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Application of standards and models in body composition analysis

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The aim of this review is to extend present concepts of body composition and to integrate it into physiology. *In vivo* body composition analysis (BCA) has a sound theoretical and methodological basis. Present methods used for BCA are reliable and valid. Individual data on body components, organs and tissues are included into different models, e.g. a 2-, 3-, 4- or multi-component model. Today the so-called 4-compartment model as well as whole body MRI (or computed tomography) scans are considered as gold standards of BCA. In practice the use of the appropriate method depends on the question of interest and the accuracy needed to address it. Body composition data are descriptive and used for normative analyses (e.g. generating normal values, centiles and cut offs). Advanced models of BCA go beyond description and normative approaches. The concept of functional body composition (FBC) takes into account the relationships between individual body components, organs and tissues and related metabolic and physical functions. FBC can be further extended to the model of healthy body composition (HBC) based on horizontal (i.e. structural) and vertical (e.g. metabolism and its neuroendocrine control) relationships between individual components as well as between component and body functions using mathematical modelling with a hierarchical multi-level multi-scale approach at the software level. HBC integrates into whole body systems of cardiovascular, respiratory, hepatic and renal functions. To conclude BCA is a prerequisite for detailed phenotyping of individuals providing a sound basis for in depth biomedical research and clinical decision making.

4-Compartment model: MRI: Fat mass: Fat free mass

In vivo body composition analysis (BCA) is within the centre of integrative physiology on understanding the body responses to internal and external factors at different biological levels. BCA applies concepts of cellular/molecular physiology, biochemistry and experimental approaches to understand the function at the level of whole body or its individual organs and tissues. Within clinical nutrition BCA is used to identify obese patients and malnutrition, to characterize weight gain and weight loss and to diagnose sarcopenia (i.e. a reduced quantity of skeletal muscle) and cachexia (i.e. involuntary weight loss and underweight). BCA is part of cardio-metabolic risk assessment and adds to characterize hyper- and dehydration, development and growth, ageing as well as physical performance. In contrast to BCA crude estimates of the nutritional status such as BMI and waist circumference inadequately characterize nutritional status, health risks and morbidity[1–6]. Thus, BMI and waist circumference cannot provide a sound basis for nutritional assessment, understanding physiology of metabolism, clinical decision making, personalized medical nutrition, prediction of prognosis in patients and for in depth biomedical research.

Abbreviations: ADP, air displacement plethysmography; BCA, body composition analysis; CT, computed tomography; DXA, dual X-ray-absorptiometry; FBC, functional body composition; FFM, fat free mass; FM, fat mass; HBC, healthy body composition; LST, lean soft tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

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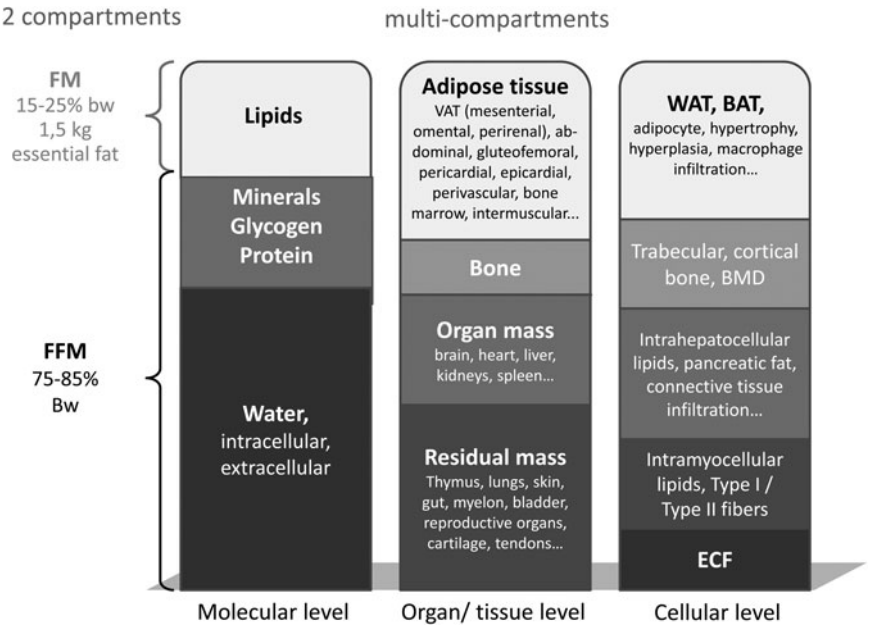

