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REVIEW

Functional body composition: insights into the regulation of energy metabolism and some clinical applications

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The application of advanced methods and techniques and their continuous development enable detailed body composition analyses (BCAs) and modeling of body composition at different levels (e.g., at atomic, molecular, organ-tissue and whole body level). Functional body composition integrates body components into regulatory systems (e.g., on energy balance). Regulation of body weight is closely linked to the mass and function of individual body components. Fat mass is part of the energy intake regulatory feedback system. In addition, fat-free mass (FFM) and fat mass are both determinants of resting energy expenditure (REE). Up to 80% of the variance in energy intake and energy expenditure is explained by body composition. A deviation from normal associations between body components and function suggests a metabolic disequilibrium (e.g., in the REE–FFM relationship or in the plasma leptin–fat mass association) that may occur in response to weight changes and diseases. The concept of functional body composition adds to a more sophisticated view on nutritional status and diseases, as well as to a characterization of biomedical traits that will provide functional evidence relating genetic variants.
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Introduction

Recent methodological and technological advances enable (1) an accurate and detailed body composition analysis (BCA) as well as (2) the development of new models and concepts in body composition research; for example, a 4-component model reaches a high accuracy in the estimates of fat mass, taking into account tissue hydration, protein and mineral content of fat-free mass (FFM) (Heymsfield, 2002). In addition, a multicomponent model that takes into account individual organ masses explained ~85% of the variance in resting energy expenditure (REE) (Gallagher and Elia, 2005). BCA is now a standard in investigations on energy and macronutrient metabolism. At present, the number of scientific publications on BCA is steadily increasing, and a new scientific society has been founded recently (International Society of Body Composition Research, ISBCR; http://www.isbcr.org). The introduction of valid field methods (such as bioelectrical impedance analysis) also led to broader applications of BCA within epidemiological and clinical studies (e.g., in the context of weight management both in underweight and overweight patients). As more and more BCA data accumulate, one may inquire about the meaning and the appropriate use of BCA data in clinical practice.

Assessment of body components and modeling of body composition at molecular, cellular and tissue levels result in different parameters (e.g., tissue hydration, electrical resistance, mineral content, as well as kilograms of fat and FFM) (Shen *et al.*, 2005). Within epidemiology, these data can be used to generate population-specific reference values and suitable cutoffs (e.g., by using percentiles to characterize overweight and underweight individuals) (Pichard *et al.*, 2000, Bosy-Westphal *et al.*, 2005). BCA data (such as on body fat distribution) may also be included in scores used for the

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assessment of cardiometabolic risk (Klein *et al*., 2007, Assmann *et al*., 2008). Individual body components help to identify specific types of malnutrition by the assessment of body fat and muscle mass (e.g., sarcopenia with a reduced skeletal muscle mass at normal or with an increased fat mass in patients with rheumatoid arthritis; Baumgartner, 2005). BCA data are also associated with clinical prognosis (e.g., a low phase angle as assessed by bioelectrical impedance analysis was shown to predict survival in severely ill patients; Selberg *et al*., 1997; Bosy-Westphal *et al*., 2006). Assessment of body components and their changes with nutrition, development, inflammation and/or wasting disease is mandatory for understanding changes in metabolism (e.g., in response to starvation; Hall, 2006) and health (e.g., muscle mass is one determinant of bone health; Goulding *et al*., 2005).

Functional body composition aims at integrating body components into a broader perspective of regulatory systems. Thus, the major applications of BCA are (1) interpretation of body functions and their disturbances in the context of body components and vice versa and (2) interpretation of the meaning of individual body components in the context of their functional consequences. Functional body composition adds to an understanding of energy balance and thus to clinical investigation and decision making. This article sets out to apply the concept of functional body composition to studies on energy metabolism.

Functional aspects of fat mass and FFM

Fat-free mass and fat mass determine both sides of energy balance. Data obtained from large populations covering a wide weight range suggest that FFM is the major determinant of energy expenditure, explaining about 60–80% of its variance (Ravussin and Bogardus, 1989; Elia, 1992; Korth *et al*., 2007). The higher the FFM the higher is the REE. On the other side of the energy balance equation, there exists a close and exponential association between fat mass and plasma leptin concentrations (which is supposed to be a major signal in appetite and thus in energy intake regulation; Ostlund *et al*., 1996). The higher the fat mass the higher are the plasma leptin levels. Functional consequences of changes in body composition in response to weight loss include increases in energy intake brought about by a low leptin secretion rate and/or a decrease in REE with decreasing FFM. Conversely, increases in body weight and also obesity are associated with high plasma leptin levels (at increased fat mass) and high REE (associated with increased FFM).

This idea suggests a dichotomy of fat mass and FFM with respect to the regulation of the two sides of energy balance. Contrary to that view, fat mass (in addition to FFM) also adds to the variance in REE. Overweight and obese individuals have a higher REE than their lean controls, even after adjustments for FFM and age (Schulz and Schoeller, 1994; Prentice *et al*., 1996; Müller *et al*., 2004). After a further adjustment for fat mass, most of the between-group differences in REE disappeared.

Table 1 Age-adjusted covariate effects of fat-free mass (FFM) and fat mass (FM) on resting energy expenditure (REE) by grade of adiposity (% FM) in 1306 females (REE, kcal per day = K1† × FFM, kg + K2† × FM, kg + intercept). Data are from Bosy-Westphal *et al.* 2009

FM, %	*REE (kcal per day) =*	*Ratio of coefficients*	R^2
⩽10	15.4 × FFM + 17.9 × FM + 356.3	17.9/15.4 = 1.16	62.4
>10–⩽30	11.8 × FFM + 14.4 × FM + 629.2	14.4/11.8 = 1.22	52.7
>30–⩽40	5.5 × FFM + 19.3 × FM + 926.3	19.3/5.5 = 3.51	42.6
>40–⩽50	12.0 × FFM + 10.4 × FM + 886.0	10.4/12.0 = 0.87	63.3
>50	11.5 × FFM + 7.1 × FM + 1097.2	7.1/11.5 = 0.62	80.5

R^2, covariate variance.
†All regression coefficients were significant at $P<0.001$.

