

# Role of Adaptive Thermogenesis in Unsuccessful Weight-Loss Intervention

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Future Lipidology. 2007;2(6):651-658.

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## Abstract and Introduction

### Abstract

Numerous studies have been performed to examine the existence of a relationship between a weak thermogenic potential and the risk of developing obesity. These studies used a large variety of methodological approaches that have frequently revealed a potential physiological vulnerability in obesity-prone individuals. However, from a quantitative standpoint, they have not allowed the demonstration of differences or experimental effects that could explain large variations in energy balance. As discussed in this paper, a definition of adaptive thermogenesis as being a greater than predicted change in energy expenditure in response to changes in energy balance leads to clinically meaningful observations. This is particularly the case in the context of a weight-reducing program in which adaptive changes in thermogenesis can be sufficient to compensate for a prescribed decrease in daily energy intake. This paper also presents evidence suggesting that these thermogenic adaptations might indirectly contribute to the protection of body homeostasis by attenuating the decrease in the dilution space of some lipid-soluble pollutants.

### Introduction

Energy expenditure is subjected to variations that are rarely of a pathological nature, which may explain why no reference value of 'metabolic rate normality' exists to diagnose physiological dysfunctions. In fact, when excess deviations in energy expenditure are observed in a patient, the medical diagnosis is generally made by referring to other variables as in the case of hypo- and hyperthyroidism. Another reason potentially explaining why energy expenditure has not been traditionally used in obesity as a variable of clinical diagnosis pertains to the inability of basic and clinical research to identify and characterize a thermogenic defect in obesity-prone individuals. However, in a context where the prevalence of obesity is increasing in an accelerated manner, it remains relevant to question whether variations in energy expenditure may be a matter of physiological vulnerability for some individuals.

In the present paper, we document this issue by specifically focusing on the hypothesis that adaptive thermogenesis might be a cause of unsuccessful body weight loss. In addition, factors that may well explain these variations, particularly those that are difficult to investigate under free-living conditions because of ethical considerations, will also be discussed.

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## Adaptive Thermogenesis: A Historical Perspective & a Definition

Neumann was probably the first investigator who reported evidence documenting the possible existence of an adaptive component of energy expenditure. His personal observations pertained to the ability to maintain a stable body weight at various levels of energy intake, suggesting that compensations in energy expenditure have the potential to prevent deviations in energy balance when energy intake is changing. The experiments of Neumann<sup>[1]</sup> were followed by those of Gulick<sup>[2]</sup> who also demonstrated body weight stability despite significant variations in the diet. From a technical standpoint, these experiments emphasized the ability to document the existence of adaptive thermogenesis based on the measurement of the energy intake of weight maintenance.

The early works of Neumann and Gulick were followed by numerous investigations in which a large variety of experimental approaches were used. In this regard, presents the main methodological strategies that were tested in humans over recent decades with the preoccupation to document the existence of a thermogenic deficit in obesity-prone individuals. These approaches are, in general, well justified from a conceptual standpoint and they are still in use in many laboratories by relying on the most rigorous procedures of standardization. In many cases,

the results provided by the studies referenced in revealed some thermogenic deficit or related physiological vulnerability in individuals predisposed to obesity. In addition, it is relevant to note that these effects were more easily detectable in weight-reduced obese individuals compared with when obese subjects were tested under conditions of habitual body weight stability. Despite the fact that many of these studies demonstrate the existence of an adaptive component of energy expenditure, the quantitative importance of the documented differences or experimental effects has not reached a level that would have led clinicians to believe that adaptive thermogenesis might be a factor which may influence the success of a weight-loss intervention.

**Table 1. Study of Thermogenesis in Humans**

Measurement of	Ref.
Thermic effect of food	3-11
Thermic effect of glucose and/or insulin	12-21
Thermic effect of catecholamines	22-25
Thermic effect of ephedrine and/or caffeine	26-30
Effects of experimental under or overfeeding	31-38
The potentiating thermogenic effect of exercise	39-44
Thermogenesis in skeletal muscle	45-48
Effects of $\alpha$ - and $\beta$ -adrenergic blockade	49-55

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In our opinion, the publication of a series of studies by Leibel *et al.* [56] has provided significant progress in the characterization of the thermogenic profile of the obese. These studies described the changes in energy expenditure in obese and nonobese individuals submitted to a 10% body weight gain and to a 10 and 20% diet-induced body weight loss. Total and resting energy expenditures were measured by indirect calorimetry at the beginning of each experiment and at each weight plateau after at least 2 weeks of body weight stability. From a technical viewpoint, these authors innovated by calculating predicted values of energy expenditure from fat-free mass and fat mass by using initial measurements as indicators of free-living normal variations in this phenotype. They used their predicted scores for comparison with measured values of energy expenditure following body weight change. In this context, adaptive thermogenesis represented the difference between predicted and measured total or resting energy expenditure values. These variations were substantial since the mean deviation from predicted total daily energy expenditure was -244 and -301 kcal/day following a 10 and 20% body weight loss, respectively. To our knowledge, this was the first time that energy expenditure was analyzed as a clinical variable, specifically, a variable that is compared with reference standardized values with the potential outcome to make a clinical diagnosis.

