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Short Communication

Adaptive reduction in thermogenesis and resistance to lose fat in obese men

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Adaptive thermogenesis is defined as a greater than predicted change in energy expenditure in response to changes in energy balance. This issue is particularly relevant in the context of a weight-reducing programme in which diminished thermogenesis can be sufficient to compensate for a prescribed decrease in daily energy intake. In the present pilot study, we investigated the adaptive reduction in thermogenesis in resting state that appears to favour resistance to further weight loss. Eight obese men (mean BMI: 33·4 kg/m^2, mean age: 38 years) participated in this repeated-measures, within-subject, clinical intervention. They were subjected to a weight-loss programme that consisted of a supervised diet (−2930 kJ/d) and exercise clinical intervention. The phases investigated were as follows: (i) baseline, (ii) after 5 (SE 1) kg loss of body weight (phase 1), (iii) after 10 (SE 1) kg weight loss (phase 2) and (iv) at resistance to further weight loss (plateau). At each phase of the weight-reducing programme, body weight and composition as well as RMR were measured. A regression equation was established in a control population of the same age to predict RMR in obese men at each phase of the weight-loss programme. We observed that body weight and fat mass (FM) were significantly reduced ($P<0·05$), while fat-free mass remained unchanged throughout the programme. In phase 1, measured RMR had fallen by 418 kJ/d, more than predicted ($P<0·05$), and this difference reached 706 kJ/d at plateau ($P<0·05$ *v.* phase 1). A positive association (r 0·64, $P<0·05$) was observed between the reduction in thermogenesis and the degree of FM depletion at plateau. The adaptive reduction in thermogenesis at plateau was substantial and represented 30·9 % of the compensation in energy balance that led to resistance to further lose body weight. In conclusion, these results show that adaptive reduction in thermogenesis may contribute to the occurrence of resistance to lose fat in obese men subjected to a weight-reducing programme.

Adaptive thermogenesis: Energy expenditure: Metabolic rate: Weight loss

The obesity epidemic that is observed in many countries of the world has a certain number of corollaries including an increasing number of obese individuals who try to lose weight or to maintain weight loss without success. Indeed, the most frequent outcome of a weight-reducing programme is a fat loss that cannot be sustained and eventually recovered. In such a context, health professionals as well as patients themselves tend to interpret this occurrence of resistance to lose fat as a demonstration of non-compliance to diet and physical activity guidelines. However, in several recent papers[1–3], we raised the possibility that in some cases, the adaptive reduction in thermogenesis can be sufficiently pronounced to counteract further weight loss, even in the compliant patients.

The concept of adaptive thermogenesis was indirectly documented at the beginning of the last century when Neumann[4] reported that body weight can remain stable despite substantial changes in daily energy intake. This study of the variations in the energy intake of weight maintenance constituted the starting point of a large number of investigations in which the detection of significant facultative thermogenesis was the central issue. As reviewed recently[2], many protocols using valid approaches revealed some differences in energy expenditure between spontaneously non-overweight persons and obesity-prone individuals. However, despite the validity of these approaches and the statistical significance of reported differences, it has never been possible to clearly establish the clinical significance of adaptive thermogenesis, including a role in the premature occurrence of resistance to lose fat in a weight-reduced obese person.

In our opinion, the experiments conducted by Leibel *et al.* [5] have provided a significant progress in the understanding of the clinical impact of adaptive thermogenesis. Briefly, they showed 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 programme by showing that the decrease in energy expenditure substantially exceeded the reduction predicted by changes in fat-free and fat mass

Abbreviation: FM, fat mass.

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(FM), both in resting[1] or active[6] state. More recently, we extended the demonstration of the clinical relevance of adaptive thermogenesis in this context by reporting the case of a woman who gained body weight despite her careful compliance to a weight-reducing programme[2]. This clinical paradox was explained by a decrease in RMR of 2043 kJ/d (488 kcal/d) at the end of the 15-week weight-loss programme. Even if the latter observation may be perceived as convincing evidence in favour of a role for adaptive reduction in thermogenesis as a determinant of resistance to lose fat, it is clear that this concept deserves a further support from relevant clinical interventions. Thus, the main aim of this pilot study was to evaluate variations in RMR in obese men who were tested when they were good responders to a weight-reducing programme, as well as when they had become resistant to further lose fat in response to this intervention. To our knowledge, the adaptive reduction in thermogenesis at a weight-loss plateau has never been studied and we hypothesised that its contribution would be more important at this moment.