On the basis of multiple regression analyses, the energy expenditure of FFM was found to be 3–7 times higher than the energy expenditure of fat mass (Elia, 1992; Nelson *et al*., 1992). Regression analyses performed in subgroups with different fat masses showed that the variance in REE explained by FFM and fat mass is variable, approximating 80% at higher levels of adiposity being <50% at overweight (Bosy-Westphal *et al*., 2009). Both fat mass and FFM are determinants of REE; however, the relative contribution of fat mass to the variance in REE increased from low to normal and elevated grades of adiposity (i.e., up to a body fat mass of <40% body weight) but sharply decreased at very high (>40% fat mass) and extreme (>50% fat mass) grades of obesity (Table 1; Bosy-Westphal *et al*., 2009). The latter finding might suggest a threshold effect of fat mass, which cannot be explained on the basis of the present knowledge. Altogether, (1) FFM is the major determinant of REE and (2) fat mass and FFM differently add to the variance of REE at different levels of adiposity.

Fat cells have a low resting metabolic rate (i.e., 19 kJ or ~5 kcal kg^{-1} d; Elia, 1992). Thus, a 'thermic' effect of fat mass may be explained by the mass-dependent secreting activity of fat cells (e.g., secretion of adipocytokines and/or hormones) as well as by metabolic, inflammatory and hemodynamic disturbances associated with overweight rather than by fat cell metabolism itself (Ahima, 2006). A high fat mass and abdominal obesity are frequently associated with metabolic disturbances (i.e., insulin resistance and increased sympathoadrenal system (SNS) activity) and comorbidity (e.g., different traits of the metabolic syndrome), which also adds to the variance in REE. Insulin resistance and increased blood pressure levels have some positive and significant associations with REE, which remain significant even after adjustments for FFM, fat mass and age (e.g., REE increased with systolic blood pressure and plasma insulin levels; Bosy-Westphal *et al*., 2008a, b).

Data on patients with partial lipodystrophy syndromes (characterized by a loss of subcutaneous fat and low plasma levels of adipocytokines associated with a higher percentage

in trunk fat as well as in ectopic fat in non-adipose tissues, such as fat in the skeletal muscle and liver) provide a further insight into the function of fat mass in regulating REE. In patients with congenital lipodystrophies, REE is increased by 20–70% of normal (Cutler *et al*., 1991). REE per kg FFM was also higher in patients with HIV (human immunodeficiency virus)-lipodystrophy compared with that in HIV-infected patients without lipodystrophy (Kosmiski *et al*., 2007). The increase in REE has been considered as a compensatory mechanism to dissipate calories that cannot be stored normally (Kosmiski *et al*., 2007). These data suggest that different fat depots (i.e., subcutaneous vs visceral vs ectopic fat), together with the storage capacity of adipocytes, differently and indirectly act on REE.

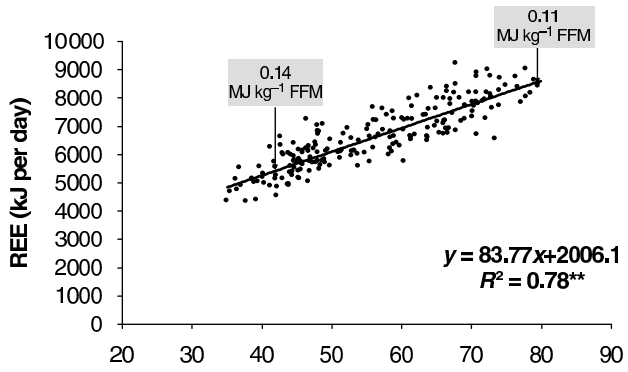
Adipocyte number is a major determinant of fat mass. In adults, the number of fat cells remains constant and ~10% of fat cells are renewed annually (Spalding *et al*., 2008). There is a curvilinear association between body fat and the mean size of adipocytes. Adipocyte cellularity and triglyceride accumulation within lipid droplets have associations with functions and morbidity. The association between adipocyte size and fat mass differs by region, that is, (1) abdominal adipocyte size is associated with visceral and subcutaneous abdominal fat, (2) femoral adipocyte size is related to percentage body fat, whereas (3) gluteal adipocyte size is related to visceral fat (Tchoukalova *et al*., 2008). Enlarged subcutaneous fat cells are associated with insulin resistance independent of fat mass (Weyer *et al*., 2000). Therefore, a high fat cell size may also result in a relatively higher REE. There is initial evidence obtained from experimental data that lipid droplet structure (large unilocular vs smaller multilocular droplets) is associated with mitochondrial oxidative metabolism, and that smaller droplets increased the rate of lipolysis and energy expenditure (Puri and Czech, 2008). Thus, the effect of fat mass on REE varies with fat depots, fat cell size and lipid droplet structure. Future studies have to extend BCA into cellular morphology and microstructure.

