EDITORIAL

Explaining the failures of obesity therapy: willpower attenuation, target miscalculation or metabolic compensation?

The ancient prescription of Hippocrates (400 BC) that the obese should 'eat less and exercise more' is still today, and for the foreseeable future, the cornerstone approach to treat obesity despite its well-documented failures. In most obese individuals, the amount of weight loss is far less than that expected from the imposed energy deficit, and in the overwhelming majority, the lost weight is regained within a few years.[1] Most become weight cyclers, as they attempt again and again at losing weight, encouraged by their families and friends, health professionals, media that promote a slim image and a prosperous diet-industry that constantly innovate in generating hopes for better slimming successes. In the meantime, the reality begs the question: why is the short-term and long-term success rates of dieting/exercise so low?

LACK OF WILLPOWER

The most common explanation centers on the failure of the obese to follow the dietary advice and prescribed exercise regimen; the dieters 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 centers upon terms like 'disinhibition' or 'loss of inhibition' to describe self-regulatory failure. Such periodic disinhibition by restrained eaters has been argued as a laboratory analog of binge eating, that is, periods of dietary restriction alternating with episodes of uncontrolled overeating. This notion is strongly supported by prospective studies indicating that moderate dieters are 2–5 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.[2] Whether these findings can be interpreted as dieting, or exercise will predispose to future weight gain—or to put it bluntly: 'Dieting makes you fat'—is debatable.[2,3] It is clear, however, that the willpower to sustain dieting/exercise therapy that prevailed during the initial process of weight loss withers away in an obesogenic environment that encourages overeating and discourages physical activity. In more clinical terms, there is poor compliance to diet/exercise regimens. What physiologists will also emphasize is that willpower may also be counteracted by powerful internal signals (for example, changes in leptin, gut hormones and circulating nutrients) that sense the energy deficit or deviations in body weight and trigger compensatory mechanisms. These operate not only via the 'energy balance' control circuits in the hypothalamus and brain stem, but in addition impinge upon areas in the cortex and limbic system involved in cognitive, reward, emotion and executive brain functions important for ingestive and exercise behavior.[4] The recent advances in functional imaging technologies for the mapping of brain circuitries have no doubt opened new avenues for research toward understanding the mechanisms that underlie poor compliance to diet and/or exercise. However, as underscored by Byrne *et al.*[5] in a study published in this issue of *IJO*, factors other than lack of willpower and poor compliance can also be invoked to explain the poor outcome of diet/exercise antiobesity therapies. In this study, conducted in 19 obese men and women subjected to severe energy deficit for 3 months on a ketogenic diet and exercise intervention, and during which the tightly monitored adherence to both diet and exercise indicated high compliance, they could still observe a-third less weight loss than predicted from baseline energy deficit calculations. This discrepancy between actual and predicted weight loss, 10 kg on average but in the range of 1–22 kg, was shown to correlate strongly with reductions in the post-absorptive resting metabolic rate (RMR) and in the thermic effect of food or diet-induced thermogenesis (DIT). After adjusting for the monthly fall in RMR and DIT, with the energy conserved having been converted to the spared weight equivalent, the discrepancy between actual and predicted weight loss was markedly reduced from 10 to 3 kg on average. Consequently, the less-than-expected weight loss during dieting/exercise can also be attributed to quantitatively important reductions in energy needs of the obese individuals as they lose weight; that is, to metabolic compensations that impede weight loss.

METABOLIC COMPENSATIONS

That energy expenditure (EE) falls in response to energy deficit and that this fall in EE is highly variable between individuals have long been known,[6] but too often ignored or disregarded as insignificant pertaining to its contribution to buffer against weight loss. This may be surprising, as from a purely thermodynamic standpoint a loss in body weight will entail obligatory reductions in several compartments of daily EE, in particular:

(i) less energy would be required to sustain basal metabolism, as RMR (the major component of daily EE) is a function of body mass and in particular lean body mass, and the weight loss comprises not only fat but also lean body mass;
(ii) less energy would also be required for the amount of energy spent in performing physical activity, as from a consideration of simple mechanics it costs less energy to move a lower body mass; and
(iii) less energy would be dissipated as the thermic effect of food, that is, less DIT, as less food is consumed during dieting.

Based upon estimates that the composition of weight loss in the obese is on average ~75% fat and 25% lean body mass, and that body weight in non-athletic (sedentary) individuals is maintained at an energy cost in the range of 15–25 kcal per kg per day, 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 EE.[7] Besides this obligatory or 'passive' metabolic compensation, further reductions in daily EE can also be expected as it has repeatedly been demonstrated that the fall in EE is greater than predicted by the loss of body mass and changes in body composition, leading to the concept of adaptive thermogenesis whereby an 'active' metabolic compensation operate to conserve energy and hence further impede

weight loss. In an elaborate review about the clinical significance of adaptive thermogenesis, Major *et al.*[8] point to several weight reduction programs, including those which incorporate both diet and exercise, where values of 150–220 kcal per day on average could be ascribed to adaptive thermogenesis in the fall of sedentary EE, assessed as post-absorptive RMR and/or sleeping EE. Furthermore, adaptive thermogenesis could also operate to spare energy in the non-resting compartment of daily EE, as judged by 10–27% increases in the mechanical efficiency of walking or cycling following weight loss,[8,9] all of which would contribute to further reduce the energy needs and hence to increase further the resistance to slimming.