Fig. 1. Compartment models of body composition at different levels. Bw, body weight; BAT, brown adipose tissue; BMD, bone mineral density; ECF, extracellular fluid; FM, fat mass; FFM, fat free mass; VAT, visceral adipose tissue; WAT, white adipose tissue.

Basic models

Body composition is about models and methods[7]. About 70 years ago, the science of BCA started with the classical 'two component model', i.e. dividing the body into two major compartments, fat free mass (FFM; includes cellular water within adipocytes) or lean soft tissue (LST; the sum of all lean compartments, organs and tissues, also includes non-fat lipids; also called lean body mass) and fat mass (FM; Fig. 1). FFM includes total body water, bone minerals and protein. FM refers to chemical fat i.e. energy stores with TAG accounting for about 80 % of adipose tissue. Present models of body composition refer to 'five different levels', that is, 'atomic' (including the eleven major elements, H, O, N, C, Na, K, Cl, P, Ca, Mg, S), 'molecular' (including six components, lipid, water, protein, carbohydrates, bone minerals, soft tissue minerals), 'cellular' (that is, three or four components, cell mass, extracellular fluids, extracellular solids, where cell mass can be divided into fat and actively metabolizing body cell mass), the 'tissue-organ levels' (i.e. major tissues, adipose tissue, skeletal muscle, visceral organs, bone with further organ-level components such as brain, liver, kidneys, heart, spleen) and finally, the 'whole body level' (i.e. dividing the body into body regions, that is, brain, trunk, upper and lower limbs). All these are so-called multicomponent models (Fig. 1).

Methods and gold standards

In its early days BCA was based on anthropometrics, i.e. assessment of skinfold thickness (as an estimate of subcutaneous FM) and/or midarm or thigh circumferences (as measures of skeletal muscle mass). This approach was extended to the assessment of individual body components by reliable and valid measurements of body density by underwater weighing, to assess FM and FFM. More advanced methods include dilution techniques (D_2O to assess total body water; NaBr to measure extracellular water), dual X-ray-absorptiometry (DXA; for measuring bone mineral content, LST and FM). Air displacement plethysmography (ADP) has now replaced underwater weighing to measure body volume and, thus, density is calculated from the ratio of body mass and body volume. The assessment of major body elements (e.g. total body K, N, Ca, etc.) by whole body counting i.e. a total body K counter or neutron activation analysis is still considered as reference but of very limited use because of specialised equipment, requirements of high technical skills, high costs and a worldwide very limited availability. The results of the different measurements add up to different body components and finally to body weight.

All component models rely on certain assumptions, which are considered as stable or fixed (e.g. 73·2 % water content of FFM or a body temperature of 36 or 37°C). In addition it is assumed that an individual body component is homogenous in composition. However these assumptions do not hold true in daily practice, e.g. tissue hydration differs between newborn, children and the elderly and also between obese and normal weight patients. In addition FFM hydration changes with weight loss and throughout the course of a clinical condition, e.g. with inflammation. These alterations affect the accuracy of individual methods. For example using DXA hydration changes may affect attenuation of LST and thus result in

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Table 1. Body composition methods, outcomes and precision

	Methods	Outcomes	MDC	Precision
Gold standards	Whole body MRI/CT	AT, SAT, VAT, BAT?, MM, OM (brain, heart, liver, kidneys), ectopic fat in liver, skeletal muscle, pancreas	0·2	1·1
	4C Model	FM, FFM, hydration of FFM	1	
	DXA	Lean body mass, FM, bone mass and bone mineral density (whole body, regional)	1	2
Individual methods	Dilution methods (D_2O, NaBr)	Total body water, extra- + intra-cellular water, tissue hydration	2	1–2 (for TBW)
	Densitometry (ADP, underwater weighing)	Body volume and density	2	2–3
	QMR	FM, lean tissue, free + total water	0·2	0·7
	BIA	Resistance, reactance, phase angle, BIVA	1	1
Field methods	Skinfolds	SAT	2	>5
	Ultrasound	SAT, MM thickness, OM, liver fat	?	?

