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Review

How dieting makes the lean fatter: from a perspective of body composition autoregulation through adipostats and proteinstats awaiting discovery

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Summary

Whether dieting makes people fatter has been a subject of considerable controversy over the past 30 years. More recent analysis of several prospective studies suggest, however, that it is dieting to lose weight in people who are in the healthy normal range of body weight, rather than in those who are overweight or obese, that most strongly and consistently predict future weight gain. This paper analyses the ongoing arguments in the debate about whether repeated dieting to lose weight in normal-weight people represents unsuccessful attempts to counter genetic and familial predispositions to obesity, a psychosocial reaction to the fear of fatness or that dieting *per se* confers risks for fatness and hence a contributing factor to the obesity epidemic. In addressing the biological plausibility that dieting predisposes the lean (rather than the overweight or obese) to regaining more body fat than what had been lost (i.e. fat overshooting), it integrates the results derived from the re-analysis of body composition data on fat mass and fat-free mass (FFM) losses and recoveries from human studies of experimental energy restriction and refeeding. These suggest that feedback signals from the depletion of both fat mass (i.e. adipostats) and FFM (i.e. proteinstats) contribute to weight regain through the modulation of energy intake and adaptive thermogenesis, and that a faster rate of fat recovery relative to FFM recovery (i.e. preferential catch-up fat) is a central outcome of body composition autoregulation in lean individuals. Such a temporal desynchronization in the restoration of the body's fat vs. FFM results in a state of hyperphagia that persists beyond complete recovery of fat mass and interestingly until FFM is fully recovered. However, as this completion of FFM recovery is also accompanied by fat deposition, excess fat accumulates. In other words, fat overshooting is a prerequisite to allow complete recovery of FFM. This confers biological plausibility for post-dieting fat overshooting – which through repeated dieting and weight cycling would increase the risks for trajectories from leanness to fatness. Given the increasing prevalence of dieting in normal-weight female and male among young adults, adolescents and even children who perceive themselves as too fat (due to media, family and societal pressures), together with the high prevalence of dieting for optimizing performance among athletes in weight-sensitive sports, the notion that dieting and weight cycling may be predisposing a substantial proportion of the population to weight gain and obesity deserves greater scientific scrutiny.

Keywords: Adaptive thermogenesis, obesity dieting, weight cycling.

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Introduction

The prevalence of obesity is well known to increase rapidly, often to reach epidemic proportions, in communities and countries emerging into affluence. These transitions occur through complex interactions between genetics and changes in an environment that favour food marketing practices that provide easy access to palatable energy-dense foods all year round and where physical activity demands are low. In addition to these traditional 'Big Two' obesogenic factors, several non-traditional (non-caloric) predictors of obesity have been identified and include short sleep duration, low dietary calcium intake, microbiota composition, epigenetics and developmental programming, endocrine disruptors or other pollutants (1–3). The findings that the risk of overweight/obesity could be higher for the combination of some of these non-traditional (non-caloric) risk factors than for the combination of high dietary fat intake and low physical activity (3) emphasizes the importance of looking beyond strategies to counter the 'Big Two' factors as cornerstones of obesity prevention and treatment. Paradoxically, the use of dieting for weight control – particularly among those who are in a healthy normal range of body weight – has also emerged as a robust predictor of future weight gain and obesity, thereby raising questions about cause–effect relationships between dieting and fatness.

This paper first reviews the evidence linking dieting to future weight gain and discusses the bilateral relationships between dieting and predisposition to fatness. It then provides, from a perspective of body composition autoregulation, a mechanistic explanation as to how dieting and weight cycling may confer a greater predisposition to the lean (than to the overweight or obese) for excess weight regain and fat overshooting, thereby triggering increased risks for trajectories from leanness to fatness.

