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Effect of Over- and Underfeeding on Body Composition and Related Metabolic Functions in Humans

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Abstract

Purpose of Review Methodological limitations of body composition methods limit the validity of changes in body composition that are used to interpret metabolic outcome parameters of weight loss and weight gain.

Recent Findings Direct assessment of energy balance is necessary for the assessment of early weight changes (i.e., within the 1st week of weight change), whereas body composition analysis with a high accuracy and a low minimal detectable change is recommended to assess ongoing changes. The sequence of underfeeding and overfeeding impacts the method inherent assumptions, and the considerable day-to-day and inter-individual variance in body composition changes is a challenge to the precision of methods. Weight loss-associated changes in body composition do not resemble their changes with subsequent hypercaloric refeeding. Individual body components are related to specific metabolic functions where the structure–function relationships change with changes in energy balance.

Summary Analysis of structure–function relationships in response to weight changes needs to address (a) the validity, precision, and different outcome parameters of body composition methods and (b) the variance of results taking into account study protocols and the dynamics of weight changes. As for future studies, repeated measurements of body weight, body composition, and metabolic functions are needed before, during, and after weight changes focusing on the intra- and interindividual variances of weight change rather than on mean data only.

Keywords Body composition · Energy expenditure · Adaptive thermogenesis · Diet-induced thermogenesis · Energy balance · Obesity

Abbreviations

ADP	air displacement plethysmography
AT	adipose tissue
BCA	body composition analysis
BIA	bioelectrical impedance analysis
CT	computer tomography
DXA	dual X-ray absorptiometry
FBCP	functional body composition phenotype
FM	fat mass
FFM	fat-free mass
Ins	insulin
Lep	leptin
LST	lean soft tissue
LT	lean tissue
MDC	minimum detectable change
MRI	magnetic resonance imaging
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
REE	resting energy expenditure
QMR	quantitative magnetic resonance
SAT	subcutaneous adipose tissue
SMM	skeletal muscle mass
TAT	total adipose tissue
TBW	total body water
VAT	visceral adipose tissue

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Introduction

Weight changes are considered to be under biological control with individual body in human subjects components serving as part of different feedback systems (for recent reviews, see [1•, 2•]). Most studies on body weight control published so far have been done in clinical settings, e.g., in obese subjects before and after weight loss and in anorectic patients before and after weight gain. However clinical studies can provide limited insights only because of (a) a variable adherence to diets, physical activity, and exercise and, thus, a lack of strict experimental control, (b) not taking into account the dynamics of weight changes (i.e., their early and late phases), (c) not addressing a "true" stabilization of body weight after weight changes (i.e., reaching a new steady state), (d) lack of detailed measurements of energy and nitrogen balances together with an accurate assessment of body composition, and (e) unexplained variance in mass-independent endocrine and metabolic adaptations to weight changes.

A number of controlled under- and overfeeding studies have been conducted in humans addressing changes in body composition and related functions. Ancel Keys' "Minnesota Starvation Experiment," a 24-wk underfeeding study at − 1800 kcal/d with subsequent re-feeding for 12 to 58 weeks conducted in 1944, is still the most cited study [3•]. More recent human studies have been conducted at the University Lausanne, Switzerland [4–6], Dunn Clinical Nutrition Centre, Cambridge, UK [7–9], Tufts University, Boston, Massachusetts, USA [10, 11], Laval University, Quebec, Canada [12–14], Columbia University, New York, New York, USA [15••, 16•, 17], Royal Veterinary and Agricultural University, Frederiksberg, Denmark [18–20], National Institutes of Health, Phoenix, Arizona, USA [21, 22, 23•], Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA [24–26], University of Maastricht, Netherlands [27–29], Odense University, Denmark [30–32], University Kiel, Germany [33•, 34, 35], and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Bethesda, Maryland, USA [36•, 37].

The authors of these studies have addressed different research questions following short-term (up to 48 h) as well as medium-term (up to 3 to 5 weeks) under- and overfeeding protocols. The methodological approaches include direct assessment of energy and macronutrient balances [3•, 4–9, 15••, 18–22, 23•, 24–33, 35, 36•, 37] or different methods of body composition analysis (BCA; [3•, 7–14, 15••, 16•, 17, 23•, 25, 33•, 34]) or a combination of both [23•, 26, 33•, 38].

Changes in Body Composition in Response to Weight Changes

As a general rule, body weight, fat mass (FM), and fat-free mass (FFM) increase with overeating but decrease with caloric restriction. Following a period of more than one week of intervention, the fractions of weight changes as FM and FFM were about 70 and 30% in men and 80 and 20% in women, respectively. The "One-Fourth" or "Quarter FFM rule" assumes a constant energy density of weight change of about 7400 kcal/kg [39]. However, greater degrees of negative energy balance or tissue wasting during illness are accompanied by larger relative losses of FFM [39]. Optimizing weight loss therapy in obese subjects intends to increase the fraction of FM loss. Vice versa, weight gain in underweight patients should result from a gain in both, FM and FFM.