MDC, minimal detectable change (fat mass, kg); Precision (fat mass, %); CT, computed tomography; DXA, dual X-ray absorptiometry; ADP, air displacement plethysmography; QMR, quantitative magnetic resonance; BIA, bioelectrical impedance analysis; TBW, total body water; AT, adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; BAT, brown adipose tissue; MM, muscle mass; OM, organ mass; FM, fat mass; FFM, fat free mass; ?, not reported.

its overestimation. To minimise the shortcomings of individual methods, different methods are combined, e.g. DXA + ADP + D_2O-dilution resulting in a so-called '4-compartment- or 4C-model'[8]. This is now considered as a gold standard or criterion method with minimal assumptions. Using a 4C-model, FM (kg) can be calculated from

$$2{\cdot}747 \times \text{Volume} - 0{\cdot}71 \times \text{Total body water} + 1{\cdot}46 \times \text{Minerals} - 2{\cdot}05 \times \text{Weight}$$

(where volume is assessed by ADP, total body water by D_2O and minerals by DXA).

At the organ and tissue level body composition can be assessed by imaging technologies. Whole body MRI (based on the interaction of hydrogen nuclei, protons and the magnetic field of a field strength of 1·5 or 3·0 Tesla) or computed tomography (CT; based on ionizing radiation and X-ray attenuation) are used for accurate assessment of whole body and regional organ (i.e. skeletal muscle, brain and visceral organs) and tissue masses (i.e. regional, subcutaneous adipose tissue and visceral adipose tissue (VAT))[9,10]. Whole body CT and MRI allow reconstruction of the volumes of organs and tissues (e.g. brain, heart, liver, VAT, subcutaneous adipose tissue and skeletal muscle (SM)). Transversal images are taken at different distances (e.g. a slice thickness of 7–11 mm for abdominal organs). Cross-sectional areas are segmented. Calculation of organ volumes is based on the sum of cross-sectional areas multiplied by slice thickness and the distance between scans. The precision of MRI volume measurements is about 2 % with inter-observer differences of up to 6 %. The validity of radiographic volume measurements compared with masses determined from post mortem cadaver analyses was within the range of ±5 %. Organ/tissue volumes times organ/tissue densities then give organ/tissue masses.

When compared with MRI CT measurements can also be used to characterize muscle tissue quality[11]. The attenuation of X-rays relative to water and air depends on the molecular composition of lipids and protein in organs and tissues. Thus, intra- and extramyocellular lipid content can be separated from lean SM. In addition to MRI magnetic resonance spectroscopy measures ectopic fats (e.g. fat in liver, muscle and pancreas). More recently (non-imaging) quantitative magnetic resonance has been introduced to assess FM (and total body water) with high precision[12,13]. Contrary to MRI quantitative magnetic resonance requires only a low magnetic field (67 Gauss = 0·0067 Tesla) that can be obtained without complex equipment that entails high maintenance costs. The output of quantitative magnetic resonance is a result on FM, lean mass (without solid components that are mainly located in bone;[14]) as well as total and 'free' body water.

Presently, multicomponent models (i.e. the 4C-model) as well as whole body MRI have reached the highest level of BCA and are considered as gold standards or criterion methods (Table 1).