Prospective studies linking dieting to future weight gain

Since the early 1990s, more than 15 prospective studies (4–19), conducted over periods ranging from 1 to 15 years, have suggested that dieting to lose weight is associated with future weight gain and obesity, even after adjustment for potential confounding factors such as baseline body mass index (BMI), age and a number of lifestyle and behavioural characteristics. Some of these longitudinal studies showing that dieting predicts future weight gain have been conducted in young and middle-aged adults (4–6,8,10,11,13,15), others in adolescents as they progress into young adulthood (14,16–18), and some in children progressing into adolescence (12,19). For example, in the study of Field *et al.* (12), dieting predicted weight gain in both pre-adolescent and adolescent boys and girls even after adjustment for pubertal development, dietary intake, physical activity and BMI in the previous year, whereas in a recent study by Balantekin *et al.* (19), girls who reported early dieting (prior to age 11) with parental encouragement had greater increases in BMI percentile from 9 to 15 years compared with girls whose mothers or fathers did not encourage dieting. Particularly informative are the 3-year follow-up studies of Stice *et al.* (7) showing that adolescents with baseline dieting had three times the risk of onset of obesity than the non-dieters, and the 10-year longitudinal study of Neumark-Sztainer *et al.* (17) showing that female adolescent dieters increased their BMI by 4.6 units as compared with 2.3 units in non-dieters even after adjusting for socio-demographic characteristics and baseline BMI. Of particular interest is the 6- to 15-year follow-up study reported by Korkelia *et al.* (8) in which the risk of major weight gain (>10 kg) was found to be twofold greater in initially normal-weight subjects who were attempting to lose weight than in non-dieters. By contrast, in initially overweight men and women of this same cohort (8), the history of weight loss attempts was not found to be consistently associated with increased risk of major weight gain. Such differential findings based upon BMI status therefore suggest that the long-term impact of dieting on predisposition to future weight gain may be greater in the lean than in those who are overweight or obese. Strong support for this contention that dieting to lose weight among the lean is a robust predictor of future weight gain can also be derived from the more recent analysis by Pietiläinen *et al.* (18) of a large population-based cohort of mostly normal-weight adolescents with a follow-up from adolescence to young adulthood – which suggests a dose-dependent association between the number of lifetime intentional weight losses (i.e. the frequency of weight cycling), gain in BMI and risk of overweight. Compared with subjects with no intentional weight loss, a single episode of weight loss increased the risk of becoming overweight by three times in women and two times in men by age 25, and in addition, women who reported two or more weight loss episodes had five times greater risk of becoming overweight at age 25. Further analysis of these data (18) revealed that the rate of weight gain also differed according to three baseline BMI categories (low, intermediate and high) particularly in male, with those in the lowest baseline BMI category gaining more weight than those in the intermediate or high baseline BMI category – thereby reinforcing the contention that dieting and weight cycling most strongly predicted future weight gain in those who are the leanness.

Dieting and propensity to fatness: a bidirectional relationship

Whether dieting is a causative factor for subsequent weight gain and contributes to the current obesity epidemic has

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been a subject of considerable debate (20–22). Some have proposed that dieting *per se* may actually induce weight gain subsequently (12,16–18,22). Indeed, preoccupations with food and food obsession have often been described long after episodes of food deprivation or dietary restraint (23), and the central tenet of proponents for a causative impact of dieting on future weight gain and obesity centres upon the notion that dieting, and in particular unhealthy dieting (e.g. use of diuretics, diet pills or laxatives, vomiting), predisposes to eating disorders, disinhibition and binge eating. Others (20,21), however, argue that it is not that dieting makes people fatter, but that the fear of becoming fat makes lean people more likely to go on a diet. According to Lowe and Levine (24), normal-weight individuals who are gaining weight are more likely to attempt to lose weight by dieting than those who are not gaining weight. However, because the weight lost on a diet is usually regained, those who are susceptible to gain weight are likely to go on weight loss diets repeatedly and hence become weight cyclers. In other words, individuals predisposed to obesity are more likely to engage in unsuccessful dieting practices in order to control their proneness towards weight gain (24,25) – which is known to be strongly determined by genetic and other environmental influences (e.g. family, societal, learned behaviour).

Genetic and familial effects

The importance of genetic and familial impact on dieting behaviour is indeed strongly supported by the data from the Finnish Twin cohort study by Korkeila *et al.* (8) showing that dieting aggregated in families, and hence underscoring a familial predisposition to gain weight. Subsequent twin studies by Keski-Rahkonen *et al.* (26) have demonstrated that, like proneness for obesity, episodes of intentional weight loss has substantial genetic components, thereby underlining the possibility that individuals who are genetically most susceptible to obesity end up dieting the most and subsequently gain the most weight. Furthermore, among a large group of female twins, Enriquez *et al.* (27) reported that a younger age at dieting onset is associated with increased BMI, dieting behaviours and episodes of weight cycling. While the within-pair analyses showed that genetic and familial factors likely influence the relationship between age at dieting onset and both BMI and dieting behaviours, weight cycling episodes were associated with an earlier age at dieting onset independently of genetic and family factors. However, because of the cross-sectional nature of the analysis, the question remains whether or not dieting *per se* is a contributing factor to excess weight gain.

Beyond genetics and family factors

To directly address this issue of whether weight gain associated with dieting is more strongly related to genetic susceptibility to weight gain than to the weight loss episodes *per se*, Pietiläinen *et al.* (18) investigated the association between dieting and weight gain in more than 4,000 individual twins whose weight and height were obtained from longitudinal surveys at 16, 17, 18 and 25 years, and examined in relation to the number of lifetime intentional weight loss episodes of >5 kg at 25 years. The results showed that in monozygotic twin pairs discordant for intentional weight loss, co-twins with at least one weight loss episode were 0.4 BMI unit heavier than their non-dieting co-twins at 25 years of age, despite no differences in baseline BMI levels. Similarly in dizygotic twin pairs, co-twins with intentional weight losses gained more weight (+2.2 BMI difference) than non-dieting co-twins at 25 years of age. Taken together, these findings (18) confirm previous studies that dieters may be more prone to future weight gain and that dieters have a genetic propensity for obesity, and also provide strong evidence that, in an essentially normal-weight cohort, dieting *per se* may promote subsequent weight gain independently of genetic and familial factors. A role for dieting and weight cycling *per se* in predisposition to future weight gain, beyond genetic and family factors, is also supported by earlier findings in a national cohort of elite male athletes who had represented Finland in international sports competition between 1920 and 1965. Those who performed power sports (e.g. boxing, weight lifting, wrestling) – where weight cycling is common – showed greater gain in BMI from age 20 to 60 years over than athletes engaged in sports without weight cycling (28).

