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Review

Deep body composition phenotyping during weight cycling: relevance to metabolic efficiency and metabolic risk

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Summary

Weight cycling may lead to adverse effects on metabolic efficiency (i.e. adaptive thermogenesis or 'metabolic slowing') and metabolic risks (e.g. increased risk for insulin resistance and the metabolic syndrome). In order to investigate these topics, the partitioning of fat and lean mass (i.e. the change in the proportion of both compartments) needs to be extended to the organ and tissue level because metabolic risk differs between adipose tissue depots and lean mass is metabolically heterogeneous being composed of organs and tissues differing in metabolic rate. Contrary to data obtained with severe weight loss and regain in lean people, weight cycling most likely has no adverse effects on fat distribution and metabolic risk in obese patients. There is even evidence for an increased ability of fat storage in subcutaneous fat depots (at the trunk in men and at the limbs in women) with weight cycling that may provide a certain protection from ectopic lipid deposition and thus explain the preservation of a favourable metabolic profile despite weight regain. On the other hand, the mass-specific metabolic rate of lean mass may increase with weight gain and decrease with weight loss mainly because of an increase and respective decrease in the proportion (and/or activity) of metabolically active organ mass. Obese people could therefore have a higher slope of the regression line between resting energy expenditure (REE) and fat-free mass that leads to an overestimation of metabolic efficiency when applied to normalize REE data after weight loss. Furthermore, in addressing the impact of macronutrient composition of the diet on partitioning of lean and fat mass, and the old controversy about whether a calorie is a calorie, we discuss recent evidence in support of a low glycaemic weight maintenance diet in countering weight regain and challenge this concept for weight loss by proposing the opposite.

Keywords: Body fat distribution, insulin resistance, resting energy expenditure, weight cycling.

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Introduction

Weight cycling, the repeated loss and regain of body weight, is characterized by metabolic adaptation to weight loss and thus originally contributed to ensure increased survival capacity during alternating periods of feast and famine whereas it is suspected to lead to adverse health consequences during yo-yo dieting in modern affluent societies. It remains, however, a controversial scientific debate whether weight cycling

predisposes to weight gain and obesity-associated metabolic risk.

Regulation of energy partitioning

A precondition for the evaluation of changes in body composition with weight loss and weight regain is knowledge on the determinants of partitioning, i.e. relationship between weight gain or weight loss-associated changes in (i) fat mass (FM) and fat-free mass (FFM), (ii) organ and muscle mass as well as (iii) different adipose tissues and ectopic fat or (iv) at the molecular body composition level: glycogen, protein, water and fat. FM is the first and foremost determinant of calorie partitioning followed by others such as age, ethnicity, gender, activity (exercise) and inactivity, growth and reproduction as well as energy balance and macronutrient composition (for a review see (1)). Gilbert Forbes had found a non-linear equation that predicted the fat-free proportion of a weight change solely based on the initial body fat content ($\Delta FFM/\Delta BW = 10.4/(10.4 + FM)$) (2). From this fundamental law, it can be deduced that in obese compared with lean patients, weight loss as well as weight regain both consist of a higher proportion of FM and that a catch-up fat phenomenon and fat overshooting (with fat regain exceeding fat loss) can thus only be measured in lean subjects.

The relationship described by Forbes is also differently affected by body region in both genders (3). With increasing adiposity, the ratio of skeletal muscle to adipose tissue decreases faster at the trunk than corresponding ratios for the extremities in men. That implies a preferential accumulation of trunk adipose tissue with higher degrees of obesity in men. By contrast with weight gain in women, body fat accumulates predominantly at the extremities (3). Knowledge on normal gender-specific partitioning of lean and FM is important because a redistribution of body fat to the truncal or visceral compartments has been proposed to occur during weight regain ((4,5), see next section).

Although the empirical Forbes equation has been confirmed using larger and more diverse datasets (6), mathematic modelling of the FFM–FM relationship was more recently improved to comprise also age, height, gender and ethnicity (7). The most sophisticated dynamic model of changes in body weight and FM was developed by Hall *et al.* (8). It includes a range of baseline parameters (body weight, % FM, age, height, physical activity level, resting energy expenditure [REE], energy intake, % energy from carbohydrate [CHO], sodium intake) and intervention parameters (changes in sodium and energy intake, % energy from CHO and physical activity level) and takes water balance into account. In this model, changes in glycogen and protein content determine changes in intracellular water whereas changes in CHO intake determine sodium excretion or retention and thus changes in extracellular water. When predicted changes in body weight and body composition are subtracted from actual changes that are obtained during an intervention study, the mathematical model can be used to normalize individual patient data and facilitate interindividual comparison of energy partitioning adjusted for physiological determinants.