Applications

The use of appropriate models and methods in BCA depends on the question of interest as well as the accuracy needed to address that question. As far as energy balance is concerned, FM and FFM or lean body mass LST are suitable outcomes as assessed by either ADP, underwater weighing or DXA. During controlled over- and under-feeding quantitative magnetic resonance allows an accurate assessment of changes in energy stores[12]. Quantifying VAT and liver fat relate to metabolic risk assessment, which is based on the use of MRI, CT and magnetic resonance spectroscopy. The clinical phenotypes of sarcopenia (i.e. sarcopenia occurs at under-, normal, overweight and obese subjects and may also be associated with osteopenia) are characterized by reduced SM with or without increases in VAT and/or subcutaneous adipose tissue as can be assessed by whole body MRI or CT[15,16]. In both sexes, a single MRI scan at the level of L3 is the best compromise site to assess total tissue volumes of SM, VAT and subcutaneous adipose tissue[17]. Alternatively, DXA can be used to assess lumbar or appendicular LST (i.e. LST of the lumbar region

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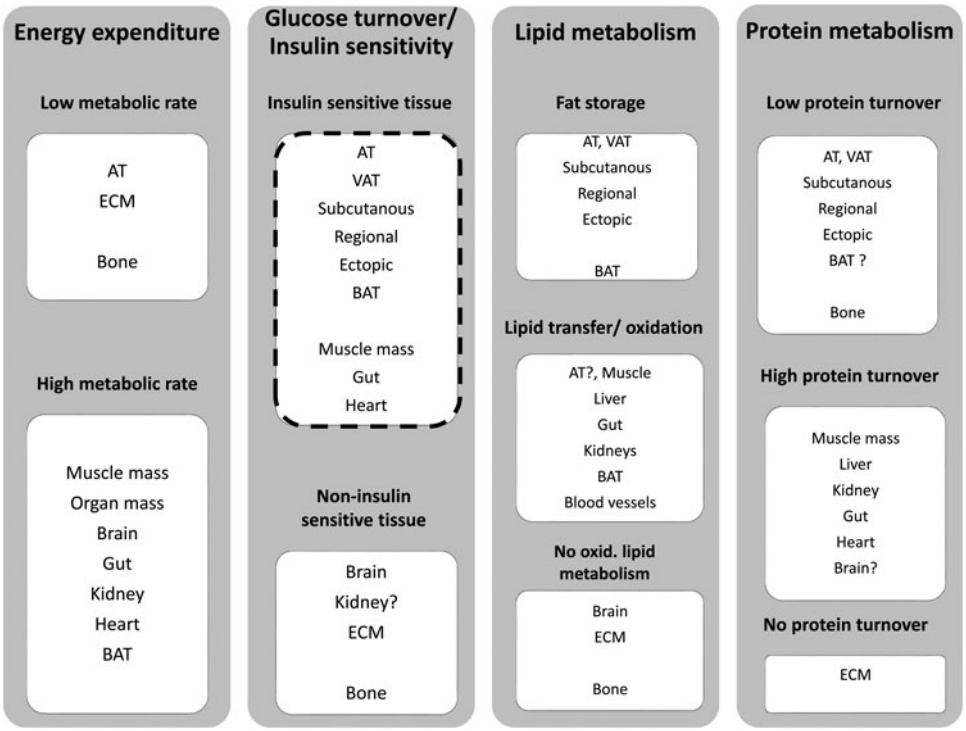

Fig. 2. Functional body composition (FBC). Proposed framework of FBC. Individual body components are grouped according to different body functions that is, energy expenditure, glucose turnover/insulin sensitivity, lipid and protein metabolism. AT, adipose tissue; BAT, brown adipose tissue; BCM, body cell mass; ECM, extracellular mass; Gut, gastrointestinal tract; TBW, total body water; VAT, visceral adipose tissue.

or extremities)[18]. As far as malnutrition is concerned FFM (or LST) is measured by either DXA, ADP, D_2O-dilution or bioelectrical impedance analysis. In malnourished patients, a low phase angle as assessed by bioelectrical impedance analysis is an estimate of poor prognosis[19–22]. In osteopenia and osteoporosis bone mineral density and trabecular structure are measured by either DXA or CT. Overhydration in cardiac failure and chronic kidney disease or dehydration in the elderly are characterized by dilution techniques and bioelectrical impedance analysis. Precision and accuracy of the different techniques are given in Table 1[23].