The so-called "Forbes rule" refers to the proportion of lean versus fat tissue with weight changes: This is a curvilinear function of initial body fat ($\Delta FFM/\Delta BW = 10.4 / [10.4 + FM]$; all values in kg) [40]. Based on this rule, in obese compared to lean subjects, greater proportions of weight loss or weight gain are accounted for by changes in FM rather than FFM due to their higher baseline FM. During weight gain, anorectic patients, who were severely depleted in FM, disproportionally increase FM when compared with changes in FFM [41]. More recently, the Forbes rule was validated in predicting changes in FFM for any given change in FM [42, 43•, 44]. The most recent NIDDK web-based body weight simulation model [45] included baseline data (body weight, age, height, physical activity level [PAL], resting energy expenditure [REE], carbohydrate [CHO] intake as % kcal, sodium intake in mg/d, % fat mass, energy intake as kcal/d) as well as specific characteristics from diet or physical activity interventions (changes in PAL, CHO and energy or sodium intake).

Specific Focus of This Review

Although controlled under- and overfeeding studies published so far provide a sound basis to model weight changes, there is a need for re-review because of the following: (a) different methods had been used to assess body composition and there is need to address their limitations; (b) there was a considerable variance in the study protocols without taking into account the dynamics of weight changes; and (c) structure–function relationships in response to weight changes have not been systematically investigated. To address these issues, we hereby mainly refer to our own data which have been published previously [33•, 34].

Methodological Issues Related to the Assessment of Body Composition During Weight Changes

BCA is about models, terminology, and methodologies [46••, 47–49]. A widely used approach is the use of a two-

compartment model dividing the body into two major components, FM and FFM. FM and FFM are frequently measured by whole-body densitometry (as assessed by underwater weighing or whole-body air displacement plethysmography, ADP) assuming their stable densities of 0.900 and 1.095 g/cm^3, respectively. FFM consists of water, proteins, minerals, and carbohydrates with individual densities of 0.993, 1.34, 3.04, and 1.52 g/cm^3. Thus, any change in the composition of FFM (e.g., as introduced by weight changes) affects its density. Adding a measure of total body water (TBW, e.g., as assessed by ^2H_2O dilution) extends the two-compartment model to a three-compartment model. After adding measures of bone mineral content (as assessed by dual-energy X-ray absorptiometry, DXA), the model can be further extended to a four-compartment model. This model requires the measurement of body weight, body volume, TBW, and bone mineral content and is considered as the gold standard of BCA at the molecular level [50].

As far as terminology is concerned, FFM (as assessed, e.g., by densitometry) and lean soft tissue (LST or lean tissue, LT, as assessed by DXA or quantitative magnetic resonance, QMR) are not interchangeable. LST is the sum of TBW, protein, carbohydrates, and minerals in the soft tissue. By contrast, LST does not include bone mass. LST and bone mineral compartments add up to FFM. Imaging techniques, such as computerized tomography (CT) and magnetic resonance imaging (MRI), further differentiate LST at the organ-tissue level [48, 51] where skeletal muscle mass (SMM) is the most prominent component of both, LST and FFM.

When compared with FM, adipose tissue (AT) comprises adipocytes including surrounding connective tissue, fibroblasts, and vasculature. About 80% of AT is FM mostly consisting of triglycerides. However, since the ratio of FM to AT is variable [52], FM and AT cannot be used interchangeably. This issue also relates to overfeeding and weight gain where AT plasticity is due to the production of collagen, fibronectin, and elastin to assure the integrity of adipocytes as well as to its vascular supply [53].

Using CT or MRI, regional depots of AT can be measured as subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and ectopic fats in the liver, SMM, and the pancreas. When compared with SAT, VAT and liver fat show disproportional gains and losses in response to over- and underfeeding, respectively [54–57]. Furthermore, individual components of FFM do not change in parallel with weight loss. Consequent to weight loss induced by a low-calorie diet, the relative loss in high metabolic rate-organ masses (i.e., the sum of brain + liver + heart + kidney masses) was significantly higher than was the change in low metabolically active FFM components (muscle, bone, and residual mass; [57]).

Methods used in BCA include bioelectrical impedance analysis (BIA; to measure TBW), whole-body densitometry (to assess FM and FFM), deuterium dilution (to assess TBW and to calculate FFM assuming its constant hydration of 0.732), whole-body counting (e.g., of body potassium or body nitrogen), imaging technologies (to assess masses of major organs and tissues), DXA (to assess LST and bone mineral content), and QMR (to measure FM, TBW, and LST). Since all these techniques differ in their specific outcomes, their underlying assumptions as well as their precision, results obtained by different methods of BCA, cannot be directly compared with each other.

With respect to controlled over- and underfeeding studies, various methods of BCA have been used, e.g., anthropometry and/or BIA [18–20, 31], densitometry [3•, 7–9, 12–14, 15••, 16•, 17, 33•], hydrometry [7–9, 33•], DXA [9, 24–27, 38], QMR [33•], and imaging technologies [12–14, 33•]. While a two-compartment model has been applied in most studies, some authors have used more advanced compartment models [7–9, 24, 27, 33•].