In continuation of the Leibel *et al.* studies, some of us investigated the impact of adaptive thermogenesis in the

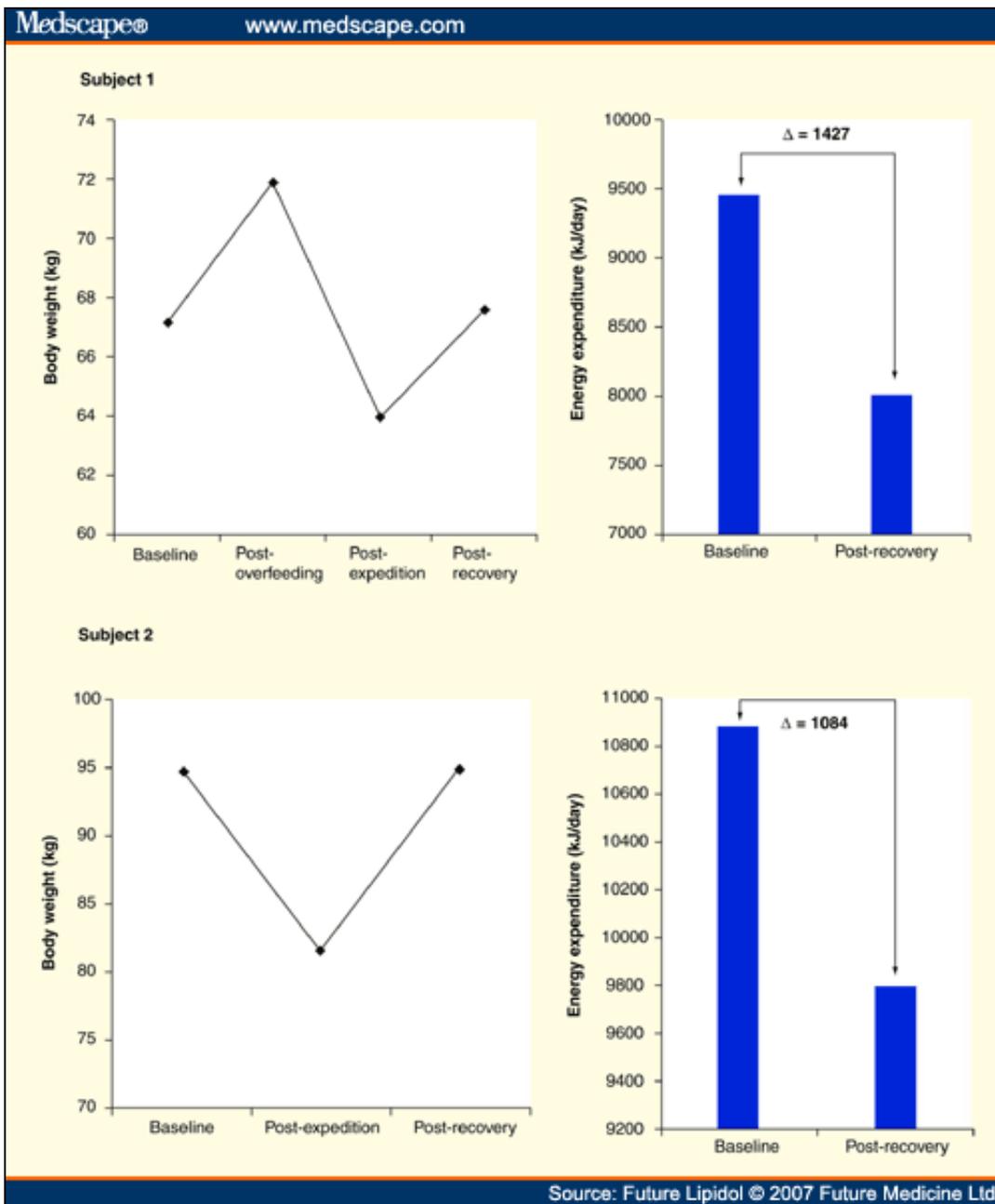
context of a standard weight-loss program. Adaptive thermogenesis was then defined as the decrease in energy expenditure beyond what could be predicted from body weight or its components (fat-free mass and fat mass) under conditions of standardized physical activity in response to a decrease in energy intake. As expected, energy expenditure, be it in the resting<sup>[57]</sup> or the active<sup>[58]</sup> state, was significantly more decreased compared with what was predicted by morphological changes. In addition, we recently reported the maximal decrease in resting energy expenditure in this study, which was sufficient to completely compensate for the prescribed energy deficit, possibly going beyond any good compliance of some subjects.<sup>[59]</sup> In the same paper, we also documented the potential impact of some normally unsuspected environmental factors on adaptive thermogenesis. As discussed in the next section, body weight instability can be considered as a factor that can induce substantial variations in energy expenditure.