Energy partitioning is also affected by metabolic and endocrine disturbances associated with diseases and hormonal changes during the life cycle. Insulin resistance occurs with acute or chronic inflammation and may contribute to shift partitioning towards a higher regain in FM with weight recovery in these patients (9–11). Changes in insulin (12) and other endocrine determinants (e.g. growth hormone, insulin-like growth factor 1 (IGF-1), estrogen, testosterone, cortisol and triiodothyronine) during growth, reproduction and senescence (e.g. puberty, pregnancy and ageing), training or weight loss also have an impact on energy partitioning (13–20).

Methodological issues of the assessment of energy partitioning

Measurement as well as prediction of changes in body composition is complicated because the fraction of weight loss or weight regain as FFM dynamically changes over time (1). During the first days, the $\Delta FFM/\Delta weight$ ratio is relatively large when weight loss or weight regain mainly consist of intracellular water bound to glycogen or protein or water associated to sodium excretion or retention. This unstable condition leads to a violation in the method's inherent assumptions such as a constant density of FFM and impedes the accurate detection of initial changes in fat and lean mass (21,22). On the other hand, a four-compartment model that provides a more accurate measurement of lean and FM independent of shifts in water balance is, nonetheless, not sensitive enough to detect small differences in fat and lean mass. Valid results thus require the use of balance methods or a minimum duration and extent of weight change (22).

Partitioning of weight loss versus weight regain

In postmenopausal women (23) and elderly people from the Health Ageing and Body Composition Study (24), the authors concluded from their data that proportionally more lean mass was lost during the weight loss period than was regained during the weight-regain period. However, a higher loss in lean mass per kilogram of weight loss was only observed for men in the Health Ageing and Body Composition Study and the results were not significant when compared with a group of elderly men who had been weight stable over the same follow-up period (24). Even the discrepancy in the composition of diet-induced weight loss and spontaneous weight regain in postmenopausal women

was only suggestive as the differences were not significant because of the small changes in lean mass that showed a high interindividual variance (23). Therefore, the results on weight cycling in elderly people are not conclusive and more data obtained under controlled conditions are needed before an adverse effect of weight cycling on body composition in the elderly can be deduced.

In contrast to these studies in elderly people, the famous Minnesota semistarvation experiment has clearly shown a discrepancy in partitioning of weight loss and regain favouring fat regain in post-starvation recovery in lean young men (25–27). This disproportional regain in FM is termed the *catch-up fat phenomenon* (27). A mechanistic explanation comes from a rat model of weight recovery showing *catch-up fat*: after 1 week of isocaloric refeeding, insulin-stimulated glucose utilization was lower in skeletal muscle (by 20–43%) but higher in white adipose tissues (by two- to threefold) (28). Because perturbations in energy balance, either by over- or underfeeding, are known to decrease and increase insulin sensitivity (29), these changes in insulin sensitivity and the increased insulin secretion during refeeding may be the main drivers of changes in energy partitioning during a weight cycle.

Although the catch-up fat phenomenon is not dependent on hyperphagia but is also observed during isocaloric refeeding (25,26), energy deficit and energy surplus have an impact on partitioning. A gain in muscle mass can only be achieved during the anabolic effect of a positive energy balance whereas a higher energy deficit during dieting leads to a more negative nitrogen balance and thus increases ΔFFM/Δweight, i.e. an accelerated loss in lean mass (30,31). From the Forbes equation, a protein sparing effect of FM can be predicted during energy restriction. In addition, consuming dietary protein at levels above the recommended dietary allowance ($0.8\ g \cdot kg^{-1} \cdot d^{-1}$) attenuates negative N-balance during caloric restriction by affecting the intracellular regulation of muscle anabolism and proteolysis (32).