An accurate assessment of changes in body composition in the dynamic phase of weight loss is a challenge to all 2-compartment methods that assume a constant composition of FFM. During the beginning of weight loss, transient decreases in nitrogen, glycogen, and sodium lead to a negative water balance that violates this assumption and leads to method-inherent bias. Densitometry (ADP and underwater weighing), deuterium dilution, and DXA all require a constant hydration of FFM to give valid results [58]. The increase in the density of FFM due to the decrease in the water content of lean mass in the first phase of weight loss leads to an overestimation of loss in fat mass by air displacement plethysmography, underwater weighing, and DXA. By contrast, deuterium dilution overestimates the loss of lean mass and thus underestimates fat loss in this condition [58]. The precision of measuring FFM and FM determines the minimal detectable change (MDC) in both compartments that corresponds to the smallest real change that can be detected beyond measurement error. For QMR, the MDC is about 200 g FM, whereas MDC is about 1 to 2 kg for densitometry, dilution methods, or the four-compartment model [46••]. Thus, QMR seems to be the method of choice to follow short-term changes in body composition in controlled feeding studies.

Impact of the Sequence of an "Underfeeding–Overfeeding Protocol" on Changes in Body Weight and Body Composition

Two sequential protocols have been performed in the same group of 10 young healthy men starting with one week of underfeeding (at − 60% of individual energy needs) followed by one week of hypercaloric re-feeding (at + 60% of individual energy needs) in the 1st run (for details of the protocol, see [34]). The order of feeding interventions was reversed in the

2nd run. Comparing the results of the two runs, underfeeding resulted in similar mean weight losses of − 3.04 ± 0.42 kg (1st run) and − 3.35 ± 0.77 kg (2nd run). By contrast, overfeeding increased body weight by + 3.09 ± 0.97 kg in the 1st run while the effect was + 1.61 ± 0.86 kg in the 2nd run. Thus, despite an identical positive energy balance, weight gains differ between overfeeding and hypercaloric re-feeding. Concomitantly, the between-run differences in gains in FM were + 1.43 ± 1.16 kg in the 1st run and + 0.66 ± 1.17 kg in the 2nd run.

There is a considerable inter-individual variance in changes in body weight and body composition with between-run differences in response to overfeeding. Furthermore, with underfeeding, the sequence of the protocol matters. Although variable, mean decreases in FFM were − 0.46 ± 1.24 kg (1st run) and − 1.43 ± 2.07 kg (2nd run). With overfeeding, glycogen depots are filled which are depleted during subsequent underfeeding with a loss of body water explaining the predominant loss in FFM during the 2nd run. By contrast, hypercaloric re-feeding after underfeeding results in greater increases in FFM compared with overfeeding, because glycogen stores and TBW, and thus FFM, preferentially increase with hypercaloric re-feeding compared with overfeeding (mean increases in FFM of + 1.66 ± 1.42 kg vs + 1.02 ± 1.37 kg, respectively; [34]).

Taken together, within one week of feeding, the sequence of under- and overfeeding impacts the changes in body weight and body composition. This is true for a positive as well as a negative energy balance. Even under controlled feeding conditions, there is a considerable inter-individual variance in changes in body weight and body composition.

Do Decreases in Body Weight and Body Composition During Underfeeding Resemble Their Increases Observed During Hypercaloric Refeeding?

Comparison of data obtained in 32 healthy normal weight men undergoing a sequential two-week underfeeding (at − 50% of their energy needs) and two-week hypercaloric refeeding (at 150% of their energy needs) revealed that decreases in body weight were not fully re-gained during refeeding (Fig. 1a; mean changes in body weight: − 4.59 ± 0.79 kg/2 wks vs. + 3.48 ± 1.16 kg/2 wks) [33, 59]. Plotting the intra-individual changes revealed that this was due to a limited re-gain in FM with hypercaloric refeeding (Fig. 1b). There was a huge inter-individual variance in the association between losses and gains in FFM (Fig. 1c; mean changes in FFM during underfeeding − 2.6 ± 2.2 kg/2 wks vs. +1.5 ± 2.9 kg/2 wks with refeeding). Since with hypercaloric refeeding, the positive nitrogen balance markedly exceeded the negative nitrogen balance with underfeeding (Fig. 1d; mean values − 59.3 ± 24.3 g/2 wks vs. + 138.7 ± 68.5 g nitrogen/2 wks), the variance in the associations between changes in FFM with underfeeding vs. hypercaloric refeeding is most likely due to the variances in changes in TBW.

How Do Changes in Body Composition Relate to Metabolic Function?

Functional body composition addresses the associations between individual body components and their functional or risk correlates [46••]. This approach integrates individual body components into regulatory systems, i.e., by relating body components to their corresponding in vivo functions. Functional body composition is a "multilevel–multisystemic approach" to address the associations between masses of organs and tissues as well as between these masses and their related metabolic functions, in the context of their neurohumoral control (e.g., insulin, leptin, sympathetic nervous system activity, thyroid hormones), and finally in relation to systemic outcomes like body temperature, heart rate, glomerular filtration rate, and respiration.