How then does dieting and weight cycling *per se* promote future weight gain? In addressing this question, it should be pointed out that the transition from weight cycling to future weight gain and obesity can be envisaged to occur with or without weight and fat overshooting, the latter being defined as the phenomenon occurring in response to an episode of weight loss and weight regain whereby the amount of weight and fat regained are greater than what had been lost. It is our contention here that in normal-weight individuals, the occurrence of weight and fat overshooting after each cycle constitutes an important feature of the transition from weight cycling of large amplitudes to future weight gain and obesity. What evidence is there that dieting in normal-weight individuals may lead to fat overshooting?

Post-starvation fat overshooting

Support for this contention that dieting *per se* may lead to overshoot in body weight and fat can, in fact, be derived from classic studies of food deprivation and refeeding in normal-weight individuals showing that more weight and fat are recovered than are lost, and in whom hyperphagia persisted well after body weight (and fat) were fully recovered (Fig. 1). These phenomena of post-starvation

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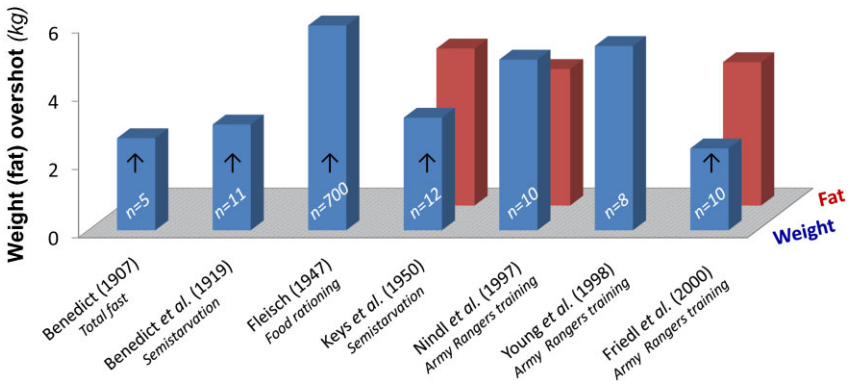

Figure 1 Fat overshooting after one cycle of weight loss and weight regain in normal-weight humans. The data obtained from different studies represent post-starvation weight and fat overshooting (kg), as well as hyperphagic overcompensation in normal-weight men during studies of recovery from experimental and semi-experimental food deprivation. The black arrow pointing upwards (↑) indicates that energy intake was measured in the study, and that hyperphagia was found to persist for some time after weight or fat had been completely recovered. This figure is drawn from the tabulated data published previously (30); see text for details.

hyperphagic overcompensation and weight overshoot (29,30) were first documented by Benedict (31,32) in studies of experimental total fasting or partial starvation. They were subsequently observed at the end of World War II during follow-up studies of food rationing in Switzerland by Fleisch (33,34), as well as in male volunteers subjected to experimental semi-starvation and refeeding in the Minnesota Experiment conducted by Keys *et al.* (35). In the latter classic study, 32 healthy volunteers completed the study that comprised 12 weeks of control baseline period, 24 weeks of semi-starvation (~25% weight loss) and 12 weeks of restricted refeeding. Among 12 of them who remained in the laboratory during the first 8 weeks of *ad libitum* refeeding, food intake increased markedly above the pre-starvation level. This hyperphagic response persisted for several weeks after body weight had been fully recovered and contributed to weight overshooting mostly as fat.

In more recent years, similar weight and fat overshooting, as well as hyperphagic overcompensation, have also been reported in young men recovering from much more modest weight loss than in the Minnesota Experiment, namely at the U.S. Army Ranger School where about 12% of weight loss was observed following 8–9 weeks of training in a multi-stressor environment that includes energy deficit (36–38) (Fig. 1). Nindl *et al.* (36) reported that at week 5 in the post-training recovery phase, body weight had overshot by 5 kg, reflected primarily in large gains in fat mass, and that all the 10 subjects in that study had higher fat mass than before weight lost. Similarly, in another 8 weeks of U.S. Army Ranger training course that consisted of four repeated cycles of restricted energy intake and refeeding, Friedl *et al.* (38) showed that more weight was regained than was lost after 5 weeks of recovery following training cessation, with substantial fat overshooting (~4 kg on average) representing an absolute increase of 40% in body fat compared with pre-training levels. From the data obtained in a parallel group of subjects (38), they showed that hyperphagia peaked at ~4 weeks post-training, thereby suggesting that hyperphagia was likely persisting over the last week of refeeding, during which body fat had already exceeded baseline levels.

