Collateral Fattening: When a Deficit in Lean Body Mass Drives Overeating

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In his last review entitled "Some Adventures in Body Composition," Gilbert Forbes reminded us that "lean body mass and body fat are in a sense companions." To what extent the lean body mass (or fat-free mass) component in this companionship impacts on energy intake is rarely a topic for discussion, amid a dominant adipocentric view of appetite control. Yet an analysis of the few human studies that have investigated the relationships between objectively measured food intake and body composition reveals a potentially important role for both an increase and a decrease in fat-free mass in the drive to eat. These studies are highlighted here, together with the implications of their findings for research directed as much toward the elucidation of peripheral signals and energy-sensing mechanisms that drive hunger and appetite, as toward understanding the mechanisms by which dieting and sedentariness predispose to fatness.

Obesity (2017) **25**, 277-279. doi:10.1002/oby.21734

Introduction

The first report about the relationships between body composition and objectively measured *ad libitum* food intake can be traced to the 1989 publication of Lissner et al. (1) in women who, for periods ranging from 14 to 63 days, came to a metabolic unit to consume their daily meals. They found that energy intake for weight maintenance was not correlated with percent body fat or with fat mass (FM) but was positively associated with fat-free mass (FFM). These findings were ignored or overlooked for the next two decades until the report in 2012 by Blundell et al. (2) that FFM, but not FM, was positively associated with self-selected meal size and total energy intake in individuals with overweight and obesity. Between these two reports, however, the publication of a reanalysis of the classic Minnesota Starvation Experiment revealed that FFM depletion, independently of FM depletion, predicted the degree of hyperphagia during post-starvation *ad libitum* refeeding (3). From an integration of these findings (1-3), a plausible conclusion (4) is that although the increase in FFM that accompanies FM gain contributes to an increase in energy needs as obesity develops (thereby explaining a higher energy intake in the obesity state relative to the lean state), a deficit in FFM is also a factor that drives energy intake, as depicted in Figure 1.

Increase in FFM as a Factor Driving Energy Intake

The impact of obesity-associated increase of FFM on energy intake is expected given that FFM is a major determinant of energy expenditure accounting for ~70% of the variance in resting metabolic rate (5). Indeed, the application of statistical models to data on body composition, energy expenditure, and energy intake has suggested that FFM has no direct effect on energy intake, but rather indirectly influences daily hunger, self-selected meal size, and daily energy intake via its effect on resting metabolic rate (6,7). According to Hopkins et al. (6), such FFM-induced energy needs represent a physiological source of hunger that drives food intake at a level proportional to basal energy requirements and helps ensure the maintenance and execution of key biological and behavioral processes. Furthermore, the findings of Weise et al. (8) of a link between FFM, hunger, and cerebral blood flow in specific midbrain structures involved in the homeostatic control of appetite suggest that such a link could be part of a system that transforms FFM-induced energy demand into feeding behavior. While the mechanisms by which the body's energy needs are coupled to motivated eating behaviors remain to be elucidated, these above findings suggest that FFM-induced energy intake is driven by energy expenditure *per se* rather than a molecular signaling pathway arising from FFM. By contrast, the existence of appetite-controlling signals arising from lean tissue seems much more plausible when examining the relationship between deficits in FFM and increased energy intake.

Deficits in FFM as a Factor Driving Energy Intake

The reanalysis of data from the Minnesota Experiment revealed not only that the FM deficit and FFM deficit independently predicted

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Funding agencies: This research work was supported by the Swiss National Science Foundation (grant no. 310030152870).

Disclosure: The author declared no conflict of interest.

Received: 28 September 2016; **Accepted:** 11 November 2016; **Published online 11 January 2017. doi:10.1002/oby.21734**

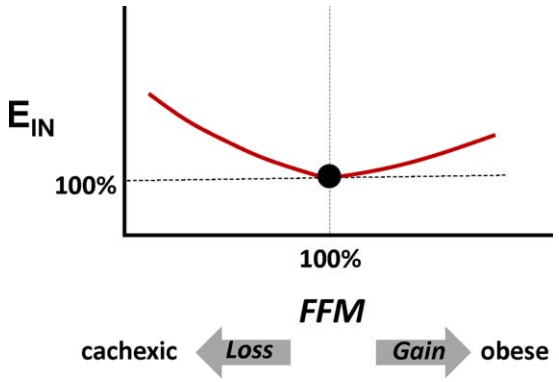

Figure 1 Schematic diagram depicting, in a normal-weight individual, the impact of changes in fat-free mass (FFM) on energy intake (E_{IN}) (adapted from Ref. 4). If the individual enters into a chronic positive energy imbalance, the resulting weight gain will comprise not only fat but also FFM (20%–30% of excess weight), thereby resulting in an increase in resting metabolic rate and hence in an increase in energy needs. A new steady state of body weight (*albeit* higher than before) is reached when the increase in energy needs matches the positive energy imbalance. Thus, at the new steady state body weight, the energy intake of this individual with obesity would be higher than before the positive energy imbalance occurred, in large part because of the higher FFM-induced energy needs. This can be referred to as a "passive" influence of FFM on energy intake. By contrast, a more "active" role of FFM on energy intake is postulated to occur if the normal-weight individual loses FFM. In this case, the deficit in FFM will trigger a feedback signaling pathway arising from FFM to increase energy intake in an attempt to restore FFM, as depicted in Figure 2.

post-starvation hyperphagia, but also that despite the complete recovery of weight and FM, hyperphagia persisted until FFM was completely recovered to pre-starvation levels (3). Thus, the autoregulatory component of the hyperphagic response to weight loss goes beyond an explanation based solely on the lipostatic or adipostatic theory. The existence of a control system whereby the loss or deficit in FFM triggers an increase in energy intake in an attempt to restore FFM, with consequential increase in FM—i.e., "collateral fattening" (Figure 2)—has several implications for research in energy balance and obesity.