Numerous metabolic functions are related to body weight and individual body components [60]. REE increases with increases in body weight (and FFM) and vice versa. Similarly, plasma leptin concentrations increase and decrease with changes in FM (and SAT). Further associations exist between SMM and muscle strength, kidney mass and glomerular filtration rate, and VAT and insulin resistance [60]. Recently, three functional body composition phenotypes (FBCPs) have been defined based on physiologic structure–function relationships [61], which are as follows: a "REE on FFM-FBCP," a "plasma leptin concentration on FM-FBCP" ("Lep on FM-FBCP"), and a "plasma insulin concentration on VAT (or on %liver fat)–FBCP ("Ins on VAT or LF%-FBCP"). "Normal FBCPs" were defined by the respective residuals inside a ± 25P range of the respective regression lines of the "REE on FFM," "Lep on FM," or "Ins on LF%" associations with positive and negative residuals at > 75P and < 25P.

The associations between individual body components and physiological functions are affected by age. For example, the slope of the "REE on FFM" association decreases from childhood to advanced age [62]. The association between insulin and VAT serves as another example for an age-dependent change of an association between structure and function where the cut-offs for VAT indicating insulin resistance increased from childhood to adulthood [63]. When compared to age, sex had no effect on the "REE on FFM" and "Ins on VAT" association [62, 63].

Weight changes in response to over- and underfeeding affect the relationships between body composition and metabolic functions. Adaptive thermogenesis has been defined as the decrease in energy expenditure independent of the decrease in FFM [64, 65••, 66••, 67••]. Although most authors propose metabolic adaptations with weight loss only, there is some but

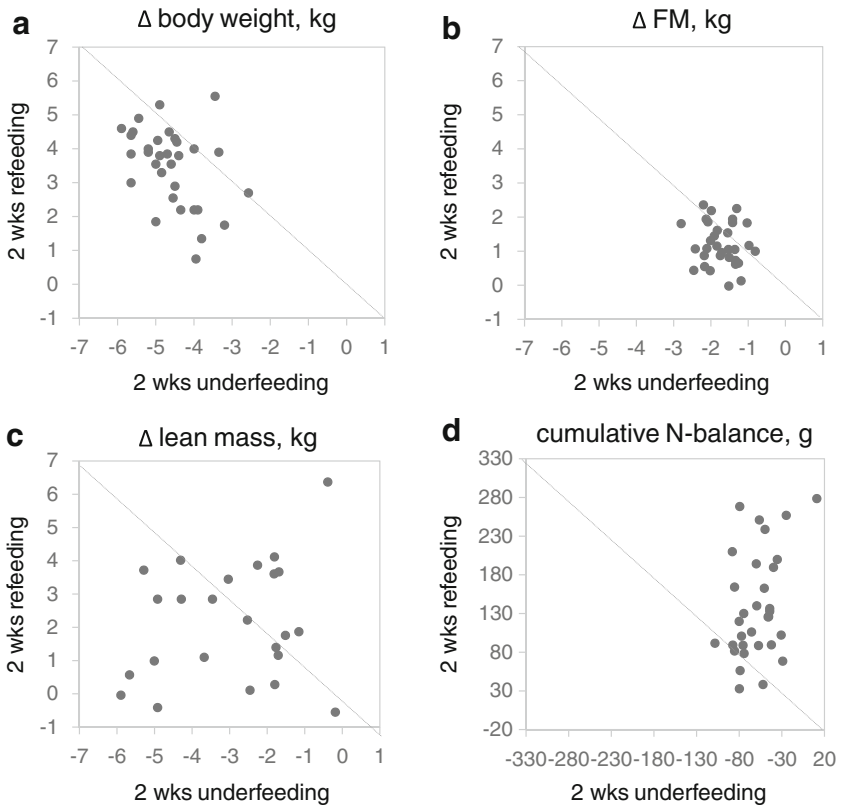

Fig. 1 Intra-individual association between decreases in body weight and body composition during underfeeding with their increases observed during subsequent hypercaloric re-feeding (**a**, changes in body weight; **b**, changes in fat mass; **c**, changes in fat-free mass; **d**, changes in cumulative nitrogen balance). Thirty-two healthy young men aged 20–37 yrs with BMI range of 20.7–29.3 kg/m^2 were studied during a total 6-wk period with subsequent overfeeding (at + 50% of individual energy needs) for 1 week followed by 3 weeks of caloric restriction (at − 50% of individual energy needs) and finally 2 weeks of hypercaloric refeeding (at + 50% of energy needs). Mean changes in body weight were + 1.8 kg (overfeeding), − 6.0 kg (underfeeding), and + 3.5 kg (refeeding). To compare the effects of underfeeding and refeeding, data obtained before and at the end of a 2-week period were used. Body composition (FM, fat mass, and lean mass) was measured by quantitative magnetic resonance (QMR). In addition, cumulative nitrogen balance (N-balance) was assessed as a measure for net losses and net gains of total body protein. For further details, see text and Ref. [33]