In the study of Byrne *et al.*[5] physical activity and its energy cost were not assessed, nor was the contribution of adaptive thermogenesis evaluated from their data on RMR. However, judging from their data on monthly changes in body composition indicating modest and statistically insignificant loss of lean body mass (perhaps due to the anabolic effects of the exercise therapy and high protein content of the diet), a considerable component of the fall in RMR could hence be attributed to adaptive thermogenesis. This contention is supported by the report of Goele *et al.*[10] that in about half of 48 overweight or obese women losing weight on a restricted diet, and where measured weight loss was only 44% of the predicted value, nearly 40% of this discrepancy could be explained by adaptive thermogenesis in the fall in RMR. Furthermore, the possibility that part of the residual discrepancy between actual and predicted weight loss after adjusting for the fall in RMR and lower DIT may reside in compensatory reductions in physical activity between the periods of imposed exercise bouts or in improved mechanical efficiency of movements, and hence in adaptive thermogenesis operating in the non-resting compartment of daily EE, cannot be disregarded.

TARGET MISCALCULATIONS

What also should not be disregarded in the study of Byrne *et al.*[5] are potential errors in the evaluation of the discrepancy between actual vs predicted weight loss. First, DIT was not measured but estimated as a fixed component (10%) of daily energy intake. However, the authors argue that because of the very large difference in energy intake for baseline weight maintenance compared with the energy restricted diet (2958 vs 597 kcal per day), the error incurred in the estimates in the fall in DIT, including any improved efficiency of postprandial meal processing, would be small in absolute terms. Second, errors occur in the calculation of the energy deficit and hence in predicted or target weight loss, particularly in the estimation of daily energy requirement for weight maintenance before the intervention, which was calculated as RMR $\times$ a physical activity level (PAL) of 1.5. As underlined by Heymsfield *et al.*,[11] if the estimated baseline energy requirement of the obese person is 100–200 kcal per day higher or lower than measured, then even perfect adherence to a diet will result in an error of 2–4 kg in predicted weight change over a year. However, Byrne *et al.*[5] point out that any such miscalculations are likely to be small in their study on the basis of a previous validation study in a similar cohort of sedentary obese individuals, indicating that weight stability over 4 weeks could be maintained by the same approach for calculating energy requirements for weight maintenance. Third, the predicted weight loss was calculated using the Wishnofsky's constant of 7700 kcal kg^{-1} based upon a composition of weight loss, that is, 79% fat and 21% lean mass. This composition of weight loss can of course vary with treatment regimens and across subjects, which would hence translate into caloric equivalents different from the Wishnofsky's constant. In considering this variability, Byrne *et al.*[5] showed that further reduction in the discrepancy between actual weight loss and that predicted, such that almost 90% of this discrepancy could be explained by taking into account all three factors: the fall in RMR, the diminished DIT and the composition of weight lost.

INTER-INDIVIDUAL VARIABILITY IN RESISTANCE TO SLIMMING

The merits of the study of Byrne *et al.*[5] cut across a study design that optimized compliance to the diet/exercise therapy while assessing RMR and body composition at monthly interval during the dynamic phase of weight loss. Under these conditions, the prediction of expected weight loss takes into account the fact that the reductions in EE that occur during energy restriction are greater than is often evident after the weight loss period when energy balance is essentially restored. Furthermore, the analytical and statistical approaches that they utilize fully capture the large inter-individual variability in weight loss, the composition of weight loss and in the metabolic compensations in RMR and DIT. In addressing the clinical significance of such metabolic compensations, it is clearly important to go beyond the 'mean' values of reported data and to focus on the large inter-individual variability in the capacity to conserve energy. In addition to the passive metabolic compensation resulting from diminished energy intake and changes in body weight and composition, there are clearly individuals capable of showing a large capacity for adaptive thermogenesis amounting to 300–400 kcal per day,[6–10] that is, an active metabolic compensation that in some individuals could be quantitatively as important as the passive metabolic compensation of 300–500 kcal that, as discussed above,[7] would occur after losing 20 kg. Such compensatory energy-conservation mechanisms, which impede weight loss and subsequently facilitate weight regain,[3] would most likely have conferred survival advantage in an ancestral lifestyle of famine and intermittent food scarcity that have characterized much of human evolution. Indeed, a role for genes in determining the capacity for such metabolic compensation and the large inter-individual variability in weight loss has been demonstrated by Hainer *et al.*[12] in studies on identical obese twins treated with a very low energy diet. The bottom line of all these studies[5–12] is that at least some of the weight loss deficits result from physiological metabolic adaptations and do not necessarily result from lack of compliance of the patient. People are different in their response to energy deficit, be it due to dieting, exercise or to both combined. Such metabolic compensations are clearly capable of modifying the outcome of a weight loss intervention, albeit to varying degrees, and success in the clinical management of obese individuals has to be tailored according to individual variations for any relevant phenotype, including the capacity to show metabolic compensations.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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