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## Adaptive Thermogenesis & Body Weight Instability

Body weight instability, which is also generally referred to as the 'yo-yo phenomenon', seems to be the normal biological reaction to uncontrolled and quantitatively important negative energy balance. The weight regain that generally follows this large energy deficit may exceed weight loss so that a net weight gain may be the outcome of such a weight cycle. Approximately two decades ago, the yo-yo effect was tested as a factor that could explain, *per se*, the proneness to a positive energy balance in animals.<sup>[60-62]</sup> Although this valuable testing demonstrated the potential to induce an increase in food efficiency and/or weight gain, subsequent human studies have not provided a clear support to this concept.<sup>[63-65]</sup> This may not be so surprising if one considers that clear demonstration of weight cycling on energy expenditure is practically untestable for ethical reasons. Indeed, it would be ethically unacceptable to submit individuals to one or several severe weight cycles when an investigator cannot exclude the possibility of a permanent handicap in the accuracy of energy-balance regulation as a consequence of the testing.

As previously reported,<sup>[59]</sup> we had the opportunity to complete two case studies in which we could test the effect of weight cycling on adaptive thermogenesis under well-standardized conditions. In the first study, an athletic male explorer was first tested in the Laval University respiratory chamber under well-standardized experimental conditions.<sup>[66]</sup> As shown in Figure 1, this measurement was followed by pre-expedition overfeeding that induced a 5 kg weight gain. After overfeeding, he engaged in a 22-day cross-country skiing expedition through Greenland that resulted in a weight loss of 8.5 kg. Figure 1 also shows that indirect calorimetry measurements were repeated after he had recovered his baseline morphological profile. It is also important to note that this post-expedition measurement was performed under conditions similar to baseline measurement for energy and macronutrient intake, as well as for spontaneous physical activity in the chamber. Despite this optimal standardization for factors influencing 'obligatory thermogenesis', daily energy expenditure was reduced by 1.4 MJ (approximately 350 kcal) following the expedition.



**Figure 1.**

Variations in body weight and daily energy expenditure in response to a weight cycle imposed by an expedition in Greenland (Subject 1) and in Antarctica (Subject 2).

A comparable result was obtained in the second study, which involved the testing of another male explorer who was also subjected to whole-body indirect calorimetry measurements before and after a 65-day expedition in Antarctica. As expected, the expedition induced a considerable body weight loss (13.2 kg) that had to be recovered following the expedition before a second series of measurements could be performed in the respiratory chamber. Thus, as for case study 1, this subject was tested at the same body weight and composition status before and after the expedition as well as under standardized nutritional and activity conditions in the chamber. Figure 1 shows that the weight loss/regain cycle again resulted in a marked decrease (1.0 MJ/day) in daily energy expenditure, which provides further evidence of the impact of weight cycling on adaptive thermogenesis.

### Adaptive Thermogenesis as a Cause of Unsuccessful Weight Loss

The main implication that can be derived from the observations presented above is that adaptive thermogenesis can be sufficiently pronounced in some individuals to interfere with successful weight loss. On the basis of the

studies of Leibel *et al.* and those performed in Laval University, this phenomenon could appear as an adaptation that promotes the early occurrence of resistance to lose fat. Indeed, in these two series of studies, greater than predicted decreases in energy expenditure were observed in subjects having experienced some weight loss.

Our clinical experience also reveals that such an adaptation can happen sufficiently early during the course of a weight-reducing program to totally prevent the achievement of weight loss. This is the case of a woman who participated in a weight-reducing program at Laval University several years ago. As shown in , she experienced weight gain after 15 weeks of careful nutritional supervision aimed at promoting weight loss. This table also shows that this subject was compliant to nutritional guidelines since she was reporting a decrease in daily energy intake of approximately 500 kcal at the end of the study compared with initial measurements. Interestingly, indirect calorimetry measurements offered an explanation of the apparent paradox revealed by the weight gain at the same time as the subject was reducing her energy intake. Indeed, shows that the decrease in daily resting metabolic rate was equivalent to the reported reduction in energy intake. If one considers that the energy efficiency displayed by the subject in the resting state at the end of the study was also likely to be present in the nonresting state, it becomes easily understandable that weight gain occurred when the subject was compliant to nutritional guidelines promoting a decrease of caloric intake. This agrees with the observations of Miller and Parsonage<sup>[67]</sup> who found that some subjects were resistant to slimming despite a rigorous control over energy intake.