controversial evidence for mass-independent increases in REE in response to overfeeding [22, 23•]. The latter becomes evident after overfeeding a low protein diet, i.e., nutrient-deficient or unbalanced diet [68], where diet-induced thermogenesis is considered as wasting of excess energy while regulating the supply of essential nutrients. By contrast, adaptive thermogenesis with underfeeding is considered as an energy-sparing mechanism. It is worthwhile to mention that metabolic adaptation with underfeeding relates to REE and thus energy expenditure of SMM and internal organs like liver, kidneys, and heart (with the exception of brain which keeps its oxygen consumption constant in response to weight changes) whereas adaptive thermogenesis with overfeeding is explained by an increase in diet-induced thermogenesis which, in humans, mainly relates to postprandial increases in hepatic energy expenditure [64, 69].

Following our sequential underfeeding and hypercaloric refeeding protocol [33•], three FBCPs defined before [61] were characterized at baseline (see Fig. 2, upper panel). As for the impact of weight changes on the individual FBCPs (Fig. 2, lower panel), the "REE on FFM-FBCP" showed a decrease with underfeeding with no effect of hypercaloric refeeding. Furthermore, the "Lep on FM-FBCP" decreases with underfeeding and increases again with hypercaloric refeeding. By contrast, the "Ins on %LF-FBCP" was unaffected by either under- or overfeeding and seems to be "fixed" to the changes in liver fat (or VAT). It becomes obvious that the three FBCPs differ in their responses to under- and refeeding. They reflect different dimensions of normality and do not overlap with each other.

Inter- and Intra-Individual Variances in Changes in Body Weight and Body Composition

Up to now, the intra- (or within) individual variances of changes in body weight (and body composition) in response