Changes in the partitioning of fat and lean mass may also occur in response to changes in cellular energetic efficiency. Metabolic pathways such as *de novo* lipogenesis, ketogenesis, urea synthesis and glyconeogenesis have a high energy cost. If energy is wasted, less energy is available as adenosine triphosphate (ATP) for anabolic processes, such as protein or fat synthesis. Energetic efficiency is influenced by diet composition (i.e. the administration of high doses of glucose leads to *de novo* lipogenesis) and energy balance (i.e. energetic efficiency is increased during caloric restriction and may persist during refeeding). The latter idea is supported by evidence suggesting that (besides hyperinsulinaemia and insulin resistance) suppressed thermogenesis in skeletal muscle contributes to the accelerated fat regain during refeeding (33,34).

An increased propensity to regain FM after massive weight loss may also be explained by an improved fat storage capacity in adipose tissue. This idea is supported by studies in rats that showed a higher fatty acid synthase activity in adipose tissues from refed animals than from fed controls (28). In addition, regain in body weight was associated with adipocyte hypercellularity suggesting recruitment of preadipocytes (35). In humans, diet-induced weight loss led to enhanced subsequent *in vitro* expression of genes involved in *de novo* lipogenesis and increased adipogenic capacity of preadipocytes (FASN, DGAT2, SCD1, ACLY and ChREBPα) and shifted their secretions towards a lower inflammatory profile (36). The authors suggested that augmented *de novo* lipogenesis together with higher insulin sensitivity represent intrinsic characteristics of adipocytes reprogrammed by weight loss. Other authors found that abdominal subcutaneous lipoprotein lipase (LPL) activity after weight reduction was negatively related to weight regain in women, whereas in men both the post-weight loss abdominal subcutaneous α2-adrenoreceptor density and the α2-/β-adrenoreceptor balance were positively associated with weight regain (37).

In contrast to previous studies, we examined in 14 healthy young men, who underwent a controlled diet-induced weight cycle (38), the change in adipose tissue gene expression during weight regain (at the end the refeeding period) relative to that at the end of caloric restriction. Weight regain led to a marked downregulation of expression of C/EBPα (a stimulator of adipogenesis, although also implicated as an inhibitor of adipocyte growth (39)) by threefold (0.36 ± 0.38; $P < 0.001$) whereas the expression of proliferator-activated receptor γ (PPARγ, a stimulator of lipid uptake and adipogenesis) was significantly up-regulated by threefold (2.96 ± 2.94; $p < 0.01$, Fig. 1). If C/EBPα was up-regulated after caloric restriction (a 2.4-fold up-regulation was shown after 16% weight loss in obese women (40)), it may well be down-regulated again at the end of refeeding whereas additional fat storage is then facilitated by up-regulation of PPARγ. We found that the increase in PPARγ expression during refeeding was associated with an increase in the regain of FM adjusted for the fat regain predicted by the Hall model (8) ($r = 0.54$; $P < 0.05$).

Finally, the endocrine explanation of the *catch-up fat* phenomenon can be provided not only by insulin and insulin sensitivity but also by leptin. After weight loss, the low leptin secretion of small lipid-depleted adipocytes can, not only increase appetite and thus facilitate fat regain (41), but may also trigger a cellular programme controlling the recovery of adipose tissue mass (42). Leptin deficiency thus led to the transient deposition of large amounts of glycogen within lipid-depleted adipocytes followed by a rapid reaccumulation of fat in those cells (42). Because the repletion of lipid in adipocytes was associated with a coordinated induction of glycolytic genes and pathways of lipogenesis, the authors concluded that fat is synthesized via a glycogen intermediate.