The feedback mechanism of the effect of fat mass on energy metabolism is unknown, but leptin was considered as a candidate for such a signal from fat (Leibel *et al*., 1995; Leibel, 2002; Prentice *et al*., 2002). Animal data have suggested a thermic effect of leptin (Hwa *et al*., 1996; Porter and Andrews, 1998; Wang *et al*., 2000a; Solinas *et al*., 2004; Summermatter *et al*., 2008). Leptin directly stimulated thermogenesis in mouse skeletal muscle (Solinas *et al*., 2004). With regard to the mechanisms, (1) an effect of leptin on uncoupling proteins (Porter and Andrews, 1998) and (2) an increased substrate cycling between *de novo* lipogenesis and mitochondrial lipid oxidation (Solinas *et al*., 2004; Summermatter *et al*., 2008), explained by diminished phoshatidylinositol-3 kinase and adenosine monophosphate-activated protein kinase signaling (Summermatter *et al*., 2008), have been proposed. When compared with animal data, a thermic effect of leptin is equivocal in humans. Observational studies do not provide evidence for a thermic effect of leptin in normal weight or obese individuals (Johnstone *et al*., 2005; Blaak *et al*., 2007). Treating a child with a congenital leptin deficiency (Farooqi *et al*., 1999, 2002) or obese patients with increased plasma leptin concentrations (Westerterp-Platenga *et al*., 2001) with leptin resulted in a substantial weight loss but was without effect on REE, and REE adjusted for FFM was reduced rather than increased. In obese individuals, leptin administration does not seem to accelerate weight loss as a supplement to diet intervention, unless it is administered in supra-physiological doses (Heymsfield *et al*., 1999). In the latter study, leptin administration had a dose-dependent effect on weight loss, wherein no dose dependency on energy intake was observed, thus providing indirect evidence for a 'thermic' effect of leptin, which is in contrast to the data of Westerterp-Platenga *et al*. (2001). Substituting leptin for the physiological decrease in plasma leptin concentrations in 10% weight-reduced normal weight or overweight healthy individuals had no effect on REE or REE adjusted for FFM (Rosenbaum *et al*., 2005). Leptin was also administered to treat patients with generalized lipodystrophy (characterized by very low plasma leptin concentrations) and reduced REE by ~17% (Oral *et al*., 2002; Javor *et al*., 2005). Concomitantly, energy intake and body weight decreased in parallel to the decrease in REE, suggesting that leptin's ability to decrease food intake explains the fall in REE. The latter idea is questioned by pair feeding in one patient with lipodystrophy, suggesting an independent effect of leptin replacement on metabolism (Javor *et al*., 2005). In any case, the effects of leptin administration in lipodystrophic patients are confounded by the resolution of diabetes and insulin resistance.

Taken together, the concept of functional body composition adds to explain energy balance. A simple two-component model (fat mass, FFM) is insufficient, and thus a more detailed perspective on body components (e.g., on adipocyte cellularity) will provide further insights. In humans, the feedback mechanism relating fat mass to energy expenditure remains to be characterized.

FFM composition and REE

Body size-related interindividual variations in REE are considered to be mainly because of (1) FFM; (2) proportional contributions of different organ masses (e.g., skeletal muscle, masses of the brain, liver, heart and kidneys) to FFM; (3) variations in organ metabolic rates; and (4) adaptations of specific metabolic rates in response to both overfeeding and underfeeding (i.e., adaptive thermogenesis). The slope of REE on FFM is lower at high FFM, whereas a higher specific metabolic rate (i.e., REE per kg FFM) is observed at low FFM (Figure 1). Thus, REE on FFM decreases with increasing FFM (Ravussin and Bogardus, 1989; Elia, 1992; Weinsier *et al*., 1992; Wang *et al*., 2000b; Müller *et al*., 2002; Gallagher and Elia, 2005; Later *et al*., 2008). This phenomenon is mainly explained by the composition of FFM.



FFM	30–40 kg	40–50 kg	50–60 kg	60–70 kg	70–80 kg
MM (kg)	16.74	20.83	26.57	31.59	36.05
OM (kg)	2.53	2.82	3.05	3.37	3.64
MM/OM	6.59	7.44	8.09	9.43	9.94

Figure 1 Relationship between resting energy expenditure (REE) and fat-free mass (FFM) and increasing muscle mass (MM), organ mass (OM) and MM–OM ratio with increasing FFM category in 202 healthy individuals. $^{**}P<0.01$. Data are from Later *et al.*, 2008.

Fat-free mass is the sum of (at least) two functional body components, namely metabolically active FFM and very low metabolically active or (for simplicity) 'non-metabolically active' tissues. Muscle and organ masses (brain plus heart plus liver plus kidney masses or taken as a whole) add up to a metabolically active FFM. Skeletal muscle, brain and visceral organs substantially differ with respect to their masses, growth rates as well as to their individual or specific metabolic rates. Organ metabolic rates of the brain, heart, liver and kidney are approximately 10–20 times the figure for the body as a whole, and can thus be considered as high-metabolic rate organs (Elia, 1992; Weinsier *et al.*, 1992; Wang *et al.*, 2000a, b; Müller *et al.*, 2002; Gallagher and Elia, 2005). Organ metabolic rates per kg organ mass vary between 837 and 1841 kJ (200–440 kcal) for internal organs and between 54 and 63 kJ (13–15 kcal) for skeletal muscle. Thus, in adults, 70–80% of REE is derived from organs that comprise approximately only 5% of body weight (Figure 1). Resting metabolic requirements of splanchnic tissues, brain and kidney vary little under a relatively constant tissue mass (Gallagher and Elia, 2005; Wolfe, 2006; Later *et al.*, 2008). In contrast, there are large variations in mass as well as in protein turnover rates in skeletal muscle (Wolfe, 2006).