Desynchronization in recovery of fat mass and fat-free mass

It should be noted that in some of the above-mentioned studies (Fig. 1) where body composition was assessed, the amount of fat overshot was greater than the amount of weight overshot (35,38). This discrepancy in fat vs. weight overshooting can be explained by the fact that fat-free mass (FFM) was still not fully recovered, i.e. below pre-starvation level, at the end of the study. Indeed, a striking observation from the Minnesota Experiment (Fig. 2) is that it showed that when their body fat had been completely recovered (i.e. 100% control values), the FFM was not yet fully recovered and the hyperphagia, which was still very much evident, only disappeared when FFM was fully recovered (35).

These observations about hyperphagic overcompensation and its relationship with the pattern of body composition recovery and fat overshooting raise fundamental questions about how control systems operate to re-establish fat mass and FFM during weight recovery, namely:

- What is the relative importance of fat vs. FFM depletion as determinants of post-starvation hyperphagia?
- What drives the faster rate of fat mass recovery relative to FFM recovery? Since the latter preferential catch-up fat

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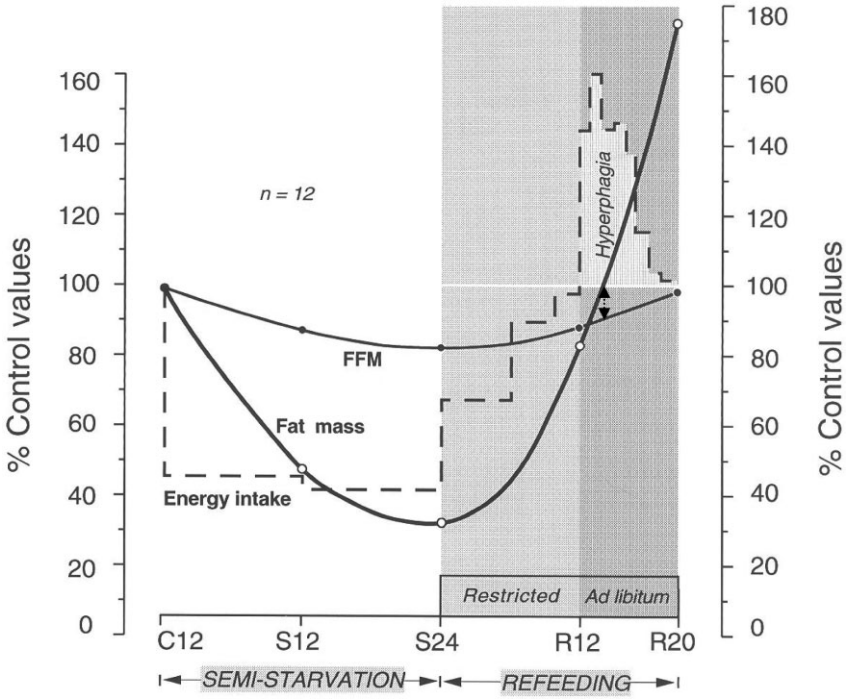

Figure 2 Dynamics of body composition changes in men participating in all phases of the Minnesota Experiment. The data are plotted to show the pattern of changes in energy intake, body fat and fat-free mass (FFM) during semi-starvation and refeeding in the 12 men who completed all phases of the Minnesota Experiment (including the ad libitum phase of refeeding). All values are expressed as percentages of corresponding values during the control (pre-starvation) period. C12: end of 12 weeks of control period; S12 and S24: end of 12 weeks and 24 weeks of semi-starvation, respectively; R12 and R20: end of 12 weeks of restricted refeeding and 8 weeks of *ad libitum* refeeding, respectively. The double-headed arrow indicates that at the time point when body fat had been fully recovered (i.e. 100% of control period value), FFM recovery is still far from complete, with hyperphagia persisting until completion of FFM recovery. Adapted from Dulloo *et al.* (42).

is evident even in the absence of hyperphagia (as observed in the period of restricted refeeding, S24-R12) (Fig. 2), could it be explained by an adaptive reduction in energy expenditure (i.e. adaptive thermogenesis) that occurs during weight loss and which persists during weight recovery? What then is the relative importance of fat mass and FFM depletion as determinants of such adaptive suppression of thermogenesis during weight regain?

- What are the determinants of the large inter-individual variability in partitioning of energy into FFM and fat mass during weight recovery, and in the extent of fat overshooting?

These questions were previously addressed by revisiting the Minnesota Experiment and applying more elaborate statistical and analytical tools in a re-analysis of the data on the dynamic changes in body composition, energy intake and basal metabolic rate in response to the 24 weeks of semi-starvation, 12 weeks of restricted refeeding and subsequent 8 weeks of *ad libitum* refeeding. The methodological approaches and results of this reanalysis have been reported and discussed in detail elsewhere (39–44), and the main results are summarized below.

Control systems in autoregulation of body composition driving fat overshooting

The main findings from our re-analysis of the data from the Minnesota Experiment, which provides insights into the determinants of control systems that operate through the control of body energy partitioning, adaptive thermogenesis and hunger/appetite during weight recovery, have been incorporated into a conceptual model of autoregulation of body weight and body composition, and are depicted in Fig. 3a.

