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Suppressed thermogenesis as a cause for resistance to slimming and obesity rebound: adaptation or illusion?

According to Hippocrates (400 BC), the obese should '*eat less and exercise more*'. This ancient prescription has never ceased to be the cornerstone approach in the treatment of obesity, and will remain so for the foreseeable future despite its well-documented failures. Indeed, several long-term follow-up studies conducted over the past decades have repeatedly demonstrated that the overwhelming majority (>90%) of patients who manage to lose weight will have returned close to their starting weight within 1–5 years – findings which are encapsulated in a commentary made by Albert Stunkard[1] some 50 years ago, to quote:

> Most obese persons will not stay in treatment for obesity. Of those who stay in treatment, most will not lose weight and of those who do lose weight, most will regain it.

Yet every year, scores of millions of people, who are fatter than they want to be, attempt to lose weight on some form of diet and/or exercise therapy, encouraged by their families and friends, health professionals, media that promote a slim image, and a diet-industry that in the US and Europe alone has an annual turnover in excess of $150 billion. At the same time, those who have tried dieting with or without exercise, and who have experienced that it does not work, will keep asking the same old questions: 'Why is weight loss so difficult to achieve? Why is maintaining the lost weight an even greater challenge?'

Self-regulatory failure

According to the classical theory, resistance to slimming and obesity recidivism occur because the patients sooner or later revert back to the same lifestyle of 'gluttony and sloth' that made them obese in the first place. Psychologists, however, prefer an explanatory mechanism that is inferred by work on dietary restraint, and which centres upon terms like 'disinhibition' or 'loss of inhibition' to describe self-regulatory failure.[2] Such periodic disinhibition by restrained eaters has been argued as a laboratory analogue of binge eating (i.e. periods of dietary restriction alternating with episodes of uncontrolled overeating) – a notion that is strongly supported by several prospective studies in adolescent girls and young adults.[2] These studies have indicated that moderate dieters are two to five times more likely than their non-dieting peers to develop an eating disorder, and that dieting, restrained eating or exercise for weight control actually predict weight gain. Whether these findings can be interpreted as dieting (or exercise) will facilitate subsequent weight gain – or to put it bluntly: 'Dieting makes you fat'[3] – is debatable.[2–4] It is clear, however, that the willpower to sustain dieting/exercise therapy that prevailed during the process of weight loss withers away in the face of environmental influences that promote obesity. In more clinical

(and contemporary) terms, there is poor compliance to diet/exercise regimens in an obesigenic environment that encourages overeating and discourages physical activity. What is less well recognized is that willpower may also be counteracted by powerful internal signals that sense the deviations in body weight and trigger compensatory mechanisms. These mechanisms operate on both sides of the energy balance equation in an attempt to restore body weight, that is by enhancing food-seeking behaviour as well as by slowing down the rate of metabolism and hence conserving energy through the suppression of thermogenesis.

Biological feedbacks

There is indeed compelling evidence that such compensatory biological feedback systems play a crucial role in the regulation of body weight in animal models. Fantino *et al.*[5,6] showed that hoarding behaviour of food-deprived rats was inversely proportional to the fat content of the body, and MacLean *et al.*[7] demonstrated that an enhanced metabolic efficiency was quantitatively as important as an elevated appetite in the high rate of fat regain after weight loss in obese rats. However, the existence of these compensatory feedback mechanisms in response to weight loss in obese humans remains ill-defined. Progress in understanding these physiological aspects of the human's weight defence system is hampered by practical and methodological difficulties for obtaining reliable data on changes in energy intake and in energy expenditure across several months, if not years, during which the relapse of obesity is 'expected' to occur. In fact, much of our knowledge (and conceptual development) in this area of human energetics derives from the classic 'Minnesota Experiment' in which the food intake, basal metabolic rate (BMR) and body composition were meticulously documented in 32 normal-weight men (mostly conscientious objectors of war) who volunteered to be subjected to 24 week of semistarvation, followed by 12 week of restricted refeeding, before they were allowed *ad libitum* access to food for 8 weeks. By applying a system-analysis approach in a re-evaluation of these data, evidence was presented showing that the hyperphagic response to food deprivation was dictated as much by the psychobiological responses to dietary restraint as by the extent to which body fat, and to a lesser extent fat-free-mass (FFM), were depleted.[8] This same analytical approach, applied to the changes of BMR of the Minnesota men after adjusting for changes in FFM and fat mass (an index of energy conservation through suppressed thermogenesis), also revealed that the extent to which thermogenesis was suppressed during the phases of weight loss and weight recovery was dictated not only by the food energy deficit *per se* but also by the extent to which body fat was depleted.[9] These experiments in humans, like in the laboratory rat,[5–7] demonstrate that the drive to overeat or to conserve energy (through adaptive suppression of thermogenesis) can be explained, at least in part, as the outcome of autoregulatory control systems that operate to restore body weight and body composition. Within the context of an ancestral hunter-gatherer lifestyle characterized by periodic famine, the teleological argument can be put forward that these weight regulatory mechanisms that drive 'food-seeking behaviour' and 'suppressed thermogenesis' in response to starvation must have evolved to enhance survival capacity, and can hence be considered as adaptive. Whether similar lipostatic (or adipostatic) control of food intake and thermogenesis also operate to defend the obese state in humans losing weight in response to therapeutic dieting remains to be demonstrated, but there is increasing recognition that adaptive suppression of thermogenesis could constitute an important component in the overall energy economy that tends to oppose the efficacy of weight reduction programs.