**Table 2. Daily Energy Intake and Resting Metabolic Rate Before and After a 15-week Weight-reducing Program in a Woman Resistant to Weight Loss**

Variable	Before	After
Body weight (kg)	79.7	81.8
Energy intake (kcal/day)	2358	1870
Resting metabolic rate (kcal/day)	1479	927

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In summary, there seem to be some obese individuals who clearly overreact in energy expenditure when they are exposed to a negative energy balance. This adaptive thermogenesis may then clearly reduce the ability to achieve a successful body weight loss. To date, there is no clear explanation for the occurrence of such a phenomenon but, as discussed in the next section, we cannot exclude the possibility that it might happen so as to protect body homeostasis.

## Adaptive Thermogenesis as a Protective Mechanism Against Environmental Hazards

The research conducted in Laval University during the past 10 years on body organochlorines (OCs) and obesity probably offers the best example to discuss the issue of a protective role for adaptive thermogenesis. As previously described, the interest for OCs in the study of obesity is related to their lipid soluble properties.<sup>[68]</sup> Despite the fact that the use of these compounds has now been banned in many countries for several decades, they persist in the body of every person on the planet because of their long half-life and their transport via air from countries where they still remain in use.<sup>[69-71]</sup> As summarized in , their effects on thyroid function and mitochondrial functionality theoretically confer to these compounds an antithermogenic profile.

**Table 3. Potential Detrimental Effects of Organochlorines on Adaptive Thermogenesis**

Effects	Ref.
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Decrease in thyroid hormone synthesis	72
Decrease in plasma T3 and T4	73-74
Increase in thyroid hormone clearance	75
Decrease in skeletal muscle oxidative potential	76
Inhibition in enzyme activities of the mitochondrial electron transport chain	77

At the end of the 1970s, Backman and Kolmodin-Hedman were the first investigators to report a significant increase in circulating OCs with body weight loss.<sup>[78]</sup> This hyperconcentration in plasma OCs depends on body weight loss, specifically, the importance of the decrease in their dilution space. In this regard, it was recently demonstrated that the increase in the plasma concentration of OCs corresponded to 388% of baseline values in obese patients tested 1 year after bariatric surgery.<sup>[79]</sup>

The integration of these observations also led some of us to examine the potential impact of OCs as an explanatory factor for the decrease in thermogenesis favored by weight loss in humans. Since this issue also cannot be directly tested for ethical reasons, a stepwise multiple regression analysis was used to quantify the contribution of various factors, including OCs, on the variance of changes in sleeping metabolic rate induced by body weight loss. The main finding of this study was that changes in plasma OC concentration explained half of the variance in the greater than predicted decrease in sleeping metabolic rate measured by whole-body indirect calorimetry.<sup>[80]</sup>

This finding is ecologically important since it provides an indication of the potential detrimental role of chemical pollution on the control of human energy expenditure. Since the documentation of this effect is the outcome of an association study rather than of a direct experimental demonstration, it is clear that it will not be possible to get a definitive proof of this concept. However, biological common sense would suggest that the accentuation of the thermogenic decrease occurring with weight loss appears to be useful to attenuate the decrease in the dilution space of OCs and to prevent more pronounced perturbations of body homeostasis.

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## Conclusion

The observations presented in this paper indicate that greater than predicted decrease in energy expenditure may happen in response to weight loss in obese individuals. The extent to which this may represent a thermogenic defect is debatable, but its ability to interfere with weight loss seems to be much clearer. Furthermore, this paper suggests that such a decrease would not occur randomly since it appears to be, at least partly, the consequence of fluctuations in body pollutants, which are known to produce detrimental effects on health and factors involved in the control of body thermogenesis.

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## Future Perspective

This paper provides evidence suggesting that equations estimating metabolic rate may not be adequate to determine energy needs in some individuals. This is likely the case for some obese individuals who are tested after weight loss when metabolic rate can be substantially lower than what is predicted by changes in body weight or composition. In this context, it is likely that the clinical evaluation of obese and weight-reduced individuals may require a greater level of sophistication by incorporating techniques such as indirect calorimetry in the evaluation setting. Without such an improvement in clinical characterization, the physiological vulnerability and the good compliance of some patients might remain unrecognized realities.

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## Sidebar: Executive Summary

- This paper documents the clinical significance of adaptive thermogenesis that is defined here as a greater than predicted change in energy expenditure in response to changes in energy balance.

- In some patients tested after a weight-reducing program, this excess decrease in energy expenditure may reach 1 MJ/day or even more.
- This adaptation reduces the ability to tolerate a prescribed energy deficit and may compromise the success of a weight-reducing program.
- This decrease in thermogenesis can also be viewed as a protective mechanism by preventing a substantial decrease in the dilution space of lipid soluble pollutants.

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Future Lipidology. 2007;2(6):651-658. © 2007 Future Medicine Ltd.