1. The control of energy partitioning between lean and fat compartments confers to the individual's 'basal' or intrinsic energy partitioning characteristic (Pc). The demonstrations (39,43) that the initial adiposity (i.e. initial percentage fat) explains most of the inter-individual variability in Pc, and that the Pc of the individual during weight loss is conserved during weight recovery (39), suggest that the initial body composition expressed as percentage body fat (which reflects the ratio of fat to FFM) provides the individual with a 'memory of partitioning', which dictates an autoregulatory control system that underlies partitioning between protein and fat during weight loss and subsequent weight recovery.

2. Thermogenesis, which is suppressed during weight loss, was found to remain suppressed during weight recovery as a function of fat depletion, but unrelated to FFM depletion (40). This led to the concept for the existence of a 'fat-stores memory', which governs an adaptive suppression of thermogenesis as a function of the replenishment of the fat stores (referred to as *adipose-specific* control of adaptive thermogenesis). Its functional importance is to accelerate specifically fat replenishment, thereby contributing to the disproportionate rate of body fat relative to lean tissue recovery.

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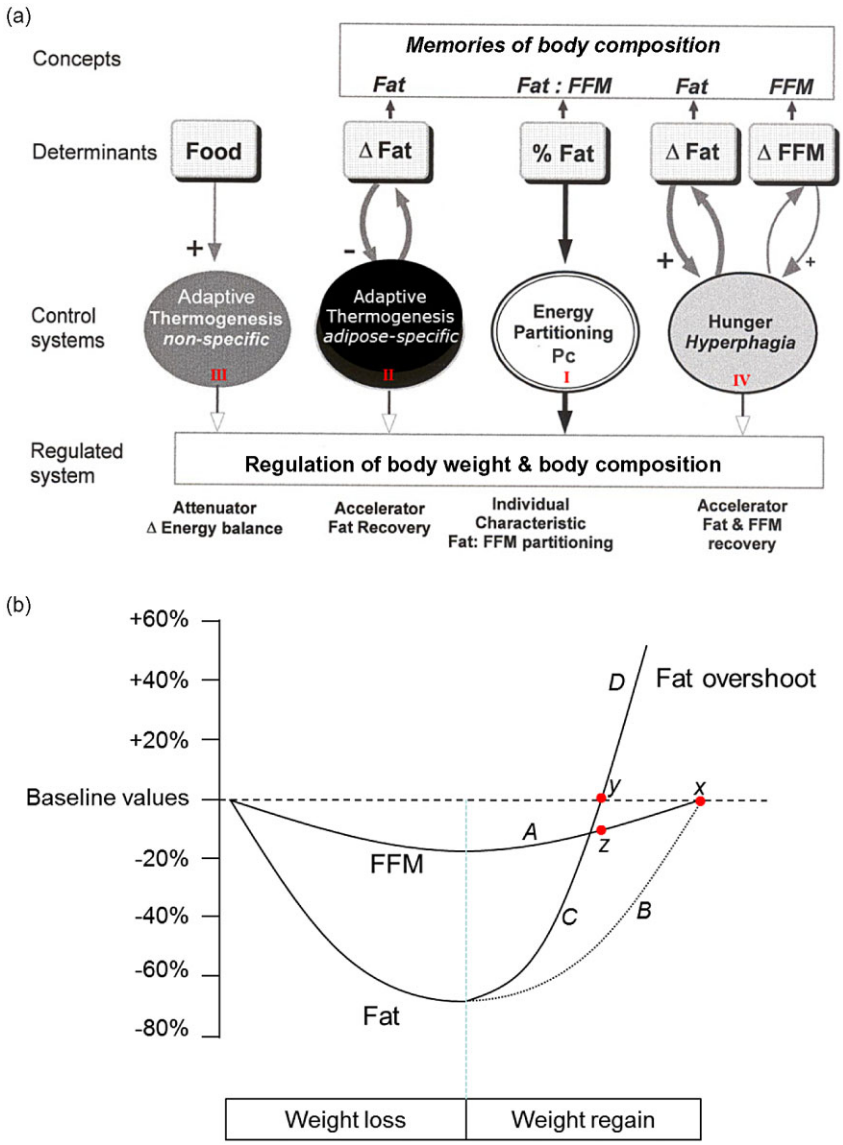

Figure 3 (a) Conceptual model for autoregulation of body composition during weight recovery depicting the various control systems involved, namely (i) the control of energy partitioning between fat-free mass (FFM) and fat compartments, which determines the partitioning characteristic (Pc) of the individual as a function of initial percentage body fat (or fat : FFM ratio); (ii) the *adipose-specific* control of thermogenesis, which specifically accelerates fat recovery; (iii) the '*non-specific'* control of thermogenesis which functions as an attenuator of energy imbalance and is dictated by the food energy flux rather than by fat depletion and (iv) hunger-appetite drive leads to hyperphagia, the magnitude of which is determined by the extent to which body fat and FFM are depleted. Adapted from Dulloo & Jacquet (43). (b) Schematic diagram showing dynamics of body composition changes as fat mass and FFM during one cycle of weight loss and weight regain in lean humans. The lines 'A' and 'B' represent the fully synchronized recovery of FFM and fat mass, respectively, as determined by control of energy partitioning and the partitioning characteristic (Pc) of the individual (see panel (a) above), and with both FFM and fat mass theoretically reaching complete recovery simultaneously at time point 'x'. The line 'C' represents the observed value with excess fat recovery, i.e. beyond that determined by the control of partitioning and Pc of the individual; this preferential catch-up fat being driven by an adaptive suppression of thermogenesis through the adipose-specific control of thermogenesis (see panel (a) above). The consequence of this catch-up fat phenomenon is that the recovery of fat and FFM are now desynchronized, with body fat being completely recovered before that of FFM, i.e. at the time point 'y' when fat mass is fully recovered, FFM is still far from complete recovery (time point 'z'). In order to complete the recovery of FFM, hyperphagia persists due to the continued operation of proteinstatic signals linking the deficit in FFM to food intake, i.e. between ΔFFM and hunger (as depicted in panel (a) above). As a consequence of the continued operation of the control of energy partitioning to complete FFM recovery, fat also continues to be deposited above baseline levels (line 'D'), resulting in the phenomenon of fat (and weight) overshooting.

