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REVIEW

Adaptive thermogenesis can make a difference in the ability of obese individuals to lose body weight

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The decrease in energy expenditure that occurs during weight loss is a process that attenuates over time the impact of a restrictive diet on energy balance up to a point beyond which no further weight loss seems to be possible. For some health professionals, such a diminished energy expenditure is the normal consequence of a progressive decrease in the motivation to exercise over the course of a weight-reducing program. Another explanation of decreased energy needs during weight loss is the decrease in body energy stores (that is, fat mass and muscle mass) and its related obligatory costs of living. Many studies have also documented the existence of adaptive thermogenesis in the context of weight loss, which represents a greater-than-predicted decrease in energy expenditure. In this paper, we pursue the analysis of this phenomenon by demonstrating that an adaptive decrease in thermogenesis can have a major role in the occurrence of resistance to further lose fat in weight-reduced obese individuals. Evidence is also presented to support the idea of greater hunger sensations in individuals displaying more pronounced thermogenic changes. Finally, as the decrease in thermogenesis persists over time, it is also likely associated with a greater predisposition to body-weight regain after weight loss. Globally, these observations suggest that the adaptive reduction in thermogenesis that accompanies a prolonged negative energy balance is a major determinant of the ability to spontaneously lose body fat.

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INTRODUCTION

The study of an adaptive component of energy expenditure is an issue that has more than a century of age. Indeed, at the beginning of the last century, it was reported that body weight stability could be maintained despite substantial variations in daily energy intake (EI).[1] This was followed by a long series of investigations that confirmed the body's potential to adapt its energy expenditure to attenuate the impact of fluctuations in energy balance on body energy stores. As reflected by the epidemic of obesity, the long-term matching of EI to energy expenditure is not easily achieved for a large proportion of the population. In light of this, one can assume that the coupling between EI and energy expenditure goes beyond naive allusions to the lack of good dietary compliance. One of the culprits that has also been frequently proposed to be part of the determinants of obesity is adaptive variations in thermogenesis. Specifically, a reduced capacity to increase energy expenditure in a context of overfeeding would result in an increase in body fat accumulation over time. Conversely, a greater-than-predicted decrease in energy expenditure in response to a negative energy balance may damper efforts to lose body fat. In recent papers, we reported the quantitative importance of adaptive thermogenesis for weight-reduced obese individuals,[1,2] which may in fact be more important than initially perceived. In the present paper, we pursue this analysis by documenting some issues that are directly related to obesity management. These include the contribution of adaptive thermogenesis to resistance to lose fat, the inability to reach satiety at energy balance in a weight-reduced obese state and the long-term persistence of depressed thermogenesis following weight loss amongst other things.

MATERIALS AND METHODS

As described in the Introduction section, this paper presents a conceptual extension of the review articles recently published by the authors. Specifically, its main goal is to integrate recent research developments that could be translated into clinically relevant questions. Thus, this review is not the outcome of a systematic literature survey based on key words and selection criteria. It rather represents a conceptual integration of papers that are deemed to provide the best answers to the following questions: (i) What is the clinical meaning of adaptive thermogenesis? (ii) Why is adaptive thermogenesis occurring? (iii) What is the relationship between adaptive thermogenesis, resistance to lose fat, appetite control and rate of weight loss? Globally, the answers to these questions help discussing the extent to which it is relevant to intervene in reduced-obese individuals.

Adaptive thermogenesis: what does it mean for the clinician?

Adaptive thermogenesis has been defined as the change in energy expenditure following acute and/or long-term overfeeding and underfeeding. In some studies, it has also been investigated by using catecholamines, caffeine, ephedrine and adrenergic blockers to induce changes in thermogenesis. As previously described,[1] these stimuli were found to induce statistically significant changes in thermogenesis. However, the quantitative estimates of adaptive thermogenesis derived from these studies were found to be of little significance from a clinical perspective.