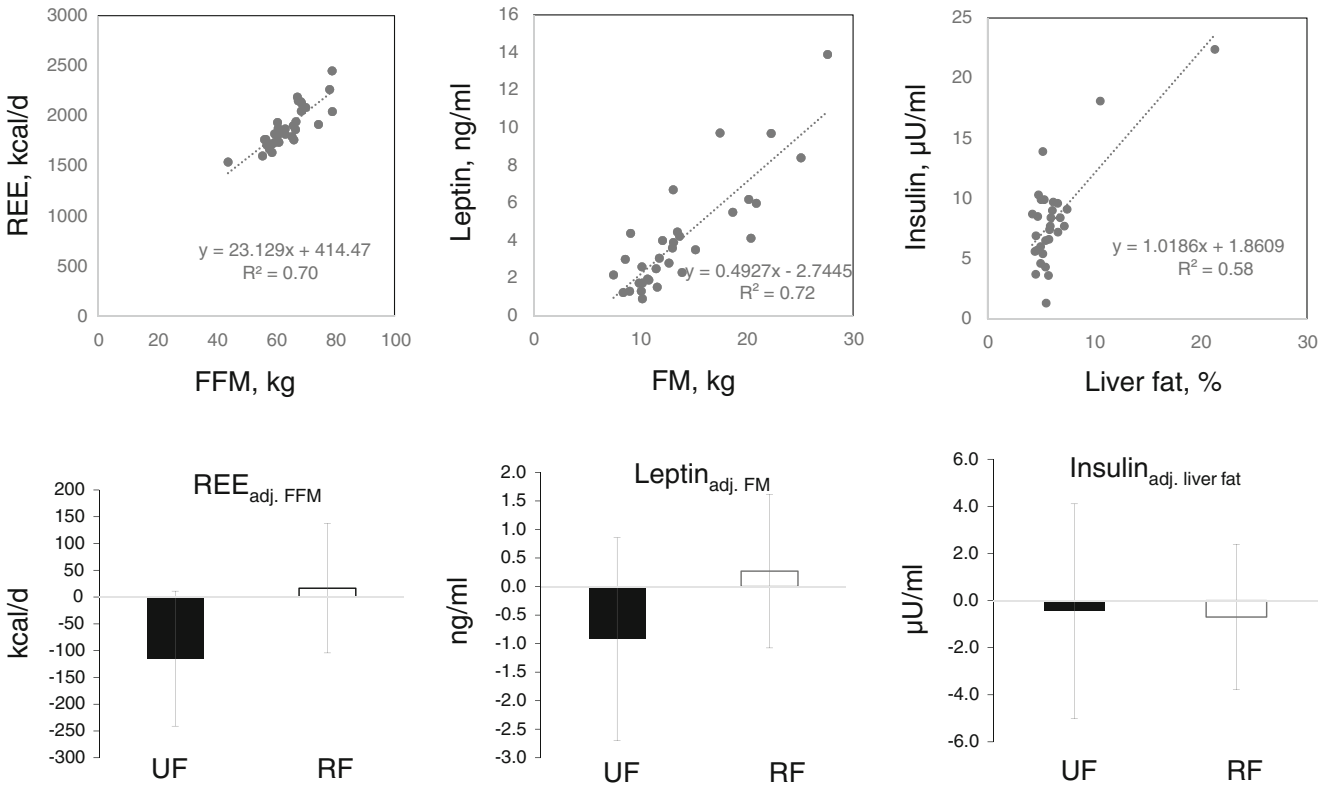

Fig. 2 Defining functional body composition phenotypes (FBCPs) according to structure–function relationships between fat-free mass (FFM) and resting energy expenditure (REE), fat mass (FM) and plasma leptin concentrations, and percentage liver fat (liver fat, %) and plasma insulin levels (see from left to right in the upper panel). Baseline data were taken for the 32 healthy normal weight male participants of the underfeeding and subsequent re-feeding study described in Ref. [33]. "Normal FBCPs" were defined by the respective residuals inside a ± 25P range of the respective regression lines of the "REE on FFM," "lep on FM," or "insulin on LF%" associations with positive residuals > 75P and negative residuals < 25P. Negative and positive residuals of the three FBCPs with either underfeeding (UF) or hypercaloric refeeding (RF) are shown in the lower panel. For details of the FBCP concept, see Refs. [46••, 60]

to controlled under- and over-feeding have not been systematically studied. Variance is a mathematical property. If the intra-individual variance (intra-CV) in changes in body weight (or in FM and FFM) is high, inter-personal variance (inter-CV) in these outcomes is difficult to relate to biological factors. In our underfeeding and subsequent hypercaloric re-feeding study [33•], we found considerable intra- (day-to-day) as well as inter-individual variances in changes of weight, FFM, and FM [33•, 69]. The intra-CV exceeded the inter-CVs of weight changes. Despite controlled under- and over-feeding, and thus a "defined" energy balance, there is no "stable" decrease and increase in body weight and its components, with 69, 78, and 74% of the inter-individual variance in changes of body weight in response to over-, under-, and hypercaloric re-feeding explained by the 13 variables included in the NIDDK body weight simulation model [45].

This day-to-day variance of body weight and its changes in response to over- and underfeeding brings us back to a widely used definition of the so-called "stable body weight" which, in the baseline state, remains within a ± 1.5 kg range. Thus, strictly spoken, a "stable" body weight cannot be considered as "true stable"; it may vary by up to 3 kg. It is obvious from our data that this is also true for weight changes which we may consider as "unstable."

To address the intra-individual reproducibility of weight loss, a 1-week controlled caloric restriction trial (at − 50% of individual energy needs) was carried out twice in a subgroup of 8 subjects with about 1 year between the two runs [33•]. A strong intra-individual correlation was observed between baseline measurements of body weight, FM, and FFM taken at the two occasions. However, the between-run differences in the changes of either body weight, FFM, or FM were − 0.13, − 0.14, and 1.69 kg for the first 3 days and − 0.04, 0.21, and − 0.25 kg for the whole week, respectively. FM and FFM obtained during the two identical runs were correlated with an *r* value of about 0.6. In addition, there was a similar decrease in REE (− 226 ± 138 kcal/d in the 1st run compared with − 208 ± 144 kcal/d in the 2nd run) with a considerable day-to-day as well as inter-individual variance of the data. These results are in line with another study investigating the reproducibility of short-term overfeeding-induced changes in metabolic balance in 14 subjects with an intraclass correlation coefficient of 24 h

energy expenditure and the thermic effect of food at 0.88 and 0.65, respectively [22].

Faced with the intra-individual variances, repeated measurements of body weight and body composition are needed before, during, and after weight changes. Taking a random sample does not provide a sound basis for conclusions. In addition, the reproducibility of the findings has to be tested. To address the high inter-individual variance in weight changes, the adjustment of results for at least the 13 variables as proposed in the NIDDK advanced model (see [45]) is recommended.

Dynamics of Weight Changes with Under- and Overfeeding

Changes in body weight and body composition in response to under- and overfeeding are non-linear ending with a new equilibrium between energy intake and energy expenditure [2•, 70•]. The composition of weight changes is not constant; it is time-dependent and affected by baseline body composition, the intervention itself, the caloric deficit, exercise, age, and disease-related catabolism. The fractional contributions of FM and FFM to weight changes explain the degree of body weight change as well as the variance of the timeframe over which body mass changes.

Calculating the half-life of decreases in body weight in lean subjects resulted in a two-phase weight loss model: An early (or 1st) phase of about two to four days has to be differentiated from a longer 2nd phase with a half-life of about 100 d [71]. The different phases are explained by fractional contributions of FM and FFM to body weight loss and gain, which vary over time with the duration of the feeding protocol.