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3. The above-mentioned *adipose-specific* control of adaptive thermogenesis, which specifically accelerates fat recovery, is distinct from the '*non-specific*' control of thermogenesis which functions as an attenuator of energy imbalance and is dictated by the food energy flux rather than by fat depletion *per se*; it is under the influence of leptin/insulin–sympathetic–thyroid neurohormonal axis (41).

4. Hunger-appetite drive leads to hyperphagia, the magnitude of which was shown to be determined by the extent to which body fat and FFM are depleted, with the degree of fat depletion being the stronger determinant (42). This hyperphagic response therefore seems to be dictated not only by a 'memory' of the initial fat stores but also by a 'memory' of the initial FFM compartment. The functional importance of this increase in the hunger-appetite sensation, with consequential hyperphagia, is to accelerate the restoration of both lean and fat compartments, as defined by the Pc of the individual.

Thus, besides the control of partitioning *per se*, other control systems operating via the control of food intake and thermogenesis with feedback loops from the lean and/or fat tissue compartments are conceptualized to be dictated by 'memories' of the FFM and/or fat compartment. These are viewed as attenuators of energy imbalance and/or accelerators of tissue recovery that are superimposed over a more 'basal' control of energy partitioning. As can be observed in Fig. 3a, there is a sharp contrast between the determinants of the two accelerators of tissue recovery: whereas the control system operating through increased hunger-appetite is dictated by the degree of depletion of both fat and FFM, that operating through the *adipose-specific* suppression of thermogenesis is dictated specifically by the degree of depletion of the body's fat mass only (and not by FFM depletion). As previously pointed out (30,39), this differential relationship of hyperphagia and suppressed thermogenesis with regard to the two main energy-containing compartments underscores an asymmetry in the way FFM and fat mass are recovered, with fat being recovered at a faster rate than FFM – a phenomenon that we have referred to as preferential catch-up fat (45). Thus, the greater the severity of weight loss (and the degree of fat and FFM depletion), the more the suppression of thermogenesis that enhances specifically fat recovery (and not FFM recovery) and hence the greater the disparity in the rate of fat vs. FFM recovery (Fig. 3b). As we previously emphasized (30), this would provide an explanation for the fact that when fat recovery in the Minnesota men or Army Rangers reached 100% of pre-starvation values, the FFM recovery was still far from complete. Since depleted FFM can also drive hyperphagia (42), a consequence of the disparity between complete fat recovery and incomplete FFM recovery is that the hyperphagia is prolonged until FFM is also fully recovered. However, since the completion of FFM recovery can only be achieved through the process of energy partitioning, more body fat is also deposited, which hence underscores the phenomenon of fat overshooting. In other words, excess gain in fat mass (i.e. fat overshoot) appears as a prerequisite to allow complete recovery of FFM.

Inverse relationship between adiposity prior to weight loss and fat overshooting

The critical event that eventually leads to the prolongation of hyperphagia beyond the complete recovery of fat mass (and hence fat overshooting) resides in the adaptive suppression of thermogenesis which drives fat recovery at a rate that is greater than that determined by the Pc of the individual. As this enhanced metabolic efficiency (*adipose-specific* suppression of thermogenesis) that drives fat acceleration is a function of fat depletion, and the prolongation of hyperphagia beyond complete recovery of fat mass is a function of depleted FFM still to be recovered, the extent of fat overshooting would therefore depend upon the extent to which both fat mass and FFM are depleted. This, in turn, depends upon the Pc of the individual, which is dictated primarily by the initial percentage body fat, i.e. the level of adiposity prior to weight loss (Fig. 4a): the lower the initial adiposity, the greater the proportion of energy mobilized as body protein (referred to as P-ratio) during weight loss. The steep part of the negative exponential curve lies between 8–20% body fat, and a shift from the upper to the lower values in this range, generally considered to reflect a 'normal' range of adiposity for men living in affluent societies, results in 2.5- to 3-fold increase in the P-ratio; the latter constitutes a proxy of the fraction of weight that is lost as FFM since protein belongs to the FFM compartment. This extremely high sensitivity of the P-ratio with regard to the initial body composition emphasizes the critical importance of even small differences in the initial percentage body fat in dictating the individual's energy-partitioning characteristic and, hence, the pattern of lean and fat tissue deposition during weight loss and subsequent weight regain, in turn, determining the extent of fat overshooting. Indeed, from our most recent re-analysis (30) of the individual body composition data of the 12 men who completed all phases of the Minnesota Experiment, the extent of fat overshooting was shown to be negatively related to the initial percentage body fat in a non-linear fashion (Fig. 4b). The lower the initial adiposity, the higher the amount of fat overshot. From a perspective of autoregulation of body composition therefore, lean dieters are at greater risk for fat overshooting than the overweight dieters, let alone the obese dieters.