Body mass and body composition account for the overwhelming fraction of REE variance. This idea is based on data obtained from heterogeneous populations with a wide range of body mass. However, when narrow ranges of body mass are considered, the explained variance decreases from approximately 80–20% (Deriaz *et al.*, 1992; Bouchard *et al.*, 1994). Using the whole data set of Later *et al.* (2008), FFM, age and gender taken together explained 77% of the variance of REE. At narrow ranges of FFM (i.e., 40–50, 50–60, 60–70 kg), the common variance between REE and FFM decreases to 12–25%. Replacing FFM by muscle and organ masses explained variances that increased up to 0.5, despite the given low variances in body components within the narrow FFM ranges. Thus, a detailed BCA suggests that, from a biological point of view, body composition is a true determinant of REE, which has been questioned before by some authors (Bouchard *et al.*, 1994).

Comparing the associations between REE and FFM in different age groups, there is a progressive sloping of the REE–FFM relationship with age (Gallagher *et al.*, 2000; Müller *et al.*, 2004, 2005; Baumgartner, 2005), suggesting that REE per kg FFM decreases with age. This finding can be explained by two different factors. First, there is evidence for an age-related decrease in cellular metabolism; for example, $^{13}C/^{31}P$-nuclear magnetic resonance (MR) spectroscopy showed that rates of mitochondrial oxidative and phosphorylation activity were reduced by −40% in elderly individuals compared with those in young controls (Petersen *et al.*, 2003). Concomitantly, energy expenditure due to protein synthesis ranges from ~485 kcal per day in well-muscled young men to ~120 kcal per day in active elderly individuals (Wolfe, 2006). Second, mass and composition of FFM change with age (Gallagher *et al.*, 2000; Bosy-Westphal *et al.*, 2003; Baumgartner, 2005; Müller *et al.*, 2005). Comparing groups of normal and overweight young and older individuals, considerable differences in muscle (−20.3 and −26.2% in older women and older men, respectively) and organ masses (−23.3 and −21.0%, respectively) were found (Gallagher *et al.*, 2000; Bosy-Westphal *et al.*, 2003; Wolfe, 2006). The sum of organ masses increased with FFM in young and in elderly individuals (Keys *et al.*, 1973; Bosy-Westphal *et al.*, 2003). There were no differences in slopes, but at a given FFM, masses of the brain, liver and kidney were lower in the elderly. By contrast, heart mass per FFM was higher in elderly individuals compared with that in young individuals. In our population, five elderly individuals were found to have cardiac hypertrophy (i.e., a heart weight >500 g). After the exclusion of these individuals from further analyses, there was no evidence of age-related alterations in organ metabolic rates (Bosy-Westphal *et al.*, 2003).

Up to now, little is known about the changes in individual FFM components with either weight gain or weight loss. Long-term overfeeding in healthy normal weight individuals increased body weight and skeletal muscle mass, but non-muscular lean tissue remained unchanged (Deriaz *et al.*, 1992). Concomitantly, REE increased, which was correlated with changes in muscle mass. In obese individuals, weight loss-associated changes in FFM were mainly explained by losses in skeletal muscle mass, but additional losses were observed in liver and kidney mass (Bosy-Westphal *et al.*, 2008a, b). MR spectroscopy showed that the loss in liver mass is mainly explained by a loss in liver fat. Weight loss-associated changes in REE were closely linked to changes in FFM and its major component, skeletal muscle mass.

The composition of FFM explains gender differences in REE and metabolic alterations associated with clinical

conditions (e.g., in both overweight and underweight individuals, spinal cord-injured patients with a low REE and 'hypermetabolic' cancer patients or patients with liver cirrhosis; Müller *et al.*, 1999; Heymsfield, 2002; Bosy-Westphal *et al.*, 2004; Peng *et al.*, 2007). Hypermetabolism in patients with liver cirrhosis provides a further example. In a clinical setting, hypermetabolism was defined as measured REE exceeding the predicted value by >20%, wherein prediction is based on standard formulae using weight, height, age and sex (Müller *et al.*, 1999). Using this definition, hypermetabolism was observed in more than 30% of clinically stable cirrhotic patients (Müller *et al.*, 1999). However, a more detailed analysis of body components (e.g., by estimating total body protein by neutron activation or by assessing body cell mass by total body potassium) provided evidence that only 15% of the cirrhotic patients suffer from 'true' (i.e., body mass-independent) hypermetabolism (Selberg *et al.*, 1999; Peng *et al.*, 2007). In cirrhosis, mass-independent hypermetabolism was explained by hemodynamic alterations and/or increased SNS activity, and thus should be considered for further treatment (e.g., with propranolol; Müller *et al.*, 1999; Müller, 2007; Peng *et al.*, 2007). In clinical practice, stratification of cirrhotic patients is necessary, and a detailed BCA (e.g., assessment of body cell mass) is recommended in hypermetabolic patients. Hypermetabolism that is associated with a low body cell mass then serves as a basis for pharmacological (in addition to nutritional) treatment.

Metabolic adaptations during weight changes

Both weight loss and weight gain are associated with metabolic adaptations, contributing to long-term weight regulation in underweight as well as in overweight individuals. Metabolic adaptations result from changes in body composition and from alterations in the metabolism of individual body components (Figure 2).

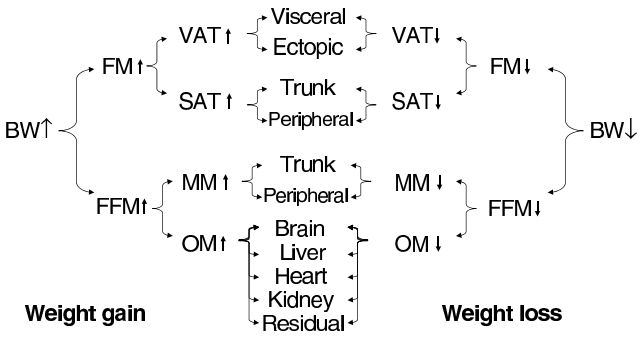


Figure 2 Changes in body weight and energy balance are characterized by detailed changes in body composition that again contribute to metabolic adaptations to weight loss and weight gain. BW, body weight; FM, fat mass; FFM, fat-free mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; OM, organ mass; MM, muscle mass.