Early weight loss is characterized by loss of LST (with losses of its molecular components, including glycogen, protein, water, and electrolytes). By contrast, late weight loss is characterized by a linear decrease in FM [33•]. The early weight loss has a decay constant of -0.78 ± 0.19 kg body weight/d (k1) when compared to -0.19 ± 0.03 kg body weight/d for the late phase (k2). K1 is closely correlated with changes in fluid balance. This is because both glycogen and protein are hydrated, and the mobilization of 1 g of either glycogen or protein is thus accompanied by loss of -1.5 to -2.7 g or -1.6 g water, respectively [71, 72]. During the early phase of caloric restriction, about 250 g of glycogen is mobilized, which is associated with a loss of about 500 g of water together with losses in sodium (−30 to 60 mMol/d in obese subjects) and potassium (−40 to 50 mMol/d) [68]. In line with these considerations, the rate of weight loss during days 1–4 was higher (0.69 kg/d) than during days 5–14 (0.18 kg/d). The corresponding rate of losses in FM and lean mass measured by QMR was 0.15 and 0.51 kg/d during days 1–4 and 0.11 and 0.07 kg/d during days 5–14. With hypercaloric refeeding, there are again two different phases of weight change, i.e., an early phase comprising the first 4 days and a later phase thereafter [33•]. While the early phase is associated with a positive fluid balance, the late phase reflects the positive fat and nitrogen balance. Likewise, the rate of weight regain during days 1–4 was higher (0.56 kg/d) when compared with days 5–14 (0.13 kg/d). The corresponding rate of regain in FM and lean mass measured by QMR was 0.08 and 0.49 kg/d during days 1–4 and 0.10 and 0.01 kg/d during days 5–14.

It is obvious that during the dynamic phases of weight change, a non-steady state exists which invalidates the underlying assumptions of methods used for BCA. By contrast, during weight maintenance, a new steady state is reached [2•, 15••, 16•, 17, 59••, 69]. Besides the methodological issues, the structure–function relationships differ between periods of weight changes and during weight maintenance. This is known for adaptive thermogenesis during weight loss which reflects control of REE during early weight loss but refers to non-resting energy expenditure during weight maintenance after weight loss [59••]. While the former is related to changes in insulin secretion, fluid balance, and composition of LST, the latter is explained by decreases in plasma leptin levels, and thus FM [59••].

Taken together, weight change and weight maintenance differ in their association with body composition as well as in their metabolic correlates. During loss and gain of body weight, there is need to distinguish between (a) early and late phases of weight change as well as (b) weight maintenance after weight change. To address the specific nature of early and late changes of body weight and weight maintenance, different methodological approaches are needed. While methods to assess energy and macronutrient balance (so-called balance techniques) are suitable for the assessment of early changes in body composition, BCA can address its later changes and periods of weight maintenance [72].

Assessment of Energy and Nitrogen Balances as Obtained by Either Energy and Nitrogen Balances or Changes in Body Composition

Assessing energy and macronutrient balances derived from energy/macronutrient intake and energy expenditure/macronutrient oxidation combined with urinary and fecal nitrogen losses serves as a "gold standard" for the assessment of changes in body composition. Under metabolic ward conditions, where physical activity is restricted and activity and food intake are controlled, the errors of estimates of energy intake, energy expenditure, and energy losses are about 2, 4, and 2%, respectively [72]. Thus, balance techniques are considered as most sensitive to assess changes in fat mass with a precision between 0.03 and 0.71 kg and a MDC for FM of 0.51 kg [73]. Since

however balance data measure changes over time, they have to be complemented by BCA before weight changes.

Alternatively, energy and nitrogen balances can be indirectly calculated from changes in body composition [65••]. The assessment of energy imbalance from changes in FM and FFM requires assumptions about their energy density. During overfeeding and weight gain, the coefficients for tissue gain were 13.1 kcal/g for FM and 2.2 kcal/g for FFM gained covering both the energy content of the tissues plus the energy costs of tissue gains [26]. By contrast, during underfeeding, the coefficients of tissue losses were 9.3 kcal/g FM and 1.1 kcal/g FFM [24]. The energy density of FFM is calculated from the energy densities of its protein and glycogen content, i.e., 4.7 and 4.2 kcal/g, respectively [65••].

Direct and indirect approaches to assess energy balance have been compared with each other in controlled feeding experiments [24, 26, 33•, 38]. In these studies, methodological issues include the assessment of energy and macronutrient intake, using metabolizable energy instead of gross energy, assuming the energy content of individual body components, difficulties, and methodological problems of measuring energy expenditure (either by doubly labeled water or within a respiratory chamber), adaptations in metabolism and physical activity to either under- or overfeeding, and using either energy or nitrogen or macronutrient balances.

When compared with balance data, a two-compartment model using DXA was accurate to assess changes in fat mass in response to either 21-d underfeeding or 56-d overfeeding (both in overweight subjects) with a difference below 10% between direct and indirect estimates [24, 26]. In addition, two different three-compartment models in 12-d under- and overfed normal weight subjects were found to be precise and accurate to assess changes in energy balance [38].