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In our opinion, a significant progress has been achieved in this field by the group of Leibel *et al.*[3] who quantified adaptive thermogenesis by calculating the difference between measured energy expenditure and a value predicted by variations in fat-free mass and fat mass. These investigators showed that body weight loss induced a greater than predicted decrease in resting energy expenditure, which on average ranged between 250 and 300 kcal per day. Our measurements in obese individuals subjected to a weight-reducing program provided comparable estimates.[4,5] We have also shown that this adaptive reduction in thermogenesis is seemingly present in the active state.[6] Furthermore, we have emphasized that there are substantial inter-individual response variations, suggesting that adaptive thermogenesis probably exerts a much greater influence on fluctuations of energy balance in some individuals.[2] At the other end of the spectrum, an increase of 760 kJ per day has been shown to occur after 3 days in overfed subjects. Similar to energy deprivation, a large range of responses (− 110 to 1610 kJ per day) was noted,[7] again emphasizing that inter-individual variations might therefore be important to consider when assessing factors that may limit weight loss and/or weight gain. For the clinician, the calculation of the greater-than-predicted decrease in energy expenditure in response to a weight-loss program provides a useful clinical marker that may reflect the ability of an obese individual to be a 'good responder' to the intervention. Indeed, as it is difficult to prescribe food intake that imposes an energy deficit exceeding 700–800 kcal per day to obese individuals, the decrease in energy expenditure in response to weight loss can entirely compensate for this prescribed deficit.[1] In this regard, it is also relevant to point out that aging can affect the response to a weight-loss intervention, as it has been shown to be associated with a greater-than-predicted decrease in resting energy expenditure.[8]

Adaptive thermogenesis: why is it occurring?

Adaptive thermogenesis may represent a defense mechanism that is set to protect energy stores from accelerated growth or depletion. The first explanation that has been proposed to explain thermogenic variations in animals is related to the activity of brown adipose tissue (BAT). As described by Rothwell and Stock,[9] BAT activity has sufficient impact on energy metabolism to explain individual variations in the proneness to obesity. In animals, this observation has been corroborated by many investigators, but the demonstration of relevance in humans has generally failed to provide a substantial quantitative importance of BAT in energy metabolism. However, interest for this aspect has been recently reactivated by a series of papers providing evidence of seemingly important amounts of BAT in human adults and of an impact on energy metabolism that might be greater than previously considered.[10–12] In this regard, the fact that glucose uptake by BAT represents an index of its metabolic activity has prompted the development of new phenotypic characterization.[13,14] Recent progress in position emission tomography scanning has permitted to obtain BAT imaging by using uptake of 2[^{18}F] fluoro-2-dioxy-glucose.[15] For instance, Yoneshiro *et al.*[16] tested healthy men who underwent fluorodeoxyglucose positron emission tomography measurements after 2 h of cold exposure. Compared with the measurement in a warm environment, cold exposure increased energy expenditure to a substantially different extent between the BAT-positive and -negative groups (410 vs 42 kcal per day). More recently, the demonstration of a specific role of BAT on thermogenesis in humans was done with even more specificity by Ouellet *et al.*[17] who tested healthy men under control cold-exposure conditions. These investigators showed that cold-induced increase in total energy expenditure was related to an activation of oxidative metabolism in BAT but not in adjoining skeletal muscles and subcutaneous adipose tissue.

Beyond the demonstration of validity of the greater-than-predicted change in energy expenditure as a measure of adaptive thermogenesis,[3] Rosenbaum *et al.*[18] have also contributed to identify some metabolic correlates of this variable. Indeed, a decrease in thermogenesis in weight-reduced obese individuals was found to be associated with a decrease in plasma T3 and leptin, as well as sympathetic nervous system activity.[18] They also showed that low-dose leptin administration reverses autonomic and neuro-endocrine adaptations occurring with weight loss[19] and the decrease in energy expenditure that normally occurs with weight loss.[20] Our research experience is also concordant with the notion of an important role of leptin in variations of adaptive thermogenesis in humans. Indeed, the decrease in plasma leptin was significantly correlated with the greater-than-predicted decrease in energy expenditure both at rest and during exercise in obese individuals having experienced weight loss.[5,6]