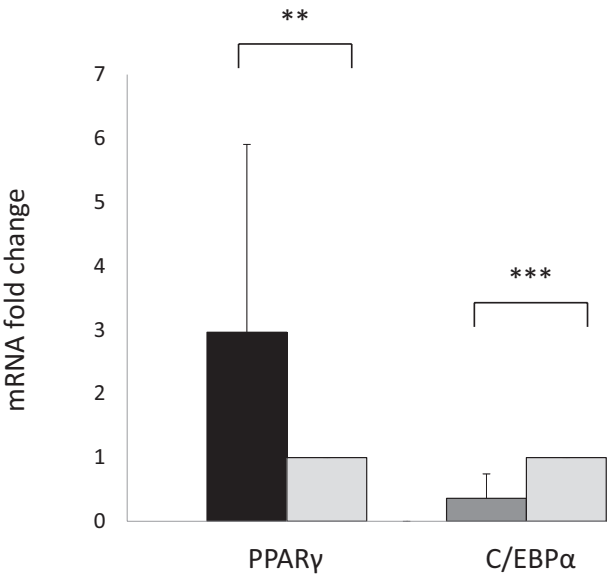

Figure 1 Effect of refeeding on gene expression in subcutaneous adipose tissue in 14 healthy young men who underwent 3 weeks of calorie restriction followed by 2 weeks of refeeding (38). Needle (aspirate) biopsies were taken from abdominal subcutaneous adipose tissue laterally of the umbilicus. For gene expression analysis, total RNA was isolated using an RNeasy mini kit (Qiagen, Hilden, Germany). Transcription of RNA into cDNA was performed by a high capacity cDNA reverse transcription kit (Applied Biosystems, Weiterstadt, Germany). Quantitative Real-Time (RT)-PCR of mRNA for peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer binding protein alpha (C/EBPα) was done using a qPCR SYBR-Green ROX Mix (ABgene, Hamburg, Germany) and the Mastercycler Realplex system (Eppendorf, Wesseling, Germany). mRNA expression after refeeding (dark columns) was calculated relative to the end of caloric restriction and normalized to glyceraldehyde 3-phosphate dehydrogenase expression using ΔΔ Ct method ($n = 14$); one sample *t*-test with test value = 1; $^{**}P < 0.01$; $^{***}P < 0.001$.

Mathematical modelling of changes in the composition of lean mass during the Minnesota semistarvation experiment revealed glycogen as an important determinant of partitioning (43). The model predicted a rapid initial drop of glycogen stores with caloric restriction but at the onset of semistarvation the glycogen content increased again and was even predicted to exceed baseline levels because of the progressive reduction in physical activity with weight loss. During refeeding, the model predicted high rates of *de novo* lipogenesis caused by the elevated glycogen content with a simultaneous high carbohydrate intake. The impact of macronutrient composition of the diet on partitioning is discussed in the succeeding text. The importance of glycogen for partitioning (i.e. the fuel mix oxidized) was proposed by Flatt (44) who claimed that recent changes in the food supply and a decline in physical activity could have led to an increase in the glycogen levels and thus contributes to the obesity epidemic. When glycogen stores were lowered by exhaustive exercise, obese subjects were capable of rapidly adjusting fat oxidation to high fat intake (45). The effect of exercise on glycogen content could thus contribute to the improved weight maintenance with exercise (i.e. a high energy flux) after diet-induced weight loss. However, high oxidative capacity because of chronic exercise training has been shown to attenuate the lipid-induced reduction in non-oxidative glucose disposal (46). Trained subjects thus partly maintained their insulin sensitivity with lipid infusion by maintaining glycogen synthesis (46). By contrast, glycogen synthesis is markedly reduced in lean patients with type 2 diabetes, obese subjects with a normal glucose tolerance, hypertensive or hypertriacylglycerolaemic patients as well as in patients with cardiovascular disease (CVD) (47). The impact of glycogen content on fuel partitioning and weight gain thus requires further investigation.

Weight cycling induced changes in fat partitioning: impact on metabolic risk

From the analysis of cross-sectional data, it was suggested that weight cycling contributes to body weight excess and abdominal fat distribution (5). A preferential trunk or visceral fat regain may occur after severe depletion of nutritional state and has been shown in studies on weight recovery in patients with anorexia nervosa (48,49) whereas others found no (50) or only a transient accumulation of visceral fat with weight restoration that is normalized within a 1-year period of weight maintenance (51). From a reanalysis of 61 studies, Chaston and Dixon (52) concluded that visceral adipose tissue (VAT) is lost preferentially with modest weight loss, but the effect is attenuated with greater weight loss. This is confirmed by a simple allometric model of changes in visceral versus total body FM that predicts that increasing weight loss attenuates the preferential loss of VAT versus subcutaneous adipose tissue (SAT) (53). It is thus tempting to speculate that visceral fat is preferentially lost or regained at the beginning of weight loss or weight regain. In contrast to data in anorectic patients, results in obese patients did not confirm an effect of weight cycling on visceral fat accumulation (54,55) or even found an increased gynoid pattern of fat redistribution after weight regain (56–58). Our results confirm the absence of a preferential accumulation of visceral fat with weight regain and showed a sex-specific redistribution of subcutaneous adipose tissue at the trunk in men and at limb depots in women (59). This is very consistent with the preferential deposition of subcutaneous limb adipose tissue in women or trunk adipose tissue in men with increasing FM in cross-sectional data (3).