A functional approach to body composition

BCA has a sound theoretical and methodological basis, but the results are merely descriptive. Normative approaches give rise to reference values, age- and sex-specific centiles and cut offs to define overweight, cachexia and sarcopenia[15,16]. However, these cut offs do not take into account organ and tissue functions and, thus, the different metabolic, physical and inflammatory properties of individual body components. As different body functions and metabolic processes are differently related to individual body components, organs and tissues as well as the relationships between them, functional body composition (FBC) extends the view of traditional BCA (Fig. 2; [24,25]). FBC crosses as well as combines different methods and body composition models. For example in a traditional 2-compartment model FM includes brown adipose tissue. By contrast using FBC for energy expenditure brown adipose tissue belongs to the group of high metabolic rate organs and thus is a functional part of FFM. Suitable applications of FBC are (i) interpretation of body functions (e.g. energy expenditure or insulin sensitivity) and their disturbances in the context of body components and *vice versa* and (ii) interpretation of the meaning of individual body components in the context of their functional consequences (e.g. energy expenditure)[3].

Healthy body composition: horizontal and vertical approaches

FBC provides a conceptual framework to enter the next era of body composition research. In depth phenotyping needs detailed BCA in the context of metabolism, endocrine determinants and health risks. Future concepts of healthy body composition (HBC) will focus on relationships between individual body components and between organ and tissue masses (rather than on their isolated masses) in the context of age-and sex- specific metabolic or functional traits (e.g. energy expenditure, insulin sensitivity, muscle strength, physical performance) and health risks. This idea is supported by the findings that (i) changes in weight (during either weight loss or weight

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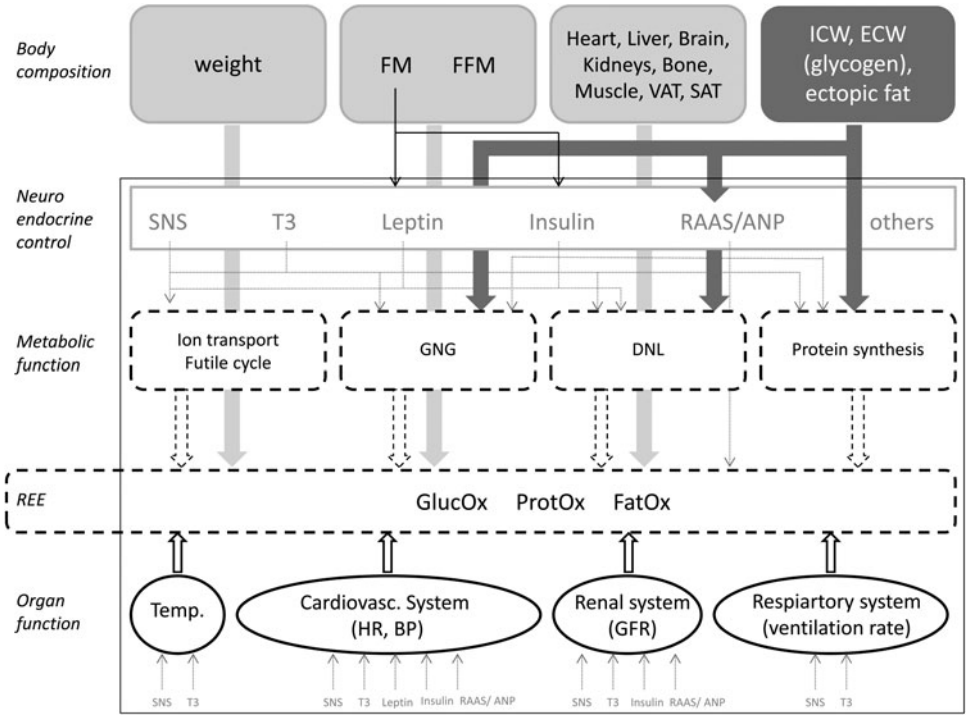