Another explanation of thermogenic variations in humans pertains to the environmental interference with metabolic regulation. In this case, the main problem is related to the impact of some persistent organic pollutants (POPs), which promote detrimental effects on the control of energy expenditure as far as maintaining lower levels of adiposity is concerned. It has been shown that POPs alter the development of the thyroid gland in animals,[21] promote a decrease in concentrations of thyroid hormones in animals[22,23] and humans,[24,25] and accentuate their body clearance.[26,27] Furthermore, POPs have been found to decrease skeletal muscle oxidative enzymes[28] and inhibit mitochondrial activity.[29,30] We also reported that changes in POP levels with weight loss were the best predictor of the decrease in resting metabolic rate (RMR) in obese individuals.[31] Subsequently, we compared the predictability of the greater-than-predicted decrease in sleeping metabolic rate in response to weight loss by changes in plasma leptin and POPs.[32] As expected, both variables significantly predicted the adaptive reduction in thermogenesis, but the contribution of POP changes was greater than that attributable to leptin changes.

Available data support a role of heredity on inter-individual variations in energy expenditure, in conditions of overfeeding or underfeeding leading to weight loss. To investigate this issue, Bouchard *et al.*[33] tested monozygotic twins in whom the within-pair resemblance relative to the between-pair resemblance in changes in energy expenditure provided an indication of a genotype–environment interaction effect. In twins tested under short-term (22 days) and long-term (100 days) conditions of overfeeding and underfeeding, resting and exercise energy expenditure were measured under standardized conditions. In general, a significant within-/between-twin pair variance ratio was observed,[34–38] suggesting a role of heredity in thermogenic adaptations to a positive or negative energy balance.

The analysis of factors potentially influencing thermogenesis also imposes to consider some mechanistic explanations that have not been, up to now, the object of systematic investigation. Among these factors, the impact of probiotics has been examined by Lee *et al.*[39] in mice with diet-induced obesity, which were supplemented with *Lactobacillus rhamnosus* TL60, a strain which produces conjugated linoleic acid, over 8 weeks. Following this treatment, mice showed reduced body weight without any change in energy expenditure. In humans, this issue does not seem to have been directly studied. The investigation of this issue would require to take into account that heat produced by gut bacteria is not measured by indirect calorimetry, which is 'blind' to energy-consuming anaerobic processes.[40]

Dietary calcium is another factor that has been studied for its potential thermogenic effect. In transgenic mice, which expressed the *agouti* gene in adipose tissue under the control of the aP2 promoter, the anti-obesity effect of dietary calcium and dairy products was confirmed in a series of studies.[41,42] In addition, high-calcium diets were found to inhibit lipogenesis, stimulate lipolysis, increase thermogenesis and suppress fat accretion and weight gain in animals fed isocaloric diets.[41] This is consistent with human studies that evaluated the effects of high calcium intake on RMR and thermic effect of a meal. In 11 subjects having participated in a randomized within-subject meal protocol comparing low to high calcium intake, diet-induced thermogenesis was significantly increased by an isoenergetic high-calcium meal.[43] Accordingly, St-Onge *et al.*[44] reported an increase in resting energy expenditure after 1 week of milk supplementation compared with a supplementation with sugar-only beverage in children. However, when studied in the context of a weight-loss program, calcium supplementation was not found to promote significant changes in energy expenditure.[45,46]

Among other factors that have the potential to influence thermogenesis, adenovirus-36 seropositivity is relevant, as its association with obesity was confirmed both in adults[47] and children.[48] However, to our knowledge, no animal or human studies have directly tested the effects of adenovirus-36 on adaptive thermogenesis. Finally, the impact of short sleep duration is also worth considering, as its link with the risk of obesity is also well documented.[49,50] In this regard, sleep deprivation in rats was found to promote an increase in both EI and energy expenditure. This increase in energy expenditure seemed to be mediated by an elevation of the expression of uncoupling proteins (UCP), for example, UCP1 in BAT[51] and UCP2 in skeletal muscle.[52] Further research will also be useful to determine if this stimulation of UCPs is the consequence of the sleep-induced hyperphagia[53] or the stress related to inadequate sleep-related recovery. In humans subjected to a reduced calorie diet, Nedeltcheva *et al.*[54] reported that sleep deprivation induced a decrease in relative fat oxidation.