A preferential regain in subcutaneous contrary to visceral fat depots is also consistent with long-lasting improvements in liver fat and metabolic risk that were reported despite a substantial body weight regain after dietary weight loss in

obese patients (60). Other authors found that a very low calorie diet (VLCD) reduced body weight, pericardial fat, hepatic triglyceride content, visceral and subcutaneous abdominal fat volumes to 78, 83, 16, 40 and 53% of baseline values, whereas after follow-up on a regular diet, the reduction in pericardial fat volume was sustained, despite a substantial regain in body weight, visceral abdominal fat and hepatic fat content (90, 83 and 73% of baseline values (55)).

Increased metabolic risk in obesity is related to limited lipid storage capacity and dysfunction of hypertrophic adipocytes. It is thus tempting to speculate that enhanced fat storage capacity/adipocyte hyperplasia in subcutaneous adipose tissue resulting from weight cycling could lower lipid overflow, ectopic lipid storage and lipotoxicity and improve insulin sensitivity. A drawback of increased adipogenesis after weight loss could, however, be a compromise of weight loss maintenance. As the rate of basal lipolysis is higher in enlarged adipocytes (61,62), the higher availability of fat-derived fuel could reduce protein catabolism and preserve lean mass during caloric restriction. This is supported by a tendency towards an inverse relationship between adipocyte cell size or a positive association with adipocyte number and nitrogen deficit during fasting (19).

Weight cycling could have an adverse effect on bone health because bone marrow adipose tissue decreases with diet-induced weight loss and shows a disproportional high recovery during spontaneous weight regain that occurred concomitant to a decrease in bone mineral density (63). This could be explained by an increased expression of PPARγ with weight regain because the PPARγ pathway not only determines adipocyte differentiation from mesenchymal progenitors, but also inhibits osteoblast differentiation (64) and an increased risk for osteoporosis was observed as a side effect of glitazones (PPARγ agonists) (65).

Weight cycling induced changes in lean mass partitioning: impact on metabolic efficiency

A redistribution of skeletal muscle mass may occur with weight cycling. After diet-induced weight loss in obese men and women, the reconstitution of skeletal muscle at the trunk during spontaneous 6 months weight regain lagged behind the extremities (59). These findings are supported by Byrne *et al.* (66) who found a preferential regain of lean soft $tissue_{DXA}$ at the limbs compared with the trunk in weight regaining obese African–American and white women.

Further changes in the partitioning of lean mass with weight gain and weight loss concern the contribution of organ mass to total FFM. We found increasing masses of liver, heart and kidneys per kilogram FFM with increasing %FM whereas brain mass per FFM decreased (Table 1, (67)). Because internal organs have a very high specific metabolic rate, the higher contribution of these organ masses to FFM leads to a higher specific metabolic rate of the total FFM in obesity. Because of this observation, a regression analysis derived from participants with a higher %FM cannot be used to normalize REE in a leaner group of people without bias (67). Diet-induced weight loss in obese people lead to a decrease in organ mass per kilogram FFM with the exception of brain mass/FFM that increased after weight loss (Table 2). Therefore, the application of a regression equation before weight loss to normalize REE after weight loss may lead to an overestimation of the decrease in specific metabolic rate (i.e. adaptive thermogenesis or metabolic efficiency). Because calorie restriction along with vigorous exercise results in preservation of skeletal muscle but presumably not organ mass, the unexpected finding of a greater metabolic adaption in participants of 'The Biggest Loser' weight loss competition when compared with patients who lost the same amount of body weight after Roux-en-Y gastric bypass surgery (68) is likely also explained by a change in FFM composition.