Methods

Healthy, non-smoking, sedentary, obese Caucasian men, from 25 to 45 years of age, with a BMI between 30 and 40 kg/m^2 were recruited to participate in the present study. Participants with diabetes, high blood pressure (seated systolic/diastolic blood pressure $\geq$140/90 mmHg), cardiac or thyroid disease, or any other medical complications known to interfere with the outcome of the present study, including the medications that could affect cardiovascular function or metabolism, were excluded. Among the fifteen obese men involved in the study, four of them were dropped out for personal reasons (two at the patient's request and two because of difficulties with scheduling), all of whom were observed before the achievement of phase 1 (5 kg weight loss). Participants gave their written consent to participate in the present study that received approval of the Laval University Medical Ethics Committee.

The weight-loss programme consisted of a previously described[7] supervised diet and exercise clinical intervention that was conducted until a weight-loss plateau was observed. Briefly, a dietitian prescribed a diet plan that included a moderate energy restriction of approximately 2930 kJ/d (700 kcal/d) and nutritional recommendations that are known to favour satiety. The aerobic exercise programme was established following a progressive treadmill exercise to exhaustion (VO_{2max}) to fix exercise intensity of the physical activity follow-up, which was then fixed between 60 and 75 % of the measured VO_{2max} at a frequency of two to three times per week for a duration of 20–30 min per session. The intensity of the exercise prescription was increased progressively over a period of approximately 1–2 months, depending on the initial physical fitness of each subject. In addition, the frequency was increased to three to five sessions per week and the duration to 40–60 min per session based on our experience. To ensure proper monitoring of exercise intensity and duration, the participants had to wear a heart rate monitor (Polar Vantage XL™ HRM, Stamford, CT, USA) during their exercise sessions. On the basis of this prescribed exercise, it was estimated that exercise had the potential to accentuate the daily energy deficit by about 400 kJ/d at the beginning of the programme up to 1200–1500 kJ/d several months after its initiation. The participants came for follow-up visits every 2 weeks to verify compliance with the weight-loss programme. All the measurements were performed at the beginning of the intervention (baseline), after each 5 (SE 1) kg weight loss, and at the weight-loss plateau, even if a further 5 kg weight loss was not obtained. We defined the weight-loss plateau as no change in body weight during 1 month of intervention (i.e. $\pm$1 kg maximum). We predicted a clinical intervention of 6–10 months before reaching this plateau, which was anticipated to occur after 10–12 % decrease in the initial body weight, as shown previously[8].

Body weight and height were measured following standardised procedures[9]. Body density was determined by the underwater weighing technique[10]. The closed-circuit helium dilution method[11] was used to assess the residual lung volume. The Siri formula was used to estimate the percentage of body fat from body density[12]. Fat-free mass and FM were estimated from the body weight and the percentage of body fat. RMR measurement was obtained by indirect calorimetry in the morning, after a 12-h overnight fast, as described previously[7].

The following equation was used to predict RMR at baseline, phase 1 (5 kg weight loss), phase 2 (10 kg weight loss) and plateau (resistance to further weight loss) in the obese men involved in the weight-loss programme:

$$\text{RMR (kJ/min)} = 1{\cdot}28 + 0{\cdot}023 \times \text{FM (kg)} + 0{\cdot}052 \times \text{fat-free mass (kg)} \quad (r^2\ 0{\cdot}67,\ P < 0{\cdot}0001).$$

This reference equation was established from a control group of men (n 112) of the same age group from the Quebec Family Study, as reported previously[1]. This equation has been shown to be equally applicable to the individuals of varying degrees of adiposity within the control population[1]. In addition, changes in RMR (extrapolated over 24 h) from baseline for the measured and predicted values of RMR, respectively, were calculated as follows:

$$((\text{measured RMR at phase 1, phase 2 and plateau}) - \text{measured RMR (baseline)}) \times 1440;$$

$$((\text{predicted RMR at phase 1, phase 2 and plateau}) - \text{predicted RMR (baseline)}) \times 1440.$$

Hence, the adaptive reduction in thermogenesis was considered as the difference between the changes in the predicted RMR from the reference equation and the changes in the measured RMR. In other words, it represented the greater than predicted decrease in RMR induced by the weight-reducing programme. Furthermore, mean body energy loss was calculated from hydrostatic weighing measurements by assuming that the energy equivalent of fat and lean tissues corresponds to 38 911 kJ/kg (9300 kcal/kg) and 4268 kJ/kg (1020 kcal/kg), respectively[13]. This energy loss was used to determine the measured energy deficit (kJ/d) at each phase of the weight-loss programme.

Statistical analysis

Repeated-measures ANOVA was performed on the means of all variables. Tukey's *post hoc* test was then performed to contrast mean differences. We also used Pearson's correlation to determine the association between the adaptive reduction in thermogenesis and the degree of fat loss at plateau. We indicate that the significance of results obtained did not change if a non-parametric procedure was chosen instead of the parametric procedure. All statistical analyses were performed with JMP version 5.1.2 program (Statistical Analysis Systems Institute, Cary, NC, USA). Data are presented as means with their standard errors. Statistical significance was set at $P<0{\cdot}05$.