In summary, there is growing evidence suggesting that both BAT and white adipose tissues are involved in adaptive thermogenesis, as BAT is

metabolically well equipped to produce heat, and that molecules secreted (for example, leptin) or stored (for example, POPs) by white fat cells also appear as factors that may have an important role in adaptive thermogenesis. It thus seems of interest to investigate the interaction between the two tissues in the determinism of variations in thermogenesis observed in humans experiencing fluctuations in energy stores.

Adaptive thermogenesis and weight loss

Adaptive thermogenesis and resistance to lose fat. Although weight reduction is a difficult task, the maintenance of lost weight seems to require the deployment of even more efforts.[55] Indeed, the relapse of more than 80% of individuals to pre-weight-loss levels of body fatness after otherwise successful weight loss is likely due to the coordinated actions of metabolic, neuro-endocrine, autonomic and behavioral changes that oppose the maintenance of a reduced body weight.[56] The occurrence of an apparent resistance to lose fat (plateau) is often interpreted as being the result of a lack of dietary and/or physical activity guidelines compliance. However, the adaptive reduction in thermogenesis can be sufficiently pronounced in some cases to counteract further weight loss, even in the compliant patients.[1,2,57]

As mentioned earlier, the experiments conducted by Leibel *et al.*[3] have significantly contributed to our understanding of the clinical impact of adaptive thermogenesis by showing that the maintenance of a reduced or elevated body weight was associated with compensatory changes in energy expenditure. We confirmed these observations in obese individuals subjected to a weight-reducing program by showing that the decrease in energy expenditure substantially exceeded the reduction predicted by changes in fat-free and fat mass.[6,57] More recently, we substantiated the clinical relevance of adaptive thermogenesis by reporting the case of a woman who gained 2 kg of body weight despite her careful compliance to a 15-week weight-reducing program consisting a supervised diet (-500 kcal per day).[1] This clinical paradox was explained by a decrease in RMR of 552 kcal per day, thereby supporting the potential of adaptive thermogenesis in impeding obesity treatment in some individuals.

In an attempt to further understand the extent to which diminished thermogenesis may contribute to the occurrence of resistance to lose fat, we designed a sequential therapeutic approach requiring the testing of obese men at every 5 kg of weight loss and at resistance to fat loss. According to our previous experience, the weight-loss program was based on a low-fat diet (-700 kcal per day) supervised by a dietitian and performing exercise under the supervision of a kinesiologist. This protocol induced weight loss in the participants who became resistant to lose fat after a 12.7-kg (12.4% of initial body weight; 93.8% from fat stores) weight loss over 8 months.[58] As shown in Figure 1, the adaptive reduction in thermogenesis reached 706 kJ per day at plateau and represented 30.9% of the compensation in energy balance that led to resistance to further lose fat. Thus, even if changes in appetite control and EI occurring with weight loss remain important determinants of resistance to lose fat in obese individuals,[4] it is likely that the adaptive reduction in thermogenesis also represents an important contributor to the inability to further lose weight over time. Taken together, these studies highlight the fact that adaptive thermogenesis could be quantitatively more important than what is generally perceived by health professionals; some obese individuals display disproportionate changes in energy expenditure when exposed to conditions of negative energy balance. In turn, this then possibly impedes body weight loss.

