-$ ,  $HCO_3^-$ ) and is found in the extracellular and intracellular compartment of soft tissue (Wang et al., 2002). The whole-body STM can be measured *in vivo* by delayed- $\gamma$  NAA and is estimated roughly to reach 400 mg, that is, 0.5% of BM (St-Onge et al., 2004). Its contribution to BD is very important, because of its high density reaching  $3.317 \text{ g} \cdot \text{cm}^{-3}$ , which is higher than that of bone mineral ( $2.982 \text{ g} \cdot \text{cm}^{-3}$ ) (Heymsfield et al., 1991). The ratios of STM to extracellular water and to intracellular water are relatively stable in young adults and whole-body STM can be calculated from TBW mass (Eq. (1.42), Wang et al., 2008):

$$\text{STM (kg)} = 0.0129 \times \text{TBW (kg)} \quad (1.42)$$