Results

Among the eleven obese men who completed the programme, three of them experienced a weight-loss plateau after 10 (SE 1) kg weight loss and were thus not retested for the specific phase of resistance to further weight loss. Therefore, eight participants presented full data at four time points and were included in the present analyses. The characteristics of these eight subjects are presented in Table 1. A total of 8·1 (SE 1·3) months were necessary before reaching a plateau in weight loss. When we tested the subjects at the weight-loss plateau, a mean weight loss of 12·4 % of the initial body weight (93·8 % from fat stores) had been reached. We also observed that the measured RMR values were significantly reduced at each phase of the programme compared with baseline values ($P<0{\cdot}05$). Interestingly, a greater decline in the measured RMR occurred at plateau since the mean value was significantly different from that observed after phase 2 ($P<0{\cdot}05$). Although the predicted values of RMR were slightly reduced in response to the weight-loss programme, these differences were not statistically significant except for the phase of plateau ($P<0{\cdot}05$ *v.* baseline). We also observed that the measured RMR values at phase 1 and plateau were significantly lower than the predicted values ($P<0{\cdot}05$). This difference between the predicted and measured RMR was 0·46 and 0·66 kJ/min for phase 1 and plateau, respectively, and the adaptive reduction in thermogenesis at plateau was significantly more important when compared with the other phases ($P<0{\cdot}05$). Finally, we observed a positive relationship (r 0·64, $P<0{\cdot}05$) between the reduction in thermogenesis and the degree of FM depletion at plateau (expressed as a percentage of the initial fat content).

Table 2 shows that the period of time between phase 2 and plateau was characterised by a significantly lower measured energy deficit compared with the other phases of the programme and the prescribed dietary energy deficit ($P<0{\cdot}05$). From a quantitative standpoint, this table also shows that the compensation in energy balance that occurred during this last phase of the programme (2281 kJ/d) corresponded to 77·9 % of the prescribed energy balance. Furthermore, it is important to emphasise that the adaptive reduction in thermogenesis observed during this phase (705·6 kJ/d; Table 1) represented 30·9 % of this compensation.

Discussion

The main preoccupation underlying the present study was to evaluate the extent to which diminished thermogenesis may contribute to the occurrence of resistance to lose fat in obese men subjected to a weight-reducing programme. As described previously[1–3], we considered the adaptive reduction in thermogenesis as the decrease in energy expenditure that exceeded the value predicted by the decrease in fat-free mass and FM in a reference population. From a methodological standpoint, we thus compared the predicted and the measured change in RMR at each testing phase of the study, including the state of resistance to further lose weight/fat. The results showed that the adaptive reduction in thermogenesis was quantitatively significant in response to weight loss, as previously reported by Leibel *et al.*[5] and our research group[1,14]. The present results also confirm the concept that the adaptive reduction in thermogenesis is a phenomenon that can be detected early during the course of a weight-reducing programme[1]. In this regard, the uniqueness of the

Table 1. Characteristics of male subjects over the course of the weight-reducing programme
(Mean values with their standard errors)

	Programme phases							
	Baseline		Phase 1		Phase 2		Plateau	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (years)	38	5	–		–		–	
Body weight (kg)	102·8	4·5	97·1*	4·6	92·1†	4·8	90·1	4·7
BMI (kg/m^2)	33·6	0·8	31·4*	0·9	29·8†	0·8	29·2	0·9
Fat mass (kg)	35·6	2·9	29·3*	3·2	25·2†	3·1	23·5	3·2
Fat-free mass (kg)	67·7	3·1	67·9	2·6	67·4	2·4	66·9	2·8
Body fat (%)	34·8	1·9	30·0*	1·7	27·3†	1·9	26·1	1·8
Measured RMR (kJ/min)	5·42	0·17	5·02*	0·16	5·10*	0·15	4·65‡	0·19
Predicted RMR (kJ/min)‖	5·59	0·18	5·48§	0·18	5·36	0·17	5·31*§	0·17
Adaptive thermogenesis (kJ/d)¶	–		417·6	36·3	129·6†	10·6	705·6†‡	65

* Mean values were significantly different from baseline ($P<0{\cdot}05$).
† Mean values were significantly different from phase 1 ($P<0{\cdot}05$).
‡ Mean values were significantly different from phase 2 ($P<0{\cdot}05$).
§ Mean values were significantly different from the measured RMR values ($P<0{\cdot}05$).
‖ Predicted RMR = 1·28 + 0·023 × fat mass (kg) + 0·052 × fat-free mass (kg).
¶ Difference between the changes in the predicted RMR from the reference equation and the changes in the measured RMR.