In the classical Minnesota Starvation Study on semi-starvation, the decrease in REE was nearly 40%, and 35–50% of this metabolic adaptation was independent of body mass (Keys *et al.*, 1950, Dulloo and Jaquet, 1998). Data on controlled underfeeding suggested that the maximal adaptation to the maintenance of a reduced body weight was attained after a 10% loss in weight; there were no significant differences in energy expenditure at weight 10 or 20% below the initial weight (Leibel *et al.*, 1995), indicating the limits of metabolic adaptation that are already obvious at early weight loss.

Overfeeding resulted in increases in REE (Schoeller, 2001). However, when compared with underfeeding, small or no mass-independent increases in REE were observed (Ravussin *et al.*, 1985; Diaz *et al.*, 1992; Lammert *et al.*, 2000); for example, after 9 days of overfeeding, at 1.6-fold of maintenance requirements, body weight (+3.2 kg), FFM (+1.4 kg) and REE (+7.7%) increased in normal weight men, but there were nearly no mass-independent changes in REE (Ravussin *et al.*, 1985). By contrast, 48 h of overfeeding at 200% of energy requirements increased the sleeping metabolic rate by ~18% (or 350 kcal per day) without measurable changes in body composition (Weyer *et al.*, 2001). This is in line with data obtained from non-obese individuals after controlled overfeeding (+1000 kcal above maintenance requirements until a 10% weight gain was attained) and a subsequent weight stabilization, resulting in mass-independent increases in REE of 27 kcal per day (Leibel *et al.*, 1995). Taken together, these data suggest that the capacity to dissipate excessive energy is limited in humans.

After restoring energy balance either in the weight-gained or weight-reduced state, body mass- and body composition-independent changes in REE (i.e., increases with weight gain and decreases with weight loss) may disappear (Keys *et al.*, 1950; Leibel *et al.*, 1995; Weinsier *et al.*, 2000; Weinsier, 2001) or even persist for longer periods (for 1 year after persistent weight loss; Rosenbaum *et al.*, 2008b). Persistent reductions in REE would suggest that these adaptations do not reflect a transient carryover of metabolic changes in response to negative or positive energy balances. Discrepant results may be explained by different study designs (i.e., in-patient vs outpatient studies) and uncontrolled physical activities (which may increase after weight loss), which camouflage metabolic adaptations (i.e., the decrease in REE). Accordingly, after weight loss, overweight women had a 30% increase in physical activities (Weinsier, 2001) and a high physical activity was a major determinant of successful weight loss maintenance (Weinsier *et al.*, 2002).

Metabolic adaptations are also evident in women with anorexia nervosa and in obese women with weight loss (Figure 3a and b; Haas *et al.*, 2005; Bosy-Westphal *et al.*, 2008a, b). Using longitudinal data on either re-weight gain in underweight patients with anorexia nervosa (a mean weight gain of 5.5 kg over a period of 43 days) or weight loss in obese individuals (a mean weight loss of 8.0 kg within a period of 98 days) 0.21 and 0.78 kg per kg weight change were

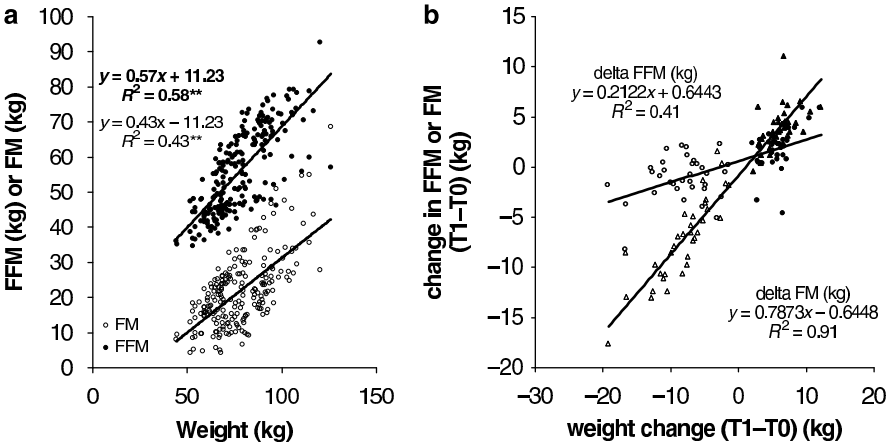


Figure 3 (**a**) Fat-free mass (FFM) and fat mass (FM) vs body weight in a cross-sectional study in 202 healthy individuals. (**b**) Changes of FFM and FM during weight loss and weight gain vs changes in body weight in 19 weight-gaining patients with anorexia nervosa (mean weight gain 5.8 kg per 43 days) and in 26 obese women during weight loss (mean weight loss 8.0 kg per 98 days (FFM = triangles, FM = circles; open symbols = obese women, closed symbols = patients with anorexia nervosa). $^{**}P<0.01$.