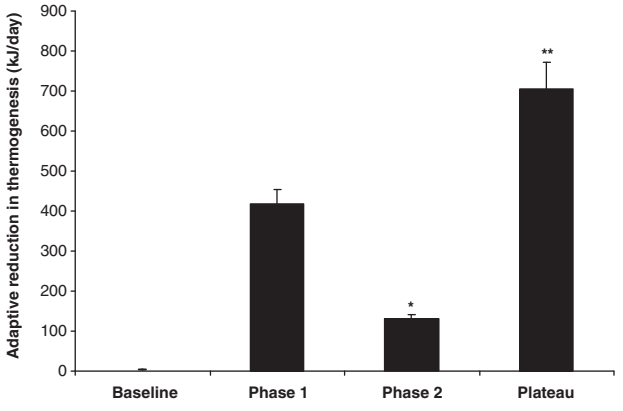

Figure 1. Adaptive reduction in thermogenesis at each phase of a weight-loss program that consisted of a supervised diet and exercise in obese men. Mean values with their s.e. Phase 1: 5 kg weight loss. Phase 2: 10 kg weight loss. Plateau: 12.7 kg weight loss (12.4% of initial body weight). Adaptive reduction in thermogenesis was defined as the greater-than-predicted decrease in resting metabolic rate induced by the weight-reducing program. *Significantly different from phase 1 and plateau ($P<0.05$). **Significantly different from phases 1 and 2 ($P<0.05$). Figure adapted from Tremblay and Chaput.[58]

Adaptive thermogenesis and appetite control. The limited ability to maintain energy balance in a weight-reduced state is the product of our difficulty in compensating for the weight-loss-induced reduction in total energy expenditure.[59] The end result, translated into the overwhelming complexity of preserving long-term weight loss, is a consequence of compromised appetite control. Indeed, there is accumulating evidence supporting that the control of food intake is compromised when body energy reserves are being depleted. Dieting has been shown to trigger counter-regulatory adaptations, possibly through downregulation (leptin, PYY and GLP-1) or upregulation (ghrelin) of peptides known to affect energy balance.[59] Despite a decrease in total energy expenditure in a weight-reduced state, there is a concomitant increase in the drive to eat,[4] an effect that is also observed early into energy deprivation[60] and that has been shown to predict weight relapse.[61] Thus, a reduction in energy expenditure as observed after weight loss is unfortunately not accompanied by a proportionate decrease in the drive to eat. The problem of maintaining energy balance after weight loss is then likely to be one of reducing EI to compensate for a chronic decrease in energy expenditure, considering that large amounts of exercise are needed to maintain weight stability after weight loss.[62]

We recently reported that changes in appetite sensations are directly related to the loss of body fat.[63] Indeed, for each kilogram of fat lost and independent of initial body weight, women subjected to a calorie-restricted diet experienced an increase in desire to eat of 5.8 mm and a decrease in fullness of 3.6 mm in their rating on 150 mm visual analog scales. These results are novel and emphasize the clinical usefulness of visual analog scales. Whether or not these could be used to identify potential weight regainers and poor weight-loss responders remains to be determined.

In an attempt to further understand the disruption in the coupling between EI and energy expenditure during weight loss, we reanalyzed data of obese subjects tested at every 5 kg of weight loss until the occurrence of a plateau, as described in the previous section. To document the ability of our participants to maintain a given energy balance over time, we divided their *ad libitum* EI during a buffet-style meal with their RMR. These rates ($EI_{buffet}/RMR_{kcal/24\,h}$) can be regarded as an indicator of their ability to deal with a negative energy balance and thereby their vulnerability of relapse. On the basis of previously reported studies, appetite is expected to increase[4,59] and RMR to decrease[3,18] with weight loss. Thus, the resulting quotient integrating changes in these two variables is a theoretical increase with weight loss. Surprisingly, phases 1 and 2 resulted in an improvement of this indicator (see Figure 2), suggesting that our weight-loss program was adequate and well tolerated by the participants. This can be explained by the functionality of our prescribed menus, which included many nutritional properties favoring satiety, as well as by the physical activity component that attenuated the decrease in fat-free mass and RMR. However, we observed an opposite trend at weight-loss plateau, that is, the phase associated with a substantial reduction in adaptive thermogenesis. Clearly, the subjects were not able to match EI with energy expenditure, and this scenario then creates optimal biological circumstances for weight regain. Interestingly, we also observed a significant association between the adaptive reduction in thermogenesis and the change in hunger (Figure 3). In other words, the greater the reduction in adaptive thermogenesis during a weight-loss program, the greater the increase in the drive to eat. This finding then suggests that it is more difficult for some individuals (that is, those experiencing an important reduction in adaptive thermogenesis) to be satiated in a reduced-obese state than for those experiencing no or little adaptive thermogenesis over the course of a weight-loss program. In addition, these observations emphasize that bringing weight loss up to a state of resistance to further lose weight is counterproductive and promotes ideal conditions for relapse.