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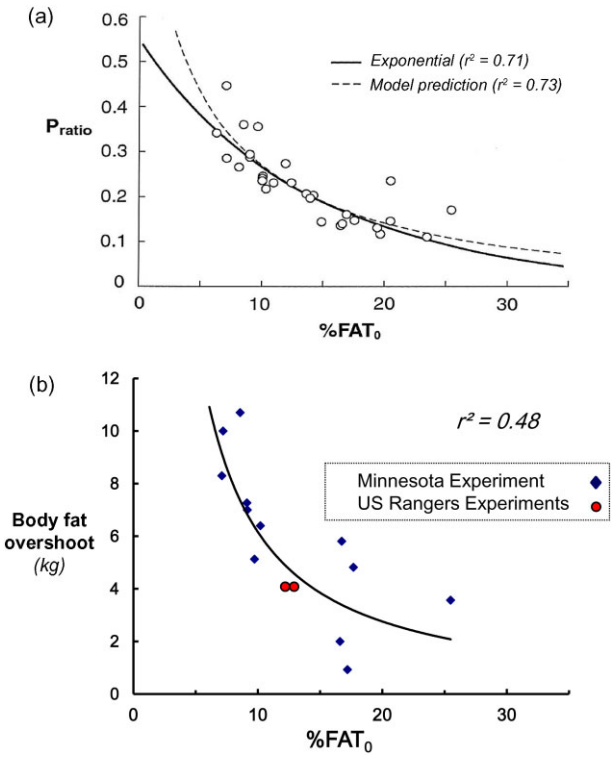

Figure 4 (a) Relationship between the proportions of energy mobilized as protein (P-ratio) during weight loss due to energy restriction and the initial percentage body fat (%FAT_0). Note that P-ratio (expressed in energy terms) is a proxy of the fraction of weight loss as fat-free mass (FFM) (i.e. ΔFFM/ΔWeight). Adapted from Dulloo *et al.* (43).
(b) Relationship between the extent of fat overshooting (kg excess fat regained) and the initial (pre-starvation) percentage body fat (%FAT_0). The exponential curve is drawn from data on the 12 men who participated in all phases of the Minnesota Experiment (data for each individual are represented by a blue-filled diamond symbol). The mean values for men (n = 10) participating in each of the Army Ranger training experiments for which body composition data are available (36,38) are shown as red-filled circles.

Body composition dynamics during weight cycling

From a perspective of autoregulation of body composition therefore, lean dieters are at greater risk for fat overshooting than the overweight dieters, let alone the obese dieters. Should the lean dieter be subjected to multiple weight cycles, while maintaining the amount of weight loss constant in each cycle, it could be predicted that the amount of fat overshot will nonetheless decrease with each successive cycle, since each cycle leads to increased adiposity and therefore decreased subsequent fat overshot. The cumulative fat overshoot over several cycles will nonetheless amount to substantial excess of body fat. These results predicting less fat overshooting in individuals whose BMI exceeds the normal range of BMI than in lean individuals are in accord with studies (46) in which overweight or obese dieters subjected to weight cycling – ranging from one cycle only (47,48) to three successive cycles (49) of dieting – failed to show significant altered body composition. They are also consistent with data from lean individuals from U.S. Ranger studies (36–38) who, during rehabilitation after losing about 12% of their weight due to food deprivation, showed substantial fat overshooting of 4–5 kg (Fig. 1). The dependency of post-dieting fat and weight overshooting as a function of initial body composition is therefore a central tenet in explaining the results from prospective studies indicating more consistent association with increased risks for major weight gain in initially normal-weight subjects than in initially overweight subjects attempting to lose weight (8,18).

Adipostats and proteinstats awaiting discovery

The mechanistic explanation of how dieting and weight cycling makes the lean fatter, based upon body composition autoregulation, underscores important gaps in knowledge about various components of feedback loops between changes in body composition and compensatory changes in energy intake and thermogenesis, and in particular about the nature and identity of adipostatic and proteinstatic signals.