By contrast, the non-invasive and rapid QMR technique, which has a high precision with a MDC of 0.18 kg of FM, was found to have a limited validity to assess short-term changes in fat mass compared to balance data [73] (Table 1). Changes in FM based on QMR estimates were lower than the respective estimates calculated from energy balance, i.e., 90 g/d during 21 d of underfeeding and 120 g/d during 14 d of hypercaloric

Table 1 Changes in body composition with 3 weeks of underfeeding (− 50% energy requirement) and two weeks of refeeding (+ 50% energy requirement) compared between QMR and balance methods (means ± SD)

	Before underfeeding (T1)	Underfeeding (UF)	Refeeding (RF)	ΔUF-T1	ΔRF-UF
Body weight (kg)	79.4 ± 7.8	73.5 ± 7.4	76.9 ± 7.9	− 6.0 ± 0.8†††	3.5 ± 1.2†††
N-intake (g/d)	22.6 ± 2.2	9.0 ± 0.2	28.0 ± 0.7	− 13.6 ± 2.4†††	18.9 ± 0.8†††
N-excretion (g/d)	17.8 ± 2.2	12.9 ± 1.8	38.0 ± 3.1	− 5.1 ± 2.0††	25.1 ± 2.5†††
N-balance (g/d)	4.8 ± 1.9	− 3.9 ± 1.6	10.0 ± 1.9	–	–
N-balance (g/phase)				− 79.0 ± 33.6†††	138.7 ± 68.5†††
$FFM_{N\text{-balance}}$ (kg)*	–	–	–	− 2.5 ± 1.1	4.5 ± 2.2
TBW_{QMR} (l)	40.4 ± 4.3	37.5 ± 4.3	38.7 ± 4.3	− 2.9 ± 1.2	1.2 ± 1.9
E-intake (kcal/d)	4083 ± 467	1361 ± 156	4083 ± 467	− 2722 ± 311†††	2722 ± 311†††
DIT (kcal/d)	352 ± 41	117 ± 14	352 ± 41	− 235 ± 28†††	235 ± 28†††
AEE (kcal/d)	572 ± 304	473 ± 210	628 ± 323	− 107 ± 233	154 ± 299
REE (kcal/d)	1946 ± 183	1720 ± 193	1914 ± 209	− 226 ± 138†††	194 ± 110†††
TEE (kcal)	2879 ± 396	2305 ± 356	2900 ± 452	− 577 ± 246†††	590 ± 363†††
$E\text{-balance}_{(E\text{-intake-TEE})}$ (kcal/phase)	–	–	–	− 44,899 ± 8360	29,753 ± 5950
FM_{QMR} (kg)	14.6 ± 5.3	12.0 ± 5.0	13.2 ± 5.0	− 2.6 ± 0.5†††	1.2 ± 0.6†††
FFM_{QMR} (kg^{Δ})	64.8 ± 7.4	61.5 ± 7.1	63.7 ± 7.3	− 3.4 ± 0.8†††	2.3 ± 0.9†††
$E\text{-balance}_{(\Delta FFM + \Delta FM)}$ (kcal/phase)	–	–	–	− 28,181 ± 4853	13,655 ± 6174
$FFM_{N\text{-balance}} - FFM_{QMR}$ (kg)	–	–	–	0.9 ± 0.9^{aaa}	2.2 ± 1.9^{aaa}
$E\text{-balance}_{(E\text{-intake} - TEE)} - E\text{-balance}_{(\Delta FFM + \Delta FM)}$ (kcal)	–	–	–	− 16,872 ± 9618^{aaa}	16,150 ± 8018^{aaa}

*$N \times 16.25$ = protein in g; $FFM_{N\text{-balance}}$ in kg = (protein × 100)/19.41/1000

$^{\Delta}$ FFM_{QMR} = body weight − FM_{QMR}

†† $p < 0.01$ difference between time points, RM-ANOVA

††† $p < 0.001$ difference between time points, RM-ANOVA

^{aaa} $p < 0.001$ differences between methods at a certain time point

AEE, activity energy expenditure; DIT, diet-induced thermogenesis; FM, fat mass; FFM, fat-free mass; REE, resting energy expenditure; TEE, total energy expenditure

re-feeding. This bias adds up to about 1.7 kg FM over the whole feeding periods. This finding is in favor of the idea that multicomponent models should be applied in steady state conditions, while balance methods are recommended to assess short-term changes in body composition in non-steady-state conditions [72].

Concluding Remarks

Today, the effects of over- and underfeeding on body weight, body composition, and related metabolic functions seem to be well established. However, faced with (a) the limitations of methods applied to assess energy balance and body composition, (b) the considerable intra- and inter-individual variances in changes in body weight and body composition and related functions in response to controlled feeding, and finally (c) the still limited number of controlled over- and underfeeding studies in humans, we consider our present textbook knowledge as a simplification. For forthcoming over- and underfeeding studies, we recommend addressing the variance of changes in body weight, body composition, and related functions.

Compliance with Ethical Standards

Conflict of Interest Manfred James Müller declares that he has no conflict of interest.

Anja Bosy-Westphal is a consultant for seca GmbH, Hamburg, Germany.

Human and Animal Rights and Informed Consent This article contains studies with human subjects performed by the authors. The respective study protocols had been approved by the local Ethical Committee of the Christian Albrechts Universität zu Kiel, Germany. After an extensive clarification, all the study participants had given their informed written consent before the study. The authors confirm that all information given in this manuscript is accurate.

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