Energy economy during obesity management

This can be illustrated in the extent to which the various compartments of energy expenditure in an 'average' obese person may be readjusted following a weight loss of say 20 kg.[10] First, it is unequivocal that the loss in body mass will entail obligatory reductions in several compartments of energy expenditure, namely because of:

- reductions in the energy cost for basal metabolism, since the BMR is related to metabolic mass and that weight loss comprises both fat and lean tissues,
- reductions in the amount of energy spent in performing work since from a consideration of simple mechanics, the energy cost of physical activity (i.e. work done on the environment) is related directly to body weight and
- reductions in the absolute level of energy dissipated as postprandial thermogenesis (i.e. the thermic effects of meals) given that less food is now required to maintain the lower body weight.

Based upon estimates that the composition of weight loss in the obese is (on average) ~75% fat and 25% FFM, and that body weight in non-athletic individuals is maintained at an energy cost in the range of 15–25 kcal per kg per day,[10] it can be calculated that a weight loss of 20 kg body weight in an obese patient will result in an obligatory reduction of 300–500 kcal in daily energy expenditure. Unless the reduced-obese individual alters his/her pre-dieting levels of food intake and physical activity accordingly to maintain the new body weight, such obligatory economy in energy expenditure alone is decisively an important factor that will precipitate the return to the obese condition. This obligatory energy economy can be further exacerbated by more 'facultative' economy in energy expenditure that could result from adaptive suppression of thermogenesis.

What constitutes evidence to support such a contention that adaptive thermogenesis might be of clinical significance in obesity management is elegantly addressed by Major *et al*.[11] in a review published in this issue of the IJO. They integrate evidence, much of which has emerged over the past decade, which underscores the occurrence of adaptive suppression of thermogenesis in the resting compartment of energy expenditure (i.e. in BMR, thermic response to food or in sleeping metabolic rate) and/or in non-resting components of energy expenditure (walking, bicycle exercise and spontaneous physical activity) during the dynamic phase of weight loss, during long-term maintenance of lower body weight, and after weight recovery.

Inter-individual variability in adaptation

One is nonetheless left with the impression that in response to dieting and weight loss, there is considerable inter-individual heterogeneity concerning the compartments and sub-compartments of energy expenditure in which adaptive suppression of thermogenesis might be occurring. There hence may be considerable inter-individual differences in metabolic strategies to conserve energy through suppressed thermogenesis. However, the final outcome seems to point in the same direction – that is a more efficient energy utilization that in most studies corresponds to mean values of 5–15% of energy expenditure in either resting or non-resting compartments. We are all aware that long-term weight maintenance requires the precise matching between energy intake and energy expenditure, and that in dynamic systems an increase in metabolic efficiency that leads to a mismatch that corresponds to only 5% of daily energy expenditure certainly can contribute to significant regain of body fat over time. Furthermore, in addressing the clinical significance of adaptive thermogenesis, it is also important to go beyond the 'mean' values of reported data and to also focus on the large inter-individual variability in the capacity to suppress thermogenesis. There clearly are individuals capable of showing a large capacity for metabolic adaptation amounting to 300–400 kcal per day; that is a facultative energy economy that is quantitatively as important as the obligatory energy economy of 300–500 kcal that would occur after losing 20 kg. As Major *et al*.[11] argue in their review, adaptive suppression of thermogenesis is capable of modifying the outcome of a weight loss intervention, albeit to varying degrees, and the success of clinical management of obese individuals have to be tailored according to individual variations for any relevant phenotype, including their metabolic efficiency.

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