

# 'Functional' body composition: differentiating between benign and non-benign obesity

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## Abstract

Recent body composition analyses, together with assessments of insulin resistance, aerobic fitness, and intima-media thickness of the common carotid artery, have shown that metabolically-benign obese subjects have a similar BMI, waist circumference, and subcutaneous abdominal fat compared with non-metabolically-benign obese subjects. Research has suggested that 25-30% of the obese population do not need either treatment or prevention of secondary disorders. Therefore, assessment of functional body composition should replace nutritional status-based risk assessments (such as the body mass index) in both metabolic research and clinical decision making. The concept of 'functional' body composition gives us a more sophisticated view on nutritional status, metabolism, endocrinology, and diseases. Knowledge of detailed body composition enables characterization of biomedical traits which will give functional evidence relating genetic variants.

## Introduction and context

The current practices to assess nutritional status include the calculation of body mass index (BMI) by dividing weight (kg) by the square of the height (m). Normative data are most frequently used to identify over- and underweight subjects. In the overweight, waist circumference is measured for additional assessment of health risks. Recent methodological and technological advances [for example, using magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DXA) technologies] have enabled accurate and detailed body composition analysis (BCA) and assisted in the development of advances in body composition, endocrine, and metabolic research. BCA is now standard in investigations on energy and macronutrient metabolism. The introduction of valid field methods such as bioelectrical impedance analysis (BIA) has led to broader applications of BCA within epidemiological and clinical studies. The present commentary aims to discuss the utility of body composition data in the assessment of metabolic, endocrine, and physical function. This article will have

a major focus on the regulation of energy expenditure and energy balance.

Assessment of body components and modeling of body composition at molecular, cellular, and tissue levels results in the identification of different characteristics of the body [for example, tissue hydration, electrical resistance, mineral content, kilograms of fat, and fat-free mass (FFM)] [1]. Within epidemiology, these data can be used to generate population-specific reference values and suitable cut-offs (for example, by using percentiles to characterize over- and underweight subjects) [2,3]. BCA data (such as body fat distribution) may also be included in scores used for assessment of cardiometabolic risk [4,5]. Characterising individual body components also helps to identify specific types of malnutrition via the assessment of body fat and muscle mass (for example, identification of sarcopenia with reduced skeletal muscle mass at normal or increased fat mass in patients with rheumatoid arthritis [6]). BCA data are also associated with clinical prognosis, for

example, a low phase angle as assessed by BIA was shown to predict survival in severely ill patients [7]. Assessment of body components and how they change with regard to nutrition, development, inflammation, and/or wasting disease is mandatory for understanding metabolism, for example, how it changes in response to starvation [8], health (for example, muscle mass is one determinant of bone health [9]), and clinical outcome (in the case of wasting diseases [7]).

## Major recent advances

### **Impact of fat mass on energy balance**

FFM is the major determinant of energy expenditure and can account for about 60-80% of the variance in energy expenditure [10]. Recent work also shows that the higher the amount of FFM, the higher the resting energy expenditure (REE). FFM is heterogeneous and the proportion of muscle and organ mass contributes to the variance in REE [11]. On the other side of the energy balance equation, there is a close and exponential association between fat mass (FM) and plasma leptin concentrations, which are considered to be a major signal in regulating appetite and thus energy intake [12]. Higher FM tends to correlate with higher plasma leptin levels. Reducing FM increases energy intake by lowering leptin secretion rates, whereas decreasing FFM lowers REE. The reverse of the previous sentence is also true; increases in FM are associated with high plasma leptin levels and increases in FFM with high REE.

### **Evidence that fat mass affects energy metabolism**

Overweight and obese subjects have a higher REE than their lean controls, mainly explained by their higher FFM. However, REE differences between lean and obese subjects remained after adjustments for FFM and age [13]. In addition, most of the between-group differences in REE disappeared after further adjustment for FM. Based on multiple regression analyses, energy expenditure of FFM was found to be three to seven times greater than energy expenditure of FM [14]. A recent study used regression analyses to show that the relative contribution of FM on the variance in REE increased from low to normal with increasing grades of adiposity (that is, up to a FM of 40% body weight) but sharply decreased at very high (>40% FM) and extreme (>50% FM) grades of obesity [15]. The latter finding might suggest a threshold effect of FM that cannot be explained on the basis of present knowledge, however, it may suggest that the metabolic rate of FM is reduced in very obese subjects, that is, FM itself has a 'thermic effect' on metabolic rate that varies with its mass.