Adaptive thermogenesis and the rate of weight loss. One of the most consistently reproduced observations in the field of obesity research is that

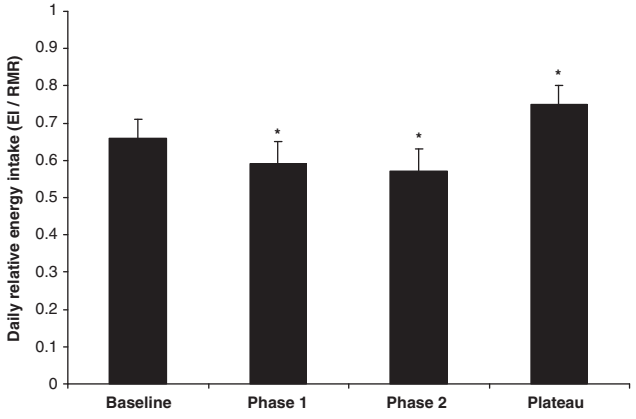

Figure 2. Daily relative energy intake at each phase of a weight-loss program that consisted of a supervised diet and exercise in obese men. Mean values with their s.e. EI, energy intake (kJ); RMR, resting metabolic rate (kJ/24 h). Phase 1: 5 kg weight loss. Phase 2: 10 kg weight loss. Plateau: 12.7 kg weight loss (12.4% of initial body weight). Daily relative energy intake is an indicator that represents the ability to deal with a negative energy balance. An increase in this quotient is generally associated with weight regain. *Significantly different from baseline ($P<0.05$). Note: the indicator significantly decreased in phases 1 and 2, and significantly increased in the plateau phase compared with baseline values.

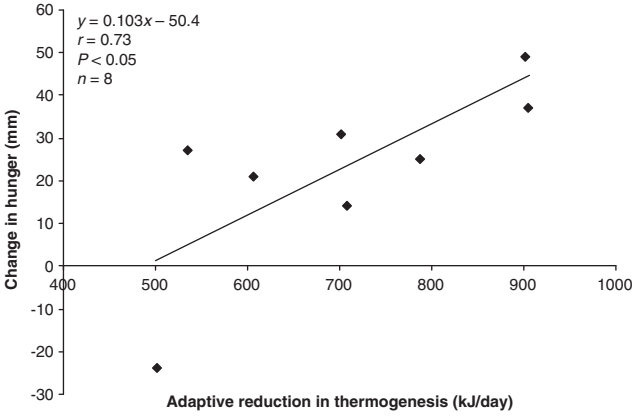

Figure 3. Association between the adaptive reduction in thermogenesis at body weight loss plateau and the change in hunger level over the course of a weight-loss program that consisted of a supervised diet and exercise in obese men. Change in hunger level: plateau − baseline. Plateau: 12.7 kg weight loss (12.4% of initial body weight). Adaptive reduction in thermogenesis was defined as the greater-than-predicted decrease in resting metabolic rate induced by the weight-reducing program.