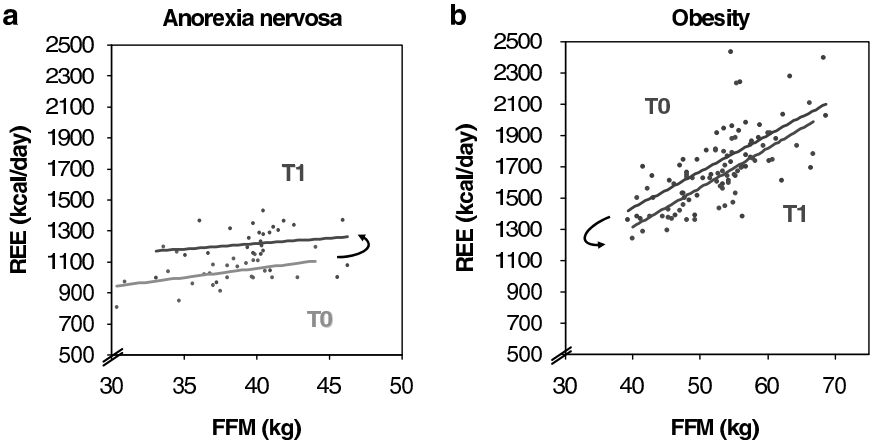


Figure 4 Resting energy expenditure (REE) vs fat-free mass (FFM) (**a**) before (T0) and after weight gain (T1) in 19 patients with anorexia nervosa and (**b**) before (T0) and after weight loss (T1) in 26 obese patients. For details see legend of Figure 3.

explained by FFM and fat mass, respectively (Figure 4b; Haas *et al*., 2005; Bosy-Westphal *et al*., 2008a, b). Initial body composition (i.e., FFM and fat mass before weight change) was the major determinant of changes in individual body components. Body composition before weight change and changes in FFM, were closely related to changes in REE (Figure 5a). However, changes in fat mass also had a close association with changes in REE (Figure 5b). In both situations, mass-independent adaptations of REE were obvious, which were associated with changes in plasma T3 (decreasing with weight loss but increasing with weight gain; Danforth *et al*., 1979; Onur *et al*., 2005, Figure 5c). T3 explained 54% of the variance in REE (Bosy-Westphal *et al*., 2008a, b) and predicted weight change in euthyroid individuals (Ortega *et al*., 2007).

Thus, metabolic adaptation to weight changes is brought about by changes in body composition plus an altered thyroid hormone economy. The unexplained variance is most probably explained by SNS activity. Fasting suppresses SNS activity, whereas plasma levels, urinary excretion and turnover of noradrenaline, all increased in response to overfeeding (Landsberg and Young, 1984). Catecholamines interact with T3 and the weight change-associated changes in urinary noradrenaline excretion and in serum T3 concentrations were correlated with each other, as well as with changes in energy expenditure (Rosenbaum *et al*., 2000).

Metabolic 'elasticity'

A broader concept of functional body composition includes both mass-dependent plus mass-independent alterations in body function. The latter reflects metabolic 'elasticity' and

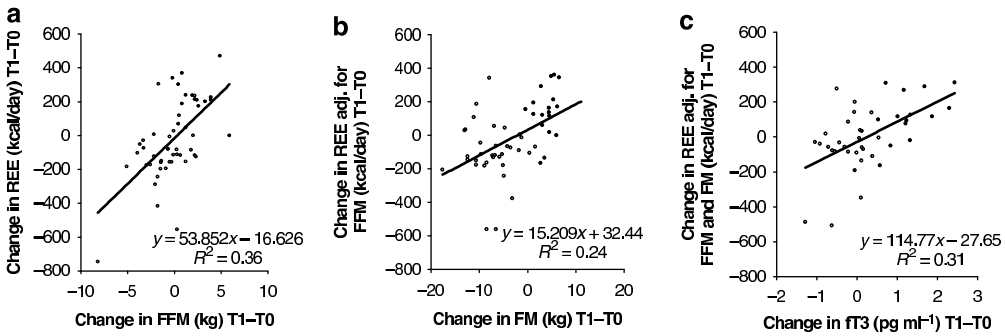


Figure 5 Relationship between (**a**) changes in resting energy expenditure (REE) vs fat-free mass (FFM), (**b**) changes in REE adjusted for FFM vs fat mass (FM) and (**c**) changes in REE adjusted for FFM and FM vs changes in free triiodothyronine levels (fT3) in women with anorexia nervosa during weight gain and in obese women during weight loss (for details, see legend of Figure 4) open circles = obese women, closed circles = women with anorexia nervosa.

includes mass-independent changes in metabolism in response to different stimuli, such as fasting, feeding, workload, short sleep, disease or stress. It is tempting to speculate that the interindividual variance in metabolic 'elasticity' adds to energy balance and health. The first evidence for this concept was obtained from intra-individual and interindividual comparisons of metabolic responses to short-term overfeeding and fasting (Weyer *et al.*, 2001). From these studies, two different phenotypes became evident: first, the *spendthrift phenotype* showing large increases in REE to overfeeding, but small decreases in response to fasting; and second, the *thrifty phenotype*, characterized by large decreases in energy expenditure in response to fasting at small increases to overfeeding (Weyer *et al.*, 2001). These data suggest intra-individual and interindividual differences in 'elasticity' in response to either fasting or overfeeding.

To explain metabolic 'elasticities,' detailed BCAs may provide a clue. Comparing obese individuals with large decreases in REE in response to caloric restriction with those who have only small diet-induced adaptations showed that the former patients were thrifty (i.e., weight loss in response to hypocaloric nutrition was 8 kg compared with 10 kg in the non-thrifty group) and could conserve FFM, liver and kidney mass at a concomitantly higher decrease in plasma T3 concentration (Bosy-Westphal *et al.*, 2008a, b). 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 the conservation of FFM and its composition, as well as to T3 production. Thus, for a clinician, body composition data should be seen in the context of plasma thyroid hormone concentrations and/or biomarkers of stress to characterize the metabolic phenotype.