First, it raises the possibility that following dieting-induced weight loss, the loss of FFM as a factor for weight regain (9) can be attributed not only to the diminished resting metabolic rate resulting from a lower energy cost for maintenance of a lower FFM, but also to the impact of the deficit in FFM in enhancing the drive to eat.

Second, the existence of a negative feedback loop between FFM and energy intake provides a mechanistic explanation for the observation that dieting and weight cycling pose a greater risk for future weight gain in those who are of normal body weight than in those who have obesity (10). The basis for this explanation resides in the fact that the fraction of weight loss as FFM is greater in the lean than in those with obesity, and that a faster recovery of FM than FFM (i.e., preferential catch-up fat) is a characteristic feature of normal-weight individuals recovering from substantial weight and fat losses due to experimental semi-starvation or more moderate energy deficit, as well as in patients recovering from anorexia nervosa, famine, or disease cachexia (reviewed in Refs. 4 and 10). Such a temporal desynchronization in the restoration of the body's FM versus FFM results in a state of hyperphagia that persists beyond complete FM recovery, since it continues to be driven by FFM deficit until full recovery of FFM. However, as the completion of FFM recovery is also accompanied by fat deposition, excess fat accumulates—resulting in the phenomenon of fat overshooting, whereby the FM regained is greater that the FM lost. In other words, fat overshooting is a prerequisite to allow complete recovery of FFM. The demonstration, using data on body composition from the Minnesota Experiment, that the extent of fat overshooting increases exponentially with decreasing initial (pre-starvation) percent body fat (10) provides proof of concept that the nonobese dieters are at greater risk for fat overshooting than the dieters with obesity. Given the increasing prevalence of dieting among those in the normal weight range (due to pressure for a slim image, body dissatisfaction, or for athletic performance), the notion that post-dieting fat overshooting through repeated dieting and weight cycling would increase the risks for trajectories from leanness to fatness is particularly relevant to public health.

Third, there is now mounting evidence of a J-shaped relationship between physical activity level and energy intake (7), with tight coupling of energy intake to energy expenditure at moderate and high levels of physical activity but weak coupling and increased adiposity in those displaying low levels of daily physical activity and sedentariness. One may also argue that as individuals become sedentary and muscle contractile function diminishes, the resulting muscle disuse is likely to lead to progressive muscle atrophy and loss of FFM. Such deficits in FFM may thus trigger the negative feedback loop between FFM and energy intake, such that a compensatory increase in energy intake, in an attempt to re-establish the skeletal muscle mass, would be accompanied by an increase in body fat.

Last but not least, the existence of a control system between FFM deficit and energy intake assumes the existence of sensors and signals arising from FFM. While it is not known what exactly is being sensed (protein mass, muscle mass, other organ size, or metabolic activity), the discovery that several hundreds of factors are secreted by skeletal muscle (11) opens new avenues in the search for FFM-sensitive feedback signals to the brain hunger-appetite centers. In this context, it has recently been shown that diet-induced obese mice that were slimmed down by caloric restriction before Roux-en-Y gastric bypass surgery subsequently ate more and showed weight

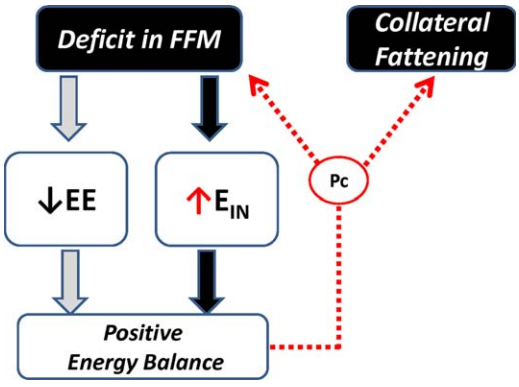

Figure 2 Concept of collateral fattening. A deficit in fat-free mass (FFM) results not only in a lower energy expenditure (EE) and hence lower energy needs for weight maintenance, but also in the activation a feedback loop that drives energy intake (E_{IN}) in an attempt to restore FFM through the lean-to-fat partitioning characteristic (Pc) of the individual (4).

regain that was exclusively accounted by FFM (12). This mouse model whereby Roux-en-Y gastric bypass surgery selectively abolished the defense of a higher fat mass, while remaining sensitive to the defense of lean mass, therefore provides an interesting model in the search for molecular signal pathways from the lean mass that drive appetite.

Concluding Remarks

In line with the remarks of Gilbert Forbes (13) that FM and FFM are "companions," the body's attempt to restore FFM by increasing energy intake will inevitably result in an accompanying increase in body fat. To what extent this phenomenon of "collateral fattening" will keep operating over time in situations of limited capacity to rebuild lean tissues (e.g., in older age, feeding on poor-quality diets) and underlie certain forms of sarcopenic obesity are also intriguing questions for future research to address. Overall, the phenomenon of collateral fattening is a further reminder of the importance of promoting both healthy diets and physical activity as protection against FFM deficits in strategies directed at both the prevention and treatment of obesity. O

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