weight loss is accompanied by a decrease of energy expenditure.[5,64] To obtain a more comprehensive overview of the effects of weight loss on energy expenditure, we recently conducted a systematic review on this issue.[65] From these analyses, we reported that when all types of weight-loss interventions are combined, the resulting figure for weight-loss-induced reduction in resting energy expenditure is 15.4 kcal kg^{-1} per day. As can be seen in Figure 4, there are important differences between the modes of interventions. As the energy deficit, that is, the gap between energy expenditure and EI, is likely the greatest at the onset of interventions, we were also interested in comparing short- and long-term interventions aimed at inducing weight loss. As initially anticipated, the analysis of a subset of studies for this systematic review revealed that short-term interventions (<6 weeks) produced a reduction in energy expenditure that was twice as much (–28 kcal kg^{-1} per day) than that observed for the longer-term interventions (> 6 weeks; −13 kcal kg^{-1} per day; Figure 5). As such, one could postulate that in some individuals,

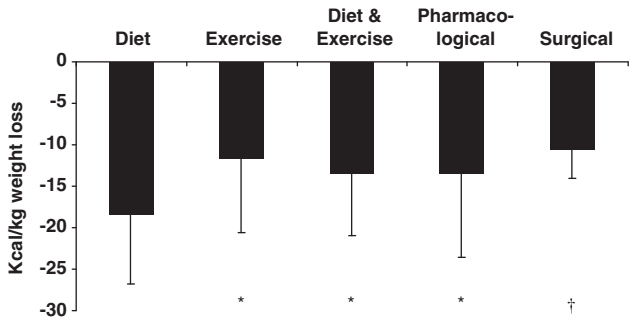

Figure 4. Comparison of the mean rate of changes in resting EE relative to weight loss with different weight loss interventions in all males and females ($n=2983$). * and † indicate significant difference from diet at $P<0.05$ and $P<0.001$, respectively.

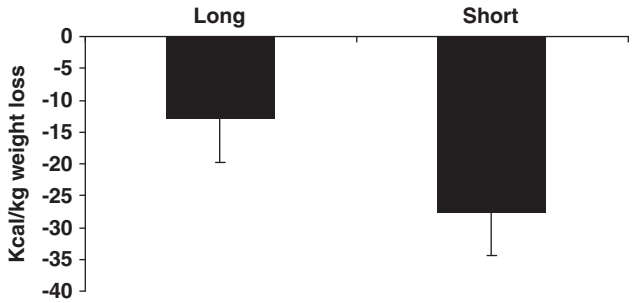

Figure 5. Comparison of the effect of time on the mean rate of changes in resting EE relative to weight loss with long (⩾6 weeks) and short (<6 weeks) interventions. Differences were statistically significant ($P<0.001$).

a greater energy restriction may not systematically yield the expected weight loss if it downplays the magnitude of the energy deficit through a more aggressive response in the depression of energy expenditure. Together, the results presented throughout this review would thus tend to suggest that adaptive thermogenesis may impede the rate of body energy mobilization, but testing this provides a challenge from an experimental point of view. Indeed, as greater-than-predicted depressions in energy expenditure have been noted both for the resting[57] and non-resting[3,6] components of energy expenditure, this implies precise measurements of total, physical activity and resting energy expenditure. It also implies a good control of the EI measurement throughout the weight-loss trial. Accordingly, not many studies have been performed to test whether alterations in energy metabolism could represent a barrier to weight loss in some individuals. Among these, Miller and Parsonage[66] published the results of a study in 29 women who claimed that they could not lose weight. The participants were secluded in a house for 3 weeks, where they were fed a standard 1500 kcal per day diet. Under these very controlled conditions, 19 women lost weight, 9 lost no weight and 1 woman actually gained weight. What is more, energy expenditure was measured on three occasions during the 3-week period. In the end, the authors concluded that women with the lowest basal metabolic rate were the ones who did not lose weight under very well-controlled conditions. These observations lend credibility to the postulation that adaptations to energy-restricted diets, under very controlled conditions, may indeed impede weight loss attempts in some individuals.