A more complete picture will be reached by characterizing intra-individual 'elasticity' to different stimuli (e.g., fasting, overfeeding and sleep deprivation, at different work loads and stress). This approach will also enable to conceptualize metabolic changes associated with severe diseases; for example, hypermetabolism in liver cirrhosis had no association with etiology and clinical markers of the severity of liver disease (Müller *et al.*, 1999; Müller, 2007; Peng *et al.*, 2007). In this situation, hypermetabolism is an expression of the allostatic load, which is the cumulative burden exacted on the body and its components through attempts to adapt to the demands of stress associated with disease. Hypermetabolism thus reflects the 'wear and tear' on the regulatory systems and is a new metabolic steady state that is at the end or even outside the normal range of metabolism. It is thus not surprising that hypermetabolic compared with normometabolic patients more frequently suffer from complications and have a higher mortality (Selberg *et al.*, 1997). As (1) both the clinical and biochemical markers of liver disease and hypermetabolism, add to prognosis but (2) were unrelated to each other, these data suggest that they reflect two different features of disease (i.e., specific liver damage, plus the overall burden of disease). To understand this idea, disease load, liver damage and function, as well as body composition, should be analyzed separately. Characterizing the burden of disease requires a new operationalization of the allostatic load, which includes REE adjusted for body composition, together with parameters of the hypothalamic–pituitary–adrenal axis, SNS activity, insulin resistance and other metabolic disturbances associated with disease, providing the clinical 'dimension' of the concept of functional body composition.

Genetics of functional body composition

Body composition and metabolism have underlying genetic components. These may influence either body components and/or metabolism. In family studies, heritability estimates of individual body components are variable (e.g., 0.05 for body mass index but 0.25 for percent body fat; Bouchard and Perusse, 1994) and may exceed 0.50 for individual variables (Bosy-Westphal *et al.*, 2008b; Chung and Leibel, 2008). After adjusting REE for FFM, FM, age and sex, a considerable

variance of ~150 kcal per day remained (Bouchard *et al.*, 1994). This variance remains to be explained. Adjusted REE was moderately heritable (i.e., ~0.30; Bogardus *et al.*, 1986; Bouchard *et al.*, 1994; Bosy-Westphal *et al.*, 2008a, b), but up to now, there is no clear evidence for specific genes adding to the interindividual variance in REE (Krakoff *et al.*, 2008). In future, traits defined by measures of functional body composition (e.g., REE–FFM changes with both underfeeding and overfeeding) will provide functional evidence relating genetic variants. This approach will exceed standard questions, such as looking for the genetic determinants of body weight and body composition.

Suitable outcome variables

Nutritional status is an outcome variable of intervention studies. Functional body composition provides a sound basis for an improved characterization of clinical outcome; for example, plasma leptin concentrations and the leptin secretion rate decrease with weight loss and fasting (Rosenbaum *et al.*, 1997; Klein *et al.*, 2000). Short-term caloric deprivation results in decreasing plasma leptin concentrations by ~80% from baseline, which was independent of changes in fat mass (Rosenbaum *et al.*, 1997; Klein *et al.*, 2000), suggesting some economy of leptin secretion in response to a negative energy balance. Comparing intraindividual changes in fat mass and plasma leptin levels during weight regain in anorectic patients, it was observed that plasma leptin levels and leptin concentrations per fat mass increased, suggesting a relative leptin excess (Haas *et al.*, 2005). Conversely, there is a weight loss-associated decrease in plasma leptin levels per kg fat mass in obese patients, suggesting a relative leptin deficiency (Figure 6a–c; Bosy-Westphal *et al.*, 2008a, b). At stable body weight, there is a close and exponential association between body weight (or fat mass) and plasma leptin concentrations (Figure 1). This association alters with weight change. In weight-gaining anorectic patients, the regression line between body weight and leptin concentrations is shifted upwards, whereas a downward shift is observed in obese patients during weight loss (Figure 6a and b). In both situations, there was a