Table 1 Coefficients of correlation between organ masses per kilogram of fat-free mass (FFM) and the percentage of body fat (%FM). Data are taken from (66)

	%FM versus	
	Women ($n = 179$)	Men ($n = 122$)
Brain mass, kg FFM^{-1}, kg	–0.25**	–0.05
Liver mass, kg FFM^{-1}, kg	0.39***	0.53***
Heart mass, kg FFM^{-1}, kg	0.17*	–0.18
Kidney mass, kg FFM^{-1}, kg	0.38***	0.21*

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

Table 2 Comparison of organ masses per kilogram of fat-free mass (FFM) before and after diet-induced or bypass surgery-induced weight loss (–20.7 ± 15.1 kg) in healthy obese people (59 women and 17 men)

	Baseline ($n = 75$)	Weight loss	Paired *t*-test
Brain/FFM	0.025 ± 0.004	0.026 ± 0.004	$P < 0.001$
Liver/FFM	0.036 ± 0.008	0.033 ± 0.006	$P < 0.001$
Heart/FFM	0.0044 ± 0.0015	0.0039 ± 0.0007	$P < 0.01$
Kidneys/FFM	0.0055 ± 0.0014	0.0049 ± 0.0009	$P < 0.001$

Data were derived from the study in reference (67). Values are means ± standard deviation.

Impact of diet composition on partitioning of weight loss and weight regain

Results of the Diogenes study suggest improved weight maintenance with a modest reduction in the glycaemic index and a modest increase in protein content (69). One plausible mechanism for this observation is the reciprocal

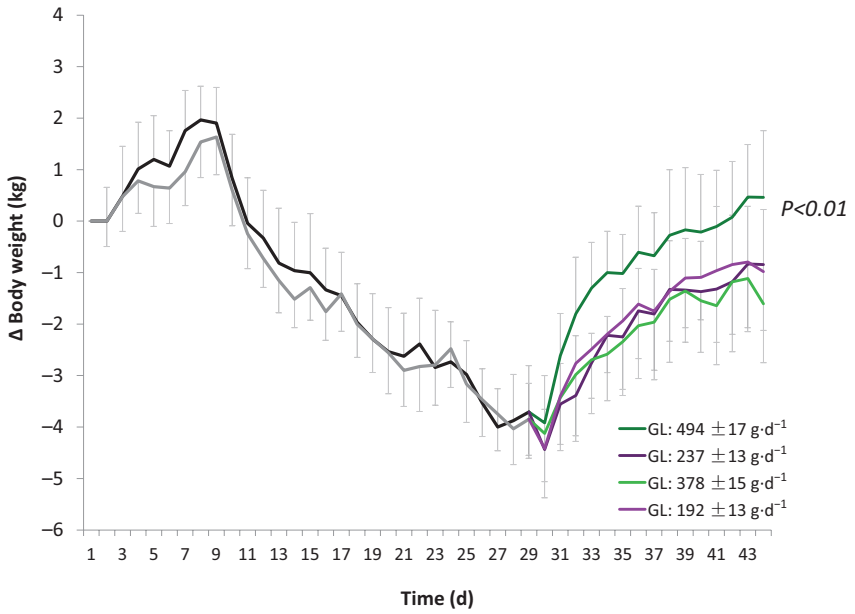

Figure 2 Changes of body weight versus time course in a controlled nutritional intervention.
Thirty-two healthy men (26.0 ± 3.9 year, body mass index 23.4 ± 2.0 kg m^{-2}) followed 1 week of overfeeding, 3 weeks of caloric restriction and 2 weeks of hypercaloric refeeding at ±50% energy requirement. During refeeding, four study groups were formed differing in carbohydrate intake (50%CHO vs. 65%CHO) and glycaemic index (GI, 40 ± 3 vs. 74 ± 3) leading to four groups with different glycaemic load (GL). During overfeeding, participants gained +1.8 ± 0.7 kg body weight, followed by a weight loss of –6.0 ± 0.8 kg and weight regain of 3.4 ± 1.1 kg. Regain in body weight was affected by CHO ($P < 0.01$) and GI × CHO interaction ($P < 0.05$, repeated-measures analysis of variance, independent factors GI and CHO). Subjects with 65%CHO diet regained more body weight (4.4 ± 0.6 kg) compared with 50%CHO-low glycemic index (LGI) (3.4 ± 1.1 kg; $P < 0.05$) or 50%CHO-high glycemic index (HGI) diet (2.5 ± 1.1 kg; $P < 0.01$). Adapted from reference (38).