### **Explaining how fat mass regulates REE**

Fat cells normally have a low metabolic rate (19 kJ or about 5 kcal/kg × d [14,16]), but another recent study suggests that the mass-dependent effect of FM may be explained, not by fat cell metabolism itself, but by the secretory activity of fat cells (for example, secretion of adipocytokines and/or hormones). It can also be explained by metabolic, inflammatory, and haemodynamic disturbances associated with being overweight [16]. A high FM and abdominal obesity are frequently associated with metabolic disturbances (such as insulin resistance and increased sympathetic nervous system activity) and co-morbidity (for example, different traits of the metabolic syndrome), which add to the variance in REE. Also, insulin resistance and elevated blood pressure are associated with higher REE, even after adjustments for FFM, FM, and age [17].

Data on patients with partial lipodystrophy syndromes (characterized by a loss of subcutaneous fat, low plasma levels of adipocytokines, and a greater percentage of trunk fat, as well as the presence of ectopic fat in non-adipose tissue such as skeletal muscle and the liver) provide further information on the role of FM in regulating REE. In patients with congenital lipodystrophies, REE is 20-70% higher than normal levels [18]. REE per kg of FFM was also higher in patients with HIV lipodystrophy compared with HIV-infected patients without lipodystrophy [19]. A recent study proposes that this increase in REE is a compensatory mechanism to dissipate calories which cannot be stored normally [19]. These data suggest that REE can be affected in different and indirect ways depending on the location of the fat depots (that is, subcutaneous, visceral, or ectopic fat), and the storage capacity of the adipocytes.

A recent study showed that, in adults, the number of fat cells stays constant and about 10% of fat cells are renewed annually [20]. The mean size of adipocytes increases with FM up to a point and then decreases. Adipocyte cellularity and triglyceride accumulation within lipid droplets is associated with morbidity. However, the association between adipocyte size and FM differs with region. Enlarged abdominal adipocytes are associated with visceral and subcutaneous abdominal fat, whereas femoral adipocyte size is related to percentage body fat, and gluteal adipocyte size is related to visceral fat [21]. Enlarged subcutaneous fat cells are associated with insulin resistance, independent of FM [22]. Therefore, large fat cells may also result in a relatively higher REE. There is now evidence from experimental data that lipid droplet structure (large unilocular versus smaller multilocular droplets) is associated with mitochondrial oxidative metabolism,

and that smaller droplets increase the rate of lipolysis and energy expenditure [23]. Thus, the effect of FM on REE varies with fat depots, fat cell size, and lipid droplet structure.

#### **Is there a feedback between fat mass and energy metabolism?**

The feedback mechanism of FM on energy metabolism is not known, but leptin has been considered as a candidate for such a signal from fat [24]. Animal data have suggested a 'thermic' effect of leptin, and leptin has been shown to directly stimulate thermogenesis in mouse skeletal muscle [25]. It has been proposed that leptin may uncouple proteins [26] and increase substrate cycling between *de novo* lipogenesis and mitochondrial lipid oxidation [25], and recent work suggests that this is diminishing phosphatidylinositol-3 kinase and AMP-activated protein kinase signaling [27]. When compared with animal data, a 'thermic' effect of leptin is equivocal in humans. Recent observational studies do not suggest that leptin has a 'thermic' effect in normal weight or obese subjects [28]. Using leptin to treat a child that had congenital leptin deficiency [29] and obese patients that had increased plasma leptin concentrations [30] resulted in substantial weight loss but did not affect REE, and REE adjusted for FFM was reduced rather than increased. In obese subjects, leptin administration does not seem to accelerate weight loss as a supplement to diet intervention unless it is given in supraphysiological doses [31]. A recent study showed that, in addition, substituting leptin for the physiological decrease in plasma leptin concentrations in weight-reduced (having undergone a 10% reduction in body-weight), normal-weight, or overweight healthy subjects had no effect on REE or REE adjusted for FFM [32]. These data argue against a 'thermic' effect of leptin in humans. However, contrary to dose-response characteristics of many hormones, leptin may not have effects at high plasma concentrations; its 'thermic' effect may become obvious below a certain threshold level only. In fact, new data in patients with anorexia nervosa suggest a steep association between plasma leptin levels and REE in underweight patients, which disappears after weight gain (V Haas, K Gaskin, MJ Müller, unpublished data). It is unclear whether the threshold may be changed (for example, in obese subjects with chronically elevated leptin levels).

#### **Metabolic adaptations during weight changes and disease**

A broader concept of functional body composition includes both mass-dependent and mass-independent alterations in body function. The latter reflects metabolic 'elasticity' and includes mass-independent changes in metabolism in response to different stimuli such as fasting, feeding, work load, short sleep, disease, or stress.