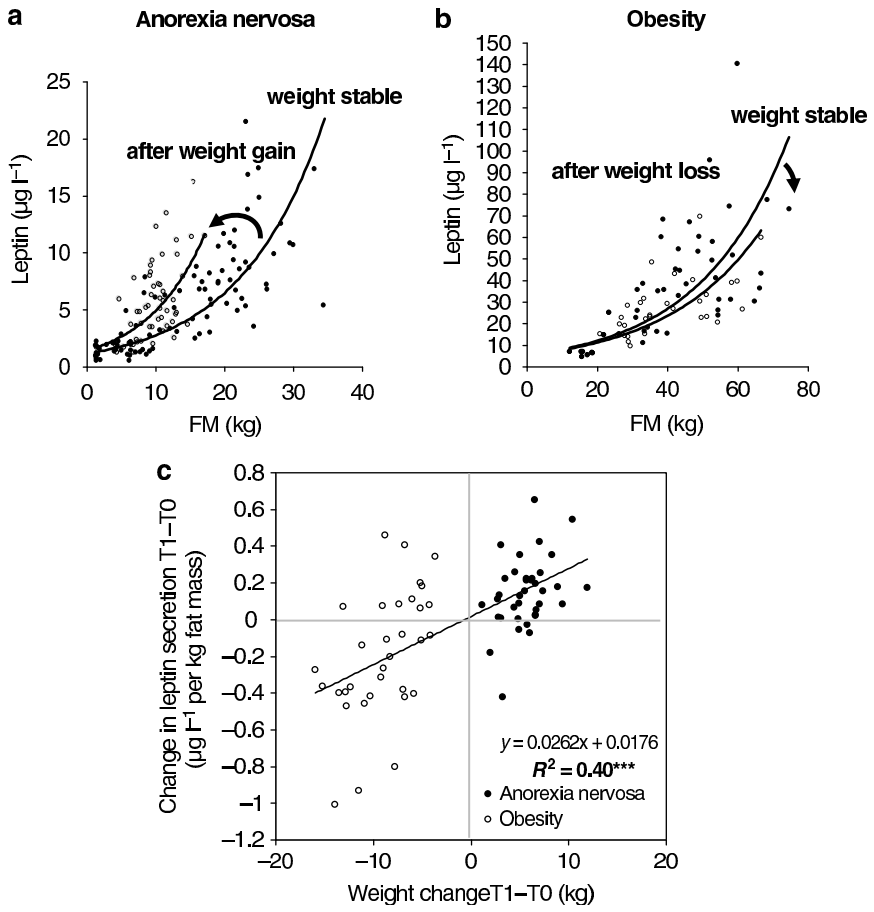


Figure 6 Relationships between plasma leptin levels and fat mass (FM): (**a**) before and after weight gain in 19 women with anorexia nervosa and (**b**) before and after weight loss in 26 obese women. For details, see legend of Figure 4. (**c**) The impact of weight change (weight gain in 19 women with anorexia nervosa and weight loss in 26 obese women) on changes in leptin secretion (leptin/fat mass). ***$P<0.001$.

significant association between weight changes and changes in plasma leptin levels per kg fat mass (Figure 6c). These data suggest that a 'new' association between fat mass and plasma leptin levels has been established in response to weight change. A 'new' leptin–body weight relationship may facilitate the return of individuals to their initial weight. This idea is in line with the clinical observation that in the long term, most underweight individuals lose their regained weight, whereas obese individuals tend to regain lost weight.

Both relative leptin excess with weight regain in anorectic patients and relative leptin deficiency with weight loss may trigger a counter regulation for attaining a stable body weight (or fat mass) at a higher and lower level, respectively. In fact, in obese individuals, maintaining a 10% weight loss substituting the weight loss-associated decrease in plasma leptin concentrations counteracted metabolic adaptation, that is, it increased 24 h energy expenditure, skeletal muscle work efficiency, sympathetic nervous system activity and circulating concentrations of thyroid hormones (Rosenbaum *et al.*, 2002, 2005). More recent functional MRI (magnetic resonance imaging) data on food-related activities in different brain regions suggested leptin-reversible changes, resulting in a disinhibition of food intake in weight-reduced obese patients (Rosenbaum *et al.*, 2008a). Thus, in anorectic patients, reduced energy expenditure, plus increased food intake, favors weight regain.

Over the long term, weight loss- and weight gain-associated changes in FFM also serve to compensate for low- and high-energy intakes by altering energy expenditure, aiming to achieve a stable body weight (Jequier and Tappy, 1999). The 'final' body weight then resembles a set point (as reflected by a normal leptin–body weight relation at a given FFM and REE–FFM ratio) in which there is no need for further adaptations. As both situations, namely weight regain and weight loss, are characterized by similar regulatory patterns, these data argue against the idea that energy homeostasis is inherently biased toward weight gain (Schwarz *et al.*, 2003; Rosenbaum *et al.*, 2005). However, the situation may differ between underweight patients regaining weight and normal weight individuals becoming overweight.

The characterization of clinical outcome of interventions that aimed at weight gain or weight loss should include a measure of functional body composition (e.g., the leptin–fat mass ratio or the REE–FFM relationship), rather than nutritional status alone.

Perspectives of body composition research

As regulatory systems within the body are redundant, BCA cannot provide the complete answer for the regulation of energy balance and body weight. However, faced with the concept of functional body composition definitions of both, overweight and malnutrition should be reconsidered; for example, the use of suitable cutoffs of body weight and/or body components (e.g., based on percentiles or health outcomes) does not take into account their functional aspects. It is likely that future definitions of overweight and malnutrition will be more in terms of function (i.e., metabolism and inflammation) in the context of body composition, rather than mere nutritional status.

To give an example, current guidelines recommend weight loss therapy for patients with a body mass index $\geqslant 30\,kg\,m^{-2}$ and those with a body mass index $\geqslant 25\,kg\,m^{-2}$, who additionally have a high-risk waist circumference and other risk factors. However, there is substantial heterogeneity within obese individuals with regard to their overweight-associated health risks (Stefan *et al.*, 2008; Widman *et al.*, 2008). On the basis of cross-sectional data on 5440 adult participants of the National Health and Nutrition Examination Survey (NHANES) 1999–2004 study, 51.3% of overweight and 31.7% of obese adults were metabolically healthy as defined by the absence of cardiometabolic abnormalities, including increased blood pressure levels, hyperlipidemia, insulin resistance and elevated serum levels of C-reactive protein (Widman *et al.*, 2008). Correlates of no or low risk in overweight and obese individuals were young age, ethnicity, high leisure time physical activity and a small waist circumference. In another clinical study, 25.4% of obese individuals were characterized as being metabolically benign (Stefan *et al.*, 2008). BCAs (by MRI, measurement 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-benign obese individuals had a similar body mass index, waist circumference, subcutaneous abdominal fat, slightly lower visceral fat mass but higher ectopic fat deposits in muscle particularly in the liver (Stefan *et al.*, 2008). These data suggest that between 25 and 30% of the obese population need neither treatment nor prevention of secondary disorders. Clearly, detailed body composition measurements have to be combined with a measure of ectopic fat and/or insulin resistance to explain the meaning of nutritional status. Functional body composition thus has to replace nutritional status-based risk assessments and needs to be included in clinical decision making.

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