Adipostats: beyond leptin

The adipocyte-releasing hormone leptin – which acts on brain areas to induce satiety and enhance sympathetic control of thermogenesis – is often integrated in the lipostatic (or adipostatic) theory of weight regulation. Yet, the role of leptin as a circulating 'adipostatic' signal controlling body fat is questionable in view of the poor correlation between the kinetics of circulating leptin and dynamic changes in body fat in response to energy deprivation and refeeding (50). Furthermore, a closer examination of the outcome of the parabiotic studies in rodents (which demonstrated that circulating factors are involved in the long-term control of food intake and energy balance) reveals that leptin alone does not explain all of the findings of the parabiotic experiments (51,52), thereby suggesting that other as yet unidentified factor(s) may be involved in energy balance regulation. Other adiposity signals and hormones implicated in the control of food intake (insulin, amylin, ghrelin, peptide YY), which are altered in response to weight loss also do not appear to sustain the signal of depletion as body fat is being regained (50). To-date, the adipostat(s) inherent in the feedback loop between fat depletion and post-starvation compensatory hyperphagia and suppressed thermogenesis (depicted in Fig. 3a) is (are) unknown.

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Proteinstat: beyond amino acids

Similarly, the proteinstatic signal(s) inherent in the feedback loop between FFM depletion and compensatory hyperphagia (Fig. 3a) – as suggested by the re-analysis of the Minnesota Experiment (42) is (are) unknown, amid almost total disregard for its existence in the field of appetite control today. Yet, the existence of an appetite mechanism driven by the demands for protein generated by the growth of lean tissues have long been known to be consistent with the animal and human literature indicating that the nutrient requirements during growth or catch-up growth and the control of food intake are dominated by the impetus for lean tissue growth (53–55). More recently, the notion that a signal associated with lean tissues exerts a determining effect over self-selected food consumption has also been proposed by Blundell *et al*. (56). In a re-assessment of food intake data obtained from an intervention period of 3 months in adult humans, they found that it was FFM, but not fat mass or BMI, which predicted (as well as correlated with) meal size and daily energy intake, leading them to postulate that this signal may interact with a separate class of signals generated by fat mass (56). Two decades earlier, Millward (55) in describing proteinstat mechanisms that regulate lean body mass has emphasized that its mode of operation would require an aminostatic component of appetite regulation in which food intake is adjusted to provide the amino acids and protein needs for lean tissue growth or maintenance. A role for dietary protein intake and fluctuations in circulating amino acids in the regulation of food intake was indeed proposed more than 50 years ago by Mellinkoff *et al*. (57), with considerable interest in the 1990s for amino acids such as phenylalanine and tryptophan that are precursors of monoamine neurotransmitters, which are known to have potent influence on food intake, and more recently reviewed by Bray (58). However, the evidence in support of the aminostatic theory are fragmentary, and the extent to which the protein requirements for lean tissue (re)growth and appetite control are mediated by plasma changes in amino acids is unknown.

Novel adipokines and myokines

In addition to more than 100 different adipokines that have been clearly identified based upon gene expression, and the demonstration that the encoded protein is secreted from adipocytes, proteomic studies indicate that there are several hundred adipokines in total (59,60). Similarly, recent applications of proteomic approaches to investigate factors secreted by skeletal muscle (59,60) have revealed that myocytes are capable of producing several hundred secreted proteins (i.e. myokines), the identity and function of most of which remain to be unravelled. The discovery that a multiplicity of factors is secreted by adipocytes and myocytes opens new avenues in the search for adipostatic and proteinstatic feedback signals in the regulation of body composition.

Conclusions

From our analysis of the bidirectional relationships between dieting and proneness for fatness, it is concluded that, in addition to the possibility that dieting to lose weight in normal-weight people represents an attempt to counter genetic and familial predispositions to obesity and/or a psychosocial reaction to the fear of fatness, dieting to lose weight *per se* may also confer risks for fatness. Our proposed mechanistic explanation as to how dieting *per se* predisposes more the lean to fatness than the overweight or obese rests upon evidence of a much greater propensity of lean individuals to exhibit fat overshooting during weight regain, which, in turn, resides in a temporal desynchronization in the restoration of the body's fat vs. FFM (i.e. preferential catch-up fat driven by an adaptive suppression of thermogenesis). Such an asymmetry in fat and FFM recoveries during weight regain results in a state of hyperphagia that persists beyond complete recovery of fat mass and until complete recovery of FFM, thereby conferring biological plausibility for post-dieting fat overshooting – which through repeated dieting and weight cycling – would increase the risks for progressing from leanness to fatness. In addition to the search towards the identification of the underlying putative adipostatic and proteinstatic signals, an intriguing question for future research is whether the mechanisms that leads to catch-up fat and fat overshooting in the lean also underlie a causative association between weight cycling and cardiovascular morbidity, which is also more readily seen in those of normal body weight, rather than those overweight or obese; the latter associations being documented in a companion paper by Montani *et al*. (61). Given the increasing prevalence of dieting in normal-weight female and male among young adults, adolescents and even children who perceive themselves as too fat (due to media, family and societal pressures), together with the high prevalence of dieting for optimizing performance among athletes in weight-sensitive sports (61), the notion that dieting and weight cycling may be predisposing a substantial proportion of the population to weight gain and obesity deserves greater scientific scrutiny. Among strategies to control the obesity epidemic, primary preventive measures that target the lean 'dieting-prone' population groups may turn out to be as important as traditional strategies (centred on diet quality and physical activity) to counter the 'Big Two' obesogenic factors.

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Conflict of interest statement

All authors declare no conflict of interest.

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