Table 2. Prescribed and measured daily energy deficit at each phase of a weight-loss programme in obese men

(Mean values with their standard errors)

	Time period					
	Baseline to phase 1		Phase 1 to phase 2		Phase 2 to plateau	
	Mean	SE	Mean	SE	Mean	SE
Number of days	78·1	14·3	63·7	12·1	105·2*†	11·8
Prescribed dietary energy deficit (kJ/d)	2930	–	2930	–	2930	–
Measured energy deficit (kJ/d)§	3129	234	2539*	205	649*†‡	66
Daily energy compensation (kJ/d)‖	−199	18*	391*	32	2281*†	276

* Mean value was significantly different from baseline to phase 1 ($P<0·05$).
† Mean value was significantly different from phase 1 to phase 2 ($P<0·05$).
‡ Mean value was significantly different from the prescribed dietary energy deficit ($P<0·05$).
§ Mean body energy loss (38 911 and 4268 kJ/kg for fat mass and fat-free mass, respectively) multiplied by the number of days.
‖ Prescribed dietary energy deficit − measured energy deficit.

present study pertains to the demonstration that the adaptive reduction in thermogenesis becomes significantly greater when resistance to lose weight/fat occurs.

In order to quantify the relative importance of the adaptive reduction in thermogenesis at plateau, we had to rely on indicators reflecting targeted and measured energy balance during the programme. We thus estimated the body energy deficit during each phase of the programme by calculating the energy equivalent of morphological changes measured with the hydrostatic weighing technique. Moreover, we used the targeted dietary restriction as a constant reference value of theoretical energy deficit, while keeping in mind that the targeted 2930 kJ/d deficit was susceptible to vary according to the good perception of the subjects and the variations in physical activity practice. Thus, the comparison of a theoretical and measured body energy deficit gave us the opportunity to derive an index of compensation in energy balance during the course of the programme. In this regard, data presented in Table 2 provide a significant support to the value and the usefulness of our estimates since the prescribed and measured energy deficit were comparable during the first two phases of the programme. Indeed, the subjects were maintaining weight loss at a rate of 75 g/d during these phases, corresponding to a mean measured energy deficit of 2864 kJ/d. This weight loss stability, however, drastically changed in the plateau phase where mean body weight loss was 19 g/d before reaching a zero value. During this period, compensation in energy balance (2281 kJ/d) corresponded to 78 % of the theoretical energy deficit. Furthermore, it is important to note that at plateau, the high level of observed adaptive reduction in thermogenesis at rest explained about 30 % of this compensation in energy balance. Since the adaptive reduction in thermogenesis also occurs in the active state[6], it is likely that we could have been able to measure a greater contribution of thermogenic adaptations to changes in energy balance over time if we could have measured total daily energy expenditure in the present study. Therefore, even if changes in appetite control and energy intake occurring with weight loss remain important determinants of resistance to lose fat in obese individuals[15], it is likely that the adaptive reduction in thermogenesis also represents an important contributor to the inability to further lose weight over time.

The link observed between the adaptive reduction in thermogenesis and the degree of fat loss suggests that the greater the percentage reduction in body fat, the greater the reduction in adaptive thermogenesis, and hence the greater the total thermogenic economy. This agrees with the results from Dulloo & Jacquet[16], showing that in response to food deprivation in non-obese men subjected to semi-starvation, the amount of reduction in thermogenesis during weight loss was largely predicted by the degree of body fat depletion. According to these authors, this may reflect the operation of a control system with a negative feedback loop between a component of regulatory thermogenesis and the state of depletion of fat stores.

In a recent study, we used sleeping metabolic rate measured by whole-body indirect calorimetry to estimate thermogenic changes observed in response to weight loss. We used the same strategy of comparison of the predicted and measured scores of energy expenditure, which revealed a difference of about 400 kJ/d at the time the subjects were not losing any more weight and fat[17]. Interestingly, the present study also allowed an analysis of the potential determinants of thermogenic changes induced by weight loss. We were surprised by the results which showed that half of the variance in the greater than predicted decrease in sleeping metabolic rate was explained by the changes in plasma concentration of organochlorine compounds that are known to negatively impact on thyroid function[18], skeletal muscle oxidative enzyme potential[19] and mitochondrial functionality[20].

In conclusion, a growing body of evidence supports the potential of the adaptive reduction in thermogenesis in attenuating the success of obesity treatment. In this regard, the present study added critical information to the literature by documenting the contribution of the adaptive reduction in thermogenesis during the phase of weight-loss plateau that seems to be substantially greater than what has been traditionally considered by health professionals and scientists.

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