Fig. 3. Proposed model of metabolism (REE, resting energy expenditure; GluOx, ProtOX and FatOx: substrate oxidation rates) based on its structural and functional determinants (FFM, fat free mass; FM, fat mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SNS, sympathetic nervous system activity; T3, 3,5,3′ triiodothyronine; RAAS, rennin angiotensin aldosterone system; ANP, atrial natriuretic peptide; GNG, gluconeogenesis; DNL, *de novo* lipogenesis; GlucOx; glucose oxidation; ProtOX, protein oxidation; FatOx, lipid oxidation; HR, heart rate; BP, blood pressure; GFR, glomerular filtration rate; Temp, body temperature) defining healthy body composition (HBC) by hierarchical multi-level-multi-scale analysis.

gain) are associated by concomitant changes in body composition, which are not independent of each other (e.g. FM and FFM both decrease with weight loss[26–28], while muscle mass decreases whereas FM increases in the case of age-related sarcopenia[15,16]) (ii) body weight control hinges on the relationship between organs and tissues[24,25].

Applications of an HBC-model relate to (i) generate normal values of HBC based on multi-regression analysis taking into account body component-body function-relationships and (ii) mathematical modelling to address complex metabolic processes and pharmacokinetics using a multi-level/multi-scale approach at the software level (Fig. 3). A multi-level/multi-scale approach integrates and combines data horizontally (i.e. between compartments, organs and tissues and at the cellular level) and vertically (from masses to functions taking into account neuroendocrine control, metabolism and different organ systems). Different scales are added, e.g. age (time), BMI (kg/m^2) and/or sex (male, female). Using that hierarchical model, body composition can be seen at a horizontal (i.e. a structural) level as well as vertically (i.e. a functional level; Fig. 3). Structures include the whole body, two chemical compartments (i.e. FFM + FM), organ and tissues (e.g. individual organ masses and fat distribution) and the cellular level (e.g. tissue hydration). The vertical approach refers to metabolism (e.g. resting energy expenditure) and physical functioning as well as their determinants (e.g. hormones, cytokines, inflammation). The multi-level/multi-scale approach further integrates metabolic function into organ and tissue systems (e.g. cardiovascular system, liver and renal function and respiration).

Finally, HBC can be defined individually taking horizontal and vertical perspectives related to different outcomes (i.e. energy expenditure, insulin sensitivity, physical performance). The HBC-approach (Fig. 3) gives insights into the inner dependencies between the quantities of components, organs and tissues and their relationships to individual body functions which then give rise to new and dynamic normal values, i.e. defining body composition as a prerequisite for health. HBC can also be used (i) to model and predict the magnitude and rate of weight change for a given change in energy intake, physical and disease activity, (ii) to understand the regulation of energy expenditure as part of energy balance and (iii) to assess if a certain medication impacts resting energy expenditure and energy balance.

Given the differences in body composition throughout a person's life span, changes in body components as well as body component units that relate to specific body functions can be identified. This may serve as a basis of prevention and treatment of specific age- and performance-related conditions. Examples of functional

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body component units are (i) age- and sex-specific ranges of the SM mass–VAT–inflammation (C-reactive protein)-unit for characterization of a sarcopenic phenotype, (ii) bone mineral content–SM mass–muscle strength relationship in an extended characterization of frailty and osteoporosis, (iii) the liver fat–VAT–muscle mass-unit to characterize positive energy balance and insulin resistance and (iv) the muscle mass–organ mass–FM–T3-unit to explain variances in energy expenditure and metabolism. The HBC-concept gives rise to the next area of body composition research and application.

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Conflict of interest

M. J. M. and A. B. W. serve as consultants of seca GmbH & Co. KG, Hamburg.

Authorship

M. J. M. and A. B. W. had the ideas, developed the concepts and wrote the manuscript, W. B., M. P. and C. G. provided data, did data analyses and provided tables and figures. All authors have read and discussed the manuscript.

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