Inter-individual variance in metabolic 'elasticity' contributes to energy balance. Detailed body composition analyses may provide a clue to explain metabolic 'elasticities'. A recent study comparing obese subjects who had large decreases in REE in response to caloric restriction with those who had only small diet-induced adaptations revealed that the former patients were 'thrifty' (that is, weight loss in response to hypocaloric nutrition was 8 kg compared with 10 kg in the non-thrifty group) and they could conserve fat-free, liver, and kidney mass at a concomitant greater fall in plasma triiodothyronine ( $T_3$ ) concentration [33]. The 'thrifty' phenotype could not be identified by any *a priori* measure of body composition, fat distribution (including liver fat), metabolism, or plasma hormone concentrations. These data suggest that adaptive thermogenesis is related to conservation of FFM and its composition, as well as to  $T_3$  production. Thus, for a clinician, data on body composition and metabolism should be seen in the broader context of plasma thyroid hormone concentrations and/or biomarkers of stress in order to characterize the metabolic phenotype.

#### **Future directions**

##### **Genetic basis of energy metabolism**

Body composition and metabolism have underlying genetic components. In family studies, heritability estimates of individual body components are variable, for example, 0.05 for BMI compared with 0.25 for percent body fat (and may exceed 0.50 when individual variables are taken into account) [34,35]. After adjusting REE for FFM, FM, age, and sex, a considerable variance of about 150 kcal/d remained [36,37] that has not yet been explained. Adjusted REE was moderately heritable (around 0.30 [16,35-37]) but presently there is no clear evidence that specific genes add to the interindividual variance in REE [38,39]. In future, research into traits defined by measures of functional body composition (for example, changes in REE-FFM with under- and overfeeding) will provide functional evidence relating genetic variants.

##### **Use of cut-offs in body composition research**

The definitions of both 'overweight' and 'malnutrition' should be reconsidered now that we are faced with the concept of functional body composition. Suitable cut-offs of body weight and/or body components (such as those based on percentiles or health outcomes) do not take into account functional aspects. In future, it is likely that the terms 'overweight' and 'malnutrition' will be defined more in terms of function in the context of body composition (for example, by their affect on metabolism and inflammation) rather than mere nutritional status. Current guidelines recommend weight-loss therapy for patients with a BMI  $\geq 30$  kg/m<sup>2</sup> and for patients with a

BMI  $\geq 25$  kg/m<sup>2</sup> who additionally have a high-risk waist circumference amongst other risk factors. However, there is substantial heterogeneity within obese subjects as to their overweight-associated health risks [40,41], suggesting the need for detailed assessment of body composition together with energy, glucose, and lipid metabolism (that is, an assessment of 'functional' body composition).

#### **Are there healthy obese subjects and can they be identified by assessment of detailed body composition?**

Based on cross-sectional data on 5,440 adult participants of the NHANES (National Health and Nutrition Examination Survey) 1999-2004, 51.3% of overweight and 31.7% of obese adults were metabolically healthy as defined via the absence of cardiometabolic abnormalities including elevated blood pressure, hyperlipidemia, insulin resistance, and elevated serum levels of C-reactive protein [40]. Correlates of no- or low-risk in overweight and obese subjects were young age, ethnicity, high leisure time, physical activity, and a small waist circumference. In another clinical study, 25.4% of obese subjects were characterized as metabolically benign [41]. Body composition analyses (including measurements of ectopic fat in the liver and muscle by MR-spectroscopy) together with assessments of insulin resistance, aerobic fitness, and intima-media thickness of the common carotid artery, showed that metabolically-benign compared with non-metabolically-benign obese subjects had a similar BMI, waist circumference, and subcutaneous abdominal fat, but had slightly lower visceral fat mass and higher ectopic fat deposits in muscle and particularly in the liver [40]. These data suggest that 25-30% of the obese population do not need either treatment or prevention of secondary disorders. Clearly, detailed body composition measurements have to be combined with a measure of ectopic fat and/or insulin resistance in order to explain the meaning of nutritional status.

To summarize, assessment of functional body composition should replace nutritional status-based risk assessments and needs to be included in metabolic research and clinical decision making.

#### **Abbreviations**

BCA, body composition analysis; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual energy X-ray absorptiometry; FFM, fat-free mass; FM, fat mass; MRI, magnetic resonance imaging; NHANES, National Health and Nutrition Examination Survey; REE, resting energy expenditure; T<sub>3</sub>, triiodothyronine.

#### **Competing interests**

The authors declare that they have no competing interests.

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