relationship between glucose and fat metabolism: glucose utilization is associated with higher insulin levels that inhibit lipolysis and thus facilitates lipid storage. Individuals with higher insulin sensitivity or a higher insulin secretion may thus be vulnerable to a high glycaemic load (GL) diet. Such an interaction between glucose metabolism and diet has been reported to affect body weight regulation after weight loss (70,71). Because of the inverse relationship between insulin sensitivity and insulin secretion in healthy subjects, both parameters need to be taken into account when the effect of glucose metabolism on body weight regulation is investigated. Lower insulin sensitivity may also be advantageous under fasting conditions (i.e. a higher reliance on fat oxidation). However, insulin resistance is associated with an impaired metabolic flexibility that contributes to a higher rate of gluconeogenesis under fasting conditions (i.e. an energy consuming metabolic pathway) and a higher reliance on fat oxidation under postprandial conditions (which may lead to a decrease in fat balance). Therefore, the impact of glucose metabolism on body weight regulation remains complex and only poorly understood with a lot of controversial results from previous studies (for review see (72)).

In a controlled dietary-induced weight cycle (overfeeding, caloric restriction and refeeding), we investigated the effect of GL on changes in insulin sensitivity and body composition with weight loss and weight regain (38,73), changes in body fat being measured by quantitative magnetic resonance (QMR, EchoMRI, Echo Medical Systems, Houston, TX, USA) and changes in protein and lean mass were assessed by nitrogen balance. We found that insulin sensitivity was improved after weight loss irrespective of the diet whereas it decreased again with weight regain on a high GL diet. By contrast, insulin sensitivity was maintained on a refeeding diet with low GL. Although weight was similar between diet groups, weight regain on a high GL diet was significantly higher (Fig. 2) and regain in FM tended to be higher (1.7 ± 0.6 vs. 1.0 ± 0.6 kg, $P < 0.05$ when the two subgroups with the lowest and highest GL were compared by a *t*-test (74)).

We had put forward the hypothesis that the impact of GL on changes in body composition differs for weight loss and weight regain. Because a high GL diet could attenuate the decrease in insulin and leptin levels with weight loss (75) and a low GI diet could reduce insulin secretion with weight regain, anti-cyclical diet could be recommended to counteract metabolic and endocrine adaptation to weight loss and weight regain. In line with our hypothesis, stepwise regression analysis revealed that GL during caloric restriction was a positive predictor (39% explained variance) and GL during refeeding a negative predictor of the regain in protein (ΔN balance) during refeeding

($R^2 = 0.60$). In order to evaluate the observed changes in partitioning with refeeding (Δlean mass by nitrogen balance/Δbody weight) independent of differences in body composition, we adjusted them by predicted changes (based on FM before weight regain) using the Forbes model (2). The results remained the same and GL during caloric restriction and refeeding together explained 42% of the variance in adjusted changes in partitioning with refeeding. During caloric restriction, glucose is known to have a larger protein-sparing effect than lipids, which is partly explained by increased insulin secretion because insulin inhibits muscle proteolysis, hepatic gluconeogenesis and renal ammoniogenesis (for a review see (76)).

Besides GL, a further determinant of the discrepancy between measured and predicted changes in partitioning was the change in basal fat oxidation (Δfasting non-protein respiratory quotient, ΔNPRQ) (r = 0.53 for caloric restriction and r = 0.51 for refeeding, both $P < 0.01$). This result implies that the ability to increase basal fat oxidation with weight loss or to maintain basal fat oxidation under refeeding conditions favourably affects the composition of weight loss and weight gain.

Conclusion

Body weight regulation needs to be investigated by analysing weight partitioning rather than body weight *per se*. Because of differences in their specific energy content and metabolic consequences, the loss and regain of fat and lean mass are more meaningful for our understanding of the regulation of energy balance and metabolic risk. Interpretation of changes in fat and lean mass requires knowledge on their physiological determinants in order to appropriately normalize the data (e.g. for baseline body composition). Deep body composition phenotyping revealed an overestimation of the often claimed adverse effects of weight cycling on metabolic efficiency and metabolic risk. The impact of dietary GL on the regulation of partitioning deserves further studies using more accurate, precise and sensitive technologies for the assessment of small changes in body composition as well as controlled dietary interventions.

Conflict of interest statement

The authors declare no conflict of interest.

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