Persistence of adaptive thermogenesis over time. Ravussin *et al.*[67] reported that low rates of energy expenditure was a risk factor for weight gain. More relevant to this review, is the relationship between low rates of energy expenditure and the maintenance of a reduced body weight. Along these lines, it has been shown that individuals who regain the most weight over a 16-month follow-up are also those in whom the greatest depression in 24-h energy expenditure is witnessed during the weight-loss intervention.[61] As such, the magnitude of the decrease in energy expenditure that occurs as a response to prolonged energy deficits

leading to weight loss seems to be an important determinant of the long-term success of weight-loss interventions. In fact, greater reductions in energy expenditure may increase the degree of difficulty to bridge the gap with a manageable EI, as weight loss also increases appetite,[4] food reward and palatability of foods[68] as mentioned previously. Then, addressing whether or not the greater-than-predicted changes in energy expenditure persist in the weight-reduced state, if somehow individuals manage to maintain weight stability after weight loss, becomes interesting and important. The re-analysis of the semi-starvation data from the classic experiment of Keys *et al.*[69] provided some of the first evidence that the depression of energy expenditure persisted at least for a short period after the end of the 24 weeks of severe energy deprivation.[70] In fact, basal metabolic rate remained ~10% below predicted values after 12 weeks of refeeding while the subjects had almost entirely recovered their pre-starvation body weight. Although these data support the existence of a depression in energy expenditure that persists beyond the energy restriction, under conditions where individuals are consuming food *ad libitum* after weight loss, it may be argued that this effect may be a carry-over from subjects having been recently semi-starved. Through the meta-analysis approach, Astrup *et al.*[71] provided further documentation of the possible durability of depressed energy expenditure. They compiled results from 124 formerly obese women who were compared with 121 women who had never been obese. Results from the analyses showed that resting energy expenditure was 5.1% lower in the formerly obese subjects after all appropriate corrections for differences in body mass had been performed. Unfortunately, little information was provided as to the time at which the post weight-loss assessment of energy expenditure was performed in the formerly obese subjects. More recently, the predicted and measured values of energy expenditure were compared in subjects who had just completed a weight-loss intervention designed to induce a 10% body weight reduction or in subjects who managed to maintain a 10% weight reduction for at least 1 year.[72] It was reported that the difference between predicted and measured total energy expenditure and non-resting energy expenditure remained similar after 1 year of weight stability at a lowered body weight as that observed soon after weight loss. Collectively, these results underline the possibility that the metabolic adaptations that occur in response to prolonged energy deficit persist in time and that constant efforts may need to be deployed in the form of increased energy expenditure from exercise or strict adherence to lowered EI, similar to the characteristics of successful long-term weight-loss maintainers.[55]

Is it relevant to intervene in reduced-obese individuals?

As presented and discussed in this review, the increase in the drive to eat and the seemingly persistent depression of different components of energy expenditure after weight loss, may well complicate the maintenance of energy balance at that point, which is supported by the overwhelming level of weight relapse. These observations provide an interesting platform for investigating approaches that may normalize weight-loss-induced effects on energy balance. Some studies have investigated the potential of exogenous leptin administration to attenuate the effects of weight loss on appetite and changes in energy expenditure. In the first of these two studies, it was reported that administrating recombinant leptin to human subjects after weight loss partly corrected some of the weight-loss-induced defects in energy expenditure.[20] Similarly, administration of leptin during weight loss has also been shown to attenuate the appetite and hunger responses that normally occur under such circumstances.[73] Finally, results from a recent functional imagery trial also showed that administration of recombinant leptin reestablished the brain response to food cues to levels comparable to pre-weight-loss patterns.[74] Collectively, these results show that changes in appetite and energy expenditure that occur in response to weight loss may be partially reversed with exogenous leptin administration. Whether or not this approach would lead to improved long-term weight stability after weight loss remains to be determined.

In conclusion, the observations presented and discussed in this paper indicate that a decrease in thermogenesis may occur in obese individuals maintaining a supervised diet–exercise program promoting weight loss. This adaptation explains a substantial decrease in daily energy needs and is related to changes in appetite sensations promoting compensation possibly through increased EI. As these thermogenic changes would seem to persist over time, they likely contribute to body weight regain following body weight loss. It thus seems important to further investigate adaptive thermogenesis in humans, be it for the development of relevant biomarkers or to improve diagnosis about individual determinants of the predisposition to obesity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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